Summary Table of Study Protocol

Title	Retrospective Analysis of Second Primary Malignancies (SPM) Data From ASPIRE and ENDEAVOR Studies
Protocol version identifier	20220146 version 1.0
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EU Post Authorization Study (PAS) Register No	Yes
Active Substance	carfilzomib
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Joint PASS	No
Research Question and Objectives	• Describe the incidence rate of SPM, time to onset and outcome of SPM. • Describe baseline characteristics of patients with SPMs and without SPM.
Country(ies) of Study	Global
Author	PPD Amgen Inc Global Clinical Development Thousand Oaks, CA PPD

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen
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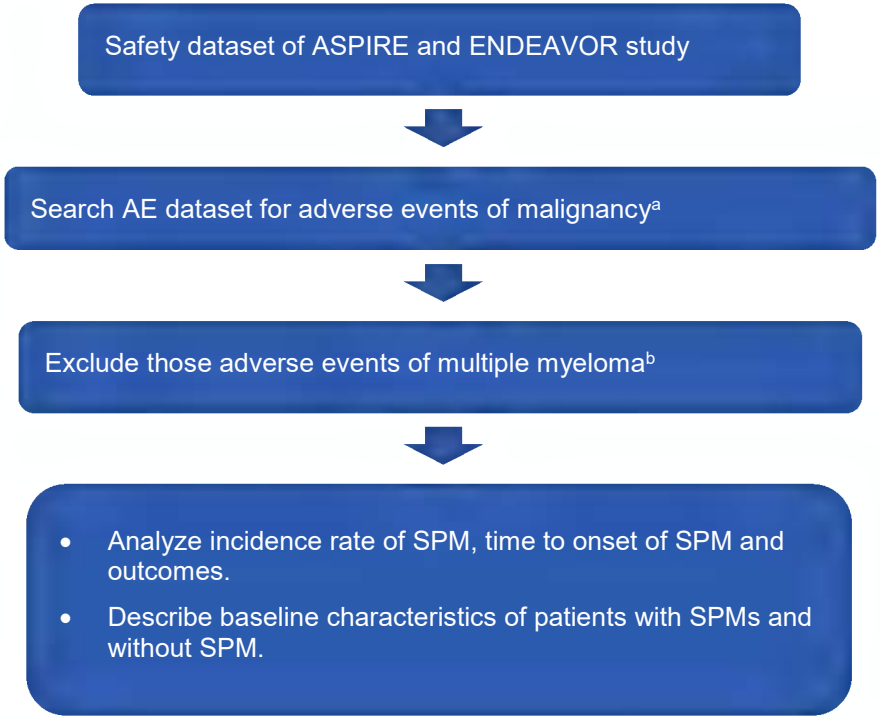
Protocol Version	Date of Protocol	Page Header Date
Original, Version 1.0	20 January 2023	20 January 2023

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Figure 1. Study Design Schema



[a] Malignant tumours SMQ (Narrow scope) and Tumours of unspecified malignancy SMQ (Narrow scope) are used in adverse events data search.

[b] Excluding the following PTs: Plasma cell leukaemia, Plasma cell leukaemia in remission, Plasma cell myeloma, Plasma cell myeloma in remission, Plasma cell myeloma recurrent, Plasma cell myeloma refractory, Plasmacytoma.

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2. List of Abbreviations

Abbreviation or Term	Definition or Explanation
AE	Adverse event
ASCT	Autologous Stem Cell Transplantation
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FDA	Food and Drug Administration
ICF	Informed Consent Form
IMiD	Immunomodulatory drugs, including thalidomide, lenalidomide and pomalidomide.
ISS	International Staging System
Kd	Carfilzomib in combination with dexamethasone
KRd	Carfilzomib in combination with lenalidomide and dexamethasone
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
RRMM	Relapsed or refractory multiple myeloma
R-ISS	Revised International Staging System
RCT	Randomized controlled trial
Rd	Lenalidomide in combination with dexamethasone
SAP	Statistical Analysis Plan
SMQ	Standard MedDRA Queries
SPM	Second primary malignancy
TEAE	Treatment-Emergent Adverse Event
Vd	Bortezomib in combination with dexamethasone

3. Responsible Parties

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4. Abstract

- Study Title

  Retrospective analysis of second primary malignancies (SPM) data from ASPIRE and ENDEAVOR

- Study Background and Rationale

  With the introduction of multiple novel therapeutics including immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies and advances in autologous stem cell transplantation, the overall survival in multiple myeloma patients has drastically improved recently. As survival increases, patients have been observed to develop second primary malignancies after initiation of myeloma therapy. An understanding of whether an elevated rate of development of second primary malignancies is related to, or independent of, the therapeutic agents used for myeloma treatment will further the optimization of myeloma care. Currently there is no evidence showing increased SPM risk in patients receiving proteasome inhibitors. The aim of this analysis is to describe incidence rate of SPM, time to onset and outcomes of SPM and baseline characteristics of patients with SPMs in patients included in the treatment arms, or carfilzomib-free control arms, in two phase 3 randomized clinical trials (ASPIRE,NCT01080391, and ENDEAVOR,NCT01568866). The Safety Analysis Set of these trials will be used in the analysis.

- Study Feasibility and Futility Considerations

  In ASIPIRE study, 781 subjects were randomized and treated with study drug (392 subjects in KRd arm and 389 subjects in Rd arm). In ENDEAVOR study, 919 subjects were randomized and treated with study drug (463 subjects in Kd arm and 456 subjects in Vd arm). Descriptive analysis will be done to estimate incidence rates of SPM that arises after initiation of Study therapy and is reported in the Adverse Events form in each arm of the two studies. Baseline characteristics of patients with SPM will be summarized and listed side-by-side with those without SPM.

- Research Question and Objective(s)

Objectives	Endpoints
Primary	
• Describe the incidence rates of SPM in each arm of ASPIRE and ENDEAVOR	• Overall subject incidence of SPM and of SPM by categories (solid tumor [skin or non-skin cancer], hematologic malignancies, or other non-specified malignancies). • Exposure-adjusted incidence rate of SPM and SPM by category
Secondary	
• Describe the characteristics of SPM in each arm of ASPIRE and ENDEAVOR	• Time to onset of SPM • Outcome of SPM
• Describe the baseline demographic and disease characteristics of patients with SPM and without SPM.	• Baseline demographic and disease characteristics

  - Hypothesis(es)/Estimation

    No formal hypothesis testing is planned for comparison between arms in each of the studies (ASPIRE and ENDEAVOR). All analyses will be descriptive.

- Study Design/Type

  This is a retrospective, post hoc analysis of two phase 3 randomized controlled trials of carfilzomib-based regimen vs non-carfilzomib regimen in patients with relapsed or refractory myeloma after 1 – 3 prior lines of therapy.

- Study Population or Data Resource

  The study population is the safety population from ASPIRE and ENDEAVOR.

- Summary of Subject Eligibility Criteria
  - Subjects signed ICF and enrolled in ASPIRE and ENDEAVOR
  - Subjects randomized and treated with study drug(s)
- Follow-up

  In this analysis based on data from ASPIRE and ENDEAVOR, patient follow-up continued from first dose of any study drug until the end of study (ie, subject withdrew consent for further participation, was lost to follow-up, died, or the sponsor made decision to close the study). Overall duration of follow up on study is defined in months as the time from date of the first dose of any study drug to patient's end of study date.

- Variables
  - Outcome Variables
  - Overall subject incidence of SPM and subject incidence of SPM by category of solid tumor [skin or non-skin cancer], hematology malignancies, or other non-specified

    The subject incidence of SPM in each arm is defined as the number of subjects with the event of SPM divided by the total number of subjects in each arm.

  - Time to onset of SPM

    Time from 1st dose of study treatment to second primary malignancy (date of AE reporting).

  - Outcome of SPM

    Outcomes of SPM include resolved, resolved with sequelae, not resolved, death, unknown. If there are two or more SPM events for one patient, the worst outcome among SPMs will be used in analysis for this patient.

  - Exposure Variables
  - Overall study treatment exposure

    It is defined in months as the time from the date when first dose of any study drugs was started to the date when last dose of all study drugs has ended

  - Exposure to each study drug

    The extent of exposure to each study drug (including duration of treatment and the number of cycles of treatment) will be provided by treatment arm and SPM category. Duration of treatment with a study drug (eg, carfilzomib) is defined as the time from the start date of the first dose to the end date of the last dose. The number of treatment cycles is defined as the total number of treatment cycles in which at least one dose of study drug is administered

  - Other Covariates

    Below list of baseline demographic and disease characteristics contains the covariates that will be described in this analysis.

List 1. Baseline Demographic and Disease Characteristics That may Lead to Increased Cancer Risk

Basline Characteristics	Description (*if relevant)*
Age	<75 vs ≥75 years
Gender	Male vs female
Race	White, Black, Asian, not reported and other
ISS staging at study entry	I vs II vs III
R-ISS staging at study entry	I or II vs III vs not classified
Number of previous lines of therapy	1 vs >1
Time from initial MM diagnosis (months)	
Cytogenetic abnormality (del(17p), t(4;14), t(14;16))	At least one vs. none
ECOG PS at baseline	0 or 1 vs >1
Neutrophil count (10^9/L) at baseline	
Hemoglobin (g/L) at baseline	
Platelet count (10^9/L) at baseline	
Lymphocyte count (10^9/L) at baseline	
Beta 2-microglobulin (mg/L) at baseline	
Serum LDH (IU/L) at baseline	
Albumin (g/L) at baseline	
Previous treatment with IMiD	Yes vs No
Previous treatment with alkylating agents*	Yes vs No
Previous treatment with etoposide	Yes vs No
Previous treatment with platinum-based agents(cisplatin, carboplatin and oxaliplatin)	Yes vs No
Previous treatment with proteasome inhibitors	Yes vs No
Prior history of malignancy(non-myeloma)	Yes vs No
Prior history of ASCT	Yes vs No
Prior history of radiation therapy	Yes vs No
Type of region	Sunny [Australia / Brazil / Spain / Greece / Italy / Turkey] vs Non-sunny [Canada / Czech Republic / France / United Kingdom / Hungary / Japan / Korea, Republic of / New Zealand / Russian Federation / United States]

- * alkylating agents include melphalan, cyclophosphamide, bendamustine, carmustine

- Study Sample Size

  In the ASPIRE study, 781 subjects were randomized and treated with study drug (392 subjects in KRd arm and 389 subjects in Rd arm). In the ENDEAVOR study, 919 subjects were randomized and treated with study drug (463 subjects in Kd arm and 456 subjects in Vd arm). The precision of the subject incidence of SPM was estimated by 95% confidence intervals for a range of potential subject incidence as shown in Table 8-1.

- Data Analysis

  The descriptive statistics will be provided by treatment arm for subjects with SPM and without SPM. Continuous variables are summarized by the non-missing sample size (n), mean, standard deviation, median, interquartile range, minimum, and maximum. Categorical variables are summarized by the number of subjects and percentage in each category.

  – Demographics and baseline characteristics

  Baseline demographic characteristics, MM characteristics, and Prior anti-myeloma treatments (**List 1**) will be described by treatment arm and SPM category (solid tumor [skin or non-skin cancer], hematology malignancies, or other non-specified).

  – Overall study treatment exposure

  Overall extent of exposure will be described by treatment arm and SPM category (solid tumor [skin or non-skin cancer], hematologic malignancies, or other non-specified).

  – Exposure to each study drug

  The extent of exposure to each study drug (including duration of treatment and the number of cycles of treatment) will be provided by treatment arm and SPM category (solid tumor [skin or non-skin cancer], hematology malignancies, or other non-specified).

  – Overall duration of follow up on study
  – Subject Incidence of SPM and characteristics of SPM

  A listing of patients who reported second primary malignancies during the study will be provided.

Malignant tumours SMQ (Narrow scope) and Tumours of unspecified malignancy SMQ (Narrow scope) are used in adverse events data search to identify patients with SPM. Following PTs would be excluded: Plasma cell leukaemia, Plasma cell leukaemia in remission, Plasma cell myeloma, Plasma cell myeloma in remission, Plasma cell myeloma recurrent, Plasma cell myeloma refractory, Plasmacytoma.

This listing will include at least the following items: the PT, the study day of diagnosis (from first dose of study treatment), prior exposure to anti-myeloma treatments, outcome, action taken, grade, causal relationship to carfilzomib, seriousness, subsequent anti-MM therapies (treatment name and initiation date). Listing of deaths of patients with SPM will be also provided.

Subject incidence of SPM and SPM by category (solid tumor [skin or non-skin cancer], hematologic malignancies, or other non-specified) will be summarized based on the listing. Outcomes of SPMs will be summarized by arms.

In addition, the description of SPM will be provided by category and by decreasing incidence of PT for:

- Combined treatment-emergent and post-treatment AEs
- All TEAEs

The following summaries will be provided by SPM category (solid tumor [skin or non-skin cancer], hematologic malignancies, or other non-specified):

- Time from 1st dose of study treatment to second primary malignancy ($<$3, 3 - 6, 6 - 12, 12 - 24, 24-36, $>$36 months)

- Exposure-adjusted analyses of TEAEs

The event rate per patient-year of overall extent of exposure of all study drugs, carfilzomib exposure and event rate per patient-year of time on study will be provided for all SPM TEAEs , and by tumor type (solid tumor [skin or non-skin cancer], hematologic malignancies, or other non-specified).

For subjects with an event, the person-year is calculated as the sum of the time (years) to first TEAE of SPM for all subjects in each arm. For subjects without an SPM event, the entire exposure time for carfilzomib (up to 30 days after the last dose) is considered in the sum of the time for the event rate per patient-year of carfilzomib exposure; the entire exposure time for study drugs (up to 30 days after the last dose of any study drugs) is considered in the sum of the time for the event rate per patient-year of study drug exposure; the entire time from study day 1 up to

patient's end of study date is considered in the sum of the time for the event rate per patient-year of time on study.

5. Amendments and Updates

None.

6. Rationale and Background

This study protocol was developed to address a specific request from US FDA to characterize second primary malignancies (SPM) observed in trials across the carfilzomib development program.

6.1 Diseases and Therapeutic Area

Multiple myeloma (MM) is a malignant neoplasm characterized by the proliferation of neoplastic plasma cells and monoclonal immunoglobulin production. It is the second most common hematologic malignancy, constituting 1–2% of neoplasms worldwide and 2% of all cancer deaths (Siegel RL, et al. 2019). The association between MM and second primary malignancies (SPM) as a long-term risk has long been recognized. Population studies conducted in several countries since 1950s reported an increased incidence of hematologic malignancies, specifically acute leukemia, in MM patients compared with general population (Poh C, et al. 2021). For example, an analysis of the Swedish Family Cancer Database between 1958 and 1996 noted an excess of hematologic SPM in MM patients compared to the general population with a standardized incidence ratio (SIR) of 2.19 (95% CI: 1.74-2.71), indicating that the observed rate of hematologic malignancy development was 2.19 times that of the general population (Dong C, et al. 2001). Another study utilizing the SEER 13 registries to analyze three cohorts of MM patients diagnosed during 1995-1999 (pre-thalidomide, limited use of ASCT), 2000-2004 (post-thalidomide, pre-lenalidomide and bortezomib, increased utilization of ASCT) and 2005-2009 (post-lenalidomide and bortezomib, highest utilization of ASCT) showed the 7.5-year cumulative incidences of SPM to be 4.7%, 6.0% and 6.3% respectively (Costa LJ, et al. 2018). With the introduction of novel therapeutics including immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies and advances in autologous stem cell transplantation, the overall survival in multiple myeloma patients has drastically improved recently (van de Donk N, et al. 2021). As survival increases, SPMs are increasingly relevant considerations for both patients and clinicians. An increased incidence of invasive second primary malignancy has been observed in patients with myeloma receiving lenalidomide, although the observed difference in incidence rate of SPM was attributed to the

increased occurrence of nonmelanoma skin carcinoma (Dimopoulos M, et al. 2012). In a recent study comparing elotuzumab, lenalidomide and dexamethasone (ERd) with lenalidomide and dexamethasone (Rd) in patients with RRMM, the proportion of patients with SPM was 12% in ERd arm and 9% in Rd arm after a minimum follow-up of 70.6 months. The most common SPMs were basal cell carcinoma and squamous cell carcinoma of the skin (Dimopoulos MA, et al. 2020).

Although there is ample literature on increased incidences of SPMs after diagnosis of MM, studies that have considered outcomes have found that not all SPMs lead to death. Instead, the primary cause of death among MM survivors, even for those who develop SPM, is often MM (Alexanian R, et al. 1985; Murakami H, et al. 1992). A population study utilizing the SEER 13 registries to analyze three cohorts of MM patients diagnosed during 1995–99 (pre-thalidomide, limited use of ASCT), 2000–04 (post-thalidomide, pre-lenalidomide and bortezomib, increased utilization of ASCT) and 2005–09 (post-lenalidomide and bortezomib, highest utilization of ASCT) demonstrated a decline in overall mortality over time among MM patients due to a decrease in MM-associated and cardiovascular mortality with no increase in risk of death from SPMs (Costa LJ, et al. 2018). Since the risk of death from MM was significantly higher than the risk of death from SPMs, IMWG panel recommended that the risk of SPMs should not alter the current therapeutic decision-making process in MM. SPM risk should be carefully discussed with the patient in the context of benefits and risks of different treatment options (Musto P. et al. 2016).

With ongoing increase in incidence of myeloma, and increase in duration of therapy and survival, a question of rate of development of SPM in myeloma patients, and its possible relation to myeloma therapy, remains an area of investigation.

6.2 Rationale

SPM risk is multi-factorial in etiology, likely due to a combination of intrinsic and extrinsic risk factors. Intrinsic risk factors include host-related factors such as sex, age, race/ethnicity, comorbidities, genetic predispositions and disease related-factors such as MM disease characteristics (Thomas A, et al. 2012). Extrinsic risk factors include treatment regimen and duration and lifestyle factors known to increase cancer risk such as smoking, sun exposure, obesity (Khan N, et al. 2010). Prolonged treatment with alkylators, especially melphalan, was associated with an increased hematologic SPM risk; likewise, autologous stem cell transplantation appeared to minimally increase SPM risk. Immunomodulatory drugs, specifically lenalidomide, was associated with an

increased SPM incidence, although most studies concluded that the benefits of therapy outweighed any risks of SPM (Poh C, et al. 2021). And generally, the risk of developing hematologic SPMs rose with longer duration of follow-up after MM diagnosis; risk appeared to start 12 months after MM diagnosis and increased with time, with highest rates usually seen at 5–10 years after diagnosis (Costa LJ, et al. 2018). Currently there is no evidence showing increased SPM risk in patients receiving proteasome inhibitors. The aim of this analysis is to describe incidence rate of SPM, time to onset and outcomes of SPM and baseline characteristics of relapsed or refractory myeloma patients treated with or without carfilzomib, developing SPMs in the Safety Analysis Set, in two phase 3 randomized clinical trials (ASPIRE and ENDEAVOR).

ENDEAVOR is a randomized, phase 3, open-label, multicentre study in patients with relapsed or refractory multiple myeloma who had one to three previous treatments. Patients were randomly assigned (1:1) to receive carfilzomib with dexamethasone or bortezomib with dexamethasone. Between June 20, 2012, and June 30, 2014, 929 patients from North America, Europe, South America, and the Asia-Pacific region were randomly assigned to treatment (464 to the carfilzomib group and 465 to the bortezomib group). ASPIRE is a randomized, phase 3, open-label, multicentre study in patients with relapsed or refractory multiple myeloma who had one to three previous treatments and patients were randomly assigned in a 1:1 ratio to receive carfilzomib with lenalidomide and dexamethasone (carfilzomib group) or lenalidomide and dexamethasone alone (control group). Between July 2010 and March 2012, a total of 792 patients in North America, Europe, and the Middle East underwent randomization. (Stewart AK, et al. 2015; Dimopoulos MA, et al. 2016)

6.3 Feasibility and Futility Considerations

In the ASPIRE study, 781 subjects were randomized and treated with study drug (392 subjects in KRd arm and 389 subjects in Rd arm). In the ENDEAVOR study, 919 subjects were randomized and treated with study drug (463 subjects in Kd arm and 456 subjects in Vd arm). Descriptive analysis will be done to estimate incidence rates of SPM in each arm of the two studies. Baseline characteristics of patients with SPM and without SPM will be summarized. The study data of ASPIRE and ENDEAVOR have been published and contain the data elements needed to support this post hoc analysis.

6.4 Statistical Inference (Estimation or Hypothesis[es])

No formal hypothesis testing is planned. All analysis will be descriptive.

7. Research Question and Objectives

7.1 Primary

Describe the incidence rates of SPM in each arm of ASPIRE and ENDEAVOR

7.2 Secondary

Describe the characteristics of SPM in each arm of ASPIRE and ENDEAVOR and the baseline demographic and disease characteristics of patients with SPM and without SPM.

8. Research Methods

8.1 Study Design

This is a retrospective, post hoc analysis of two phase 3 randomized controlled trial of carfilzomib-based regimen vs non-carfilzomib regimen.

8.2 Setting and Study Population

The study population is safety population from ASPIRE and ENDEAVOR. The data source is clinical study database of ASPIRE and ENDEAVOR.

8.2.1 Study Period

Both ASPIRE (conducted from July 14, 2010 to April 28, 2017) and ENDEAVOR (conducted from June 20, 2012 to Feb 5, 2018) have been completed already. Data needed for this analysis will be derived from existing clinical study databases.

8.2.2 Subject Eligibility

8.2.2.1 Inclusion Criteria

- Subjects signed ICF and enrolled in ASPIRE and ENDEAVOR
- Subjects randomized and treated with study drug(s)

8.2.2.2 Exclusion Criteria

NA

8.2.3 Matching

NA

8.2.4 Baseline Period

The baseline period is defined as the period from screening up to the time before the first dose of protocol-specified treatment was given, during which the data obtained. If multiple values were obtained during this time period, then the most recent value prior to the first dose of protocol-specified treatment will be used as the baseline parameter.

8.2.5 Study Follow-up

In this analysis based on data from ASPIRE and ENDEAVOR, patient follow-up continued from first dose of any study drug until the end of study (ie, subject withdrew consent for further participation, was lost to follow-up, died, or the sponsor made decision to close the study). Overall duration of follow up on study is defined in months as the time from date of the first dose of any study drug to patient's end of study date. No additional follow-up visits after study end date will be conducted.

8.3 Variables

8.3.1 Exposure Assessment

Overall extent of exposure of study drugs including carfilzomib will be described by treatment arm.

- Overall study treatment exposure

  It is defined in months as the time from the date when first dose of any study drugs was started to the date when last dose of all study drugs has ended

- Exposure to each study drug

  The extent of exposure to each study drug (including duration of treatment and the number of cycles of treatment) will be provided by treatment arm and SPM category. Duration of treatment with a study drug (eg, carfilzomib) is defined as the time from the start date of the first dose to the end date of the last dose. The number of treatment cycles is defined as the total number of treatment cycles in which at least one dose of study drug is administered

8.3.2 Outcome Assessment

- Primary endpoints:
  - Overall subject incidence of SPM and SPM by categories of solid tumor [skin or non-skin cancer], hematology malignancies, or other non-specified.

    Malignant tumours SMQ (Narrow scope) and Tumours of unspecified malignancy SMQ (Narrow scope) are used in adverse events data search to identify patients with SPM. Following PTs would be excluded: Plasma cell leukaemia, Plasma cell leukaemia in remission, Plasma cell myeloma, Plasma cell myeloma in remission, Plasma cell myeloma recurrent, Plasma cell myeloma refractory, Plasmacytoma.

- Exposure-adjusted incidence rate of SPM

  The event rate per patient-year of overall extent of exposure of all study drugs, carfilzomib exposure and event rate per patient-year of time on study will be provided for all SPM TEAEs , and by tumor type (solid tumor [skin or non-skin cancer], hematology malignancies, or other non-specified).

- Secondary endpoints
  - Time to onset of SPM

    Time from 1st dose of study treatment to second primary malignancy (date of AE reporting).

  - Outcome of SPM

    Number and proportion of patients with different outcome of SPM in each arm of the two studies. Outcomes of SPM include resolved, resolved with sequelae, not resolved, death, unknown. If there are two or more SPM events for one patient, the worst outcome among SPMs will be used in analysis for this patient.

  - Baseline demographic and disease characteristics (shown in List 1) will be collected and summarized .

8.3.3 Covariate Assessment

Below list of baseline demographic and disease characteristics summarizes the covariates that will be described in this analysis.

List 1. Baseline Demographic and Disease Characteristics That may Lead to Increased Cancer Risk

Basline Characteristics	Description (*if relevant)*
Age	<75 vs ≥75 years
Gender	Male vs female
Race	White, Black, Asian, not reported and other
ISS staging at study entry	I vs II vs III
R-ISS staging at study entry	I or II vs III vs not classified
Number of previous lines of therapy	1 vs >1
Time from initial MM diagnosis (months)	
Cytogenetic abnormality (del(17p), t(4;14), t(14;16))	At least one vs. none
ECOG PS at baseline	0 or 1 vs >1
Neutrophil count (10^9/L) at baseline	
Hemoglobin (g/L) at baseline	
Platelet count (10^9/L) at baseline	
Lymphocyte count (10^9/L) at baseline	
Beta 2-microglobulin (mg/L) at baseline	
Serum LDH (IU/L) at baseline	
Albumin (g/L) at baseline	
Previous treatment with IMiD	Yes vs No
Previous treatment with alkylating agents*	Yes vs No
Previous treatment with etoposide	Yes vs No
Previous treatment with platinum-based agents (cisplatin, carboplatin and oxaliplatin)	Yes vs No
Previous treatment with proteasome inhibitors	Yes vs No
Prior history of malignancy (non-myeloma)	Yes vs No
Prior history of ASCT	Yes vs No
Prior history of radiation therapy	Yes vs No
Type of region	Sunny [Australia / Brazil / Spain / Greece / Italy / Turkey] vs Non-sunny [Canada / Czech Republic / France / United Kingdom / Hungary / Japan / Korea, Republic of / New Zealand / Russian Federation / United States]

* alkylating agents include melphalan, cyclophosphamide, bendamustine, carmustine

8.3.4 Validity and Reliability

NA

8.4 Data Sources

All subject data in the ASPIRE and ENDEAVOR were recorded on the Clinical Research Form (CRF). All adverse events of malignancy reported in each arm of the two studies were captured in the Adverse Events Form. The investigator verified the accuracy of data entries by signing the CRF. Clinical monitors performed source data verification to confirm that CRF data are accurate. The sponsor data management department performed the edit check outlined in the data management plan on file. The analysis datasets and variables of each individual clinical trials in this analysis have been validated by sponsor. All data among sources can be linked based on the unique identifier for each subject.

8.5 Study Size

In ASIPIRE study, 781 subjects were randomized and treated with study drug (392 subjects in KRd arm and 389 subjects in Rd arm). In ENDEAVOR study, 919 subjects were randomized and treated with study drug (463 subjects in Kd arm and 456 subjects in Vd arm). The precision of the subject incidence of SPM was estimated by 95% confidence intervals for a range of potential subject incidence as shown in Table 8-1.

Table 8-1. 95% Confidence Interval for a Potential Subject Incidence of SPM

Study/arm	Sample size (N)	Subject incidence of SPM = 1% 95% CI (width)	Subject incidence of SPM = 5% 95% CI (width)	Subject incidence of SPM = 10% 95% CI (width)
ASPIRE	781	0.44, 2.01 (1.57)	3.57, 6.76 (3.19)	7.97, 12.31 (4.34)
KRd	392	0.28, 2.59 (2.31)	3.14, 7.77 (4.63)	7.17, 13.35 (6.18)
Rd	389	0.28, 2.61 (2.33)	2.97, 7.52 (4.55)	7.23, 13.45 (6.22)
ENDEAVOR	919	0.45, 1.85 (1.40)	3.69, 6.62 (2.93)	8.15, 12.14 (3.99)
Kd	463	0.35, 2.50 (2.15)	3.17, 7.36 (4.19)	7.37, 13.03 (5.66)
Vd	456	0.36, 2.54 (2.18)	3.22, 7.47 (4.25)	7.48, 13.23 (5.75)

95% CIs for subject incidence were estimated using the Clopper-Pearson method.

8.6 Data Management

8.6.1 Obtaining Data Files

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data (from the clinical trial database) to be used in the planned analyses. The data of individual clinical trial were entered in Onyx owned clinical databases and Amgen RAVE database. The data handling and electronic transfer of data are described in the data management plan on file. No linking of data files is necessary. For further details, please see Section 8 of the SAP.

8.6.2 Linking Data Files

NA

8.6.3 Review and Verification of Data Quality

The database of each individual clinical trial was subject to edit checks outlined in the data management plan during study execution. Data inconsistencies and suspicious values were reviewed and resolved before the database was locked years ago for analyses in clinical study report. The analysis datasets and variables in each individual clinical trial had been validated by sponsor before database lock. For our analysis (study 20220146), final clinical databases of ASPIRE and ENDEAVOR will be used.

8.7 Data Analysis

8.7.1 Planned Analyses

The planned analysis includes the primary analysis which will be based on the subjects from the ASPIRE and ENDEAVOR that meet the eligible criteria outlined above. The methodology used for each objective is described in the sub-sections below. More details are included in the SAP.

8.7.1.1 Primary Analysis

The primary analysis will be conducted after protocol and SAP are finalized. Primary analysis will include both primary and all secondary endpoints in the protocol. Details of statistical methods used in endpoints analysis are summarized in Section 8.7.2.4. The analysis will be based on the data used for the final analysis of ASPIRE and ENDEAVOR, including subjects that meet the eligible criteria outlined in section 8.2.2.1. The SPM event will be defined based on Malignant tumours SMQ (Narrow scope) and Tumours of unspecified malignancy SMQ (Narrow scope).

For the primary endpoints, subject incidence of SPM and exposure-adjusted incidence rate will be summarized by SPM category and by decreasing incidence of PT. The results will be presented side-by-side for each treatment arm.

For the secondary endpoints, time to onset of SPM will be summarized by the following time categories in months: <3, 3 - 6, 6 - 12, 12 - 24, 24-36, >36 while the number of subjects and percentage in each time category will be presented by SPM category in each treatment arm. The outcome of SPM (resolved, resolved with sequelae, not resolved, death, unknown) will be summarized by the number of subjects and percentage in each category of outcome and by SPM category in each treatment arm. For baseline demographic and disease characteristics (List 1), descriptive statistics will be provided for subjects with SPM and without SPM by treatment arm, Continuous variables are summarized by the non-missing sample size (n), mean, standard deviation, median, interquartile range, minimum, and maximum. Categorical variables are summarized by the number of subjects and percentage in each category.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

All analyses will be descriptive. No formal hypothesis testing is planned.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

The descriptive statistics will identify the extent of missing data. Any relevant information will be included in the SAP for this study. for this analysis, the imputed start date of adverse events will be used in the calculation of time to event onset. The rules for imputing the start date of adverse events and death date are detailed in each SAP of ASPIRE and ENDEAVOR. No imputation will be done for the analysis of subject incidence of SPM and outcome of SPM. Regarding missing (or unknown) values of baseline characteristics in this study, the missing values for continuous variables will not be imputed; the missing values for categorical variables in each individual trial will be reported and classified as Unknown category.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

The subjects will be enrolled based on eligibility criteria outlined in Section 8.2.1.

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

- Demographics and baseline characteristics

  Baseline demographic characteristics and MM characteristics and Prior anti-myeloma treatments (**List 1**) will be described by treatment arm and SPM category (solid tumor [skin or non-skin cancer], hematologic malignancies, or other non-specified). The descriptive statistics will be provided for subjects with SPM and without SPM by treatment arm, Continuous variables are summarized by the non-missing sample size (n), mean, standard deviation, median, interquartile range, minimum, and maximum. Categorical variables are summarized by the number of subjects and percentage in each category.

- Overall study treatment exposure

  Overall extent of exposure will be also described by treatment arm and SPM category (solid tumor [skin or non-skin cancer], hematologic malignancies, or other non-specified). Duration of the overall study treatment will be calculated as the time from the date when first dose of any study drugs was started to the date when last dose of all study drugs has ended.

- Exposure to each study drug

  The extent of exposure to each study drug (including duration of treatment and the number of cycles of treatment) will be provided by treatment arm and SPM category. Duration of treatment with a study drug (eg, carfilzomib) is defined as the time from the start date of the first dose to the end date of the last dose. The number of treatment cycles is defined as the total number of treatment cycles in which at least one dose of study drug is administered

- Subject incidence of SPM and characteristics of SPM

  A listing of patients who reported second primary malignancies during the study will be provided.

  Malignant tumours SMQ (Narrow scope) and Tumours of unspecified malignancy SMQ (Narrow scope) are used in adverse events data search to identify patients with SPM. Following PTs would be excluded: Plasma cell leukaemia, Plasma cell leukaemia in remission, Plasma cell myeloma, Plasma cell myeloma in remission, Plasma cell myeloma recurrent, Plasma cell myeloma refractory , Plasmacytoma.

This listing will include at least the following items: the PT, the study day of diagnosis (from first dose of study treatment), prior exposure to anti-myeloma treatments, outcome, action taken, grade, causal relationship to carfilzomib, seriousness, subsequent anti-MM therapies (treatment name and initiation date). Listing of deaths on patients with SPM will be also provided.

Subject incidence of SPM and SPM category of solid tumor [skin or non-skin cancer], hematologic malignancies, or other non-specified will be summarized based on the listing. The subject incidence of SPM in each arm is defined as the number of subjects with the event of SPM divided by the total number of subjects in each arm. Outcomes of SPMs (resolved, resolved with sequelae, not resolved, death, unknown) will be summarized by the number of subjects and percentage in each category of outcome and by SPM category in each treatment arm.

In addition, the description of SPM will be provided by category and by decreasing incidence of PT for:

- Combined treatment-emergent and post-treatment AEs
- All TEAEs

The following summaries will be provided by category (solid tumor [skin or non-skin cancer], hematologic malignancies, or other non-specified):

- Time to onset of SPM will be calculated only for subjects who experienced the SPM event and is defined as the time from 1st dose of study treatment to the first onset of second primary malignancy (<3, 3 - 6, 6 - 12, 12 - 24, 24-36, >36 months).

- Exposure-adjusted analyses of TEAEs

The event rate per patient-year of overall extent of exposure of all study drugs, carfilzomib exposure and event rate per patient-year of time on study will be provided for all SPM TEAEs , and by tumor type (solid tumor [skin or non-skin cancer], hematologic malignancies, or other non-specified).

The exposure-adjusted incidence rate is defined as the number of subjects with SPM event divided by the total person-year of exposure time. For subjects with an event, the person-year is calculated as the sum of the time (years) to first TEAE of SPM for all subjects in each arm. For subjects without an SPM event, the entire exposure time for carfilzomib (up to 30 days after the last dose) is considered in the sum of the time for the event rate per patient-year of carfilzomib exposure ; the entire exposure time for study drugs (up to 30 days after the last dose of any study

drugs) is considered in the sum of the time for the event rate per patient-year of study drug exposure ; the entire time from study day 1 up to patient's end of study date is considered in the sum of the time for the event rate per patient-year of time on study.

8.7.2.5 Sensitivity Analysis

NA

8.7.2.5.1 Subgroup Analysis

NA

8.7.2.5.2 Stratified Analysis

NA

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

NA

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

The SPM event will be defined based on Malignant tumours SMQ (Narrow scope) and Tumours of unspecified malignancy SMQ (Narrow scope) as described in Section 4. Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later will be used to code all AEs to a system organ class (SOC) and a preferred term (PT). The analyses of SPM will be summarized based on the safety analysis set. The methods are described in Section 8.7.1.1 and 8.7.2.4, and more details are included in the SAP.

8.8 Quality Control

Biostatical programmers will write and execute the analytics. A programmer will be assigned to quality control and verify the results from the analyses.

8.9 Limitations of the Research Methods

This is a post-hoc analysis to describe the incidence rate and characteristics of SPM in RRMM patients treated with carfilzomib based on two phase 3 RCT. While there are inherent limitations to post-hoc analysis, the randomized controlled trial design of the source data studies provides a relatively well-balanced patient distribution . Additionally, the control arms in ASPIRE and ENDEAVOR were lenalidomide plus dexamethasone and bortezomib plus dexamethasone respectively. There was no carfilzomib in control arm. Therefore, at this time, applying this method on database of ASPIRE and ENDEAVOR is considered the most appropriate method to investigate SPM in RRMM patients treated with carfilzomib that may be attributable to carfilzomib. Meanwhile, it is

appropriate to note that this analysis may have limitations due to its relatively small SPM cases and potential short duration of follow-up.

9. Protection of Human Subjects

9.1 Informed Consent

All subjects enrolled in this study had signed ICF in study ASPIRE or ENDEAVOR. As per ICF v 12.0 of the ASPIRE study and ICF v 11.0 of the ENDEAVOR study, the results of studies can be reanalyzed by sponsor and may be combined with results of other studies. No study subjects will be contacted for the analysis.

9.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

This study is a retrospective analysis of existing data; therefore, IRB approval is not necessary.

9.3 Subject Confidentiality

This protocol will comply with all applicable laws regarding subject privacy. No direct subject contact or collection of additional subject data will occur. Only anonymous data will be used for the analysis. Results will be in tabular form and aggregate analyses that omit subject identification. Any publications and reports will not include subject identifiers.

10. Collection, Recording, and Reporting of Safety Information and Product Complaints

This study is analyzing secondary data from individual clinical trials (ASPIRE and ENDEAVOR) entered in Onyx owned clinical databases and Amgen RAVE database and no additional safety data will be collected.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. Amgen reserves the right to terminate the study at any time.

12. Plans for Disseminating and Communicating Study Results

As a regulatory requirement, this report will be submitted to the FDA at the agreed upon timelines; otherwise, there are no current plans to submit results for publication.

13. References

Alexanian R. Ten-year survival in multiple myeloma. Arch Intern Med 1985;145:2073–4.

Costa LJ, Godby KN, Chhabra S, Cornell RF, Hari P, Bhatia S. Second primary malignancy after multiple myeloma-population trends and cause-specific mortality. Br J Haematol 2018;182:513–20.

Dimopoulos M. A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. Blood. 2012; 119(12):2764-2767

Dimopoulos MA, Moreau P, Palumbo A, et al; ENDEAVOR Investigators. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016 Jan;17(1):27-38.

Dimopoulos MA, Lonial S, White D, Moreau P, et al. Elotuzumab, lenalidomide, and dexamethasone in RRMM: final overall survival results from the phase 3 randomized ELOQUENT-2 study. Blood Cancer J. 2020 Sep 4;10(9):91.

Dong C, Hemminki K. Second primary neoplasms among 53159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. Br J Cancer. 2001;85:997–1005.

Khan N, Afaq F, Mukhtar H. Lifestyle as risk factor for cancer: Evidence from human studies. Cancer Lett. 2010;293:133–43. [PubMed: 20080335]

Murakami H, Nemoto K, Miyawaki S, Shinonome S, Nogiwa E, Shimano S, et al. Ten-year survivors with multiple myeloma. J Intern Med 1992;231:129–31.

Musto P, Anderson KC, Attal M, et al. International Myeloma Working Group. Second primary malignancies in multiple myeloma: an overview and IMWG consensus. Ann Oncol. 2018 Apr 1;29(4):1074.

Poh C, Keegan T, Rosenberg AS. Second primary malignancies in multiple myeloma: A review. Blood Reviews 2021;46:100757

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69: 7–34.

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. New Engl J Med. 2015;372:142–152.

Thomas A, Mailankody S, Korde N, et al. Second malignancies after multiple myeloma: from 1960s to 2010s. Blood. 2012;119:2731–7.

van de Donk N, Pawlyn C, Yong KL. Multiple myeloma. Lancet. 2021;397(10272):410-427

14. Appendices

Appendix A. ENCePP Checklist for Study Protocols

Study title: Retrospective analysis of second primary malignancies (SPM) data from ASPIRE and ENDEAVOR

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☒	☐	
1.1.2 End of data collection[2]	☐	☒	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results.	☐	☐	☒	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.4
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	8.7.2
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.2.1
	4.2.2 Age and sex	☐	☐	☒	
	4.2.3 Country of origin	☐	☐	☒	
	4.2.4 Disease/indication	☒	☐	☐	8.2.2
	4.2.5 Duration of follow-up	☒	☐	☐	8.2.5
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	8.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (eg, dose, duration)	☒	☐	☐	8.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.5

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (eg, confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.3.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3.1
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3.2
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.7.3
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☒	☐	☐	8.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7.2
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.5
10.3 Are descriptive analyses included?	☒	☐	☐	8.7.2
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.2.2
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☐	☒	☐	
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	6.3

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☐	☐	☒	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:
