Summary Table of Study Protocol

Title	Postmarketing Surveillance Study for Kyprolis® (carfilzomib) in Korea (study number 20160117)
Protocol version identifier	Final version 1.0
Date of last version of the protocol	29 March 2016
EU Post Authorisation Study (PAS) Register No	
Active Substance	carfilzomib
Medicinal Product	Kyprolis®
Product Reference	NA
Procedure Number	
Sponsor	Amgen Korea
Joint PASS	No
Research Question and Objectives	To assess safety and effectiveness of Kyprolis® in post-marketing real-life setting
Country(-ies) of Study	Korea
Author	[redacted] Sr. medical advisor, region (Asia) Amgen

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Confidentiality Notice

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This document must not be disclosed to anyone other than the site study staff and members of the Institutional Review Board/Independent Ethics Committee/Institutional Scientific Review Board or equivalent, as applicable.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the research without the prior written consent of Amgen Inc.

Investigator's Agreement

I have read the attached protocol entitled Postmarketing Surveillance Study for Kyprolis® (Carfilzomib) in Korea, dated 29 March 2016, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator Date (*DD Month YYYY*)

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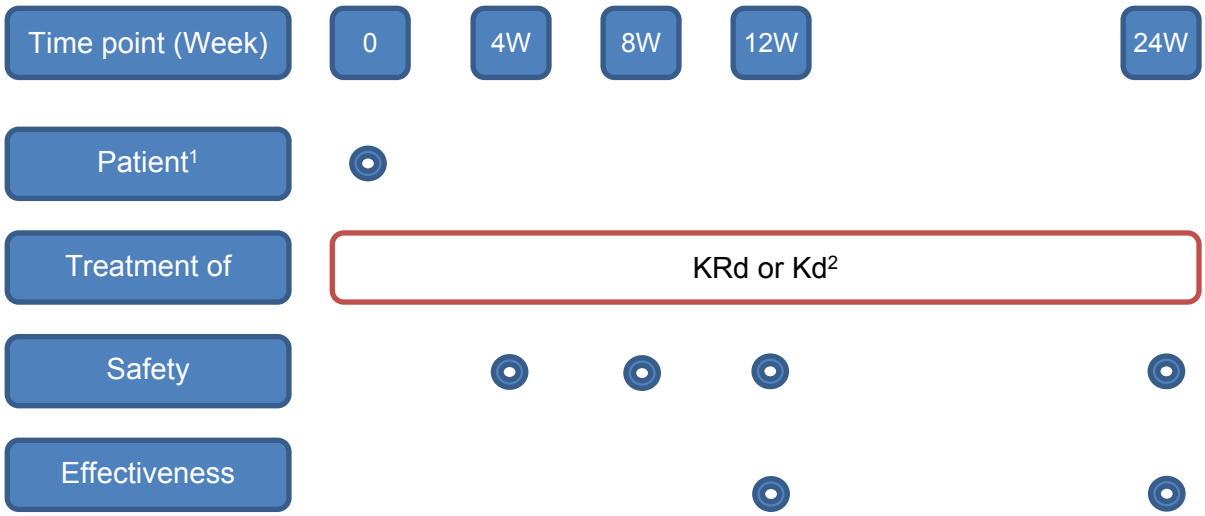
Study Design Schema



1. Patient with multiple myeloma who have received at least on prior therapy.
2. KRd (Kyprolis (carfilzomib), Revlimid (lenalidomide) and low-dose dexamethasone) or Kd (Kyprolis (carfilzomib) and low-dose dexamethasone) administered on D1, 2, 8, 9, 15, 16 per cycle, 1 cycle: 28 days (Refer to Table 1 and Table 2 for details).

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1. Table of Contents

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2. List of Abbreviations

Abbreviations	Definition of the Terms
ADR	Adverse Drug Reaction
AE	Adverse Event
CRF	Case Report Forms
CI	Confidence Interval
CR	Complete Response
sCR	stringent Complete Response
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
ECOG	Eastern Cooperative Oncology Group
FLC	Free Light Chain
HR	Hazard Ratio
ICMJE	International Committee of Medical Journal Editors
IMWG	International Myeloma Working Group
INN	International Nonproprietary Name
IRB	Institutional Review Board
ISS	International Staging System
IV	Intravenous(ly)
KIDS	Korea Institute of Drug Safety and Risk Management
Kd	Kyprolis (carfilzomib) and low-dose dexamethasone
KRd	Kyprolis (carfilzomib), Revlimid (lenalidomide) and low-dose dexamethasone
K-RMP	Korea Risk Management Plan
MFDS	Ministry of Food and Drug Safety
ORR	Overall Response Rate
PFS	Progression-Free Survival
PMS	Post Marketing Surveillance
PR	Partial Response
Rd	Revlimid (lenalidomide) and low-dose dexamethasone
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
TTP	Time to Progressive
VGPR	Very Good Partial Response
Vd	Velcade (Bortezomib) and low-dose dexamethasone

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3. Responsible Parties

Sponsor: Amgen Korea

Investigators: Investigators at medical institutions with active contracts for this study, Korea.

4. Abstract

- Study Title

Postmarketing Surveillance Study for Kyprolis® (Carfilzomib) in Korea

- Study Background and Rationale

According to local regulation, a regulatory post-marketing surveillance study is required for new medicines approved in Korea to collect safety and effectiveness data in routine clinical practice.

Korea Risk management plan (K-RMP) of Kyprolis® includes this study as a part of pharmacovigilance plan.

- Research Question and Objective
  - Primary Objective

    The primary objective of this study is to determine the incidence of adverse events (AEs), serious AEs and adverse drug reactions (ADRs) among patients with at least 1 prior therapy receiving Kyprolis® in real-life setting in its registered indication(s) as required by MFDS. Kyprolis is indicated in combination with lenalidomide and dexamethasone or just with dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
  - Secondary Objective

    The secondary objective of this study is to investigate effectiveness of Kyprolis® (Overall Response Rate).
  - Hypothesis(es) / Estimation

    There is no hypothesis to be tested. Instead, the proposed study will provide descriptive data on real-life use of Kyprolis® and adverse event occurrence in patients in Korea.

- Study Design/Type

Prospective observational study in post marketing setting without a comparator arm

- Study Population or Data Resource

Patients for whom Kyprolis® is prescribed at participating medical institutions in accordance with the approved Korea prescribing information (Kyprolis is indicated in combination with lenalidomide and dexamethasone or just with dexamethasone for the

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treatment of patients with multiple myeloma who have received at least one prior therapy).

The investigator, or a person designated by the investigator will collect the patient's data using the case report forms (CRF) authorized by Amgen Korea. The patient's information needed for analysis and reporting will be entered/transmitted into the validated database or data system. Study data management will be performed according to applicable standards and data cleaning procedures. The database will be locked once the quality control procedures are completed. The original CRFs will be retained by Amgen Korea. The final data collection for each patient will be performed at the time point of 24 weeks (6 cycles) or drop-out. Most of major severe AE should be detected within 6 cycles based on ASPIRE study.

- Summary of patient eligibility criteria

Inclusion criteria: A patient can be included into the study only if all of the following criteria are met:

1. Signed and dated informed consent
2. Patients diagnosed with multiple myeloma who have received at least one prior therapy
3. Patients who are prescribed with Kyprolis® (in combination with lenalidomide and dexamethasone or in combination with dexamethasone) for the first time

Exclusion criteria: All contraindications specified in the local product information have to be considered. In addition, patients treated with any regimens not specified in the approved prescribing information of Kyprolis® in Korea should be excluded from the study.

- Follow-up
  - The total follow-up period is 24 weeks.
    - Safety assessment will be performed at 4 weeks, 8 weeks, 12 weeks and 24 weeks.
    - Response assessment will be performed at 12 weeks and 24 weeks.
  - The study protocol does not define exact referral dates for follow-up visits. Follow-up visits occur during routine practice. The investigator documents the date of initial visit and follow-up in the case report form and follows the study procedures (usually pertaining to data collection only) for the visit.

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- Variables
  - *Outcome Variables*
    - Patient demographics and medical history
    - Diagnostic information
    - Prior and Concomitant medication
    - Prior anti myeloma therapy
    - Myeloma characteristics eg, cytogenetic risk
    - Safety: Adverse events (AEs) including serious adverse events and adverse drug reactions (ADRs)
    - Effectiveness: Overall response rate (ORR, %) according to the International Myeloma Working Group (IMWG) uniform response criteria to assess the tumor response (sCR, CR, VGPR, or PR) (Appendix F)
    - Laboratory values

- Study Sample Size

The sample size will be 700 patients (at least 600 patients required for satefy analysis according to local regulation).

- Data Analysis

Patient demographics, baseline characteristics, medical history and concomitant drug use will be summarized. For the safety analysis, adverse event will be presented using the number of treated patients, incidence proportion and number of patients with events. For the effectiveness analysis, overall response rate at 12 and 24 weeks after drug administration will be analysed.

5. Amendments and Updates

None.

6. Milestones

The given period of re-examination is 6 years from the time of product approval obtained as a new medicine in Korea.

Regular interim reports should be submitted to MFDS every 6 months for the first 2 years and annually afterward during the period of re-reexamination. The due date for submission of each regular interim reports date will be determined depending on the approval date of Kyprolis® in Korea.

The re-examination report (ie, the final study report) will be prepared and submitted to MFDS within the specific timeline, in three months after completion of re-examination period, according to local regulation.

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7. Rationale and Background

7.1 Diseases and Therapeutic Area

Multiple myeloma is an incurable and fatal plasma cell malignancy and is the second most common lymphoid malignancy worldwide [1],[2]. Three drugs that have been commonly treated to patients with relapsed multiple myeloma are lenalidomide (Revlimid, R), an IMiD; bortezomib (Velcade, V), a proteasome inhibitor; and liposomal doxorubicin (in combination with bortezomib)[3]. There is significant room for improvement as none of these agents have been reported to extend median disease-free intervals (PFS or TTP) past 14 months in large, registrational Phase 3 trials [4]-[6].

As of 19 January 2016, Overall, an estimated 3040 subjects (2522 subject-years) have been exposed to carfilzomib in clinical trials conducted by Onyx since the beginning of the development program. The results from the PX-171-009 (ASPIRE) study demonstrated that Kyprolis® may provide an important treatment option for patients with relapsed multiple myeloma. This Phase 3 study was a randomized, open-label, multicenter study comparing 2 treatment regimens (carfilzomib, lenalidomide, low-dose dexamethasone [“KRd”] versus lenalidomide, low-dose dexamethasone [“Rd”]) for patients with relapsed multiple myeloma with 1 to 3 prior therapies. A total of 792 patients were enrolled (396 per arm). The trial demonstrated that Kyprolis® improved progression-free survival (PFS) with a hazard ratio (HR) of 0.69 (95% confidence interval [CI]: 0.57, 0.83; $p < 0.0001$). The patients in the KRd treatment arm had a significantly longer duration of PFS than did the patients in the Rd arm, with a median PFS duration of 26.3 months (95% CI: 23.3, 30.5) versus 17.6 months (95% CI: 15.0, 20.6), respectively—a difference of 8.7 months at the median.

In addition, the results from Phase 3 study 2011-003 (ENDEAVOR) in relapsed multiple myeloma demonstrated superiority of Kd (Kyprolis (carfilzomib) and low-dose dexamethasone) over Vd (Velcade (Bortezomib) and low-dose dexamethasone), a current standard of care for this patient population, based on a 9.3 month improvement in PFS for those randomized to Kd (median PFS 18.7 months versus 9.4 months; HR 0.53; 95% CI: 0.44, 0.65, p-value < 0.0001).

7.2 Rationale

According to local regulation, regulatory post-marketing surveillance study is required for new medicines approved in Korea to collect safety and effectiveness data in a routine clinical practice.

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Korea Risk management plan (K-RMP) of Kyprolis® includes this study as a part of pharmacovigilance plan.

7.3 Statistical Inference (Estimation or Hypothesis [es])

There is no formal hypothesis to be tested. Instead, the proposed study will provide descriptive data on real-life use of Kyprolis® and adverse event occurrence in patients in Korea. While the study does not target any specific patient sub-populations, it will collect data on patient characteristics with respect to "important missing information for safety" in MFDS.

8. Research Question and Objectives

To obtain the safety information and effectiveness of the product in the real-life use of Kyprolis® in Korea.

8.1 Primary

The primary objective of this study is to determine the incidence of adverse events (AEs), serious AEs and adverse drug reactions (ADRs) among patients receiving Kyprolis® in real-life setting in its registered indication(s) as required by MFDS.

8.2 Secondary

The secondary objective of this study is to investigate effectiveness of Kyprolis® (Overall Response Rate).

8.3 Exploratory Objective(s)

The exploratory objective of this study is to identify patients characteristics associated with the safety and effectiveness of Kyprolis®.

9. Research Methods

9.1 Study Design

This regulatory PMS is a single-arm prospective observational study on the patients with multiple myeloma who have received at least one prior therapy and then Kyprolis® in combination with lenalidomide and dexamethasone or just with dexamethasone in real-life setting. The decision to treat a patient with Kyprolis® must be independent of the patient's inclusion in the study. No study drug will be provided by Amgen Korea. There will be no control group. All data required for the purpose of this study will be collected during routine visits.

700 patients will be enrolled to meet the minimum requirement (600 patients for safety analysis) of MFDS. The safety assessment will be performed at 4 week, 8 week, 12 week and 24 week. The objective response assessment will be performed per routine

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clinical practice and captured at 12 week and 24 week. (Refer to.Table 3 for details.) Monitoring of adverse events (AEs) will continue until last follow-up visit (28 days after last injection or 24W after initial prescription of Kyprolis®). The given re-examination period is 6 years from the time of product approval.

9.2 Setting and Study Population

Patients prescribed with Kyprolis® in accordance with the approved Korean prescribing information at participating medical institutions will be enrolled in this study. Prior to enrolling patients, investigators should consult the full prescribing information for Kyprolis® and familiarize themselves with the safety information in the product package label. (Kyprolis is indicated in combination with lenalidomide and dexamethasone or just with dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy).

9.2.1 Study Period

Enrollment Period：5 year from the time of product approval

Data Collection Period：6 year from time of product approval

9.2.2 Selection and Number of Sites

This study will be performed using consecutive registration method for patient enrolment.

After a study contract is signed, the study investigator shall, until the contracted number of cases is reached, consecutively enroll the patients who are naïve to the Kyprolis® and will start to receive the study drug.

To be eligible for the study, medical institutions which have adopted or purchased Kyprolis will be selected as PMS sites.

About 40 nation-wide medical institutions, either general hospitals or cancer centers, will participate in this study and recruit patients. The centers will be asked to recruit patients consecutively wherever possible. Korean medical team reviews candidate investigators. Finally appropriate clinical sites will be selected and reviewed by functional review process in medical team in accordance with local operational instruction.

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9.2.3 Patient/Healthcare Professional Eligibility

9.2.3.1 Inclusion Criteria

A patient can be included into the study only if all of the following criteria are met:

1. Signed and dated informed consent
2. Patients diagnosed with multiple myeloma who have received at least one prior therapy
3. Patients who are prescribed with Kyprolis® (in combination with lenalidomide and dexamethasone or in combination with dexamethasone) for the first time

9.2.3.2 Exclusion Criteria

All contraindications specified in the local product information have to be considered. In addition, patients treated with any regimens not specified in the approved prescribing information of Kyprolis® in Korea should be excluded from the study.

9.2.4 Matching

No matching is used.

9.2.5 Baseline Period

The baseline data (eg, laboratory tests, concurrent medication, number of prior lines, cytogenetic risk, ISS, prior medication for multiple myeloma, etc.) will be collected before initial injection of Kyprolis®.

9.2.6 Study Follow-up

Each patient is followed-up at monthly visits for the first three months and then a follow-up visit at 6 months. Only safety data is collected during the first two monthly follow-up visits.

The end of follow-up for each patient is defined as death, loss to follow-up (eg, patients transferring to another clinic), 28 days from the last injection of Kyprolis® or 24 weeks after initial prescription of Kyprolis®, whichever occurs first.

* For the combination regimen with lenalidomide and dexamethasone, administer Kyprolis® intravenously as a 10-minute infusion on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 1. Each 28-day period is considered one treatment cycle.

For the combination regimen with dexamethasone, administer Kyprolis® intravenously as a 30-minute infusion on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 2. Each 28-day period is considered one treatment cycle.

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Table 1. Kyprolis® in Combination with Lenalidomide and Dexamethasone

	Cycle 1									
	Week 1			Week 2			Week 3			Week 4	
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Days 23-28
Kyprolis® (mg/m^2)	20	20	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-
	Cycles 2 to 12										
	Week 1			Week 2			Week 3			Week 4	
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Days 23-28
Kyprolis® (mg/m^2)	27	27	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-
	Cycles 13 and later[a]										
	Week 1			Week 2			Week 3			Week 4	
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Days 23-28
Kyprolis® (mg/m^2)	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-

[a] Kyprolis® is administered through Cycle 18; lenalidomide and dexamethasone continue thereafter.

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Table 2. Kyprolis® in Combination with Dexamethasone

	Cycle 1											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24-28
Kyprolis® (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-
	Cycles 2 and later[a]											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24-28
Kyprolis® (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-

[a] Treatment may be continued until disease progression or unacceptable toxicity occurs.

9.3 Variables

Information described in Sections 9.3.1-9.3.3 is collected in CRFs per a patient. CRF is used to collect data from baseline, week 4, week 8, week 12, and week 24. Adverse event and other safety information are collected throughout the follow-up period.

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Table 3. Overview of variables collected during the study

	Initial visit	Follow-up visits (week)			Last visit[6]
Schedule Procedure	Kyprolis® treatment starting	4	8	12	Final assessment (at 24 weeks) or last follow-up (28 days after last injection)
Eligibility	X				
Informed consent	X				
Demographic data[1]	X				
Myeloma history					
Previous medical history and Concomitant disease[2]	X				
Diagnostic information about multiple myeloma[2]	X				
Visit date	X	X	X	X	X
Treatment of Kyprolis®[3]	X	X	X	X	X
Adverse Events[4]		X	X	X	X
ECOG PS	X			X	X
Tumor response assessment[5]				X	X

1. Site name / Investigator's name, Patient's identifier / Patient's initials, Gender / Age, Height / Weight, Pregnancy
2. Date of diagnosis, international staging system (ISS) stage at study entry, site of metastasis and previous treatment regimen for multiple myeloma or number of previous treatment
3. Please refer to the detailed dose and administration schedule in Table 1 and Table 2.
4. AEs tracking up to 28 days after the last injection of Kyprolis® or 24 weeks after initial prescription of Kyprolis®.
5. Evaluated according to IMWG criteria. Based on the investigator's clinical assessment if a patient could not have radiological examination, , because of deterioration of medical condition
6. The last visit will occur at 28 days after the termination of treatment or the final assessment at 24W.

9.3.1 Exposure Assessment

Dosage, period (start / end date), frequency of administration, drug withdrawal (Yes or No, date, reason) of Kyprolis® with lenalidomide and dexamethasone or with dexamethasone are collected in CRF.

9.3.2 Outcome Assessment

Adverse events (including seriousness and causal relations to drug),and other safety information (eg, overdose, lack of effectiveness, pregnancy and lactation with or without adverse event) are collected as they become available throughout the follow-up period by using CRF and applicable safety reporting form.

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Laboratory values measured as a part of routine medical practice are collected in CRF for baseline, 4W (ranged; 3-5W), 8W (7-9W), 12W (11-13W), and 24W (23-25W) or at the end of follow-up.

Overall response rate: The following assessments will be required for all response categories (sCR, CR, VGPR, or PR; see definitions in Appendix F– IMWG criteria): Patients with confirmed sCR, CR, VGPR, or PR will be considered to have achieved an overall response.

9.3.3 Covariate Assessment

Data on the following covariates are collected in CRF.

Patient demographics and medical history: sex, birth Year/Month, height, weight, pregnancy, site name, investigator's name, medical history of disease (all cancers, and other diseases without relation with cancer within the last 2 years), cardiovascular disease, hepatic impairment, renal impairment, other concomitant diseases

Diagnostic information: information pertaining to Kyprolis® indication including date of diagnosis, international staging system (ISS) stage at study entry, site of metastasis, previous treatment for multiple myeloma or number of previous treatment and cytogenetic risk

Prior and Concomitant medication: Prior (at least 30 days) or concomitant medications including any prescription or over-the-counter preparation and targeted disease therapies or surgical treatments after start of Kyprolis® treatment. All the following variables are to be collected for concomitant medication: trade name or INN, start date (at least year), stop date or "continued" and daily dose (if applicable).

9.3.4 Validity and Reliability

Not applicable.

9.4 Data Sources

The original source of the data used in the study is patient medical records. Data are collected through CRFs, which are populated by the investigators.

Laboratory test values among variable data will be measured by each medical site with their own method.

9.5 Study Size

The minimum required patient number is 600 patients for the final study report. Considering follow-up loss, it is recommended 700 patients be enrolled in study.

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9.6 Data Management

It is an observational study so that variables, which can be measured at medical sites in real-life medical practice, are selected for this study in reference to prior Kyprolis® clinical trials and advice from local medical experts.

9.6.1 Obtaining Data Files

Not applicable.

9.6.2 Linking Data Files

Not applicable.

9.6.3 Review and Verification of Data Quality

Data collection will be conducted by using a validated data system. Data management will be conducted under its own standard operating procedure with oversight by the Amgen Korea.

After collection of CRF, it will be checked for completeness. Missing data should be completed or commented by the investigator. Data from the CRF will be entered in the study database and validated.

Exposures, outcomes, and all other variables observed and measured by each medical site will be collected through data system. Standardized error check will be performed through data validation program. If a logical discrepancy and clear error is identified, a query form will be prepared and delivered to the institutional site investigators for clarification and correction. Site investigators and staff will be requested to check the data against medical records, and accuracy and completeness of data consistent with information in medical records will be confirmed and attested by signature of investigators. A check for duplication of patients will be done. All details of the quality checks will be described in the data management plan.

9.7 Data Analysis

Patient disposition, demographics and baseline characteristics will be summarized. For the safety analysis, adverse event will be presented using the number of patients, incidence proportion and number of events. For the effectiveness analysis, overall response rate at 24 weeks after drug administration will be analysed.

9.7.1 Planned Analyses

Analysis of interim data will be performed at the timing of MFDS periodic interim report (every 6 months for the first 2 years and annually thereafter until re-examination). The final analysis will be conducted at the timing of MFDS re-examination (after 6 years). If

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patient enrollment reaches 700 (considering drop-out), the enrollment will stop and the final analysis will be conducted after 6years.

9.7.1.1 Interim Analysis/Analyses

There will be interim analyses to support safety reporting and assessments of effectiveness endpoints.

Under regulatory requirement, periodical analyses will be conducted in a timeline aligned to MFDS periodic interim report (every 6 months for the first 2 years and annually thereafter until re-examination). The interim result will be reported as a part of MFDS periodic interim report.

9.7.1.2 Final Analysis

The final analysis will be conducted for the re-examination report after all the study data are collected and cleaned.

Patient disposition, demographics and baseline characteristics will be summarized. For the safety analysis, adverse event will be presented using the number of patients, incidence proportion and number of events. For the effectiveness analysis, overall response rate after drug administration will be analysed.

9.7.2 Planned Method of Analysis

9.7.2.1 Analysis Populations

The data will be analyzed using 3 patient populations: CRF-collected population, Safety population and Efficacy population. Reasons for withdrawal will be described for the withdrawn patients.

- CRF-collected population: All patients from whom CRFs have been collected
- Safety population: All patients who have received at least one dose of study product and on whom a follow-up (including telephone visit) has been conducted.
- Efficacy population: All patients who have been included in the Safety population, who also have received study product per protocol, and on whom any post-baseline efficacy evaluation has been done.

9.7.2.2 General Considerations

In general, a descriptive analysis is conducted. Categorical variables are summarized with frequencies and percentages. Continuous variables are summarized with mean, standard deviation (SD), median, minimum, and maximum.

9.7.2.3 Missing or Incomplete Data and Lost to Follow-up

No imputation is to be performed.

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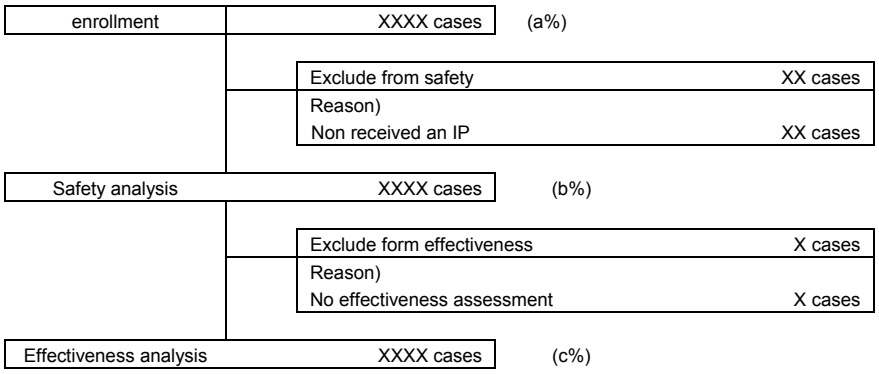
9.7.2.4 Descriptive Analysis

9.7.2.4.1 Description of Study Enrollment

All enrolled patients will be summarized in the tree of patient disposition, as described below:



Percentage of a%, b% and c% (corresponding to enrollment) will be calculated.

9.7.2.4.2 Description of Patient Characteristics

Patient characteristics will be summarized for the following variables.

- Patients demographic: sex (male, female), age(year), the aged (≤ 65 yr, > 65 yr), child (≤18 yr), pregnancy (yes, no), current disease (yes, no), height, weight, blood pressure, medical history of disease (all cancers, and other diseases without relation with cancer within the last 2 years), cardiovascular disease, hepatic impairment, renal impairment, ECOG PS, date of diagnosis, ISS stage at study entry, site of metastasis and previous treatment regimens for multiple myeloma or no of previous treatment.
- Concomitant medication

9.7.2.5 Analysis of the Primary, Secondary and Exploratory Endpoint(s)

Analysis for specified endpoints will be conducted as follows:

- Safety endpoint:
  Number of patients, subject incidence with adverse events, adverse drug reactions and serious adverse events during the observational period will be calculated and summarized (see Section 11.1 the definition of adverse event, serious adverse event, and other safety findings to be collected).
- Effectiveness endpoint:
  Overall response rate for disease assessment - Patients with confirmed sCR, CR, VGPR, or PR will be considered to have achieved an overall response.

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9.7.2.6 Sensitivity Analysis

9.7.2.6.1 Subgroup Analysis

Numbers and percentages of patients with AEs will be provided by patient baseline characteristics (gender, age, etc.), and by special populations (ISS stage, elderly patients, patients with hepatic impairment, patients with renal impairment, regimens (KRd vs Kd), dose, cytogenetics, and other special populations). Effectiveness assessment will be performed equally as well.

9.7.2.6.2 Stratified Analysis

No stratified analysis is pre-planned.

9.7.2.6.3 Sensitivity Analysis for Residual Confounding and Bias

No sensitivity analysis is pre-planned.

9.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

See Section 9.7.2.5.

9.8 Quality Control

Quality control is conducted by checking whether data management operations were conducted based on the standard operation procedures of data management, and all results of quality control, including deviations and their measurements, are documented/reported and deviations are appropriately corrected if they were found.

9.9 Limitations of the Research Methods

This is an observational study, so it has a limitation of internal validity and strength of external validity in comparison with an interventional clinical study. Limitations common to this type of study, along with how to reduce errors, are summarized below.

Limitations	How to reduce errors
Missing and incomplete data are unavoidable, because there are some cases that data could not be collected at all evaluation time points, and some patients could be lost to follow-up.	Efforts will be made to collect as complete data as possible and instructions to investigators.
Selection bias, information bias and confounding cannot be excluded.	Selection of participating medical institutions nationwide Analysis results will be interpreted with caution, acknowledging the limitations, whether or not appropriate statistical methods could be applied to address the bias.

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10. Protection of Human Patients

10.1 Informed Consent

This study requires the informed consent to collect medical data from patients with Kyprolis treatment in a routine clinical practice.

No investigator may involve a patient in this study unless the investigator has obtained the informed consent of patient.

Before starting this study, informed consent shall be documented by the use of a written consent form and signed and dated by the patient at the time of consent. A copy of the signed informed consent will be given to the patient. The original signed consent must be maintained by the Investigator.

10.2 Institutional Review Board (IRB)

This study will be conducted in accordance with any applicable local regulation, IRB requirement. This study will have the approval of a properly constituted IRB if required prior to the start of the study.

The investigator is responsible for notifying their IRB of safety information/event in scope of expedited reporting if required.

10.3 Patient confidentiality

The Investigator must ensure that the patient's confidentiality is maintained for documents submitted to Amgen Korea.

Patient medical information obtained as part of this study is confidential and must not be disclosed to third parties, except as noted below.

The Investigator/Institution will permit direct access to source data and documents by Amgen, its designee, MFDS and other regulatory authorities. The access may consist of study-related monitoring, audits/regulatory inspection and IRB/MFDS reviews.

Release of study results should be preserved for the privacy of medical information and must be carried out in accordance with applicable local regulation.

11. Collection of Safety Information and Product Complaints

11.1 Definition of Safety Events

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

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An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen Korea product prior to reporting the adverse event to Amgen Korea.

– Adverse Drug Reaction

An adverse drug reaction (ADR) is a response to a drug, which is noxious and unintended and which occurs at doses normally used and whose causal relationship to the drug cannot be ruled out. A spontaneously reported AE with unknown relationship to the drug is considered as an ADR.

– Unexpected Adverse Drug Reaction

An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the product labeling is considered unexpected.

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient 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" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient 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 dyspraxia, drug-induced liver injury, events that necessitate an

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emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving an Amgen product,
- Pregnancy and lactation exposure,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s)

11.1.4 Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

11.2 Safety Reporting Requirements

The investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) observed by the investigator or reported by the patient that occur during the pre-determined data collection period (from Initial visit to Last visit) described in Table 3 are recorded in the patient's appropriate study documentation and CRFs.

Serious adverse events and pregnancy cases must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of investigator awareness.

See Appendix C for sample Safety Report Form(s), Appendix D for Additional Safety Reporting Information regarding the adverse event grading scale & criteria for causality assessment used in this study, and Appendix E for sample Pregnancy and Lactation Notification Worksheets.

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.

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Information provided about the event must be consistent with information recorded on study Case Report Forms (CRFs) where safety data also are recorded (eg, Event CRF).

11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required to regulatory authorities, Investigators/institutions, IRBs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB or other relevant ethical review board of Serious Adverse Events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen Korea may amend the protocol at any time. If the protocol is amended, the Investigator has to follow amendments.

13. Plans for Disseminating and Communicating Study Results

The given re-examination period is 6 years from time of product approval and the recruitment period starts from the time of actual product launch. Patients will be followed up until 28 days after last injection of Kyprolis® or the final assessment at 24W after initial prescription of Kyprolis®. For submission of periodic reports to MFDS, interim data summaries will be produced annually although for the first 2 years the report will be provided biannually. Final report will be provided after 6 years.

13.1 Publication Policy

Study result will be submitted for publication as conference abstracts and/or medical journal articles.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

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- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be reviewed through applicable company review processes at Amgen Korea and Amgen prior to submission.

14. Compensation

Not applicable.

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15. References

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[3]. National Comprehensive Cancer Network [NCCN]. Multiple Myeloma Guidelines Version 3. 2016.

[4]. Dimopoulos MA, Chen C, Spencer A, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 Phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia. 2009;23:2147-2152.

[5]. Arnulf B, Pylypenko H, Grosicki S, et al. Updated survival analysis of a randomized phase III study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma. Haematologica. 2012;97(12):1925-28.

[6]. Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized Phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol. 2007;25(25):3892-3901.

[7]. International uniform response criteria for multiple myeloma, April 21, 2010, http://imwg.myeloma.org/international-myeloma-working-group-imwg-uniform-response-criteria-for-multiple-myeloma/, adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008;23:3-9.

[8]. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 14, 2010

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16. Appendices

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Appendix A. List of Stand-alone Documents

None

Approved

Appendix B. ENCePP Checklist for Study Protocols

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Appendix C. Sample Safety Reporting Form(s)

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Appendix D. Additional Safety Reporting Information

Adverse Event severity Scoring system

The NCI Common Terminology Criteria for Adverse Events 4.03 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term [**8**].

Relationship to the study product

(1) Certain

An event occurring in a plausible time relationship to use/administration of the drug, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible. The event must be definitive pharmacologically or phenomenologically using a re-challenge procedure if necessary.

(2) Probable/likely

An event with a reasonable time relationship to use/administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (re-challenge information not available)

(3) Possible

An event with a reasonable time relationship to use/administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

(4) Unlikely

A temporary occurrence which makes a causal relationship to use/administration of the drug improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

(5) Conditional/unclassified

An event about which more data are essential for a proper assessment or the additional data are under examination.

(6) Unassessible/unclassifiable

An event which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

For the reporting purposes, it is considered that the events assessed ‘unlikely’ has no reasonable possibility of a causal relationship between the event and Kyprolis®.

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Appendix E. Pregnancy and Lactation Notification Worksheets

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Appendix F. IMWG criteria [7]

Response	IMWG criteria
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable,[5] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	NA
No change/Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Plateau	NA
Progressive disease5	Increase of ≥ 25% from lowest response value in any one or more of the following: Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[6] Urine M-component and/or (the absolute increase must be ≥200 mg/24 h) Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL Bone marrow plasma cell percentage; the absolute percentage must be ≥ 10%[7] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65mmol/L) that can be attributed solely to the plasma cell proliferative disorder

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Response	IMWG criteria
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[6] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] 4. Decrease in haemoglobin of ≥ 2 g/dL [1.25 mmol/L] 5. Rise in serum creatinine by 2 mg/dL or more [177 _mol/L or more]
Relapse from CR[5] (To be used only if the end point studied is DFS)[8]	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ≥ 5% plasma cells in the bone marrow7 Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008;23:3-9.

Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

[3] Confirmation with repeat bone marrow biopsy not needed.

[4] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

[5] All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression free survival.

[6] For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

[7] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

[8] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease

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Appendix G. ECOG Performance status

Description	Status
Fully active, asymptomatic	0
Ambulatory; capable of carrying out work of a light or sedentary nature, eg, light house work, office work	1
In bed < 50% of the waking time; capable of self-care but not work	2
In bed > 50% of the waking time; capable of only limited self-care	3
Completely bedridden; incapable of self-care	4

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