Statistical Analysis Plan

NCT Number: NCT02761187

Study Title: A Global, Prospective, Non-interventional, Observational Study of Presentation, Treatment Patterns, and Outcomes in Multiple Myeloma Patients - the INSIGHT - MM Study

Study Number: NSMM-5001

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STATISTICAL ANALYSIS PLAN

A global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in multiple myeloma patients
INSIGHT-MM study

Protocol #: NSMM-5001

SAP Version:	Date of Statistical Analysis Plan:
Version 1.0	18AUG2017
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Approval Signatures

Date	Prepared by: PPD, PhD PPD, Biostatistics PPD
Date	Reviewed by: PPD, MD, MPH, MS PPD, Biostatistics PPD
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Summary of Changes

Table 1-1 Statistical Analysis Plan Amendment History

Version	Date	Summary of Changes
Version 1.0	18AUG2017	Original version
Version 2.0	08FEB2019	Editorial and administrative changes were made throughout the document for clarity, and sections 7, 8, and 9 were rearranged with additional subsections added. The summary of significant changes includes the following: **Section 3.1 Overall Study Design and Plan & Section 4.2 Sample Size:** • Reduced enrollment from minimum of 5000 patient to approximately 4200 **Section 4.5 Missing/Incomplete Dates:** • Added rules for stem cell transplant dates • Expanded rules for medical history dates **Section 5 Patient Disposition:** • Added summary for major protocol deviations **Section 7.2 Treatment Plan and Changes in Therapy:** • Modified comparisons of drug classes • Added subgroup analysis for ixazomib patients • Added expanded lists for treatments of interest for ND and R/R patients • Added specific maintenance regimes for summary • Added exposure-adjusted event rate to action taken summaries **Section 7.3 Localized MM Treatment Modalities and Supportive Care:** • Added summary for radiation therapy **Section 7.5 Treatment Patterns:** • Added treatment sequences including MOAB regimens **Section 8 Clinical Outcomes Analysis:** • Added sample size analysis for PFS based on C16010 • Added sensitivity analysis for regimens initiated within 3 months prior to enrollment **Section 8.3 Time to Next Line of Therapy & Duration on Index/Maintenance Regimen:** • Added KM analysis for index and maintenance regimen treatment durations • Ongoing censoring was modified to use non-missing quarterly therapy status visit window start and end dates instead of data cut-off date • Added sensitivity analysis to group by stem cell transplant status **Section 8.5 Best Response:** • If no regimen was assigned to best response by sites, then the prior regimen was carried forward • Added time to best response analysis **Section 9 Patient-reported Outcomes:** • Protocol amendment 2.0 reduced the scope for the number of questions required for QLQ-C30 and MY-20, and removed EQ-5D-5L

		• Added minimally importance difference of 5-points summary **Section 11.1 Adverse Events:** • Changed from exposure-adjusted incidence rate, to exposure-adjusted event rate • Added AE/SAE summary specifically for Takeda drugs **Section 12 Interim Analysis:** • Added CHMP IA to list of interim analysis **Appendices:** • Added expanded lists for treatments of interest for ND and R/R patients • Added list of tables for formal analyses • Added PRO scoring guidelines for EORTC QLQ-C30, MY-20, TSQM-9, and EQ-5D-5L
Version 2.0, Amendment 1.0	20SEP2019	Editorial and administrative changes were made throughout the document for clarity. The summary of significant changes includes the following: **Section 4 General Statistical Considerations:** • SAS v9.4 will be used for all analysis **Section 4.3 Bias and Treatment Group Comparability:** • Added checks for proportional hazards assumption in Cox survival models **Section 7.2 Treatment Plan and Changes in Therapy:** • Simplified assigning assessments of comorbidities, UPEP/SPEP, and cytogenetics to lines of therapy for ixazomib regimens based on closest to ixazomib regimen start date within +/- 12 months **Section 8 Clinical Outcomes Analysis** • Updated 95% CI width analysis for KM estimate of median PFS based on a minimum of 24-months follow-up **Section 8.1 Progression-Free Survival** • A sensitivity analysis was added to replace a patient's last adequate assessment date with their last know alive date to consider impact of missing assessment data **Section 8.2 Overall Survival** • Time since diagnosis was removed **Section 8.3 Time to Next Line of Therapy:** • Death will be analyzed as a competing risk, instead of censored • Ongoing censoring was modified to use non-missing quarterly therapy status visit window end date **Section 8.3 Duration on Index/Maintenance Regimen:** • Ongoing censoring was modified to use quarterly therapy status visit window end date if a dose modification or schedule change occurred, and to use quarterly visit window start date if patient was undergoing transplant • Clarified that death date will be used for final treatment regimen end date, if treatment regimen was not discontinued prior to death **Section 8.4 Propensity Score Modeling:** • Added checks to assess balance in propensity score distributions **Appendix 14.2 Multiple Myeloma Drugs and Classes:** • Added MM therapy drugs to make drug lists more comprehensive within

		drug classes **Appendix 14.8 List of Tables Included for Each Formal Analysis:** • Added 3 tables for ixazomib subgroup analysis • Added 10 tables for OS & PFS subgroup and sensitivity analyses • Added 6 tables for Safety analysis • Added 1 table Prior Durations analysis • Added 5 tables for PRO analysis
Version 3.0	04SEP2020	Editorial and administrative changes were made throughout the document for clarity. The summary of significant changes includes the following: **Section 3.1 Overall Study Design and Plan** • Reduced minimum follow-up from 5 years to 2 years **Section 4.5 Missing/Incomplete Data** • Added LLOQ and ULOQ for lab measurements. **Section 5 Patient Disposition and Protocol Deviations** • Added COVID-19 reasons for study discontinuation, and major protocol deviations as potential sensitivity analysis **Section 7.2 Treatment Plan and Changes in Therapy** • Added Cytotoxins and HDAC Inhibitors as drug classes of interest with specific drugs listed in Appendix 14.2 **Section 7.4 Diagnostic/Prognostic Criteria** • Updated cytogenetics risk groups definitions **Section 7.6 COVID-19 Disease Assessment** • Added summary of COVID-19 disease assessments that were implemented in updated eCRF **Section 8 Clinical Outcomes Analysis** • Excluded patients with regimens designated as clinical trials **Section 8.3 Time to Next Line of Therapy and Treatment Durations** • In addition to time to next therapy and individual treatment durations, duration of line of therapy was defined as time from start date of index regimen to end date of latest regimen (e.g. maintenance) prior to subsequent index regimen **Section 8.4 Propensity Score Modeling** • Refined list of covariates **Section 8.5 Best Response** • If a SCT date is provided, then any responses after that SCT date will not be associated with the index regimen since there must have been a peri-transplant regimen that may or may not have been entered in the eCRF. **Section 8.6 Multiple Imputation** • Multiple Imputation methods were added to account for missing data. **Section 9.0 Patient Reported Outcomes** • Updated Table 9-2 quarterly visit windows • Excluded patients with regimens designated as clinical trials **Section 9.2 PRO Analysis** • Longitudinal analysis models were added for time to deterioration and change from baseline in global health status/quality of life **Section 10 Medical Resource Utilization**

		• Excluded patients with regimens designated as clinical trials **Updated Appendixes:** • Appendixes 14.4 & 14.6 Treatments of Interest for Relapsed/Refractory & Newly Diagnosed Patients – Expanded Groups • Appendix 14.7 Summary of Analysis Topics for Each Formal Analysis • Appendix 14.8 List of Tables Included for Each Formal Analysis
Version 4.0	28SEP2021	Editorial and administrative changes were made throughout the document for clarity. The summary of significant changes includes the following: **Section 4.4 Subgroup Analysis** • Removed unused subgroups analyses **Section 5 Patient Disposition and Protocol Deviations** • Added site-level protocol deviations for data quality/integrity to be used for potential targeted analysis **Section 7.2 Treatment Plan and Changes in Therapy** • Created new combinations of drug classes for summarization **Section 7.5 Treatment Patterns** • Redefined treatment sequences for analysis **Section 8.3 Time to Next Line of Therapy and Treatment Duration** • Modified censoring to use last known alive date as an alternative to quarterly visit window dates based on Therapy Status eCRF • Allowed death to be a event, instead of competing risk for TTNT endpoint **Section 8.4 Statistical Modeling and Convergence** • Specified order for covariance structures to achieve model convergence **Section 8.5 Best Response** • Impute missing Progressive Disease date using data from other eCRF **Section 8.6 Multiple Imputations** • Added predictor variables to impute missing covariates **Section 9.2 PRO Analysis** • Updated PRO assessment windowing, removed MID, aligned subset of patients for all PRO analyses, updated model covariates, added forest plots for mixed model repeated measures results **Section 13 Changes from Analyses Planned in the Protocol** • Secondary primary malignancies for all MM therapies wasn't summarized **Appendix 14.2 Multiple Myeloma Drugs and Classes** • Added Anthracyclines as a drug class, and removed same from list of regimens in Appendix 14.4 & 14.6 Removed the following analyses from SAP scope: SCT details (Section 7.2), supportive care (7.3), radiation therapy (7.3), related surgeries (7.3), treatment strategies (7.5), on-treatment PFS (8.1), duration of line of therapy (8.3), and time to response (8.5).

List of Abbreviations

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
BUN	Blood urea nitrogen
CCI	Charlson Comorbidity Index
CI	Confidence interval
CRAB	Calcium, renal failure, anemia, and bone damage
CT	Computed tomography
DOT	Duration of therapy
DOMT	Duration of maintenance therapy
EAER	Exposure adjusted event rate
EAIR	Exposure adjusted incidence rate
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQol patient-reported, 5-dimension, 5-response outcome instrument
FISH	Fluorescence in situ hybridization
FLC	Free light chain
GEP	Gene expression profiling
HDAC	Histone deacetylase inhibitor
HRQoL	Health related quality of life
HRU	Healthcare resource utilization
IA	Interim Analysis
IADL	Instrumental activities of daily living
IPTW	Inverse Probability of Treatment Weighted
ISS	International Staging System
LDH	Lactate dehydrogenase
MGUS	Monoclonal gammopathy of unknown significance
MMRM	Mixed model repeated measures
MM	Multiple myeloma
MRD	Minimal residual disease

Abbreviation	Definition
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
ND	Newly diagnosed
NGS	Next-generation sequencing
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PH	Proportional hazards
PRO	Patient self-reported outcomes
QALY	Quality adjusted life year
QLQ-C30	Quality of Life Questionnaire - 30 item Cancer
QLQ-MY20	Quality of Life Questionnaire - 20-item Multiple Myeloma Module
R-ISS	Revised International Staging System
R/R	Relapsed/refractory
RS	Raw Score
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SMM	Smoldering multiple myeloma
TTNT	Time to Next Therapy
TSQM-9	9-Item Treatment Satisfaction Questionnaire for Medication
UPEP	Urine protein electrophoresis
US	United States

1 Introduction

Multiple myeloma (MM) is a clonal plasma cell disorder that accounts for 1% of all cancers and 10% of hematologic malignancies (National Comprehensive Cancer Network [**Error! Reference source not found.**] 2015). It is largely a disease of older people. The median age at diagnosis is 69 years, and approximately 2/3 of people are over the age of 65 at the time of diagnosis (**Error! Reference source not found.** 2012, **Error! Reference source not found.** 2015). Also, MM is more common in men than women, and in black people compared to other races (**Error! Reference source not found.** 2007). Although the reasons for these differences are not clearly understood, risk factors such as obesity, socioeconomic status, and workplace environment and exposures may have a role.

Deaths from MM are decreasing year-on-year: the 5-year survival rate in the US was 27% in 1975 compared to 53% from 2008 to 2010 (**Error! Reference source not found.** 2015, **Error! Reference source not found.** 2015), and in Europe was approximately 40% between 2006 and 2008 (**Error! Reference source not found.** 2014). The improvement in overall survival (OS) is likely due to the introduction of more effective treatments. The introduction of novel classes of agents with increased efficacy, including proteasome inhibitors (bortezomib, carfilzomib, and ixazomib) and immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide), has played a role in increasing the progression-free survival (PFS) of these patients, and has changed the natural history of the disease. In addition, agents with new mechanisms of action such as panobinostat (histone deacetylase inhibitor) and daratumumab and elotuzumab (monoclonal antibodies) have recently been approved in the United States (US) and the submission of these agents for approval globally is underway.

Although advances in chemotherapy and novel agents have improved the prognosis and disease-free survival for patients with MM, currently available data on presentation, treatment patterns, and outcomes for MM at global level are limited. By establishing an international non-interventional, observational study with multi-year inclusion and follow-up, contemporary demographics and patterns of care for MM patients can be tracked longitudinally in a large, more generalizable population.

This statistical analysis plan (SAP) prospectively (i.e. a priori) describes the types of analyses and data presentations that will address the study objectives outlined in Takeda's protocol "A global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in multiple myeloma patients – the INSIGHT MM study" version 3.0 that was amended on 11APR2018. It contains details of how the data will be handled and analyzed

including definitions of analysis populations, derived variables and statistical methods, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

2 Objectives

2.1 Primary Objectives

The primary objective of this study is to describe contemporary, real-world patterns of patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes in patients with newly diagnosed (ND) MM, and patients with relapsed/refractory (R/R) MM.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Describe patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes in ND and R/R MM patients by type of treatment facility and country.
- Describe patterns and durations of treatment combinations, sequencing, retreatment, and continuous versus fixed duration treatment strategies; and the clinical outcomes associated with different treatment regimens.
- Describe factors associated with treatment initiation, treatment modification, or treatment change over time; including whether treatment at relapse was initiated due to biochemical progression versus symptomatic progression.
- Describe health related quality of life (HRQoL) and healthcare resource utilization (HRU).
- Explore associations between patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes.

3 Investigational Plan

3.1 Overall Study Design and Plan

This is a prospective, global, non-interventional, observational study. The purpose of this study is to describe contemporary, real-world presentation, therapies, and clinical outcomes in patients with MM. The study will attempt to enroll approximately 4200 patients globally, approximately 50% ND and 50% R/R. Patients will be enrolled over a period of 3 years, and followed for a period of at least 2 years, until death, or the end of the study, whichever comes first.

No modification of standard care is assigned per protocol, and no study drug or medications will be provided. No change in the patients' management (routine clinical care or treatments) will be required as a result of this study. However, patient self-reported outcomes (PROs) will be completed by patients at routine on-site visits every quarter. Information regarding patient characteristics, diagnosis, and previous treatments will be recorded based on review of hospital or clinic records. Multiple myeloma management data will be obtained quarterly as part of routine office visits to assess clinical effectiveness (i.e. best response, OS, PFS, and time to next therapy), and healthcare resource utilization (frequency and duration of visits).

Safety data will be assessed approximately quarterly by collection of serious adverse events (SAEs) and non-serious AEs leading to treatment discontinuation (temporary and permanent) or drug modification for all MM therapies will be documented on the Action Taken eCRF. In addition, reasons for dose modification/drug discontinuation not related to AE/SAE are recorded quarterly on the Action Taken eCRF for all MM therapies. AEs/SAEs related to Multiple Myeloma therapy drug are summarized and reported for Takeda products on the AE/SAE. Second primary malignancies are reported on the quarterly AE/Pregnancy Status and Follow-Up Medical Evaluation eCRF for all MM therapies.

Patients who are not available for data collection for more than 9 months will have a follow-up for survival, i.e. the healthcare provider may search regional death indexes/registries for vital health statistics of lost to follow-up patients as per routine practice until the end of the study or the patient's death, whichever occurs earlier. The date of follow-up will be noted for censoring purposes. The data collected for this study are provided in **Appendix 14.1 Data Collection Schedule**.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

The primary outcome measures for describing contemporary, real-world pattern of patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes in patients with ND MM, and patients with R/R MM are:

- Patient demographics, co-morbidities
- Diagnostic and presenting symptoms; as well as Eastern Cooperative Oncology Group (ECOG) performance status, frailty status, assessment of myeloma cytogenetic risk, and International Staging System (ISS/Revised-ISS stage)
- Myeloma-directed therapeutic regimens, duration of each Line of Therapy, stem cell transplant status
- Overall survival, response to each regimen per International Myeloma Working Group (IMWG) criteria (**Rajkumar** 2011), and time to next therapy

3.2.2 Secondary Outcome Measures

- Describe primary outcome measures by type of treatment facility and country where appropriate.
- Patterns of treatment combinations, sequencing, and retreatment; and clinical outcomes for different strategies.
- Treatment duration and clinical outcomes between continuous treatment and fixed duration treatment strategy.
- Factors associated with treatment initiation, treatment modification, or treatment change over time; including whether treatment at relapse was initiated due to biochemical progression vs symptomatic progression.
- HRQoL, treatment satisfaction, and HRU.
- Explore associations between patient characteristics, clinical disease presentation, therapeutic regimen chosen, and progression-free survival.
- All SAEs and non-serious AEs leading to treatment discontinuation (temporary and permanent) or drug modification, and second primary malignancies.

4 General Statistical Considerations

Patients will be uniquely identified by the patient identification number concatenated with the investigator number.

The following reporting conventions apply generally to tables, listings, and figures:

- Confidence intervals (CIs) will be presented as 2-sided 95% CIs.
- Summary statistics will consist of the number and percentage of patients in each category for discrete variables, and the sample size, mean, standard deviation (SD), median, minimum, 25th percentile (Q1), 75th percentile (Q3), and maximum for continuous variables.
- All mean, median, Q1, Q3, and CI values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum will be formatted to the same number of decimal places as the measured value.
- When a count of zero is presented, the percentage will be suppressed to draw attention to the non-zero counts.
- A row denoted "Missing" will be included in tables where specified in the shells to account for dropouts and missing values. Missing will only include count (not percentage) and will not be included in denominator for summarizing a variable's distribution. However, if a selection was made in the eCRF, e.g. 'Not Reported', 'Not Available', and 'Not Done', these are not considered Missing responses and will be summarized as n, (%) and included in the denominator.
- All percentages will be rounded to one decimal place; >=99.95% to <100% will be "> 99.9%", and >0.0% to <0.05% will be "< 0.1%". The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses.
- Absolute values and change from baseline for numerical values are calculated as the post-baseline value minus the baseline value.
- All laboratory data will be reported using standard international units.
- All analysis and summary tables will include the analysis population sample size (i.e., number of Patients) in the column headings.
- Any p-values that are presented are exploratory, and will be represented as x.xxxx; if P<0.0001 then "P<0.0001", and if P>0.9999 then "P>0.9999" will be used.

All analyses will be conducted using SAS Version 9.4 or higher.

4.1 Definition of Visits

Patients will be assessed approximately every 3 months for a period of up to 5 years. In addition to calculating study day, data will be summarized by quarterly visits and labeled as follows: Inclusion, Y1Q1FU, Y1Q2FU, Y1Q3FU, Y1Q4FU, …, Y5Q1FU, Y5Q2FU, Y5Q3FU, and Y5Q4FU.

4.2 Sample Size

The study will attempt to enroll approximately 4200 patients globally. The patients included will receive various treatment regimens as determined by their healthcare provider. The planned sample size is intended to provide a sufficient number of patients to characterize treatments in a broad population. Enrollment will include 50% ND MM and 50% R/R MM patients. Patient numbers will be capped at the site level.

A formal hypothesis will not be tested in this study, and no adjustment for Type I error will be made for multiple comparisons. The planned sample size will maintain a reasonable level of estimation precision of statistics such as proportions and event rates, as well as some level of statistical power to detect differences in studies subgroups. The justifications are given below.

The Score method for a 95% CI of a proportion (p) is given by

$$\frac{2np+z^2 \pm z\sqrt{z^2+4npq}}{2(n+z^2)}$$ (**Error! Reference source not found.** 1998), where

n = group size
p = proportion estimate
z = standard normal with a 2-tailed probability alpha
q = 1 - p

Table 4-1 provides CIs of estimated proportions for individual subgroups. According to the table, a sample size of 270 patients, for a proportion estimate of 0.5 the 95% CI is from 0.441 to 0.559, and for a proportion estimate of 0.9 the 95% CI is from 0.858 to 0.930.

Table 4-1 Confidence intervals of estimated proportions based on sample size for individual groups

Proportion	n	LCL	UCL		Proportion	n	LCL	UCL
0.5	100	0.404	0.596		0.5	1000	0.469	0.531
0.6	100	0.502	0.691		0.6	1000	0.569	0.630
0.7	100	0.604	0.781		0.7	1000	0.671	0.728
0.8	100	0.711	0.867		0.8	1000	0.774	0.824
0.9	100	0.826	0.945		0.9	1000	0.880	0.917
0.5	270	0.441	0.559		0.5	4200	0.485	0.515
0.6	270	0.541	0.657		0.6	4200	0.585	0.615
0.7	270	0.643	0.752		0.7	4200	0.686	0.714
0.8	270	0.748	0.843		0.8	4200	0.788	0.812
0.9	270	0.858	0.930		0.9	4200	0.891	0.909

Abbreviations: LCL, lower confidence limit; UCL, upper confidence limit.

Comparisons between proportions of 2 groups are based on the reference proportion (p0) and the effect size (i.e., the difference, delta) between the proportions. **Table 4-2** provides sample sizes obtained from SAS ® PROC POWER using Pearson's Chi-squared test with a 2-sided critical level alpha of 0.05 and 80% power.

Table 4-2 Sample size needed to detect proportion differences between subgroups

p0	delta	n per group		p0	delta	n per group		p0	delta	n per group
50%	2%	9806		50%	8%	609		50%	14%	196
60%	2%	9336		60%	8%	564		60%	14%	176
70%	2%	8080		70%	8%	471		70%	14%	141
80%	2%	6039		80%	8%	329		80%	14%	90
50%	4%	2448		50%	10%	388		50%	16%	149
60%	4%	2311		60%	10%	356		60%	16%	133
70%	4%	1977		70%	10%	294		70%	16%	105
80%	4%	1447		80%	10%	199		80%	16%	64
50%	6%	1086		50%	12%	268				
60%	6%	1016		60%	12%	244				
70%	6%	859		70%	12%	198				
80%	6%	615		80%	12%	131				

A formal hypothesis will not be tested in this study. A sample size of about 270 (i.e. 268) in each of any 2 comparison subgroups will have at least 80% power to detect a difference between 2 proportions given the true difference is at least 12%. Since this is a disease-focused non-interventional, observational study with potential complicated confounding between

treatment assignments and outcomes, all comparative effectiveness analyses will be considered exploratory.

4.3 Bias and Treatment Group Comparability

To adjust for potential selection bias, albeit not eliminate its effect, propensity scores (**Rajkumar** 2015) may be implemented to adjust for confounding in treatment regimen selection. Additional methods may be used for reducing confounding post-baseline, such as stratification, matching, multivariable regression and weighting based on the method most efficient for a given analysis. Time-dependent confounding for post-baseline adjustment and sensitivity analyses may be conducted to assess the robustness of the primary results.

In log-rank test analysis on time to event endpoints performed for exploratory purposes and hypothesis generating when appropriate and requested by steering review committee, inverse probability weighted (IPW) Kaplan-Meier estimates (**Error! Reference source not found.**2004) may be conducted. Exploratory model-based analyses may be performed using Cox proportional hazard (PH) models or time-dependent Cox regression models, adjusting for potential confounders, e.g. propensity scores for baseline characteristics and covariates for post-baseline confounders. The PH assumption will be tested initially using a graphical approach, e.g. the log(-log(S(t))) vs. log(t) may be plotted where parallel curves across strata suggests the PH assumption holds, or Schoenfeld residuals vs. time may be plotted using locally estimated scatter plot smoothing (LOESS) where a zero slope supports the PH assumption. If there is a strong indication that the PH assumption is violated, then a stratified analysis or alternative model specifications may be explored.

4.4 Subgroup Analysis

To assess consistency of the results across subgroups, treatment patterns in ND and R/R MM patients, PRO, and clinical effectiveness endpoints may be presented by one or more of the below subgroups.

Baseline patient and disease characteristics subgroups may include:

- Age group i.e. (<50, 50-65, 66-75, >75 years), or (<65, 65-75, >75 years)
- Sex (Male/Female)
- Geographic regions:
    - United States (US), Rest of World (ROW)
    - Asia Pacific (APAC: China, Taiwan), Europe Middle East Africa (EMEA: Belgium, France, Germany, Greece, Israel, Italy, Spain, Turkey, United Kingdom),

Latin America (LA: Brazil, Columbia, Mexico), and North America (NA: United States) – these groups are more similar in available treatment options

- Country: Belgium, Brazil, China, Colombia, France, Germany, Greece, Israel, Italy, Mexico, Spain, Taiwan, Turkey, United Kingdom, United States (Midwest, Northeast, South, West)
- Type of treatment facility (i.e. academic/university, regional/local hospital, clinic/outpatient) will be imported from an Excel spreadsheet and is not included in the EDC data extraction. Regional/local hospital and clinic/outpatient may be combined as 'community'.
- Prior Peripheral Neuropathy (Yes/No)
- Stem Cell Transplant Candidate Status (Yes/No), Stem Cell Transplant (Yes/No)

4.5 Missing/Incomplete Data

Multiple imputation methods for missing data are detailed in **Section 8.6**. However, partial dates will be imputed for specific purposes as follows:

- Rules for stem cell transplant dates are given in **Section 7.2** Treatment Plan and Changes in Therapy

- Rules for dates of death, progressive disease, treatment regimen end date based on death, and new line of therapy start date are given in **Section 8**. Clinical Outcomes Analysis

- Imputation of partial or completely missing AE start dates will be imputed as follows:
    - If the start date has a month and year but the day is missing, the first day of the month will be imputed
        - If this date is earlier than the start date of the regimen associated with the AE, then the regimen start date will be used instead
        - If this date is later than the stop date of the regimen (possibly imputed), then the stop date will be used instead
    - If the start date has a year but the day and month are missing, the 1st of July will be imputed
        - If this date is earlier than the start date of the regimen associated with the AE, then the regimen start date will be used instead
        - If this date is later than the stop date of the regimen (possibly imputed), then the stop date will be used instead
    - If the start date of an AE is completely missing, then it is imputed with the regimen start date associated with the AE

- Adverse events with end dates that are partially missing will be imputed as follows:
    - If the end date has month and year but day is missing, the last day of the month will be imputed
    - If the end date has year, but day and month are missing, the 31th of December will be imputed
    - If the end date is completely missing, it will not be imputed but considered ongoing
    - After the imputation, the imputed dates will be compared against the date of death, if available. If the imputed date is later than the date of death, the date of death will be used as the imputed date instead.

- Concomitant Treatment start and end dates are required to be 100% complete and will be queried at the site if needed.

- Medical History – if dates of Initial Diagnosis of MM (MMMHDT), First Relapse (MMRRDT), Second Relapse (MMRR2DT), Third Relapse (MMRR3DT), MGUS (MMMGUSDT), Smoldering MM (MMSMMDT), AL Amyloidosis (MMALADT), or Plasmacytoma (MMEPDT) are partially missing, then impute as follows:
    - If the date has a month and year but the day is missing, the 15th day of the month will be imputed.
    - If the date of Initial Diagnosis of MM only has year, then 01JULxxxx of the given year will be imputed.

- Medical History – if a prior line of therapy *start* date was partially missing, it was imputed as follows:
    - If the date had a month and year but the day was missing, then the 1st day of the month was imputed.
    - If the date had a year but was missing month, then January 1st was imputed.
    - If the date was missing year, then no imputation was made.

  However, the order for the phase of therapy was maintained as; induction regimen, consolidation, maintenance. If the imputed date would have altered the previous order, then the latest day (if an earlier phase of therapy), or the earliest day (if a later phase of therapy) was imputed. Also, the imputed date should not be later than the informed consent date.

- Medical History – if a prior line of therapy *end* date was partially missing, it was imputed as follows:

  - If the date had a month and year but the day was missing, then the last day of the month was imputed.
  - If the date had a year but was missing month, then December 31st was imputed.
  - If the date was missing year, then no imputation was made.

  However, the order for the phase of therapy was maintained as; induction, regimen, consolidation, maintenance. If the imputed date would have altered the previous order, then the latest day (if an earlier phase of therapy), or the earliest day (if a later phase of therapy) was imputed. Also, the imputed date should not be later than the informed consent date.

- For PRO data, techniques to address missing questionaire responses data are instrument dependent and reported in **Section 9** Patient-reported Outcomes.
  - Missing PRO assessment dates are imputed as follows: if missing assessment day only and assessment month matches quarterly visit start month, then use day of quarterly visit start as assessment day, otherwise use mid-point of quarterly visit

- Lab measurements that are included in ADaM datasets with a lower limit of quantification (LLOQ) represented with <x.x will use x.x/2 for numeric calculations. Also, lab measurements with a upper limit of quantification (ULOQ) represented with >y.y will use y.y for numeric calculations.

4.6 Analysis Populations

4.6.1 All Enrolled Population

The All Enrolled (ALL) population consists of all patients that signed informed consent. All analyses will be performed using the ALL population, unless stated otherwise below. An enrollment summary overall, by cohort (i.e. ND and R/R), country and site will be provided.

4.6.2 Response Evaluable Population

The Evaluable (EVAL) population includes all patients that signed informed consent and have at least one best response assessment. A patient will be eligible to be included in the EVAL population during each Line of Therapy. The EVAL population will be used for the analyses of response rates.

5 Patient Disposition and Protocol Deviations

Patient disposition will be summarized for all enrolled patients overall and by country for ND and R/R cohorts. The number and percentage of patients enrolled in each above study population, and those who have discontinued the study with the reason for discontinuation will be provided.

The primary reasons for study discontinuation may include any of the following: patient declines participation or declines follow-up for survival, lost to follow-up, withdrew consent, physician discretion, change in physician or transfer to another treatment center, on Hospice, deceased, too ill to participate, due to study discontinued at site, patient diagnosed with COVID-19 (Confirmed Positive), patient diagnosed with COVID-19 (Suspected Positive), physician/subject discretion due to COVID-19, travel restrictions due to COVID-19, and other (reason will be specified).

The following categories will be used to summarize patient-level major protocol deviations that may occur when an patient is enrolled in the study (i.e. signed informed consent), these may be violations of: inclusion criteria, exclusion criteria, informed consent process, study procedures/assessments, data privacy, or other protocol deviations. The types of protocol deviations reportable will be controlled using the Study Deviations Rules Document approved by the client. Summaries of results may be provided excluding patients from effectiveness analyses with inclusion or exclusion major protocol deviations as a targeted analysis.

Additionally, clinical sites may be excluded from effectiveness analysis for data quality/integrity major protocol deviations as a targeted analysis. Furthermore, sites may be excluded from all analyses if the risk to data quality/integrity is egregious. In this case, a Note to File will be stored in the eTMF for each site that has data excluded from all analyses.

6 Demographics and Baseline Characteristics

6.1 Demographics

Baseline demographics will be summarized for ALL Enrolled patients overall and by country or region for ND and R/R cohorts. Following completion of enrollment, summaries of age at start of line of therapy may also be presented by Treatment Regimens of Interest (**Section 7.2**) overall and by country or region for ND and R/R cohort (or by Line of Therapy subgroups e.g. 1st, 2nd, 3rd, etc.). Age at the start of each line of therapy will be calculated as the integer part of:

Age (years) = [age at study entry – (informed consent date – line of therapy start date) / 365.25]

Baseline demographic data to be evaluated will include age, sex, race and ethnicity (from PRO; optional, based on country requirements), region of origin, distance to treatment center, reason for seeking care, duration from symptom to initial diagnosis, highest level of education, annual

income, family size, marital status, living situation, and caregiver arrangement. Age at study entry will be provided by the patient or calculated from date of birth if age is missing, as the integer part of:

Age (years) = (Informed Consent Date - Birth Date + 1) / 365.25

Age will be presented using continuous measure descriptive statistics and will also be categorized using the following groups: <50, 50-65, 66-75, >75 years. All categorical variables will be presented using frequencies and percentages.

6.2 Disease Characteristics

Disease characteristics will be summarized overall and by country or region for ND and R/R cohorts. Furthermore, by treatment regimens of interest (**Section 7.2**) following the completion of enrollment. These will include relevant past medical history, MM medical history, disease characteristics and staging, diagnostic and presenting symptoms for MM, ECOG performance status and comorbidity assessments (i.e. Myeloma Frailty Index, Charlson Comorbidity Index with components, and frailty status assessed by physician); comorbidity assessments and ECOG will be calculated at baseline and annually.

The Myeloma Frailty Index (Error! Reference source not found.2015) is a composite index that will be calculated using the below points system, which produces a range of values from 0 to 5. Patients with score 0 = fit, score 1 = intermediate, and score ≥2 = frail.

For age:
<76, add 0
76 – 80, add 1
>80, add 2

For Charlson Comorbidity Index (CCI) (**Error! Reference source not found.**1987):
CCI score 0-1, add 0
CCI score ≥2, add 1

For Activities of Daily Living (ADL) (**Error! Reference source not found.**1963):
ADL score >4, add 0
ADL score 0-4, add 1

For Instrumental Activities of Daily Living (IADL) (**Error! Reference source not found.**1969):
IADL score >5, add 0

IADL score 0-5, add 1

6.3 Medical History

6.3.1 General Medical History

A list of medical conditions will be compiled for each patient and summarized for the ALL enrolled population overall and by country or region for ND and R/R cohorts, and by Treatment Regimens of Interest (**Section 7.2**) following completion of enrollment. MM relevant medical history includes peripheral neuropathy, hypertension, thromboembolism, osteopenia/osteoporosis, osteonecrosis of the jaw, cataracts, arrhythmias, cardiac LV function (<40% vs. >=40%), myelodysplastic syndromes, radiation therapy, and orthopedic procedure/surgery.

6.3.2 Disease-Specific History

Multiple myeloma medical history at initial diagnosis will include: duration from initial diagnosis to study entry, disease stage assigned at initial diagnosis (including staging system used), cytogenetics/FISH high risk [i.e. del(17p), t(4,14), t(14,16)] vs. standard risk, presence of bone lesions at diagnosis, calcium (>11.0 mg/dL), creatinine clearance (<30, 30 to <60, >=60 mL/min), hemoglobin (<12 g/dL for males, <11 g/dL for females), ECOG Performance Status Scale (**Error! Reference source not found.**1982), and history of CNS involvement. The calculated stage at initial diagnosis will be determined as well, using beta-2 microglobulin, Albumin, LDH and cytogenetics risk with the below formulas. The aforementioned will be tabulated overall and by country or region for ND and R/R cohorts in all enrolled patients, and by Treatment Regimens of Interest (**Section 7.2**) following completion of enrollment.

Creatinine clearance will be calculated using the Cockcroft-Gault formulas as follows:

For male patients:

$$\text{creatinine clearance} = \frac{(140 - \text{Age[yrs]}) \times \text{weight[kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

For female patients:

$$\text{creatinine clearance} = 0.85 \times \frac{(140 - \text{Age[yrs]}) \times \text{weight[kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

Integer values will be used.

The derivation of ISS is based on β2-microglobulin and albumin levels:

Stage	Criteria
Stage I	Serum β2-microglobulin < 3.5 mg/L and Serum albumin ≥ 3.5 g/dL
Stage II	Neither Stage I nor Stage III
Stage III	Serum β2-microglobulin ≥ 5.5 mg/L

The derivation of R-ISS is based on ISS, chromosomal abnormalities (CA), and lactate dehydrogenase (LDH) (**Error! Reference source not found.**2015):

Stage	Criteria
Stage I	ISS Stage I and standard risk CA by FISH and normal LDH (i.e. <=300 U/L)
Stage II	Neither R-ISS Stage I nor Stage III
Stage III	ISS Stage III and either high risk CA by FISH or high LDH (i.e. >300 U/L)

Prodromal plasma cell disorders at baseline will be tabulated overall and by country or region for ND and R/R cohorts in the all enrolled population. Summaries will include frequency and duration of MGUS, SMM, AL amyloidosis (including organ involvement), and plasmacytomas (including location and number of lesions).

6.4 Medical and Prescription Insurance Types

Medical and prescription insurance types will be collected at baseline and annually for all Patients. In the US, medical insurance types will be categorized as: commercial/private, Medicaid, Medicare (fee for service, HMO/managed care), military health insurance, Indian Health Services, and not insured. Prescription insurance types in the US will include: commercial/private, Medicaid, Medicare (fee for service, HMO/managed care), Medicare with private supplement, Indian Health Service, indigent/free care, and not insured. For Rest of World medical and prescription insurance types will be categorized as public only, private only, public supplemented with private and uninsured. Summaries will be provided by calendar year for medical and prescription insurance by treatment regimens of interest (**Section 7.2**).

7 Treatments

7.1 Definition of Baseline

A Line of Therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplant, followed by maintenance is considered 1 Line of Therapy. For all enrolled patients, there will be the following baselines defined: a study entry baseline, a baseline for each treatment regimen, and a baseline for each Line of Therapy. The study entry baseline is defined as the date of informed consent. The Line of Therapy baseline will be the start date a new Line of Therapy was initiated and will equal the earliest regimen start date entered in the eCRF if more than one exists in a particular line of therapy. Clinical outcomes, e.g. OS, PFS, and time to next therapy, will use the Line of Therapy baseline start date or the treatment regimen start date as day 1, which may be prior to informed consent date. Each TLF will specify in the footnote what type of baseline was used for the summary table.

There may be multiple regimens within a Line of Therapy, and multiple drugs with different mechanism of action within a Regimen. Once a Treatment Regimen of Interest is completely discontinued the last drug end date will be used as the Treatment Regimen of Interest end date, which is captured in the eCRF. The patient will not be reclassified with a new Treatment Regimen of Interest until they initiate another Regimen. When an unplanned drug is added to a patient's regimen, it should be entered into the eCRF as a new regimen and a new Line of Therapy (**Rajkumar** 2015).

7.2 Treatment Plan and Changes in Therapy

All lines of therapy for ND and R/R MM will be collected in the eCRF. The duration from date of initial diagnosis to the start date of each Line of therapy will be calculated and may be used as a covariate in statistical models.

Patients will be grouped by their Line of Therapy as entered in the eCRF, and following the completion of enrollment by Treatment Regimen of Interest or Treatment Class of Interest (used interchangeably throughout this SAP) for analyses. The concept of an 'index' regimen is used to define an induction regimen for a ND patient, or a treatment for relapse regimen in a R/R patient.

1) Lines of Therapy - All patient assessments will be categorized by their Line of Therapy at the time of the assessment as entered on the MM Regimen Therapy Plan eCRF.

- Newly Diagnosed: Frontline (or 1st Line)
- Relapsed/Refractory: 2nd Line
- Relapsed/Refractory: 3rd Line
- Relapsed/Refractory: 4th Line
- Relapsed/Refractory: >4th Line (the last two categories may be combined as >=4th Line)

2) All patients will be grouped based on whether their Line of Therapy included treatment drug classes of interest. The drugs belonging to each class are given in **Appendix 14.2 Multiple Myeloma Drugs and Classes**. Each Line of Therapy for a patient may have a different drug class, and the index regimen in the Line of Therapy will be used for analysis.

   For analysis the following treatment class groups will be used: mAB, mAB/IMID, mAB/PI, mAB/Alkylator, mAB/IMID/PI, Cytotoxic, PI, IMID, PI/IMID, Alkylator, PI/Alkylator, IMID/Alkylator, PI/IMID/Alkylator ,and Other. A patient's therapy may belong to more than one class, e.g. VRD would belong to PI, IMiD, and Steroid, and similarly dara-VD would belong to MOAB, PI and Steroid. In order to assign a patient to a single group the following rules were applied in order:
   a) mAB: Any monotherapy or combination that includes mAB but not (IMID or alkylator or PI);
   b) mAB/IMID: Any combination that includes mAB and an IMID but not (alkylator or PI);
   c) mAB/PI: Any combination that includes mAB and PI but not (IMID or alkylator);
   d) mAB/Alkylator: Any combination that includes mAB and alkylator but not (PI or IMID);
   e) mAb/IMID/PI: Any combination that includes mAB and an IMID and PI but not alkylator
   f) Cytotoxic: Regimens that contain 1 or more agents from the cytotoxics category
   g) IMID: Any monotherapy or combination that includes IMID but not (PI or alkylator or mAB);
   h) PI: Any monotherapy or combination that includes PI but not (IMID or alkylator or mAB);
   i) Alkylator: Any combination or monotherapy that includes an alkylator but not (IMID or PI or mAB);
   j) PI/IMID: Any combination that includes PI and an IMID but not (alkylator or mAB);
   k) PI/Alkylator: Any combination that includes PI and alkylator but not (IMID or mAB);
   l) IMID/Alkylator: Any combination that includes IMID and alkylator but not (PI or mAB);

m) PI/IMID/Alkylator: Any combination that includes IMID, an alkylator, a PI but not a mAB
n) Other

3) An Ixazomib subgroup will be defined based on line of therapy, retrospective versus on-study exposure, and phase of regimen as listed below. **Appendix 14.8** identifies which tables will include Ixazomib subgroup analysis, in which formal deliverables.
   a. Line of therapy may include: 1st, 2nd, 3rd, 4th, and >4th (the last two categories may be combined as >=4th Line); however, relapsed/refractory is only considered 2nd line of therapy or higher
   b. Exposure will be retrospective if the regimen ended prior to the informed consent date. On-study 'prospective' exposure will be when the regimen was ongoing at date of informed consent or initiated after study enrollment
   c. Index regimen or maintenance regimen are phases of interest for analysis
   d. The patients in the R/R Ixazomib subgroup will be summarized for each line of therapy (i.e. 2nd, 3rd, 4th, and >4th, the last two categories may be combined as >=4th Line)) that they received Ixazomib as the index regimen in the corresponding line of therapy. To select the quarterly assessment (or annual in the case of comorbidities) relative to the Ixazomib regimen start date for a corresponding line of therapy multiple approaches were implemented depending on the type of assessment. The relevant approach was detailed in the corresponding footnotes of the analysis table.

4) Treatment Regimens of Interest Basic Groups for R/R Patients are listed in **Appendix 14.3.** For the 1000 patient IA and CHMP IA, all treatments will be classified using these regimen groups for descriptive analysis. In future analyses, the Expanded Groups list may be used (**Appendix 14.4**) for the Treatment Regimens of Interest.

   In addition, the actual regimens will be summarized from most frequent to least frequent regimen based on total counts. The summary will also include by line of therapy (i.e. 2nd, 3rd, 4th, and >4th, the last two categories may be combined as >=4th Line). An additional overall (R/R and ND patients combined) summary of treatment regimens by country will be tabulated.

   If a patient enters "ixazomib/placebo" or something similar that indicates the patient was on a randomized clinical trial and may have been exposed to either ixazomib or placebo, that regimen will be coded as 'Other' due to the ambiguity.

5) Treatment Regimens of Interest Basic Groups for ND Patients are listed in **Appendix 14.5**. For the 1000 patient IA and CHMP IA, all treatments will be classified using these

regimen groups for descriptive analysis. In future analyses, the Expanded Groups list may be used (**Appendix 14.6**) for the Treatment Regimens of Interest.

In addition, the actual regimens will be summarized from most frequent to least frequent group based on total counts. The summary will also include by SCT Candidate Yes, SCT Candidate No, and Unknown.

If a patient enters "ixazomib/placebo" or something similar that indicates the patient was on a randomized clinical trial and may have been exposed to either ixazomib or placebo, that regimen will be coded as 'Other' due to the ambiguity.

Since a patient may progress along lines of therapy, Treatment Regimens of Interest may change over time within a patient, e.g. when summarizing response to therapy a patient may enroll ND on PI therapy, and then relapse and initiate PI + IMiD on their 2nd Line of Therapy. The patient would be represented in separate summary tables at each Line of Therapy that was experienced (i.e. frontline, 2nd, 3rd, etc.) and classified with the Treatment Regimens of Interest corresponding to each Line of Therapy (**Figure 1**).

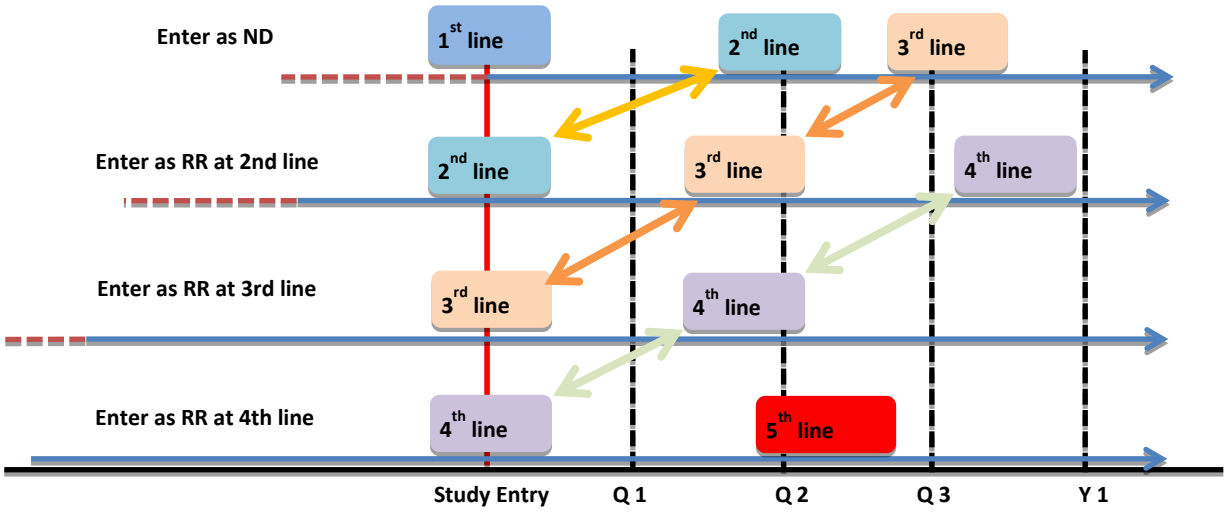


Figure 1. Grouping Patients by Lines of Therapy

For R/R patients the frequency of the Treatment Regimens of Interest will be summarized by region or country for up to 4 previous lines of therapy each including regimens grouped into one of the Treatment Regimens of Interest using the Basic or Expanded regimen classifications in **Appendixes 14.3 to 14.6**, and maintenance regimen with corresponding durations. The maintenance regimens to summarize included: lenalidomide, bortezomib, lenalidomide + bortezomib, ixazomib, ixazomib + lenalidomide, daratumumab, daratumumab + lenalidomide,

ixazomib + daratumumab, thalidomide, and other. In addition, whether stem cell transplant or consolidation post-transplant was part of each Line of Therapy, the number of prior lines of therapy, and the following durations: diagnosis to 1st relapse, diagnosis to 2nd relapse, diagnosis to 3rd relapse, 1st relapse to 2nd relapse, and 2nd relapse to 3rd relapse will be summarized.

Multiple Myeloma therapy at baseline will be tabulated as yes (drug therapy, or undergoing transplant), or no due to the following reasons: treatment not started yet, patient has completed planned therapy, patient refused treatment, drug holiday with intention to resume treatment, unknown, financial or insurance constraints, patient is not receiving drug therapy or undergoing transplant, other, therapy not indicated due to: advanced age, comorbid illness, frailty, toxicity concerns, or other. These will be summarized by region or country, and by Line of Therapy (i.e. 1st, 2nd, 3rd, etc.).

Treatment duration, intent of regimen (until progression, fixed duration, to best response/plateau, or planned therapy change/switch), if fixed duration then the number of months or cycles, and if the regimen is part of a clinical trial will be summarized. If the number of cycles were provided, they were converted into number of months by multiplying times the longest schedule for the corresponding MM Therapy drug in the regimen. For ND patients the reasons for drug initiation include: renal failure, anemia, bone involvement, hypercalcemia, insurance/financial, or other. For R/R patients, additional reasons for drug initiation are: biochemical PD, clinical PD, resistance to ongoing therapy, toxicity, or completed course of regimen. Phase of regimen will be summarized as induction, consolidation, maintenance, treatment for relapse, or peritransplant (from mobilization to 30 days post-transplant). All information will be summarized by Treatment Regimens of Interest overall and by country or region for ND and RR cohorts (or by Line of Therapy subgroups e.g. 1st, 2nd, 3rd, etc.).

A change in regimen occurs with the substitution or addition of a new drug; however, a discontinuation of a drug is not a change in regimen. The dose, schedule, and route of administration will be captured in the eCRF for each current and prospective drug for all patients, but not included in summary tables.

However, actions taken for regimens (i.e. dose increased, delayed, reduced, or permanently discontinued) categories will be summarized, and reasons for dose modifications (i.e. AE related to drug, AE not related to MM therapy drug, dose delay due to toxicity, biochemical PD, clinical PD, patient/family preference, treatment fatigue, dose increased, planned change, other, COVID-19 diagnosis confirmed positive, COVID-19 diagnosis suspected positive, COVID-19 restrictions and lack of response) will be summarized by drugs of interest overall and by country or region for ND and RR cohorts (or by Line of Therapy subgroups i.e., 1st, 2nd, 3rd, etc.). The

types of actions taken will also include an estimate of the Exposure-Adjusted Event Rate (EAER) per 100 patient-years; the calculation for EAER is given in **Section 11.1**.

To examine reasons that patients changed therapy, the actions taken for discontinuing therapy will also be summarized on the same table. Specifically, when a drug is Discontinued Permanently the Action Taken for Administered/Prescribed MM Therapy Drugs for Regimen eCRF provides the following reasons:

- Adverse Event/Toxicity Related to Drug
- Adverse Event/Toxicity Not Related to Drug
- Relapse – Biochemical Progression
- Relapse – Symptomatic/Clinical Progression
- Resistance to Therapy
- In Remission
- Planned Therapy Ended
- Patient/Family Preference
- Drug Holiday
- Insurance Change
- Treatment Fatigue
- Financial Toxicity
- Lack of Response
- Death
- Unknown
- COVID-19 Diagnosis (Confirmed Positive)
- COVID-19 Diagnosis (Suspected Positive)
- COVID-19 Restrictions
- Other

Stem cell transplant (SCT) status will be summarized (Yes/No) at baseline by ND/RR cohorts overall and by country; and ongoing following the completion of enrollment by Treatment Regimens of Interest overall and by country for ND and R/R cohorts.

The following additional SCT details will be collected, but not summarized. The source, quantity, conditioning regimen, whether stem cells were harvested for: storage or part of a research protocol. Also, if SCT was for myeloma, the type of transplant (autologous, allogeneic, tandem autologous/allogenic, not specified), if autologous (single, tandem), if allogeneic (myeloablative or non-myeloablative), and reason for transplant. In addition, MRD assessment, response assessment at time of transplant, and timing of transplant.

- If date of SCT was partially missing, it was imputed as follows:
    - If the date had a month and year but the day was missing, then the 1st day of the month was imputed.
    - If the date had a year but was missing month, then January 1st was imputed.
    - If the date was missing year, then no imputation was made.

  However, the date for SCT < the date for consolidation therapy. If the imputed date would have altered the previous order, then the latest day prior to consolidation therapy was imputed.

7.3 Localized MM Treatment Modalities and Supportive Care

Supportive care for MM patients is part of an overall therapy plan and will be collected quarterly for all enrolled patients, but not summarized. These data will include: transfusions, bisphosphonates, growth factors, anti-Zoster therapy, anticoagulation therapy, pain medications, peripheral neuropathy therapy, and anti-depression therapy.

Radiation therapy related to myeloma will be collected quarterly for all enrolled patients, but not summarized. These data include: the number of fractions given, number of days of radiation therapy, total dose, reason for therapy, and whether inpatient or outpatient. In addition, surgeries related to myeloma with the type of procedure and if administered as an inpatient or outpatient were collected.

7.4 Diagnostic/Prognostic Criteria

Bone marrow aspirate and/or biopsy will be assessed at baseline and quarterly follow up. For ND patients, diagnostic marrow should be included. For R/R patients diagnostic marrow (if available), otherwise most recent not in remission should be included. The greatest value of plasma cells whether based on aspirate or biopsy for that assessment will be categorized as follows: <=10%, >10% to <=30%, >30% to <=60%, >60%, or not done. Summaries will be overall and by country or region for ND and R/R patients.

Detailed cytogenetics analysis by FISH and/or Karyotype will be assessed at baseline and quarterly follow up and summarized by treatment regimens of interest for ND and R/R patients overall and by country or region. FISH methodology will be reported with Yes/No results for the following tests: deletion (17p)/p53, translocation (4,14), and translocation (14,16); karyotype analysis results will be used for deletion (17p)/p53 only if FISH results are missing for that test. Karyotype analysis results will also report: deletion (13). Either method may report deletion (1p), 1q amplification, or hyperdiploid. These individual tests will be combined to determine High Risk, Definitive Standard Risk, or Presumed Standard Risk using traditional and alternative

definitions as below. Once a patient is defined as High Risk at any time including from medical history, then that patient will remain High Risk for all analyses.

Table 7-1 Cytogenetics Tests and Risk Group Definitions

Test Method	Abnormality	Flag
FISH	Del (17p) / p53	X1
	t(4,14)	X1
	t(14,16)	X1
Karyotype	Del(17p) / p53	X2
FISH or Karyotype	Chromosome 1p Deletion	X3
	Chromosome 1q Amplification	X3

Traditional Definition - If any of X1, X2 is 'Yes' then High risk; else if 3 of X1 are all 'No' then Definitive Standard risk; else if any of 3 of X1 is 'No' then Presumed Standard risk.

Alternative Definition - If any of X1, X2, X3 is 'Yes' then High risk; else if 3 of X1 and 2 of X3 are all 'No' then Definitive Standard risk; else if any of (3 of X1 or 2 of X3) is 'No' then Presumed Standard risk.

Type of paraprotein may be assessed at baseline and quarterly by serum and/or urine, which will be tabulated overall and by country or region for ND and R/R patients. The types of paraprotein include: IgG Kappa, IgG Lambda, IgA Kappa, IgA Lambda, free light chain kappa, free light chain lambda IgD, IgM, IgE, and not done.

7.5 Treatment Patterns

The number and proportion of patients treated with various index and subsequent regimen therapies will be summarized in shift tables (i.e. drug regimen changes from 1st to 2nd, 2nd to 3rd, etc.) to describe changes in treatment patterns over time. All enrolled patients will be summarized overall and by country or region. Shift tables may be used prospectively and/or retrospectively for R/R patients with up to 3 prior lines of therapy. Shift tables will be summarized for all patients among the treatment regimens of interest for the following changes in lines of therapy:

- 1st to 2nd line
- 2nd to 3rd line
- 3rd to 4th line

In addition, shift tables will be summarized for all patients within drug classes (**Appendix 14.2**). Frequency (%) of drug re-treatment will be summarized along the main-diagonal of the shift tables. Within class shift tables may be generated ad-hoc for other drug classes based on **Appendix 14.2**.

Sequences of treatments are of interest; for R/R patients a table summarizing up to 4 sequences since their front-line induction therapy will include therapies prior to study entry and prospective therapies. In addition, the clinical responses will be included in the clinical outcomes' effectiveness analyses (e.g. OS, PFS, DOT, TTNT). For R/R patients' treatment regimens of interest, the treatments received in 1st line including: induction, SCT (Yes/No) and maintenance regimen will be concatenated and summarized by descending total frequency. Likewise, the index regimens across 1st, 2nd, 3rd, and 4th lines will be concatenated and summarized for these patients. These same sequencing tables will be created for Ixazomib patients and summarized by region.

The treatment strategy of continuous versus fixed duration therapy will be summarized for select treatments. Fixed duration treatment will be defined with the intent from the MM regimen therapy plan to be 'Planned Fixed Duration of Therapy' or 'Planned Treatment to Best Response/Plateau'; otherwise, if the intent is 'Planned Treatment Until Progression' or 'Planned Therapy Change/Switch' these will be considered continuous strategies.

7.6 COVID-19 Disease Assessment

Due to the COVID-19 pandemic, the database and eCRF were modified to capture the impact of COVID-19 on accessibility to health care and outcomes by adding additional categorical responses on several forms, which will be summarized descriptively.

- Vital Status Information - During vital status assessment the result of attempted contact were expanded to include: 'Patient is alive, COVID-19 diagnosis (Suspected Positive), expected to return to clinic'; or 'Patient is alive, COVID-19 diagnosis (Confirmed Positive), expected to return to clinic'.
- Action Taken for Administered/Prescribed MM Therapy Drugs for Regimen - When there is a drug dose modification or discontinuation, the expanded reasons include: COVID-19 Diagnosis (Confirmed Positive), COVID-19 Diagnosis (Suspected Positive), or COIVD-19 Restrictions.

- Study Discontinuation - If the patient discontinued the study, it may additionally be: Due to Study Discontinued at Site, Patient Diagnosed with COVID-19 (Confirmed Positive), Patient Diagnosed with COVID-19 (Suspected Positive), Physician/Patient discretion due to COVID-19, or Travel Restrictions due to COVID-19. If a patient died due to Multiple Myeloma, the primary cause of death could be COVID-19 Diagnosis (Confirmed Positive) or COVID-19 Diagnosis (Suspected Positive).
- PRO Completion - It was also considered that a patient may not have completed their quarterly PRO assessment due to COVID-19.

A separate COVID-19 information eCRF was implemented to report the 6 combinations of symptomatic or asymptomatic with COVID-19 test results Positive, Negative, or Not Tested, or COVID-19 status was unknown. These responses will be summarized with descriptive statistics as n (%).

8 Clinical Outcomes Analysis

Time-to-event effectiveness endpoints, i.e. OS, PFS, TTNT, duration of therapy (DOT), and duration of maintenance therapy (DOMT) may be summarized by line of therapy [e.g. 1st, 2nd, 3rd, 4th, >4th, and R/R (i.e. 2nd and higher lines)] for ND and RR cohorts based on Kaplan-Meier methods in a descriptive fashion overall and by country or region. After a better understanding of confounding factors, missing patterns, selection biases, etc., further model adjustments using Inverse Probability Treatment Weighted (IPTW) Kaplan-Meier method (**Error! Reference source not found.**2004) with product limit estimator stratified by regimens of interest and/or lines of therapy may be performed during the interim or final analysis. After enrollment has been completed then the modeling strategy, including covariates, strata, and endpoint classification may be determined for the propensity score analysis to create the weights to be used in IPTW Kaplan-Meier analysis. Cox Proportional Hazards (PH) regression may be used in addition or in place of IPTW KM analysis to adjust for confounding factors. A potential list of covariates are given in **Section 8.4**.

The protocol amendment 1 required all ND patients to be enrolled within 3 months of being diagnosed. However, R/R patients could be enrolled anytime within their therapy plan. When calculating the time since the index regimen start date for a line of therapy, there could be differential lead times for ND and R/R patients prior to joining the study. For example, a ND patient may have started their frontline of therapy 1 month prior to study entry, but a R/R patient on 3rd line of therapy may have started that line of therapy over 1 year prior to joining the study. To account for this potential differential in follow-up lead times a targeted analysis will be conducted for clinical outcomes where all patients will be restricted to having started their line of

therapy under analysis no longer than 3 months prior to study entry. This targeted analysis will be applied to effectiveness clinical outcomes only, safety analysis will contain all enrolled patients. In addition, if a patient initiated their index regimen as part of a clinical trial, that could potentially bias the rigorousness of their assessments and those patients may be excluded as well in the targeted analysis. When considering only R/R patients, a diminishing percentage across higher lines of therapy may have had SCT, these may be excluded from the targeted analysis as well.

For the above clinical outcomes, the study population used will be clearly specified in the footnotes of the analysis outputs. Median, 25th and 75th percentile estimates, and 95% confidence intervals will be presented (where calculable), and minimum and maximum durations in months. The percentage of patients event-free will be calculated at 3, 6,12, 18, and 24 months, and additionally at 12 months intervals up to 60 months as data is available with 95% CI and number of patients at risk. Also, the median follow-up in all patients and in censored patients will be determined to descriptively assess informative censoring; and the reason for censoring as defined below for each outcome will be reported.

Based on the available data from a recent study C16010, we assumed a median PFS of approximately 21 months. We also assumed the time of PFS followed an exponential distribution, and a predicted enrollment of 260 patients using Ixazomib as an index regimen in a prospective R/R setting for the whole study. To conduct a PFS analysis, 110 PFS events observed after patients were treated with Ixazomib will be needed to achieve a desirable precision of less than an 8-month 95% CI width, i.e. [17.57, 25.55] for the estimated median PFS (**PASS v15**). To determine the number of events, e.g. with a minimum of 24-months of follow-up an estimated 54.7% of patients are expected to have an event based on an exponential distribution with a median PFS of 21 months; therefore, 142 events would be expected which will result in a 95% CI width of 7.0 months. For the targeted analysis a subset of 180 patients are expected to have enrolled in the study within 3 months of starting treatment. There would be 98 events expected with a minimum of 24-months of follow up, which would result in 95% CI width of 8.5 months.

8.1 Progression-Free Survival

The investigator will assess all responses as stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (PD), or not assessed (NA). Progression-Free Survival is defined as the number of months from the line of therapy index regimen start date until the earliest of either date of death or PD (biochemical or clinical). Patients who do not experience an event (i.e. death or PD) will be censored at the date of their last adequate

assessment **Table 8-1**. A patient that changes Line of Therapy for a reason other than PD (biochemical or clinical) will be censored at the date of their last adequate tumor assessment prior to initiation of new Line of Therapy as 'New Line of Therapy'. A 'Not Assessed' response is not considered an adequate assessment and is treated as missing. Patients without an assessment but with a line of therapy start date will be censored at Day 1 as 'No Adequate Assessment' for that line of therapy, unless the patient died and then the patient will be considered as having a PD event at the date of death. When an analysis cutoff date is implemented, only data occurring on or prior to the cutoff date will be used for analysis and patients will be censored at the latest adequate assessment prior to cutoff date as 'Ongoing'. If a patient begins a clinical trial during a line of therapy they will be censored at the date of the last adequate assessment prior to the start date of the clinical trial as 'Patient Started Clinical Trial'; however, if the clinical trial start date is equal to the line of therapy start date, then they will be excluded from analysis. If a patient does not visit the clinic for 9 months, then a certified letter will be sent to the patient's last known address. If the patient fails to respond to the certified letter, that patient will be considered lost to follow-up for study disposition and censored at the date of the latest adequate assessment. 'Study Discontinued' censoring reasons include: withdrew consent, lost to follow-up, too ill to participate, patient declines participation and declines follow up for survival, physician discretion, change in physician or transferred to another treatment center, on hospice, and other.

As a sensitivity analysis to the above censoring rules a patient's last adequate assessment date will be replaced with their last known alive date on-study within current line of therapy, unless the patient started a new line of therapy for other than PD, discontinued the study, or began a clinical trial then those respective dates would be used for censoring (**Table 8-2**). In this observational study, the response assessment entered by the investigator is the only means of response assessment; therefore, if a response assessment is not recorded for any reason that would conservatively shorten the censoring follow-up duration. As an alternative censoring for a patient that does not have a PFS event, the last known alive date within that line of therapy would provide an anti-conservative censoring follow-up duration.

There may be multiple censoring conditions that identify the same adequate assessment date. For example, if a patient's last adequate assessment is on 01JAN2018, then they start a clinical trial on 01FEB2018, and then discontinue the study on 01MAR2018, it's not clear which censoring reason should be assigned to the 01JAN2018 date. Another example would be, not having an adequate assessment for a line of therapy and then withdraw consent; this condition would require censoring at day 1. Therefore, the following hierarchy will be used to assign the censoring condition to the last adequate assessment date (from highest priority to lowest): Study

Discontinued, Patient Started a Clinical Trial, New Line of Therapy, Ongoing with Assessment, and Ongoing without Assessment.

Table 8-1 Handling of Missing Assessments and Censoring for PFS Analysis

Situation	Date of Progression or Censoring	Outcome
No assessment within a line of therapy, and no death	Start date of line of therapy	Censored
Disease progression documented between quarterly visits	Date of documented disease progression	Progressed
No documented death or disease progression	Date of last adequate assessment [1]	Censored
Lost to follow-up, withdraw consent, or other reason for study discontinuation before any documented death or disease progression	Date of last adequate assessment [1]	Censored
Death or progression after more than 1 missed visit	Date of documented disease progression	Progressed
Patient begins a clinical trial during line of therapy	Date of last adequate assessment [1]	Censored
New line of therapy defined in therapy plan eCRF for reason other than PD (biochemical or clinical)	Date of last adequate assessment [1]	Censored
Death before first assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed

[1] A 'Not Assessed' response is not considered an adequate assessment and is treated as missing.

Table 8-2 Handling of Missing Assessments and Censoring for PFS Sensitivity Analysis

Situation	Date of Progression or Censoring	Outcome
No assessment within a line of therapy, and no death	Date last known alive on-study within current line	Censored
Disease progression documented between quarterly visits	Date of documented disease progression	Progressed
No documented death or disease progression	Date last known alive on-study within current line	Censored
Lost to follow-up, withdraw consent, or other reason for study discontinuation before any documented death or disease progression	Date of study discontinuation	Censored
Death or progression after more than 1 missed visit	Date of documented disease progression	Progressed
Patient begins a clinical trial during line of therapy	Start date of clinical trial	Censored
Next line of therapy defined in therapy plan eCRF for reason other than PD (biochemical or clinical)	Start date of next line of therapy	Censored
Death before first assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed

When complete dates are not available the below imputation rules will be used to calculate time-to-event outcomes. If year is missing, then dates will not be imputed (except for treatment regimen end date based on death date).

When imputing date for death from partial date:

- Missing day: use end of study day of the month and year

When imputing date for progression from partial date:

- Missing day: 15th day of the month and year, or on the end date last regimen within current line of therapy, whichever is later

When imputing start dates for line of therapy from partial date:

- Missing day: 1st day of the month and year of therapy, or one day after end date of last regimen in previous line of therapy, whichever is later
- Missing day and month (frontline induction regimen only): if date of bone marrow aspirate and/or biopsy is known then the last day of month and year of bone marrow test; otherwise, if date of initial diagnosis was known (not imputed) then last day of month and year of initial diagnosis

When imputing end dates for treatment regimen based on death date:

- If final treatment regimen end date is entirely missing and the patient has died, then impute the death date for final treatment end date

When imputing last alive date from a partial date:

- Missing day: 1st day of month and year, if imputed date is later than data cut off date, then data cut off date will be used instead

The duration of follow-up in months was defined for all time-to-event outcomes as (date of event/censor – date of line of therapy earliest regimen start date + 1) / 30.4375.

8.2 Overall Survival

Overall Survival was defined as the number of months from the index regimen start date within each line of therapy, starting with the line during study entry, until the date of death. The index regimen start date may be several months prior to study entry, but the earliest line of therapy and index regimen that will be included in analysis will match that at or after study entry (i.e. on-study). For example, if a patient enters the study on an index regimen in 2nd line of therapy and then progresses through 3rd and 4th lines and then dies, that patient would contribute an event to 2nd, 3rd, and 4th lines of therapy analysis with different durations based on each corresponding line of therapy start date. **Figure 2** shows examples of the follow-up for PFS & OS. For the All R/R and >4th Line summaries, only the earliest R/R line of therapy (i.e. >= 2nd line of therapy or >4th line of therapy, respectively) with prospective ixazomib exposure as an index regimen will

be included, to maintain independence among patients. The higher level lines may be combined e.g. >=Xth Line. The following censoring conditions will be grouped as 'Study Discontinued with Vital Status Follow-up': too ill to participate, physician discretion, change in physician or transferred to another treatment center, on hospice, lost to follow-up, and other. Other censoring is considered 'Study Discontinued without Vital Status Follow-up': when a patient declines participation and declines follow up for survival, and withdrew consent. Patients may also be censored at date of last contact or latest date known to be alive as 'Ongoing'.

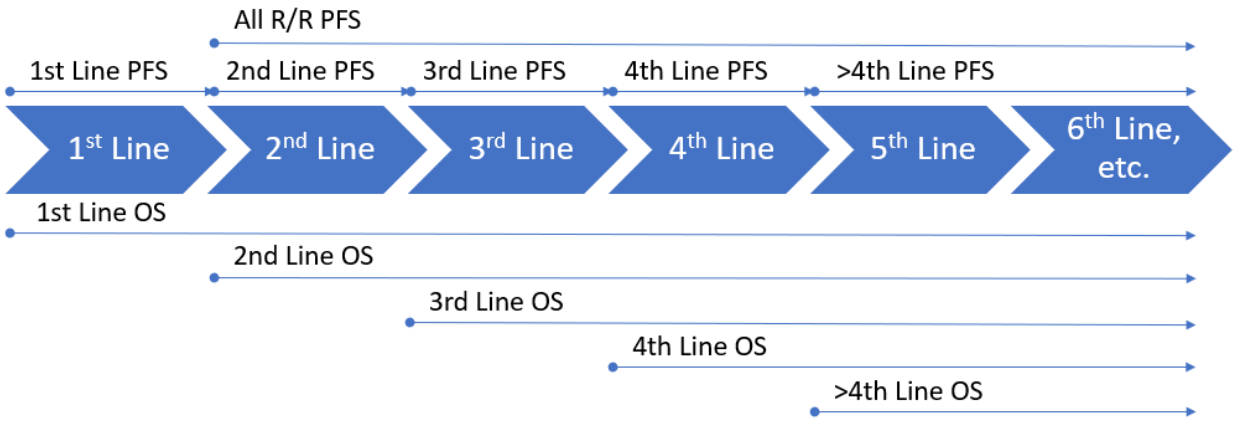


Figure 2. PFS and OS follow-up by lines of therapy

8.3 Time to Next Line of Therapy and Treatment Durations

Time to next line of therapy was defined as the number of months from the on-study index regimen start date within a line of therapy until a change in line of therapy occurred. The event will be defined as the new line of therapy start date for patients that do not die. For patients that die, the date of death may be included as a composite event (i.e. new line of therapy start date or death date), or the date of death may be included as a competing risk. If a patient discontinues therapy temporarily or permanently they will still be accruing time on the current line of therapy until a new index regimen has been initiated, which defines a new line of therapy. Patients will be analyzed on each line of therapy with an on-study index regimen. For example, if a patient enters the study in 2nd line of therapy on a maintenance regimen, then that patient would not be included in analysis until their index regimen on the 3rd line of therapy. However, if they then progressed and began a 4th line of therapy index regimen both the 3rd and 4th lines would be analyzed separately in their corresponding lines of therapy. Patients may be censored as 'Study Discontinued' with the corresponding date for the following reasons: too ill to participate, patient declines participation and declines follow up for survival, physician discretion, change in physician or transferred to another treatment center, on hospice, other, lost to follow-up, and

withdrew consent. Alternatively, a patient may be censored as 'Patient Started Clinical Trial' at their corresponding date.

For time to next line of therapy, if none of the former censoring conditions applied, then 'Ongoing' was reported and the censoring date depended on the information entered in the most recent completed Multiple Myeloma Therapy Status Quarterly visit eCRF. If the Therapy Status question 'Has the patient received Multiple Myeloma-directed Therapy during the Evaluation Period' was answered with either a Yes or No, then the window end date (i.e. start date + 90 days) was used for censoring since either condition would accrue additional time on each on-study line of therapy. If the quarterly visit window end date was beyond the data cutoff date, then the data cutoff date will be applied for censoring. If all the MM Therapy Status Quarterly visit forms were missing, then the later of the patient's informed consent date or index regimen start date was used as the censoring date. Alternatively, the patient's last know alive date was used as the censoring date; the analysis output will detail the censoring approach that was implemented.

To estimate TTNT for patients where death will be treated as a competing risk for analysis, and the survival estimates and 95% CI will be reported as (1 - cumulative incidence function, CIF) that is able to be estimated in PROC LIFETEST, in SAS v9.4. The TIME statement will include the name of the censoring variable with a parenthetical list of values that correspond to right-censoring; the EVENTCODE option will equal the value for the event of interest (e.g. indicating that a new line of therapy was initiated); death will not be included as the event of interest nor in the censoring list, thereby it will be analyzed as a competing risk. This same EVENTCODE method is available in the MODEL statement, in PROC PHREG for Cox proportional hazards analysis. The method developed by (**Brookmeyer** 1982) will be used to calculate the 95% CI for the quartile estimates. One minus the CIF will be used for the survival estimate and the CIF standard error (SE) will be used as the SE for the survival estimate along with the log-log transformation, which is the default method in SAS without competing risks.

To estimate TTNT for patients where death will be treated as a composite endpoint, standard Kaplan-Meier methods will be used with the event date being either start date of a new line of therapy or death date, whichever is earlier.

Duration on index regimen on-study was defined as time from start date to end date of index regimen, which is induction regimen for newly diagnosed patients, and treatment for relapse for relapsed/refractory patients. In both cases the start date is the index regimen start date on the corresponding line of therapy, and the event date is the regimen end date. Likewise, for duration on index (or maintenance) regimen, a patient may be analyzed in multiple lines of therapy as

long as the regimen of interest was on-study. If the patient was censored as 'Ongoing', then the censoring date depended on the information entered in the most recent completed Multiple Myeloma Therapy Status Quarterly visit eCRF. If the Therapy Status included 'No Change in Regimen from Previous Entry' or 'Dose Modification, Discontinuation or Schedule Change of any MM Drug', then the window end date (i.e. start date + 90 days) was used for censoring. It's more appropriate to use the quarterly visit window end date for the occurrence of a dose modification or schedule change since a dose modification or schedule change would not alter the treatment regimen. If a discontinuation was recorded, then there is no need to censor since the event of interest would be recorded in the Administered/Prescribed forms. However, if the Therapy Status form included 'Initiation of a New Regimen' or 'Patient is Undergoing Transplant 'then the window start date was used for censoring. If the quarterly visit window end date was beyond the data cutoff date, then the data cutoff date was applied for censoring. If all the MM Therapy Status Quarterly visit forms were missing, then the later of the patient's informed consent date or index regimen start date was used as the censoring date. Otherwise, the patient may be censored for 'Study Discontinuation' reasons, the same as time to next line of therapy. Death will not be included as a censoring event, nor a competing risk, since the study discontinuation procedures include using the death date as the latest regimen end date if the regimen was not discontinued prior to death; therefore, death would be associated with the event of interest. Duration on maintenance regimen will be similar to index regimen, except the phase of regimen must be indicated as maintenance. Also, if there was more than one maintenance regimen within a line of therapy, then the earliest regimen was used for analysis.

The time to next line of therapy, OS, PFS, and duration of therapy will be analyzed based on SCT status, i.e. all patients that had a SCT on the corresponding line of therapy will be grouped together versus all patients without SCT information available.

8.4 Statistical Modeling & Convergence

Propensity scores (**Rosenbaum** 1983) may be calculated within lines of therapy based on polychotomous logistic regression models in SAS® PROC GENMOD with a cumulative logit link (LINK=CLOGIT) and multinomial distribution, to determine the probability of being selected into their index treatment regimen of interest for the corresponding line of therapy. In this approach, each patient would have a vector of conditional probabilities estimated for each treatment regimen of interest; these patient-level conditional probabilities are available by using the PREDICTED option in the OUTPUT statement. The inverse probabilities of treatment weighted (IPTW) would then be applied in an adjusted Kaplan-Meier analysis. To reduce the influence of any extreme weights, the IPTW would be stabilized as in (**Error! Reference source**

not found.2004), i.e. the weight for each patient is defined as the marginal probability Pr(Y = y; of being in a treatment regimen of interest) divided by the conditional probability Pr(Y = y|Z; a particular treatment regimen given a vector of covariates) determined by the logistic regression model. For example, if there were 6 treatment regimens of interest, then there would be 6 weights for each patient. However, only the conditional probability corresponding to the patient's actual regimen received would be used as the denominator, and the marginal probability for the patients that received that same regimen would be the numerator (i.e. the number of patients that received the regimen of interest / total number of patients in the analysis) in the weight calculation that would be used in the WEIGHT statement for PROC LIFETEST and/or PROC PHREG. The balance in propensity scores among the index regimens of interest would be assessed graphically where non-overlap in the propensity score distributions (e.g. box & whiskers plot) indicates one or more baseline covariates are strongly predictive of regimen selection. If this occurs, then the set of covariates may require higher order polynomial terms and/or interactions to achieve overlapping distributions.

The list of covariates that may be entered into the logistic or Cox PH regression model based on subject matter expertise are provided below. The odds ratio (95% CI), or HR (95% CI), would be reported for all covariates in the final models. Covariates that were known prior to the treatment regimen assignment were considered for inclusion in the model; the below covariates would be assessed at study baseline (if fixed in study design), or within a window (-x months, +y months) compared to line of therapy or regimen start date for longitudinal measures depending on analysis. Windowing intervals will be clearly defined in the summary table footnotes.

- Geography Region: APAC, EMEA, LA, NA
- Treatment Facility Type: academic/university, community (i.e. regional/local hospital, clinic/outpatient)
- Line of Therapy 1st, 2nd, 3rd, etc.
- Patient Demographics - Age (e.g. <65, 65-75, >75 years); Sex (Male, Female)
- ECOG Performance Status (e.g. 0/1, >=2)
- Prior PI (Y/N)
- Prior PI Status (prior refractory PI, prior PI exposure immediate prior line no refractory, prior PI exposure earlier prior line no refractory, prior PI naïve)
- Prior IMiD (Y/N)
- Prior Lenalidomide Status (prior refractory Lenalidomide, prior Lenalidomide exposure immediate prior line no refractory, prior Lenalidomide exposure earlier prior line no refractory, prior Lenalidomide naïve)
- Prior Peripheral Neuropathy (Y/N)

- Comorbidities of interest: Prior MI or CHF, Prior Chronic Pulmonary Disease, Prior Diabetes with End Organ Disease, Prior Hypertension, Prior Arrhythmias/Pacemaker/AICD (Y/N)
- Charlson Comorbidity Index (e.g. CCI <2, CCI >=2)
- ISS Assigned Staging (e.g. I/II, III)
- Cytogenetics (Definitive High Risk, Definitive Standard Risk, Presumed Standard Risk); or High Risk vs Standard Risk
- Treatment Intent of Regimen (planned treatment until progression, planned fixed duration of therapy, planned treatment to best response/plateau, planned therapy change/switch)
- History of CNS involvement
- History of pneumococcal vaccine
- Prior influenza vaccine
- Stem Cell Transplant Status – prior line (Y/N), current line (Y/N)
- Duration from initial diagnosis to line of therapy start date for R/R patients (continuous or categorical, e.g. [0, 18], [>18, 36], >36 months)
- Corrected Calcium (<=11 mg/dL, >11 mg/dL)
- Renal Function (Serum Creatinine >2 mg/dL or Creatine Clearance <40 mL/min, Neither Condition)
- Anemia (>=10 mg/dL, <10 mg/dL)
- Bone Lesions (Y/N)

When conducting statistical modeling the same patient may be included in more than one line of therapy resulting in clustered patient data with only a few correlated repeated measurements by line of therapy for a small sample of patients (e.g. <5%). In the case of time-to-event endpoints using Cox PH regression (PROC PHREG) these analyses will include a robust sandwich covariance matrix estimator to account for the within patient correlation by including COVS(AGGREGATE) option on the PROC statement with an ID statement to identify the subject IDs.

In the case of repeated discrete outcomes PROC GENMOD or GLIMMIX may be used with generalized estimating equations (GEE). Since the amount of repeated data is sparse several covariance structure may not converge. The following will be tried in order until convergence is achieved for all analyses within a table: unstructured (UN), 1st-order autoregressive (AR1) for ordinal variables with at least 3 levels (e.g. line of therapy), compound symmetry (CS) and lastly variance components (VC or IND, i.e. independent). If using PROC GENMOD these TYPE options are applicable for the REPEATED statement. If using PROC GLIMMIX then the RESIDUAL option should be added to the RANDOM statement with the ordinal variable as the random effect, to indicate modeling the R-side covariance structure, then the TYPE option may be used with the same list order of covariance structures. For ordinal variables make sure the

SORT order is by subject and ascending level of the covariate. The table footnote will specify the covariance structure that was used for all analyses in the table.

8.5 Best Response

Best of best quarterly response and exact binomial 95% confidence interval (CI) will be calculated using Clopper-Pearson method by Line of Therapy, Treatment Regimens of Interest (**Section 7.2**) and/or country. If a quarterly best response is reported without a corresponding regimen, then the previous regimen will be carried forward. However, if the regimen start date is equal to the start date of a clinical trial, then that regimen (and thereby line of therapy) will be excluded from analysis. Overall response rate (ORR) and 95% CI will be calculated as achieving a response of PR or better. Clinical benefit rate (CBR) and 95% CI will also be reported as achieving a response of MR or better. Results of type of PD (symptomatic/clinical or biochemical), whether PD occurred after best response and if so, type will also be summarized. Univariate and adjusted logistic regression may be implemented based on the covariates in **Section 8.4** for ORR and CBR, to assess associations with regimens of interest within lines of therapy.

In this observational study some best quarterly responses may be missing, especially the date of PD. Additional eCRF will be used to impute a missing PD date, since it's essential for PFS outcome. If the Therapy Plan eCRF contained Relapse Biochemical Progression or Relapse – Symptomatic/Clinical Progression as a reason for initiation of an index regimen in the subsequent line of therapy, then the new index regimen start date was used as the PD date. Also, if the Action Taken eCRF contained Relapse – Biochemical Progression or Relapse – Symptomatic/Clinical Progression as a reason for regimen discontinuation on the current line, then the regimen end date was used as the PD date.

If there is a SCT date that occurred between an index regimen start date and a response assessment date, and there is no peritransplant regimen entered in the administered/prescribed eCRF, then one day prior to the SCT date will be used as the index regimen end date for the purpose of best response only. The index regimen end date is entered in the eCRF; however, for the purpose of best response only, the end date will be imputed as one day prior to the SCT date so the response assessment is not inadvertently associated with an index regimen when there must have been an intervening peritransplant regimen that may not have been entered into the eCRF.

8.6 Multiple Imputation

Due to the observational nature of this study, it is expected that several clinically meaningful variables may have a substantial amount of missing data, e.g. >10%. As a sensitivity analysis to assess the impact of missing data, multiple imputation methods will be applied to the missing covariates that are used to reduce confounding between the regimens of interest and the clinical outcomes, e.g. OS, TTNT, DOT, PFS, TTD, QoL. The Fully Conditional Specification (FCS) and Markov chain Monte Carlo (MCMC) methods will be used in PROC MI, since the missing data pattern is expected to be arbitrary and to impute continuous and categorical variables as needed. MCMC will be used for imputation of missing values of continuous laboratory measures, which are selected as explained variables of certain covariates, such as *Albumin, Creatinine Clearance*. Within the FCS method each covariate to be imputed will use the following method associated with the variable type: continuous variables will use regression, all categorical variables(binary/ordinal/nominal) will use logistic regression, and nominal variables will use discriminant function. Below is a table with a list of factors to be used for each variable with missing data that needs to be imputed.

Missing Covariate	Outcome	Predictor Variables
ECOG Performance Status	PRO, Clinical	Age, ISS Stage, Prior PN, Prior MI or CHF, Creatinine Clearance, CCI, Region
Charlson Comorbidity Index (CCI)	PRO, Clinical	ECOG, Prior MI, prior CHF, Creatinine clearance, ISS stage
Prior Hypertension	PRO, Clinical	Other cardiac comorbidities ie MI, CHF, arrythmias, creatinine clearance
Prior Peripheral Neuropathy (PN)	Clinical	Age, CCI, Region, Prior PI Status, Line of Therapy
ISS Stage	PRO, Clinical	Albumin, Creatinine Clearance
Treatment Intent of Regimen	DOT	Age, ECOG, CCI, Creatinine Clearance
Time from Diagnosis	PRO, Clinical	Age, ISS Stage, ECOG, Prior PN, Prior MI or CHF, Creatinine Clearance, CCI, Region, Line of Therapy, Treatment Facility Type
Renal Function	PRO, Clinical	Age, ISS Stage, ECOG, Prior MI or CHF, Creatinine Clearance, CCI, Region, Prior PI Status, Prior Lenalidomide Status, Line of Therapy, Treatment Facility Type, Time from Diagnosis
Anemia	PRO, Clinical	Age, ISS Stage, ECOG, Prior MI or CHF, Creatinine Clearance, CCI, Region, Prior PI Status, Prior Lenalidomide Status, Line of Therapy, Treatment Facility Type, Time from Diagnosis

The number of imputations will be set between 10 and 100 to balance the computing time with the fraction of missing information and number of subjects. The relative efficiency (RE),

relative increase in variance, is defined as RE=[1 + λ/m]-1, where m is the number of imputations and λ is the fraction of missing information. The initial number of imputations will be equal to the fraction of missing information, such that λ/m=0.01. Following the imputation phase, PROC MIANALYZE will be used to pool the parameter estimates. The results from statistical models with multiple imputations for missing covariates will be presented as supportive analyses, in addition to the primary effectiveness analyses using the same statistical models.

9 Patient-reported Outcomes (PROs)

The patient reported outcomes (PROs) in the study include the Global Health Status/Quality of Life subscale from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) (**Aaronson** 1993), the EORTC Quality of Life Questionnaire Multiple Myeloma (EORTC QLQ-MY20) (**Stead** 1999), the Treatment Satisfaction Questionnaire for Medication (TSQM-9) (**Bharmal** 2009), and the European quality of Life, 5-dimension, 5-level (EQ-5D-5L) questionnaire (**Herdman** 2011).

PRO Instrument Item Reductions

During study initiation (at enrollment/baseline), full versions of the PROs were completed either electronically (ePRO) or on paper (patients had the choice to choose their preferred modality); namely, subjects completed the full versions of the EORTC QLQ-C30, EORTC QLQ-MY20, TSQM-9 and EQ-5D-5L. It became clear during the study fieldwork that subjects were more often opting to use paper versions of the PROs as opposed to the electronic PROs, with the majority of the PROs completed on paper. In light of this information, and after approximately two years of data collection, Protocol amendment version 2.0 was implemented and involved: (1) significantly reducing the number of PRO items to decrease patient burden; (2) and removing electronic PRO data collection as an option completely. **Table 9-1** breaks down the PROs administered, the number of items per instrument, the timepoints assessed, the administration type, and the scoring calculation derivation possibilities. In summary, per protocol amendment version 2.0, all study subjects continued to complete reduced versions of EORTC QLQ-C30 and EORTC-MY20 and full version of TSQM-9 but discontinued completion of EQ-5D-5L, with all PROs completed via self-report on paper only.

The PRO item reduction that took place is expected to result in a lower sample size for the impacted measures through the duration of the study. The specific changes that were made and items affected included: (1) retaining only items 29 and 30 of the EORTC QLQ-C30, which make up the Global Heath Status/QOL subscale; (2), retaining one single item (item 43,

"Tingling in hands or feet") from the EORTC QLQ-MY20 to measure the common treatment-related side effect of peripheral neuropathy; and (3) removing the EQ-5D-5L instrument in its entirety. Thus, it is anticipated that the sample size will decrease after amendment #2 was initiated for all PRO instrument items except for items 29 and 30 from EORTC QLQ-C30, item 43 from EORTC QLQ-MY20, and the full version of the TSQM-9 as detailed in **Table 9-1**.

Table 9-1 Patient-Reported Outcome Summary of Study Assessments

		Time Point		Administration Type		
Instrument	**# of Items**	**Enroll-ment**	**Follow-Up [1]**	**Electronic or Paper [2]**	**Paper Only [3]**	**Instrument Scoring Possible?**
• EORTC QLQ-C30 subset (Overall health and QoL)	2	x	x	x	x	Yes, for all administration types
• EORTC QLQ-MY20 subset (Tingling in hands and feet)	1	x	x	x	x	Yes, for all administration types
• TSQM-9 full version	9	x	x	x	x	Yes, for all administration types
• EQ-5D-5L full version	5	x	x	x		Pre-amendment 2 protocol dataset only
• EQ-5D VAS	1	x	x	x		Pre-amendment 2 protocol dataset only
• EORTC QLQ-C30 full version	30	x	x	x		Pre-amendment 2 protocol dataset only
• EORTC QLQ-MY20 full version	20	x	x	x		Pre-amendment 2 protocol dataset only

Abbreviations: ePRO = Electronic patient-reported outcome; EORTC QLQ-C30 = Global Health Status/Quality of Life subscale from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EORTC QLQ-MY20 = EORTC Quality of Life Questionnaire Multiple Myeloma; TSQM-9 = Treatment Satisfaction European Quality of Life, EQ-5D-5L = 5-dimension, 5-level; Visual Analogue Scale (VAS).
[1] Completed quarterly at any timepoint throughout the study duration. +1 month visit window does not apply to PRO collection.
[2] Subjects had the choice to use paper or electronic PROs.
[3] All patients switched to completing only paper versions of the shortened PROs (i.e., EORTC QLQ-C30, EORTC QLQ-MY20, and full discontinuation of EQ-5D-5L) items after execution of study protocol amendment version 2.0.

PRO Compliance

Two types of PRO study compliance (completion rates) are being calculated:

1) Item-level average PRO compliance rate = sum of questions answered by all subjects and time points / sum of questions expected by all subjects and timepoints.

2) Subject-level average PRO compliance rate = average of all subject's item-level PRO compliance rates for all timepoints

Paper PRO compliance reporting includes monthly reports that provide overall compliance rates with the ability to be filtered by PRO, time point, country, site number, questionnaire, and by patient ID (furbished after protocol amendment version 2.0 and starting Jan 2019). ePRO compliance reports were derived from ERT's (ePRO vendor) electronic database system that will become static after January 31, 2019. Starting in February 1, 2019 all compliance reported will be derived from a combination of ERT's static database with RAVE ongoing data. RAVE is an electronic data capture management system by Medidata (https://www.mdsol.com/en/products/rave). Compliance will assist in better understanding the implications resulting in the migration from electronic data collection to paper fully; this will also help inform optimization of PRO data collection across sites and countries in real-time. Any additional requests for compliance reporting and analysis will be reported separately beyond this SAP.

PRO Study Visits

The early version of the electronic PRO (completed outside of RAVE by ERT prior to protocol amendment version 2.0) did not include reference to a quarterly visit; however, this was corrected during the database modification when PRO was added to RAVE. Therefore, when conducting an analysis by visit for the PRO data, if the quarterly visit information is missing, it will be imputed based on where the study day of assessment falls within the below **Table 9-2** of quarterly visit windows.

Table 9-2 PRO Quarterly Visit Windows for Imputation of Missing Visit Associated with On-going Assessments

		Quarterly Visit Window	
Quarterly Visit [1]	**Nominal Day**	**> Window Start Day**	**Window End Day**
Enrollment [2]	1	0	1
Y1Q1FU	45	1	91.3125
Y1Q2FU	137	91.3125	182.625
Y1Q3FU	228	182.625	273.9375
Y1Q4FU	320	273.9375	365.25
Y2Q1FU	411	365.25	456.5625
Etc.			

[1] Where e.g., Y1Q4FU refers to year 1, quarter 4, follow-up period.
[2] Enrollment refers to informed consent date/baseline. Note that eCRF that are only completed at Baseline/Inclusion will be assigned to that visit regardless of the study day. These data include

sociodemographic, care seeking behavior, and family history of cancer. If these data are in multiple sources (i.e. RAVE and ERT) they will be pooled together for completeness. However, if the same data point is included in both RAVE and ERT, then the RAVE data will be used.

There may be more than one set of PRO assessments within a quarterly visit window. If so, the rules below will determine how the PRO assessment should align with the single most appropriate visit.

1) A patient's informed consent date will define their enrollment (baseline) date, and then the visit window end day for each subsequent visit will be calculated by adding 91.3125 days to their study entry date.

2) If only a single PRO assessment (includes all PRO items completed during that quarter) is included within the window start and end day range, then that PRO assessment will be assigned to the corresponding quarterly visit.

3) If more than one PRO assessment is included within the quarterly visit window, then each PRO assessment will be assigned to the quarterly visit resulting in the smallest total absolute difference between the nominal day and the assessment day for each assessment in the window. For example, if a patient has PRO data at days 1, 80, 185, and 270, these would correspond to visits Baseline, Y1Q1FU, Y1Q3FU, and Y1Q3FU. However, there shouldn't be multiple assessments in a single quarter, and Y1Q2FU is missing. For Y1Q2FU the difference in days = |137 - 185| = 48 days, and |137 – 270| = 133 days if either assessment was assigned to Y1Q2FU. Similarly, the difference in days = |228 – 185| = 43 days and |228 – 270| = 42 days if either was assigned to Y1Q3FU. The overall absolute difference for the two choices equals 48 + 42 = 90 days or 133 + 43 = 176 days, so the 185-day visit should be assigned to Y1Q2FU and the 270 days visit should be assigned to Y1Q3FU to minimize the overall absolute difference.

4) If step 3 above would still result in multiple visits per quarter, e.g. if a patient had PRO assessments for Baseline, Y1Q1FU, two assessments for Y1Q2FU, and Y1Q3FU. Then, if the multiple assessments were from different data sources (i.e. RAVE and ERT), the data entered via RAVE will take priority.

9.1 Description of PROs and Scoring

EORTC QLQ-C30 (v3.0)

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) (**Aaronson** 1993) instrument contains 30 items across 5 functional scales (physical, role, cognitive, emotional, and social) and 3 symptom scales (fatigue, pain, nausea and vomiting), a Global Health Status/QoL scale, and single items assessing additional symptoms like loss of appetite, dyspnea, insomnia, constipation, diarrhea and perceived financial impact of disease (see **Table 9-3**). The instrument was used to measure general quality of life covering multiple domains (global, functioning scales, and symptom scales). Items 1 - 28 have 4 response levels ('Not at all', 'A little', Quite a bit', and 'Very much') and items 29 and 30 rely on a 7-point numeric rating scale ('Very poor' to 'Excellent').

The QLQ-C30 v3.0 is composed of both multi-item scales and single-item measures. These include five functional scales (physical functioning [5 items], role functioning [2 items], emotional functioning [4 items], cognitive functioning [2 items], social functioning [2 items]), three symptom scales (fatigue [3 items], nausea and vomiting [2 items], pain [2 items]), a global health status / QoL scale (GHS/QOL) (2 items), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). For all scales, the Raw Score (RS) is the mean of the component items. Raw scores are converted into scale scores ranging from 0 to 100 (See **Appendix 14.9** for scoring procedures). For functional scales, the score = [1 - (RS - 1) / range] x 100 and for symptoms scales/items and global health status/QoL scale, the score = [(RS - 1) / range] x 100. For functional scales and global health status/QoL scale, higher scores represent better HRQoL, whereas for symptom scales, higher scores represent worse HRQoL. A summary score of EORTC QLQ-C30 can be calculated from the mean of 13 of the 15 subscales (the Global Health Status/QoL scale and the Financial Difficulties scale are not included). If at least half of the items from the scale have been answered, all the items that were completed will be counted, and the standard equations described for calculating the scale scores will be used; any items with missing values will be ignored when making the calculations. If more than half of the items are missing, the score scale will be set to missing. As a 'rule of thumb', for multi-item measures, if at least half of the items from the scale have been answered, it will be assumed that the missing items have values equal to the average of those items which are present. If there are more than half of the items missing from a scale, then it is planned to set the scale score to missing.

As **Table 9-3** shows, the full version of the QLQ-C30 was only used prior to protocol amendment version 2.0 data collection period. Therefore, post this amendment, only two items

(overall health status and QoL) were self-reported by patients on paper forms. These items are based on a 7-point numeric scale (very poor to excellent), with higher scores representing improved health related quality of life (HRQoL). Per above, these two items were combined into a single global health status / QoL scale, ranging on a subscale/domain from 0 to 100, with higher scores representing better HRQoL.

Table 9-3 Definition of Subscale Scores of EORTC QLQ-C30

Subscale	Individual Items
Physical functioning	1-5
Role functioning	6-7
Emotional functioning	21-24
Cognitive functioning	20, 25
Social functioning	26-27
Fatigue	10, 12, 18
Nausea and vomiting	14-15
Pain	9, 19
Global Heath Status/QOL (GHS/QOL) [1]	29, 30
Dyspnea	8
Insomnia	11
Appetite loss	13
Constipation	16
Diarrhea	17
Financial difficulties	28

The majority of the QLQ-C30 data are only available prior to amendment #2; therefore, a lower sample size is expected, apart from items 29 and 30. Global Heath Status/QOL items 29 and 30 include the full dataset of both electronic and paper data collection methods, while the remaining items are only available from data collected prior to amendment #2.
[1] The study table analyses only include the Global Health Status/QoL domain.

EORTC QLQ-MY20

The EORTC Quality of Life Questionnaire Multiple Myeloma (EORTC QLQ-MY20) (**Stead** 1999) is a multiple myeloma specific questionnaire that contains 20 items across 2 functional subscales (future perspective [3 items] and body image [1 item]) and 2 symptoms scales (disease symptoms [6 items' and side effect of treatment [10 items]) (see **Table 9-4**). The questionnaire was used to assess key symptoms affected by multiple myeloma and treatments. The 20 items are assessed on a 4-point Likert scale ranging from "Not at all" to "Very much." Scores for the

symptom scale and future perspective scale are calculated by computing the RS (mean item score) and performing a linear transformation, [(RS - 1) / 3] x 100, to convert to a 0-100 scale (See **Appendix 14.10** for full scoring procedures and missing data applications). For the body image item, it is treated individually and should only be linearly transformed to a 0-100 scale. A higher score for disease symptoms and side effects of treatment represents a higher level of symptoms or problems, whereas a higher score for future perspective and body image represents better outcomes. Scores for each scale are computable if at least half of the items from the scale have been answered. For missing data imputations, each scale will have a different rule; for the disease symptoms scale, if less than 3 items have a valid score then the scale will be treated as missing. For side effects of treatment, if less than 5 items have a valid score, then it will be treated as missing. For the future perspective scale, if less than 2 items have a valid score, then it will be treated as missing. Lastly, for the body image (single-item scale), it will be a linear transformation to a 0-100 scale BI = [1 – (Q47 – 1) / 3] * 100.

The full version of EORTC QLQ-MY20 was used prior to protocol amendment version 2.0; post this amendment, only one item was retained (item 43) and collected via self-report paper format from patients. This item measures the symptom of peripheral neuropathy, or "Tingling in the hands or feet", using a 4-point Likert scale ranging from "Not at all" to "Very much". A high scale score represents a high experience of the symptom (i.e., worse outcome).

Table 9-4 Definition of Subscale Scores of EORTC QLQ-MY20

Subscale	Individual Items
Disease symptoms	31-36
Side effects of treatment [1]	37-46
Body image	47
Future perspective	48-50

Most of the QLQ-MY-20 data are only available from the electronic data collection dataset. This assessment was not included on paper in its entirety; therefore, a lower sample size is expected, apart from one item; "Tingling in hands or feet" (item 43) include the full dataset of both electronic and paper data collection methods, while the remaining items are only available from data collected prior to amendment #2.
[1] The study table analyses only include "Tingling in hands or feet" (item 43).

TSQM-9

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) (**Bharmal** 2009) captures patient satisfaction with treatment with MM-directed therapy, including the important dimension of convenience. The instrument includes 9 items either on a 5 or 7-point Likert type scale. The

TSQM-9 is composed of three domains (effectiveness [3 items], convenience [3 items], and global satisfaction scale [3 items]) (see **Table 9-5**). Scale scores are computed by adding the items in each scale. The lowest possible score is subtracted from this composite score and divided by the greatest possible score minus the lowest possible score. This provided a transformed score between 0 and 1 to be multiplied by 100, with final scores ranging on a scale from 0 to 100. Higher scores on the TSQM-9 indicate higher satisfaction, better perceived effectiveness, and better convenience. (See **Appendix 14.11** for full scoring procedures according to developers of the instrument and missing data rules). The full version of the TSQM-9 has been used and is available throughout the study.

Table 9-5 Definition of Subscale Scores of TSQM-9

Subscale	Individual Items
Effectiveness	1-3
Convenience	4-6
Global Satisfaction Scale	7-9

Full study data available for the TSQM-9.

EQ-5D-5L

The European Quality of Life, 5-dimension, 5-level (EQ-5D-5L) (**Herdman** 2011) assesses general health status. The EQ-5D-5L is composed of 5 items in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on a 5-point Likert scale (see **Table 9-6**). Each of the dimensions has 5 levels: 'No problems', 'Slight problems', 'Moderate problems', 'Severe problems', and 'Extreme problems'. The EQ-5D-5L is summarized categorically for these response levels, including 1, 2, 3, 4, and 5, respectively for each of the dimensions. The numerals 1-5 have no arithmetic properties per se and should not be used as a cardinal score. The EQ-5D-5L also includes a Visual Analogue Scale (VAS), summarized as a continuous variable (0-100). A score of 1-5 for each dimension will be combined into a 5-digit number to describe the patient's health state and transformed to a utility index (see **Appendix 14.12** for country norms and scoring procedures). The VAS asks patients to indicate how good or bad their health is today and is scored on a 0-100 scale, with higher scores indicating better health (**EQ-5D-5L User Guide** 2015). All missing values will be coded as '9' for the descriptive questions of '999' for the VAS and all ambiguous values (for example, 2 responses chosen) will be treated as missing data. The crosswalk link function will be used to calculate index values for the EQ-5D-5L based on several countries including; Denmark, England, Italy, the Netherlands, Poland and Scotland. The crosswalk index calculator is provided by the EuorQoL office.

It is important to note that this instrument was dropped in its entirety after protocol amendment version 2.0. Thus, only cross-sectional data for EQ-5D-5: will be presented at baseline (study enrollment).

Table 9-6 Definition of Scores for EQ-5D-5L

Subscale and Scoring Description	Items
Mobility	1
Self-Care	2
Usual Activity	3
Pain/Discomfort	4
Anxiety/Depression	5
Utility Index [1]	All items 1-5 (derived score)
VAS	6

EQ-5D-5L data are limited and sample size will be lower. This assessment was not included after protocol amendment version 2.0; therefore, a lower sample size is expected and data will not be available after 2018.
[1] A population-based preference weighting algorithm is used to derive health-state utility (also referred to as EQ-5D-5L index value), which is anchored on a scale of 0-1, where 0 is a health state "dead" and 1 a health state representing "best possible health", from the five response categories. EQ- 5D-5L scoring found in https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf. The health states map to the utility scale of 1 = best possible health and 0 = dead.

9.2 PRO Analysis

Line of therapy baseline was defined as the start date of the index regimen in the corresponding line of therapy. If this regimen was started more than 1 months prior to being enrolled in the study, then a line of therapy baseline could not be defined until the start of the index regimen in a later line of therapy. The baseline PRO assessment was defined as the closest assessment in the window [-3 months, +1 month] from the index regimen start date. If the regimen start date was equal to the start date of a clinical trial, then that regimen (and thereby line of therapy) was excluded from analysis. The study PROs will be analyzed by lines of therapy and/or treatment regimens (or drug classes) of interest as detailed in **Section 7.2** in the SAP.

Actual and Change from Baseline Analysis

Individual results for the final items (shown in the top half of **Table 9-1**) included in the QLQ-C30, QLQ-MY20, and TSQM-9, will be summarized using descriptive statistics of actual value and change from baseline of the scale scores for each PRO for all of the enrolled population over time (baseline, and quarterly thereafter). Total scores by PRO and subscale

domain scores for each measure will be summarized overall, and by region. Mean (SD), percentiles (25th, 50th, and 75th), min and max will be reported for the QLQ-C30, the QLQ-MY20 and TSQM-9 PRO data. The data for the QLQ-C30 and the QLQ-MY20 will be based on the full dataset (paper and ePRO) and only include the three items that were used in both datasets, per **Table 9-1** breakdown. The TSQM-9 scoring guidelines as per (**Bharmal** 2009) will be adhered to, including the three domains (**Table 9-5**) since full data capture is available. In addition, figures will plot the mean response and mean change using locally estimated scatter plot smoothing (LOESS**, Cleveland** 1979) based on the actual number of days since line of therapy baseline (not discrete quarterly visit) for each of the PRO endpoints by R-based treatment regimens, across 2nd, 3rd, >=4th lines of therapy or combined across lines of therapy as overall. EQ-5D-5L data was not presented in the individual PRO table results since the EQ-5D-5L was not used after protocol amendment version 2.0, and thus missing data was expected longitudinally.

Longitudinal Analyses

Time to Deterioration (TTD) - For the GHS/QOL subscale, the threshold endpoint deterioration was defined as a ≥16.66-point decrease on the 0-100 scale (i.e., 2 raw scale points on the scale of 2 to 14) from baseline or death. Baseline PRO assessment was defined as the closest assessment in the window [-3 months, +1 month] from the index regimen start date. If the index regimen started earlier than 1 month prior to being enrolled in the study, then a baseline was not established until the start of an index regimen in the subsequent line of therapy. Follow-up was then assessed quarterly from index regimen baseline. TTD was calculated in months from the index regimen start date to the date of assessment resulting in deterioration or death. Patients who did not have a deterioration event or discontinued the study (other than death) were censored at the date of their last EORTC QLQ-C30 assessment. The TTD was compared between R-based regimens using RD as the reference in Cox PH regression analysis, and the hazard ratio (HR) and 95% confidence interval (CI) were reported for other R-based regimens identified in the tables, e.g. IR[D], KR[D], VR[D], Dara-R[D], and Elo-R[D]. The proportional hazards (PH) assumption will be assessed by plotting Schoenfeld residuals vs. time using LOESS with a 95% confidence band, where a zero slope supports the PH assumption. The fully adjusted survival functions will be plotted by R-based regimens, and the median times will be interpolated from the figure data. The unadjusted univariate results will be reported, along with the fully adjusted results including the below covariates. Both the univariate and adjusted results will be rerun including multiple imputations for missing covariate (**Section 8.6**).

- Line of therapy (2nd, 3rd,≥4th)
- ISS stage (I/II, III)

- Prior PI Status (prior refractory PI, prior PI exposure no refractory, prior PI naïve)
- Prior Lenalidomide Status (prior refractory Lenalidomide, prior Lenalidomide exposure no refractory, prior Lenalidomide naïve)
- Prior stem cell transplant (Y/N)
- Time from diagnosis to index regimen start date (continuous or categorical, e.g. [0, 18], [>18, 36], >36 months)
- Treatment Facility Type: academic/university, community (i.e. regional/local hospital, clinic/outpatient)
- Region (US, APAC, EMEA, LA)
- Age at start of line (<65, 65-75, >75 years)
- Sex (M/F)
- ECOG (0/1, ≥2)
- Charlson Comorbidity Index (<2, ≥2)
- Prior Hypertension (Y/N)
- Baseline renal function (serum creatinine >2 mg/dL or creatinine clearance <40 mL/min vs. neither condition)
- Baseline anemia (hemoglobin ≥10 mg/dL, hemoglobin <10 mg/dL)

In addition, an unadjusted Kaplan-Meier summary stratified by R-based regimens will be presented for 2nd, 3rd, and ≥4th line of therapy and overall combined lines of therapy.

Change Over Time – Mixed Model Repeated Measures

The change from baseline in the GHS/QOL subscale was analyzed over time using a repeated-measures linear mixed-effects model (PROC MIXED) across 2nd, 3rd and >=4th lines of therapy or combined lines of therapy to exaime differences among the R-based regimens. The model included the above fixed-effects covariates in addition to time from index regimen baseline as a continuous variable, and baseline GHS/QOL score. There were interactions for treatment * time, and line of therapy * time. There may be a small percent of subjects (e.g. <5%) that have data for multiple lines of therapy; however, making the data 'doubly repeated' with a small amount of additional information is likely to cause model convergence issues so only the earliest line of therapy for each patient including the regimens of interest will be included. A random-effects intercept was used to account for the correlation within patient clusters, since time was modeled as a continuous variable. The Least Square Means (LSM) and 95% CI were reported for each covariate in the model, and the LSM differences along with 95% CI and p-values, with no adjustment for multiple comparisons, were also reported between the R-based regimens and RD. Forest plots were included for the univariate and adjusted models to plot the parameter estimates with 95% CI for each covariate.

Missing Response Data

Incomplete data is expected for the EORTC QLQ-C30 and QLQ-MY20 and during the paper administration period, as described earlier. The paper PRO dataset will not contain all domains and items for the EORTC QLQ-C30 and QLQ-MY20 (only 3 items will be represented). Details of scoring and initial handling of missing data for each PRO will be followed in accordance with developer's guidelines.

10 Medical Resource Utilization

Hospitalizations, emergency room visits, ICU, outpatient and hospice stays will be collected quarterly. These data will be summarized by Treatment Regimens of Interest and lines of therapy overall and by country for ND and R/R cohorts (or by Line of Therapy subgroups e.g. 1st, 2nd, 3rd) for the all enrolled population. However, if the regimen start date is equal to the start date of a clinical trial, then that regimen (and thereby line of therapy) will be excluded from analysis. In addition, these data may also be grouped by autologous single, autologous tandem, any allogenic, not specified or none for stem cell transplant status of newly diagnosed patients.

The number of stays for overnight hospital admissions, ER, and ICU will be tabulated; also, the number and percent of patients with at least one overnight hospital stay, ICU, and ER visits with reasons for admission during the study will be presented. The number of days the patient was seen in the clinic at the study site, the number of days that were for MM-directed drug therapy, and if the patient was admitted to hospice will be summarized. Descriptive statistics for total hospitalization length of stay during inpatient and ICU visits will also be summarized. Hospitalizations and emergency room visits per 100 patient-years and 95% CI will be presented as well. The rate will be calculated as 100 times the total number of events divided by the cumulative therapy exposure duration for all subjects in the therapy group. For summary of events by lines of therapy, patient-years will be calculated from start date to end date of line of therapy (365.25 days = 1 year). These data are captured in EDC entered by the sites based on chart review, and as Patient Reported Outcomes. The summary tables will be based on the EDC data.

11 Safety Analysis

Safety data will be assessed by collection of SAEs and non-serious AEs leading to treatment discontinuation (temporary and permanent) or drug modification, and second primary malignancies for all MM therapies. Quarterly assessment of action taken will include reasons for treatment discontinuation and reasons for drug modification. AEs/SAEs and second primary

malignancies related to Multiple Myeloma therapy drug are summarized and reported for Takeda products.

11.1 Adverse Events

Safety data will be assessed approximately quarterly by collection of SAEs and non-serious AEs leading to treatment discontinuation (temporary and permanent) or drug modification for all MM therapies on the Action Taken eCRF. In addition, reasons for dose modification/drug discontinuation not related to AE/SAE are recorded quarterly on the Action Taken eCRF for all MM therapies. AEs/SAEs related to Multiple Myeloma therapy drug are summarized and reported for Takeda products on the AE/SAE. Second primary malignancies are reported on the quarterly AE/Pregnancy Status and Follow-Up Medical Evaluation eCRF for all MM Therapies.

If there is a dose modification or drug discontinuation for an AE/SAE, then the AE will be summarized by number of unique patients and total number of events from the following: fatigue, nausea, vomiting, diarrhea, constipation, anorexia, fever, infections and infestations, infusion reactions, peripheral neuropathy, muscle cramping/pain, skin rash, heart failure, arrhythmia, shortness of breath, cough, anemia, neutropenia, thrombocytopenia, hepatic impairment, creatinine increase, febrile neutropenia, other cardiac, other pulmonary, and other. In addition to the category for AE, whether the AE was serious, and outcome (i.e. recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/unresolved, fatal, unknown, not reported) will be summarized by Drugs of Interest and Lines of Therapy overall and by region and/or country.

Exposure-adjusted event rate (EAER) per 100 patient-years will be presented for AE/SAE overall and by AE categories for drug discontinuations. The EAER per 100 patient-years is defined as 100 times the number of specific events divided by the total exposure to risk (in years) among patients included in the analysis. All occurrences of the specific events are counted for patients with multiple occurrences. The exposure to risk will be calculated from the drug start date to the drug end date, date of study discontinuation or data cut-off date, whichever is earlier. For a total-total summary, i.e. combining all drugs of interest, the exposure period will be calculated from the earliest start date to the latest end date for the drugs included in that regimen. The total exposure to risk in years is calculated by dividing the sum of exposure to risk in days over all patients included in the analysis by 365.25. The EAER per 100 patient-years is interpreted as the total number of the specific events per 100 patient-years of exposure to risk. EAER will also be calculated for total number of SAE leading to a drug discontinuation, and total number of non-serious AE leading to a drug discontinuation.

All AEs recorded in the system will be coded using MedDRA version 20.0 or later. The total number of AEs and SAEs will be presented for Takeda drugs (i.e. Bortezomib and Ixazomib) by System Organ Class, Higher Level Term, Preferred Term, and CTCAE grade entered by the physician. The summary will also include the EAER per 100 patient-years. In addition, the number of patients with at least one AE or SAE will be reported at the highest-grade level.

11.2 Clinical Laboratory Evaluations

Results of selected hematology and chemistry tests will be recorded in the study EDC system at the study baseline and quarterly, in either conventional or standard international unit. All measurements will be converted to standard international units. However, no laboratory summary tables will be created, other than summarizing the laboratory tests that are included in disease specific history (**Section 6.3.2**).

12 Interim Analysis

Three formal interim analyses are planned. The first will occur after 1000 patients have been enrolled into the study where only baseline data will be summarized to provide guidance for enrollment strategy, study design, and refinement of analysis plan. The second interim analysis will support CHMP commitment in DEC2019, where baseline data, safety and effectiveness will be evaluated for the purposes of monitoring and verifying appropriateness of analysis methods. The third interim analysis will be after completion of enrollment, and some follow-up duration to be determined by the SRC. The **final** analysis will be conducted after all patients in the study have completed at least 2 years follow-up or death, whichever occurs first. The summary of analyses that are included in each formal analysis are included in **Appendix 14.7**. In addition, biannual analysis will be performed to support steering committee meetings and publications. The set of TLF to be delivered at each analysis will be agreed upon based on the TLF table of contents and shells provided in a separate document.

13 Changes from Analyses Planned in the Protocol

Secondary primary malignancies were intended to be summarized for all MM therapies; however, due to lack of database reconciliation across all MM therapies they were only able to be summarized for Takeda products.

14 Appendices

14.1 Data Collection Schedule

Frequency	Inclusion	Quarterly from Inclusion	Annually from Inclusion
Visit Window		**+1 month**	**±1 month**
Obtaining informed consent	X		
Inclusion/Exclusion criteria	X		
Demographic information[1]	X		
Medical evaluation: Height	X		X
Medical evaluation: Weight	X		X
Vital status		X	
Insurance information	X		X
Relevant past medical history[2]	X		
Multiple myeloma medical history, disease characteristics and staging, diagnostic and presenting symptoms for MM[3]	X		
Frailty status[4]: Charlson Comorbidity Index, Katz Index of Independence in ADL, Lawton IADL scale	X		X
ECOG performance status	X		X
Follow-up medical evaluation		X	
Vaccinations	X		X
Bone marrow evaluations, Cytogenetics, FISH, MRD, GEP, NGS and investigational analysis, if available in clinical records	X	X	
Laboratory results (hematology and chemistry)[5]	X	X	
Laboratory test results (paraprotein evaluation/SPEP)[6]	X	X	

Frequency	**Inclusion**	**Quarterly from Inclusion**	**Annually from Inclusion**
Visit Window		**+1 month**	**±1 month**
Laboratory results HevyLite (if available)	X	X	
Laboratory results (UPEP) (if available)[7]	X	X	
Imaging results (if available)[8]	X	X	
Multiple myeloma related radiation therapy		X	
Multiple myeloma related surgeries and other procedures		X	
Multiple myeloma therapy prior to study entry (ND MM)[9]	X		
Multiple myeloma therapy prior to study entry (R/R MM)[10]	X		
Multiple myeloma therapy status (ND MM and R/R) (includes reason for not receiving therapy)	X	X	
Administered/prescribed MM therapy drugs for regimen (current regimen)[11]	X	X	
Multiple myeloma regimen therapy plan[12]	X	X	
Response assessment for a regimen, MRD (if available)[13]	X	X	
Patient Baseline Survey	X		
Patient self-reported outcomes[14] (Note: PRO completion can occur any time during a visit quarter. See footnote for details)	X	X[14]	
Stem cell transplants	X	X	
Multiple myeloma supportive care	X	X	
Healthcare resource utilization[15] (Note: HRU is completed by both the HCP and the patient quarterly. See footnote for details)		X	

Frequency	Inclusion	Quarterly from Inclusion	Annually from Inclusion
Visit Window		**+1 month**	**±1 month**
Study Discontinuation[16]		X	
Safety assessments (AE/SAE)[17]	X	X	
Pregnancy reporting	X	X	

Abbreviations: ADL, activities of daily living; AE, adverse event; BUN, blood urea nitrogen; CRAB, calcium, renal failure, anemia, and bone damage; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FISH, fluorescence in situ hybridization; FLC, free light chain; GEP, gene expression profiling; HCP, healthcare provider; HRU, healthcare resource utilization; IADL, instrumental activities of daily living; LDH, lactate dehydrogenase; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; MRD, minimal residual disease; MRI, magnetic resonance imaging; ND, newly diagnosed; NGS, next-generation sequencing; PET, positron emission tomography; PRO, patient self-reported outcomes; R/R, relapsed/refractory; SAE, serious adverse event; SMM, smoldering multiple myeloma; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

1 Including age, sex, race, ethnicity (optional based on country requirements), from PRO and height, weight, and geographic region.

2 Relevant medical history includes peripheral neuropathy, hypertension, thromboembolism, osteopenia/osteoporosis, cataracts, arrhythmias, assessments if available: Echocardiogram, multigated acquisition scan (MUGA), Myelodysplastic Syndromes (MDS), MM-related radiation therapy, MM-related procedures/surgeries, myeloma/skeletal-related procedures, other surgeries/procedures, and vaccinations.

3 Multiple myeloma medical history at initial diagnosis, if available, will include: disease stage at initial diagnosis, serum Beta-2 microglobulin, serum albumin, LDH, cytogenetics/FISH risk, bone lesions, calcium, BUN, creatinine, hemoglobin, MGUS/SMM, CRAB symptoms; and medical history prior to study inclusion, if available: bone marrow, FLC, MRI, M-component, immunofixation, PET/CT, GEP, amyloidosis, plasmacytoma, central nervous system involvement, and stem cell transplant.

4 The frailty index will be based on the Charlson Comorbidity Index (Charlson et al. 1987), the Katz Index of Independence in ADL (Katz 1983), and the Lawton IADL scales (Lawton and Brody 1969), all of which will be completed by the treating healthcare provider annually in eCRFs.

5 Hematology and Chemistry laboratory test results of known prognostic, predictive markers. Baseline Hematology: white blood cell count, absolute neutrophil count, hemoglobin, and platelet count. Baseline Chemistry: calcium, creatinine, alkaline phosphatase, total bilirubin, aspartate aminotransferase, alanine aminotransferase, LDH. Albumin, and serum Beta-2 microglobulin, if available in clinical records. Quarterly Hematology: white blood cell count, absolute neutrophil count, hemoglobin, and platelet count; Quarterly Chemistry: calcium, creatinine, total bilirubin, albumin, and serum Beta-2 microglobulin, if available in clinical records.

6 Paraprotein laboratory test results, if available: serum protein electrophoresis (SPEP) (serum total protein, m-spike level, serum immunofixation, serum quantitative immunoglobulins), Serum FLCs.

7 UPEP (24-hour urine, urine M-spike/BJP, urine immunofixation), or spot urine (protein, urine immunofixation). If both 24-hour and spot urine were tested, provide only the 24-hour urine results.

8 Imaging tests include skeletal survey, standard CT, MRI, PET/CT, bone mineral density, whole body assessments (low dose CT and MRI, if done for

myeloma evaluation).

9 For patients with ND MM only. Regimen, treatment durations and reasons for initiation of regimen.

10 For patients with R/R MM only. Therapy prior to study entry including 1st, 2nd, and 3rd relapses and details for number of previous lines of therapy, regimens used in 1st, 2nd, and 3rd line as applicable; whether stem cell transplant was part of 1st, 2nd, and 3rd line of therapy, and whether consolidation/maintenance was part of 1st, 2nd, and 3rd line of therapy; also, whether investigational therapy/treated on a clinical trial was part of any of these regimens.

11 Administered/prescribed MM therapy drugs for regimen for current treatment (including treatment received at study entry), including individual drug, dose, route, schedule, duration and dose modification and reasons for medication changes.

12 MM regimen therapy plan includes current (including regimen at study entry) regimen, line of therapy, phase of regimen, reason for initiation of this regimen (includes relapse), treatment intent of the regimen, duration, part of interventional clinical trial.

13 Response assessment for a regimen includes MRD, if assessed, best response achieved during the evaluation period, progression, and time to next therapy.

14 Global Health Status/QOL scale (2 items) from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - C30 (EORTC QLQ-C30), a single item on peripheral neuropathy from the EORTC Quality of Life Questionnaire - 20-item Multiple Myeloma Module (EORTC QLQ-MY-20), and the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9). A patient baseline survey will be conducted at study entry. The + 1 month visit window does not apply to PRO collection; PROs may be collected from the patient at any time within the defined quarterly visit schedule.

15 Including but not limited to inpatient and intensive care unit admissions, reasons for admission, length of stay, outpatient clinic visits, and emergency room visits. The healthcare resource utilization questionnaire is completed by the investigator in the eCRF; in this case, the frequency will be +1 month. Hospice details will also be collected on eCRFs. A healthcare resource utilization questionnaire will also be completed by the patient in the paper PRO packet.

16 Study discontinuation includes date and cause of death. After withdrawal or loss to follow-up, the patient's vital status will be assessed. The healthcare provider may search regional death indexes/registries for vital health statistics of lost to follow-up patients as per routine practice.

17 All serious AEs and non-serious AEs regardless of causality leading to treatment discontinuation (temporary or permanent) or drug modification, and second primary malignancies will be recorded on the eCRFs. All SAEs and non-serious AEs regardless of causality leading to treatment discontinuation (temporary or permanent) or drug modification of Takeda products will be reported following Section 6.5.3.

14.2 Multiple Myeloma Drugs and Classes

Class	Drug (Brand Name) Generic Name "Code"	Takeda Drugs
Proteasome Inhibitors	(Velcade) bortezomib "V", (Kyprolis) carfilzomib "K", (Ninlaro) ixazomib "I", oprozomib "O"	Velcade, Ninlaro
Immunomodulatory Drugs	(Revlimid) lenalidomide "R", (Thalomid) thalidomide "T", (Pomalyst/Imnovid) pomalidomide "Pom"	
Steroids	(Decadron) dexamethasone - high dose "D", (Decadron) dexamethasone - low dose "D", (Kordexa) dexamethasone "D", (Soldesam) dexamethasone "D", prednisone "P", prednisolone "P", methylprednisone "P", (Prednol) methylprednisolone "P"	
Alkylating Agents	(Alkeran) melphalan "M", (Cytoxan/Endoxan) cyclophosphamide "C"	
Cytotoxic	(Oncovin) vincristine "VCR", (BCNU) carmustine "BCNU", (Platinol) cisplatin "CDDP", (Bendamustine) treanda "Benda", (Ethoposide) vepesid or toposar "Etop"	
HDAC Inhibitors	(Farydak) panobinostat "PANO", (Vorinostat) zonlinza "VORI"	
Monoclonal Antibodies	(Empliciti) elotuzumab "elo", (Darzalex) daratumumab "dara", (Sarclisa) Isatuximab "isa"	
Anthracyclines	daunorubicin (dauno) / doxorubicin (A) / liposomal doxorubicin HCL (DOX) / epirubicin (Epi) / idarubicin (Ida) / mitoxantrone (Mito) / valrubicin (val)	
Other	Brand Name (Drug)	

14.3 Treatments of Interest for Relapsed/Refractory Patients – Basic Groups

Order in Tables	Code	Decode Generic Drug Combination
1	VCD/VMP	bortezomib (V) + cyclophosphamide (C) + dexamethasone (D) / bortezomib (V) + melphalan (M) + prednisone (P)
2	VRD/VTD/VPomD	bortezomib (V) + lenalidomide (R) + dexamethasone (D) / bortezomib (V) + thalidomide (T) + dexamethasone (D) / bortezomib (V) + pomalidomide (Pom) + dexamethasone (D)
3	RD	lenalidomide (R) + dexamethasone (D)
4	KRD/KPomD	carfilzomib (K) + lenalidomide (R) + dexamethasone (D) / carfilzomib (K) + pomalidomide (Pom) + dexamethasone (D)
5	KD	carfilzomib (K) + dexamethasone (D)
6	VD	bortezomib (V) + dexamethasone (D)
7	dara-VD/dara-ID	daratumumab (dara) + bortezomib (V) + dexamethasone (D) / daratumumab (dara) + ixazomib (I) + dexamethasone (D)
8	dara-RD/dara-PomD	daratumumab (dara) + lenalidomide (R) + dexamethasone (D) / daratumumab (dara) + pomalidomide (Pom) + dexamethasone (D)
9	IRD	ixazomib (I) + lenalidomide (R) + dexamethasone (D)
10	ID/I	ixazomib (I) + dexamethasone (D) / ixazomib (I)
11	PomD	pomalidomide (Pom) + dexamethasone (D)
12	dara	daratumumab (dara)
13	Other	Active treatment not included in this table
14	Elo-based combination	Any combination including elotuzumab (Elo) will take priority over above combinations
15	No Therapy	Defined in ADSL spec
16	Undetermined Therapy	Defined in ADSL spec

If a patient enters ixazomib/placebo or something similar that indicates the patient was on a randomized clinical trial and may have been exposed to either ixazomib or placebo, that regimen will be coded as ‘Other’ due to the ambiguity.

14.4 Treatments of Interest for Relapsed/Refractory Patients – Expanded Groups

Order in Tables	Code	Decode Generic Drug Combination
1	VC(D)	bortezomib (V) + cyclophosphamide (C) +/- dexamethasone (D)
2	IC(D)/KC(D)	ixazomib (I) + cyclophosphamide (C) +/- dexamethasone (D) / carfilzomib (K) + cyclophosphamide (C) +/- dexamethasone (D)
3	VR(D)	bortezomib (V) + lenalidomide (R) +/- dexamethasone (D)
4	VT(D)	bortezomib (V) + thalidomide (T) +/- dexamethasone (D)
5	VRC(D)/IRC(D)/KRC(D)	bortezomib (V) + lenalidomide (R) + cyclophosphamide (C) +/- dexamethasone (D) / ixazomib (I) + lenalidomide (R) + cyclophosphamide (C) +/- dexamethasone (D) / carfilzomib (K) + lenalidomide (R) + cyclophosphamide (C) +/- dexamethasone (D)
6	VM(P)	bortezomib (V) + melphalan (M) +/- prednisone (P)
7	V(D)	bortezomib (V) +/- dexamethasone (D)
8	RD	lenalidomide (R) + dexamethasone (D)
9	IPom(D)	ixazomib (I) + pomalidomide (Pom) +/- dexamethasone (D)
10	VPom(D)/Kpom(D)	carfilzomib (K) + pomalidomide (Pom) +/- dexamethasone (D) / bortezomib (V) + pomalidomide (Pom) +/- dexamethasone (D)
11	Pom(D)	pomalidomide (Pom) +/- dexamethasone (D)
12	dara-V(D)	daratumumab (dara) + bortezomib (V) +/- dexamethasone (D)
13	dara-I(D)	daratumumab (dara) + ixazomib (I) +/- dexamethasone (D)
14	dara-K(D)	daratumumab (dara) + carfilzomib (K) +/- dexamethasone (D)
15	dara-R(D)	daratumumab (dara) + lenalidomide (R) +/- dexamethasone (D)
16	dara-Pom(D)	daratumumab (dara) + pomalidomide (Pom) +/- dexamethasone (D)
17	dara-VR(D)	daratumumab (dara) + bortezomib (V) + lenalidomide (R) +/- dexamethasone (D)
18	dara-Rev-quad	daratumumab (dara) + carfilzomib (K) + lenalidomide (R) +/- dexamethasone (D) / daratumumab (dara) + ixazomib (I) + lenalidomide (R) +/-

		dexamethasone (D) /
19	dara-Pom-quad	daratumumab (dara) + bortezomib (V) + pomalidomide (Pom) +/- dexamethasone (D) / daratumumab (dara) + carfilzomib (K) + pomalidomide (Pom) +/- dexamethasone (D) / daratumumab (dara) + ixazomib (I) + pomalidomide (Pom) +/- dexamethasone (D)
20	dara	daratumumab (dara) alone
21	dara-other	daratumumab (dara) with any other agent not already secified
22	IR(D)	ixazomib (I) + lenalidomide (R) +/- dexamethasone (D)
23	I(D)	ixazomib (I) +/- dexamethasone (D)
24	C(D)/M(D)	cyclophosphamide (C) +/- dexamethasone (D) / melphalan (M) +/- dexamethasone (D)
25	RC(D)/PomC(D)/TC(D)	lenalidomide (R) + cyclophosphamide (C) +/- dexamethasone (D) / pomalidomide (Pom) + cyclophosphamide (C) +/- dexamethasone (D) / thalidomide (T) + cyclophosphamide (C) +/- dexamethasone (D)
26	KR(D)	carfilzomib (K) + lenalidomide (R) +/- dexamethasone (D)
27	KPom(D)/KT(D)	carfilzomib (K) + pomalidomide (Pom) +/- dexamethasone (D) / carfilzomib (K) + thalidomide (T) +/- dexamethasone (D)
28	K(D)	carfilzomib (K) +/- dexamethasone (D)
29	T(D)	thalidomide (T) +/- dexamethasone (D)
31	Steriods	Dexamethasone (D) / prednisone (P) / prednisolone (P) / methylprednisolone (MP)
32	Elo-R(D)	elotuzumab (Elo) + lenalidomide (R) +/- dexamethasone (D)
33	Elo-Pom(D)	elotuzumab (Elo) + pomalidomide (Pom) +/- dexamethasone (D)
34	Elo-other	Any combination including elotuzumab (Elo), that is not already defined above, will take priority over above combinations
35	Other	Active treatment not included in this table
36	No Therapy	If no drugs are entered and NO therapy is confirmed or missing on the MM Therapy Status CRF
37	Undetermined Therapy	If no drugs are entered but therapy is YES on MM Therapy Status

		CRF

If a patient enters ixazomib/placebo or something similar that indicates the patient was on a randomized clinical trial and may have been exposed to either ixazomib or placebo, that regimen will be coded as 'Other' due to the ambiguity.

14.5 Treatments of Interest for Newly Diagnosed Patients – Basic Groups

Order in Tables	Code	Decode Generic Drug Combination
1	VRD	lenalidomide (R) + dexamethasone (D) + bortezomib (V)
2	VCD	bortezomib (V) + cyclophosphamide (C) + dexamethasone (D)
3	VTD	bortezomib (V) + thalidomide (T) + dexamethasone (D)
4	VMP	bortezomib (V) + melphalan (M) + prednisone (P)
5	RD	lenalidomide (R) + dexamethasone (D)
6	CTD/MPT/TD	cyclophosphamide (C) + thalidomide (T) + dexamethasone (D) / melphalan (M) + prednisone (P) + thalidomide (T) / thalidomide (T) + dexamethasone (D)
7	VD	bortezomib (V) + dexamethasone (D)
8	IRD	ixazomib (I) + lenalidomide (R) + dexamethasone (D)
9	KRD	carfilzomib (K) + lenalidomide (R) + dexamethasone (D)
10	Other	Active treatment not included in this table
11	No Therapy	Defined in ADSL spec
12	Undetermined Therapy	Defined in ADSL spec

If a patient enters ixazomib/placebo or something similar that indicates the patient was on a randomized clinical trial and may have been exposed to either ixazomib or placebo, that regimen will be coded as ‘Other’ due to the ambiguity.

14.6 Treatments of Interest for Newly Diagnosed Patients – Expanded Groups

Order in Tables	Code	Decode Generic Drug Combination
1	VR(D)	bortezomib (V) + lenalidomide (R) +/- dexamethasone (D)
2	VC(D)	bortezomib (V) + cyclophosphamide (C) +/- dexamethasone (D)
3	VT(D)	bortezomib (V) + thalidomide (T) +/- dexamethasone (D)
4	VM(P)	bortezomib (V) + melphalan (M) +/- prednisone (P)
5	V(D)	bortezomib (V) +/- dexamethasone (D)
6	RD	lenalidomide (R) + dexamethasone (D)
7	CT(D)/MT(P)	cyclophosphamide (C) + thalidomide (T) +/- dexamethasone (D) / melphalan (M) + thalidomide (T) +/- prednisone (P)
8	T(D)	thalidomide (T) +/- dexamethasone (D)
9	IR(D)	ixazomib (I) + lenalidomide (R) +/- dexamethasone (D)
10	I(D)	ixazomib (I) +/- dexamethasone (D)
11	KR(D)	carfilzomib (K) + lenalidomide (R) +/- dexamethasone (D)
12	KC(D)	carfilzomib (K) + cyclophosphamide (C) +/- dexamethasone (D)
13	K(D)	carfilzomib (K) +/- dexamethasone (D)
14	C(D)/M(P)/M(D)	cyclophosphamide (C) +/- dexamethasone (D) / melphalan (M) +/- prednisone (P) / melphalan (M) +/- dexamethasone (D)
16	Steroids	dexamethasone (D) / prednisone (P) / prednisolone (P) / methylprednisolone (MP)
17	dara-R(D)	daratumumab (dara) + lenalidomide (R) +/- dexamethasone (D)
18	dara-VM(P)	daratumumab (dara) + bortezomib (V) + melphalan (M) +/- prednisone (P)
19	dara-VT(D)	daratumumab (dara) + bortezomib (V) + thalidomide (T) +/- dexamethasone (D)
20	Dara-V(D)	daratumumab (dara) + bortezomib (V) +/- dexamethasone (D)
21	dara-other	Any combination including daratumumab (dara), that is not already defined above
22	Elo-R(D)	elotuzumab (Elo) + lenalidomide (R) +/- dexamethasone (D)

23	Elo-Pom(D)	elotuzumab (Elo) + pomalidomide (Pom) +/- dexamethasone (D)
24	Elo-other	Any combination including elotuzumab (Elo), that is not already defined above, will take priority over above combinations
25	Other	Active treatment not included in this table
26	No Therapy	If no drugs are entered and NO therapy is confirmed or missing on the MM Therapy Status CRF
27	Undetermined Therapy	If no drugs are entered but therapy is YES on MM Therapy Status CRF

If a patient enters ixazomib/placebo or something similar that indicates the patient was on a randomized clinical trial and may have been exposed to either ixazomib or placebo, that regimen will be coded as 'Other' due to the ambiguity.

14.7 Summary of Analysis Topics for Each Formal Analysis

Section	Analysis Topic	IA1	IA2 CHMP	IA3	Final Analysis CHMP
4.4	Subgroup analysis – type of treatment facility	X	X	X	X
4.4	Subgroup analysis – geographic regions	X	X	X	X
4.4	Subgroup analysis – country		X		X
4.6.1	Enrollment summary	X	X	X	X
5	Patient disposition		X	X	X
5	Major protocol deviations			X	X
6.1	Demographics	X	X	X	X
6.2	Disease characteristics	X	X	X	X
6.3.1	General medical history	X	X	X	X
6.3.2	Disease specific history	X	X	X	X
6.4	Medical and prescription insurance types	X			X
7.2	Most frequent treatment regimens	X	X	X	X
7.2	R/R previous lines of therapy	X	X		X
7.2	Therapy status	X			
7.2	Therapy plan	X	X	X	X
7.2	Stem cell transplant status		X		X
7.4	Bone marrow aspirate and/or biopsy	X			
7.4	Cytogenetics	X	X	X	X
7.4	Type of paraprotein (SPEP/UPEP)	X	X	X	X
7.5	Treatment shift patterns between regimens	X			X
7.5	Treatment shift patterns between drug classes		X		X
7.5	Treatment sequences				X
7.6	COVID-19 disease assessment			X	X
8.1	KM progression-free survival			X	X
8.1	Cox PH regression PFS			X	X
8.2	KM overall survival			X	X
8.2	Cox PH regression overall survival				X
8.3	KM time to next therapy		X	X	X
8.3	Cox PH regression time to next therapy			X	X
8.3	KM duration of therapy		X	X	X
8.3	Cox PH regression duration of therapy			X	X

8.3	KM duration on maintenance regimen				
8.4	Propensity scores - descriptive	X			
8.5	Best of best response		X	X	X
8.5	Logistic regression analysis best of best response			X	
8.6	Multiple Imputations				X
9	Patient reported outcomes			X	X
10	Medical resource utilization				X
11.1	AE/SAE Takeda products		X		X
11.1	AE/SAE related dose modification, drug discontinuation		X	X	X

14.8 List of Tables Included for Each Interim Analysis

x	Table #	IA1	IA2	IA3	Columns	Description
1	14.1.1.1	x	x	x	Cohort	Summary of Enrollment by Country and Site
2	14.1.1.2	x			Country	Summary of Most Frequent Treatment Regimens Chosen by Country – Overall and by Cohort
3	14.1.1.3	x	x	x	Lines	Summary of Most Frequent Treatment Regimens Chosen in Relapsed/Refractory Multiple Myeloma Patients by Line of Therapy – Overall and by Region
4	14.1.1.3a		x	x	Lines	Summary of Most Frequent Ixazomib Treatment Regimens Chosen in Multiple Myeloma Patients by Line of Therapy
5	14.1.1.4	x	x		SCT Candidate	Summary of Most Frequent Treatment Regimens Chosen in Newly Diagnosed Multiple Myeloma Patients by Stem Cell Transplant Candidate Status – Overall and by Region
6	14.1.2.1		x	x	Cohort	Summary of Study Disposition up to Datacut for Multiple Myelomas Patients - Overall and by Region
7	14.1.2.1a		x	x	Cohort	Summary of Study Disposition up to Datacut for On-Study Ixazomib Multiple Myeloma Patients
8	14.1.2.1b			x	Cohort	Summary of Study Disposition up to Datacut for On-Study IR[D] Multiple Myeloma Patients
9	14.1.2.2			x	Cohort	Summary of Major Protocol Deviations – Overall and by Region
10	14.1.3.1	x	x	x	Cohort	Summary of Demographics for Multiple Myeloma Patients – Overall and by Region
11	14.1.3.2	x			Regimen	Summary of Age for Relapsed/Refractory Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
12	14.1.3.3	x			Regimen	Summary of Age for Newly Diagnosed Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
13	14.1.4.1	x			Regimen	Summary of Baseline Comorbidities for Relapsed/Refractory Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
14	14.1.4.1a		x		Lines	Summary of Comorbidities for Relapsed/Refractory Ixazomib Multiple Myeloma Patients by Line of Therapy
15	14.1.4.1b			x	Lines	Summary of Comorbidities for Relapsed/Refractory IR[D] Multiple Myeloma Patients by Line of Therapy
16	14.1.4.2	x			Regimen	Summary of Baseline Comorbidities for Newly Diagnosed Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
17	14.1.4.6		x		Cohort	Summary of Baseline Comorbidities for Multiple Myeloma Patients – Overall and by Region
18	14.1.5.1	x			Regimen	Summary of Myeloma-Relevant Medical History for Relapsed/Refractory Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
19	14.1.5.1a		x		Lines	Summary of Myeloma-Relevant Medical History for Relapsed/Refractory Ixazomib Patients by Line of Therapy
20	14.1.5.1b			x	Lines	Summary of Myeloma-Relevant Medical History for Relapsed/Refractory IR[D] Patients by Line of Therapy
21	14.1.5.2	x			Regimen	Summary of Myeloma-Relevant Medical History for Newly Diagnosed Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
22	14.1.5.6		x		Cohort	Summary of Myeloma-Relevant Medical History for Multiple Myeloma Patients – Overall and by Region
23	14.1.6.1	x			Regimen	Summary of Multiple Myeloma Medical History for Relapsed/Refractory Patients by Treatment Regimens of

						Interest – Overall and by Region
24	14.1.6.1a		x		Lines	Summary of Multiple Myeloma Medical History for Relapsed/Refractory Ixazomib Patients by Line of Therapy
25	14.1.6.1b			x	Lines	Summary of Multiple Myeloma Medical History for Relapsed/Refractory IR[D] Patients by Line of Therapy
26	14.1.6.2	x			Regimen	Summary of Multiple Myeloma Medical History for Newly Diagnosed Patients by Treatment Regimens of Interest – Overall and by Region
27	14.1.6.6		x		Cohort	Summary of Multiple Myeloma Medical History – Overall and by Region
28	14.1.8.1				Lines	Summary of Supportive Care at Baseline for Multiple Myeloma Patients by Line of Therapy – Overall and by Region
29	14.1.11.1	x	x		Lines	Summary of Multiple Myeloma Regimen Plan Prior to Study Entry for Relapsed/Refractory Patients – Overall and by Region
30	14.1.11.2		x		Lines	Summary of Multiple Myeloma Regimen Plan Throughout Study – Overall and by Region
31	14.1.11.3a		x		Lines	Summary of Multiple Myeloma Regimen Prior to Ixazomib Regimen for Relapsed/Refractory Patients
32	14.1.11.3b			x	Lines	Summary of Multiple Myeloma Regimen Prior to IR[D] Regimen for Relapsed/Refractory Patients
33	14.1.12.1	x	x		Cohort	Summary of Multiple Myeloma Relapsed Durations Prior to Study Entry – Overall and by Region
34	14.1.13.1	x			Lines	Summary of Multiple Myeloma Therapy Status at Baseline by Line of Therapy – Overall and by Region
35	14.1.14.1	x			Cohort	Summary of Prodromal Plasma Cell Disorders at Baseline for Multiple Myeloma Patients – Overall and by Region
36	14.1.15.1	x			Cohort	Summary of Bone Marrow Aspirate and/or Biopsy for Multiple Myeloma Patients – Overall and by Region
37	14.1.16.1	x			Regimen	Summary of Cytogenetics for Relapsed/Refractory Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region and Type of Treatment Facility
38	14.1.16.1a		x		Lines	Summary of Cytogenetics for Relapsed/Refractory Ixazomib Multiple Myeloma Patients
39	14.1.16.1b			x	Lines	Summary of Cytogenetics for Relapsed/Refractory IR[D] Multiple Myeloma Patients
40	14.1.16.2	x			Regimen	Summary of Cytogenetics for Newly Diagnosed Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region and Type of Treatment Facility
41	14.1.16.3		x		Cohort	Summary of Cytogenetics for Multiple Myeloma Patients – Overall and by Region and Type of Treatment Facility
42	14.1.19.1	x	x		Cohort	Summary of SPEP/UPEP Type of Paraprotein for Multiple Myeloma Patients – Overall and by Region
43	14.1.19.1a		x		Lines	Summary of SPEP/UPEP Type of Paraprotein for Relapsed/Refractory Ixazomib Multiple Myeloma Patients
44	14.1.19.1b			x	Lines	Summary of SPEP/UPEP Type of Paraprotein for Relapsed/Refractory IR[D] Multiple Myeloma Patients
45	14.1.20.1				Cohort	Summary of Multiple Myeloma Patients by Influenza and Pneumococcal Vaccinations and Year - Overall and by Region
46	14.1.21.1			x	R-based Regimen	Summary of Treatment and Baseline Characteristics for Relapsed/Refractory Index Regimens included in TTNT, DOT, and PFS Statistical Models
47	14.1.21.1a				R-based Regimen	Summary of Treatment and Baseline Characteristics for Relapsed/Refractory Index Regimens included in Best of Best Response Statistical Models
48	14.1.21.1b				R-based Regimen	Summary of Treatment and Baseline Characteristics for Relapsed/Refractory Index Regimens included in Time to Deterioration Statistical Models
49	14.1.21.1c			x	R-based	Summary of Treatment and Baseline Characteristics in 2nd Line of Therapy for R-based Index Regimen

					Regimen	
50	14.1.21.1d			x	R-based Regimen	Summary of Treatment and Baseline Characteristics in 3rd Line of Therapy for R-based Index Regimen
51	14.1.21.1e			x	R-based Regimen	Summary of Treatment and Baseline Characteristics in >=4th Line of Therapy for R-based Index Regimen
52	14.2.1.6				Lines	Kaplan-Meier Analysis of Overall Survival in Multiple Myeloma Patients - Overall and by Region
53	14.2.1.6a				Lines	Kaplan-Meier Analysis of Overall Survival in Ixazomib Multiple Myeloma Patients - Overall and by Region
54	14.2.1.6b				Lines	Kaplan-Meier Analysis of Overall Survival in Multiple Myeloma Patients (Sensitivity Analysis) - Overall and by Region
55	14.2.1.6c			x	Lines	Kaplan-Meier Analysis of Overall Survival in Ixazomib Multiple Myeloma Patients (Sensitivity Analysis) - Overall and by Region
56	14.2.1.6d			x	Lines	Kaplan-Meier Analysis of Overall Survival in IR[D] Multiple Myeloma Patients (Sensitivity Analysis) - Overall and by Region
57	14.2.1.6e			x	R-based Regimen	Kaplan-Meier Analysis of Overall Survival for R-based Index Regimen in Multiple Myeloma Patients (Sensitivity Analysis) - Overall and by Region
58	14.2.2.6				Lines	Kaplan-Meier Analysis of Progression-Free Survival in Multiple Myeloma Patients - Overall and by Region
59	14.2.2.6a				Lines	Kaplan-Meier Analysis of Progression-Free Survival in Ixazomib Multiple Myeloma Patients - Overall and by Region
60	14.2.2.6b				Lines	Kaplan-Meier Analysis of Progression-Free Survival in Multiple Myeloma Patients (Sensitivity Analysis) - Overall and by Region
61	14.2.2.6c				Lines	Kaplan-Meier Analysis of Progression-Free Survival in Ixazomib Multiple Myeloma Patients (Sensitivity Analysis) - Overall and by Region
62	14.2.2.6d				Lines	Kaplan-Meier Analysis of Progression-Free Survival in Multiple Myeloma Patients (Alternative Censoring) - Overall and by Region
63	14.2.2.6e				Lines	Kaplan-Meier Analysis of Progression-Free Survival in Ixazomib Multiple Myeloma Patients (Alternative Censoring) - Overall and by Region
64	14.2.2.6f				Lines	Kaplan-Meier Analysis of Progression-Free Survival in Multiple Myeloma Patients (Alternative Censoring & Sensitivity Analysis) - Overall and by Region
65	14.2.2.6g			x	Lines	Kaplan-Meier Analysis of Progression-Free Survival in Ixazomib Multiple Myeloma Patients (Alternative Censoring & Sensitivity Analysis) - Overall and by Region
66	14.2.2.6h			x	R-based Regimen	Kaplan-Meier Analysis of Progression-Free Survival in 2nd Line of Therapy for R-based Multiple Myeloma Patients (Alternative Censoring & Sensitivity Analysis) - Overall and by Region
67	14.2.2.6i			x	R-based Regimen	Kaplan-Meier Analysis of Progression-Free Survival in 3rd Line of Therapy for R-based Multiple Myeloma Patients (Alternative Censoring & Sensitivity Analysis) - Overall and by Region
68	14.2.2.6j			x	R-based Regimen	Kaplan-Meier Analysis of Progression-Free Survival in >=4th Line of Therapy for R-based Multiple Myeloma Patients (Alternative Censoring & Sensitivity Analysis) - Overall and by Region
69	14.2.2.6k			x	R-based Regimen	Cox PH Regression Univariate Analysis of Progression-Free Survival for R-based Index Regimen in Multiple Myeloma Patients

70	14.2.2.6l			x	R-based Regimen	Cox PH Regression Fully-Adjusted Analysis of Progression-Free Survival for R-based Index Regimen in Multiple Myeloma Patients
71	14.2.2.6m			x	R-based Regimen	Cox PH Regression Univariate Analysis of Progression-Free Survival for R-based Triplet Index Regimen in Multiple Myeloma Patients
72	14.2.2.6n			x	R-based Regimen	Cox PH Regression Fully-Adjusted Analysis of Progression-Free Survival for R-based Triplet Index Regimen in Multiple Myeloma Patients
73	14.2.2.6o			x	Lines	Kaplan-Meier Analysis of Progression-Free Survival in IR[D] Multiple Myeloma Patients (Alternative Censoring & Sensitivity Analysis) - Overall and by Region
74	14.2.3.6				Lines	Cumulative Incidence Analysis of Time to Next Line of Therapy in Multiple Myeloma Patients - Overall and by Region
75	14.2.3.6a		x		Lines	Cumulative Incidence Analysis of Time to Next Line of Therapy in Relapsed/Refractory Ixazomib Multiple Myeloma Patients - Overall and by Region
76	14.2.3.6b (was d)		x	x	Lines	Cumulative Incidence Analysis of Time to Next Line of Therapy in Relapsed/Refractory Ixazomib Multiple Myeloma Patients (Sensitivity Analysis) - Overall and by Region
77	14.2.3.6c (was b)		x		Lines	Cumulative Incidence Analysis of Time to Next Line of Therapy in Multiple Myeloma Patients by Stem Cell Transplant – Overall and by Region
78	14.2.3.6d (was c)		x		Lines	Cumulative Incidence Analysis of Time to Next Line of Therapy in Multiple Myeloma Patients by Stem Cell Transplant (Sensitivity Analysis) – Overall and by Region
79	14.2.3.6e			x	R-based Regimen	Cumulative Incidence Cox PH Regression Univariate Analysis of Time to Next Line of Therapy for R-based Index Regimen in Multiple Myeloma Patients
80	14.2.3.6f			x	R-based Regimen	Cumulative Incidence Cox PH Regression Fully-Adjusted Analysis of Time to Next Line of Therapy for R-based Index Regimen in Multiple Myeloma Patients
81	14.2.3.6g			x	R-based Regimen	Cumulative Incidence Analysis of Time to Next Line of Therapy in 2nd Line of Therapy for R-Based Index Regimens – Overall and by Region
82	14.2.3.6h			x	R-based Regimen	Cumulative Incidence Analysis of Time to Next Line of Therapy in 3rd Line of Therapy for R-Based Index Regimens – Overall and by Region
83	14.2.3.6i			x	R-based Regimen	Cumulative Incidence Analysis of Time to Next Line of Therapy in >=4th Line of Therapy for R-Based Index Regimens – Overall and by Region
84	14.2.3.6j			x	R-based Regimen	Cumulative Incidence Cox PH Regression Univariate Analysis of Time to Next Line of Therapy for R-based Triplet Index Regimen in Multiple Myeloma Patients
85	14.2.3.6k			x	R-based Regimen	Cumulative Incidence Cox PH Regression Fully-Adjusted Analysis of Time to Next Line of Therapy for R-based Triplet Index Regimen in Multiple Myeloma Patients
86	14.2.3.6l			x	Lines	Cumulative Incidence Analysis of Time to Next Line of Therapy in Relapsed/Refractory IR[D] Multiple Myeloma Patients (Sensitivity Analysis) - Overall and by Region
87	14.2.3.7				Regimen	Kaplan-Meier Analysis of Duration on Index Regimen in 1st Line of Therapy in Multiple Myeloma Patients - Overall and by Region
88	14.2.3.7a		x		Lines	Kaplan-Meier Analysis of Duration on Index Ixazomib Regimen in Relapsed/Refractory Multiple Myeloma Patients - Overall and by Region
89	14.2.3.7b		x	x	Lines	Kaplan-Meier Analysis of Duration on Index Ixazomib Regimen in Relapsed/Refractory Multiple Myeloma

						Patients (Sensitivity Analysis) - Overall and by Region
90	14.2.3.7c		x		Lines	Kaplan-Meier Analysis of Duration of Therapy in Multiple Myeloma Patients by Stem Cell Transplant - Overall and by Region
91	14.2.3.7d		x		Lines	Kaplan-Meier Analysis of Duration of Therapy in Multiple Myeloma Patients by Stem Cell Transplant (Sensitivity Analysis) - Overall and by Region
92	14.2.3.7e			x	R-based Regimen	Cox PH Regression Univariate Analysis of Duration of Therapy for R-based Index Regimen in Multiple Myeloma Patients
93	14.2.3.7f			x	R-based Regimen	Cox PH Regression Fully-Adjusted Analysis of Duration of Therapy for R-based Index Regimen in Multiple Myeloma Patients
94	14.2.3.7g			x	R-based Regimen	Kaplan-Meier Analysis of Duration of Therapy in 2nd Line of Therapy for R-Based Index Regimens – Overall and by Region
95	14.2.3.7h			x	R-based Regimen	Kaplan-Meier Analysis of Duration of Therapy in 3rd Line of Therapy for R-Based Index Regimens – Overall and by Region
96	14.2.3.7i			x	R-based Regimen	Kaplan-Meier Analysis of Duration of Therapy in >=4th Line of Therapy for R-Based Index Regimens – Overall and by Region
97	14.2.3.7j			x	R-based Regimen	Cox PH Regression Univariate Analysis of Duration of Therapy for R-based Triplet Index Regimen in Multiple Myeloma Patients
98	14.2.3.7k			x	R-based Regimen	Cox PH Regression Fully-Adjusted Analysis of Duration of Therapy for R-based Triplet Index Regimen in Multiple Myeloma Patients
99	14.2.3.7l			x	Lines	Kaplan-Meier Analysis of Duration on Index IR[D] Regimen in Relapsed/Refractory Multiple Myeloma Patients - Overall and by Region
100	14.2.3.8				Regimen	Kaplan-Meier Analysis of Duration on Index Regimen in 2nd Line of Therapy in Multiple Myeloma Patients - Overall and by Region
101	14.2.3.9				Regimen	Kaplan-Meier Analysis of Duration on Index Regimen in 3rd Line of Therapy in Multiple Myeloma Patients - Overall and by Region
102	14.2.3.10				Regimen	Kaplan-Meier Analysis of Duration on Maintenance in 1st Line of Therapy in Multiple Myeloma Patients - Overall and by Region
103	14.2.3.11				Regimen	Kaplan-Meier Analysis of Duration on Maintenance in 2nd Line of Therapy in Multiple Myeloma Patients - Overall and by Region
104	14.2.3.12				Regimen	Kaplan-Meier Analysis of Duration of Maintenance Therapy in 3rd Line of Therapy in Multiple Myeloma Patients - Overall and by Region
105	14.2.3.13				Lines	Descriptive Summary of Time to Response in Multiple Myeloma Patients by Line of Therapy - Overall and by Region
106	14.2.4.6		x		Lines	Summary of Best of Best Response in Multiple Myeloma Patients by Line of Therapy - Overall and by Region
107	14.2.4.6a		x		Lines	Summary of Best of Best Response for Relapsed/Refractory Ixazomib Multiple Myeloma Patients by Line of Therapy - Overall and by Region
108	14.2.4.6b			x	Lines	Summary of Best of Best Response for Relapsed/Refractory Ixazomib Multiple Myeloma Patients by Line of Therapy (Sensitivity Analysis) - Overall and by Region

109	14.2.4.7a				Lines	Summary of Best of Best Response for Relapsed/Refractory Multiple Myeloma Patients for Index IR[D] Regimen by Line of Therapy
110	14.2.4.8a				Lines	Summary of Best of Best Response for Relapsed/Refractory Multiple Myeloma Patients for Index KR[D] Regimen by Line of Therapy
111	14.2.4.9a				Lines	Summary of Best of Best Response for Relapsed/Refractory Multiple Myeloma Patients for Index R[D] Regimen by Line of Therapy
112	14.2.4.10a			x	R-based Regimen	Logistic Regression Univariate Analysis of Best of Best Overall Response Rate for R-based Regimens in Multiple Myeloma Patients
113	14.2.4.10b			x	R-based Regimen	Logistic Regression Adjusted Analysis of Best of Best Overall Response Rate for R-based Regimens in Multiple Myeloma Patients
114	14.2.4.10c			x	R-based Regimen	Logistic Regression Univariate Analysis of Best of Best Overall Response Rate for R-based Triplet Regimens in Multiple Myeloma Patients
115	14.2.4.10d			x	R-based Regimen	Logistic Regression Adjusted Analysis of Best of Best Overall Response Rate for R-based Triplet Regimens in Multiple Myeloma Patients
116	14.2.4.11a				R-based Regimen	Logistic Regression Univariate Analysis of Best of Best Clinical Benefit Rate for R-based Regimens in Multiple Myeloma Patients
117	14.2.4.11b				R-based Regimen	Logistic Regression Adjusted Analysis of Best of Best Clinical Benefit Rate for R-based Regimens in Multiple Myeloma Patients
118	14.2.4.11c				R-based Regimen	Logistic Regression Univariate Analysis of Best of Best Clinical Benefit Rate for R-based Triplet Regimens in Multiple Myeloma Patients
119	14.2.4.11d				R-based Regimen	Logistic Regression Adjusted Analysis of Best of Best Clinical Benefit Rate for R-based Triplet Regimens in Multiple Myeloma Patients
120	14.2.4.12			x	R-based Regimen	Summary of Best of Best Response in 2nd Line of Therapy for R-based Index Regimen in Multiple Myeloma Patients
121	14.2.4.13			x	R-based Regimen	Summary of Best of Best Response in 3rd Line of Therapy for R-based Index Regimen in Multiple Myeloma Patients
122	14.2.4.14			x	R-based Regimen	Summary of Best of Best Response in >=4th Line of Therapy for R-based Index Regimen in Multiple Myeloma Patients
123	14.2.5.1				Lines	PRO Descriptive Statistics at Baseline for EORTC-QLQ-C30, EORTC MY-20, TSQM-9 and EQ-5D-5L Subscales – Overall and by Region
124	14.2.5.7				R-based Regimen	Actual and Change from Regimen Baseline in Global Health Status and Quality of Life, in 1st Line of Therapy Multiple Myeloma Patients – Overall and by Region
125	14.2.5.8			x	R-based Regimen	Actual and Change from Regimen Baseline in Global Health Status and Quality of Life, in 2nd Line of Therapy Multiple Myeloma Patients – Overall and by Region
126	14.2.5.9			x	R-based Regimen	Actual and Change from Regimen Baseline in Global Health Status and Quality of Life, in 3rd Line of Therapy Multiple Myeloma Patients – Overall and by Region
127	14.2.5.10			x	R-based Regimen	Actual and Change from Regimen Baseline in Global Health Status and Quality of Life, in >=4th Line of Therapy Multiple Myeloma Patients – Overall and by Region
128	14.2.6.1				R-based	Actual and Change from Regimen Baseline in Tingling in Hands or Feet, in 1st Line of Therapy Multiple Myeloma

					Regimen	Patients – Overall and by Region
129	14.2.6.2			x	R-based Regimen	Actual and Change from Regimen Baseline in Tingling in Hands or Feet, in 2nd Line of Therapy Multiple Myeloma Patients – Overall and by Region
130	14.2.6.3			x	R-based Regimen	Actual and Change from Regimen Baseline in Tingling in Hands or Feet, in 3rd Line of Therapy Multiple Myeloma Patients – Overall and by Region
131	14.2.6.4			x	R-based Regimen	Actual and Change from Regimen Baseline in Tingling in Hands or Feet, in >=4th Line of Therapy Multiple Myeloma Patients – Overall and by Region
132	14.2.7.1				R-based Regimen	Actual and Change from Regimen Baseline in TSQM-9 Domains, in 1st Line of Therapy Multiple Myeloma Patients – Overall and by Region
133	14.2.7.2			x	R-based Regimen	Actual and Change from Regimen Baseline in TSQM-9 Domains, in 2nd Line of Therapy Multiple Myeloma Patients – Overall and by Region
134	14.2.7.3			x	R-based Regimen	Actual and Change from Regimen Baseline in TSQM-9 Domains, in 3rd Line of Therapy Multiple Myeloma Patients – Overall and by Region
135	14.2.7.4			x	R-based Regimen	Actual and Change from Regimen Baseline in TSQM-9 Domains, in >=4th Line of Therapy Multiple Myeloma Patients – Overall and by Region
136	14.2.8.2				Lines	Meaningful 10-Point Change Estimate Thresholds for Global Health Status/Quality of Life – Overall and by Region
137	14.2.9.1				Regimen	Summary of Baseline Characteristics and Health Resource Utilization in Multiple Myeloma Patients by First On-study Index Regimen and Prior Peripheral Neuropathy - Overall and by Region
138	14.2.9.2				Regimen	Summary of Baseline Characteristics and Health Resource Utilization in Multiple Myeloma Patients Received SCT by First On-study Index Regimen and Prior Peripheral Neuropathy - Overall and by Region
139	14.2.9.3				Regimen	Summary of Baseline Characteristics and Health Resource Utilization in Multiple Myeloma Patients Not Received SCT by First On-study Index Regimen and Prior Peripheral Neuropathy - Overall and by Region
140	14.2.9.4				FV Status	Summary of Baseline Characteristics and Health Resource Utilization in Multiple Myeloma Patients by Influenza Cohort — Overall and by Region
141	14.2.9.5				PV Status	Summary of Baseline Characteristics and Health Resource Utilization in Multiple Myeloma Patients by Pneumococcal Cohort — Overall and by Region
142	14.2.9.6			x	R-based Regimen	Summary of Health Resource Utilization in 2nd Line of Therapy for R-based Index Regimens – Overall and by Region
143	14.2.9.7			x	R-based Regimen	Summary of Health Resource Utilization in 3rd Line of Therapy for R-based Index Regimens – Overall and by Region
144	14.2.9.8			x	R-based Regimen	Summary of Health Resource Utilization in >=4th Line of Therapy for R-based Index Regimens – Overall and by Region
145	14.2.10.1		x		Lines	Summary of Durations for Prior R/R Ixazomib Patients - Overall and by Region
146	14.2.10.1a				Lines	Summary of Durations for Prior R/R IR[D] Patients - Overall and by Region
147	14.2.11.1				Survival Status	Summary of Influenza and Pneumococcal Vaccinations and Baseline Characteristics in Multiple Myeloma Patients by Survival Status — Overall and by Region
148	14.2.12.1			x	R-based	Kaplan-Meier Analysis of Time to Deterioration in Global Health Status/Quality of Life in 2nd Line of Therapy for

					Regimen	R-based Regimens – Overall and by Region
149	14.2.12.2			x	R-based Regimen	Kaplan-Meier Analysis of Time to Deterioration in Global Health Status/Quality of Life in 3rd Line of Therapy for R-based Regimens – Overall and by Region
150	14.2.12.3			x	R-based Regimen	Kaplan-Meier Analysis of Time to Deterioration in Global Health Status/Quality of Life in >=4th Line of Therapy for R-based Regimens – Overall and by Region
151	14.2.13.1			x	R-based Regimen	Cox PH Regression Univariate Analysis of Time to Deterioration in Global Health Status/Quality of Life for R-based Regimens
152	14.2.13.2			x	R-based Regimen	Cox PH Regression Fully-Adjusted Analysis of Time to Deterioration in Global Health Status/Quality of Life for R-based Regimens
153	14.2.13.3			x	R-based Regimen	Cox PH Regression Univariate Analysis of Time to Deterioration in Global Health Status/Quality of Life for R-based Triplet Regimens
154	14.2.13.4			x	R-based Regimen	Cox PH Regression Fully-Adjusted Analysis of Time to Deterioration in Global Health Status/Quality of Life for R-based Triplet Regimens
155	14.2.14.1			x	R-based Regimen	Summary of Least Squares Means and Differences in 2nd Line of Therapy for Change in Global Health Status/Quality of Life
156	14.2.14.2			x	R-based Regimen	Summary of Least Squares Means and Differences in 3rd Line of Therapy for Change in Global Health Status/Quality of Life
157	14.2.14.3			x	R-based Regimen	Summary of Least Squares Means and Differences in >=4th Line of Therapy for Change in Global Health Status/Quality of Life
158	14.3.2.1		x		Drug	Summary of Adverse Events for Multiple Myeloma Patients in 1st Line of Therapy on Takeda Drugs by System Organ Class, Preferred Term and CTCAE Grade - Overall and by Region
159	14.3.2.2		x		Drug	Summary of Adverse Events for Multiple Myeloma Patients in 2nd Line of Therapy on Takeda Drugs by System Organ Class, Preferred Term and CTCAE Grade - Overall and by Region
160	14.3.2.3		x		Drug	Summary of Adverse Events for Multiple Myeloma Patients in 3rd Line of Therapy on Takeda Drugs by System Organ Class, Preferred Term and CTCAE Grade - Overall and by Region
161	14.3.2.4		x		Drug	Summary of Adverse Events for Multiple Myeloma Patients in 4th Line of Therapy on Takeda Drugs by System Organ Class, Preferred Term and CTCAE Grade - Overall and by Region
162	14.3.2.4a		x		Drug	Summary of Adverse Events for Multiple Myeloma Patients in >4th Line of Therapy on Takeda Drugs by System Organ Class, Preferred Term and CTCAE Grade - Overall and by Region
163	14.3.2.5		x		Drug	Summary of Serious Adverse Events for Multiple Myeloma Patients in 1st Line of Therapy on Takeda Drugs by System Organ Class, Preferred Term and CTCAE Grade - Overall and by Region
164	14.3.2.6		x		Drug	Summary of Serious Adverse Events for Multiple Myeloma Patients in 2nd Line of Therapy on Takeda Drugs by System Organ Class, Preferred Term and CTCAE Grade - Overall and by Region
165	14.3.2.7		x		Drug	Summary of Serious Adverse Events for Multiple Myeloma Patients in 3rd Line of Therapy on Takeda Drugs by System Organ Class, Preferred Term and CTCAE Grade - Overall and by Region
166	14.3.2.8		x		Drug	Summary of Serious Adverse Events for Multiple Myeloma Patients in 4th Line of Therapy on Takeda Drugs by System Organ Class, Preferred Term and CTCAE Grade - Overall and by Region
167	14.2.3.8a		x		Drug	Summary of Serious Adverse Events for Multiple Myeloma Patients in >4th Line of Therapy on Takeda Drugs by System Organ Class, Preferred Term and CTCAE Grade - Overall and by Region

168	14.3.3.1				Cohort	Summary of Action Taken for Administered/Prescribed Multiple Myeloma Therapy Drugs – Overall and by Region
169	14.3.3.2				Cohort	Summary of Adverse Events Leading to a Dose Modification or Drug Discontinuation of MM Therapy – Overall and by Region
170	14.3.3.3		x		Drug	Summary of Drug Action Taken for Administered/Prescribed Therapy in 1st Line of Therapy – Overall and by Region
171	14.3.3.4		x		Drug	Summary of Drug Action Taken for Administered/Prescribed Therapy in 2nd Line of Therapy – Overall and by Region
172	14.3.3.5		x		Drug	Summary of Drug Action Taken for Administered/Prescribed Therapy in 3rd Line of Therapy – Overall and by Region
173	14.3.3.5a		x		Drug	Summary of Drug Action Taken for Administered/Prescribed Therapy in 4th Line of Therapy – Overall and by Region
174	14.3.3.5b		x		Drug	Summary of Drug Action Taken for Administered/Prescribed Therapy in >4th Line of Therapy – Overall and by Region
175	14.3.3.6		x		Drug	Summary of Adverse Events of Interest Leading to a Drug Discontinuation in 1st Line of Therapy – Overall and by Region
176	14.3.3.7		x		Drug	Summary of Adverse Events of Interest Leading to a Drug Discontinuation in 2nd Line of Therapy – Overall and by Region
177	14.3.3.8		x		Drug	Summary of Adverse Events of Interest Leading to a Drug Discontinuation in 3rd Line of Therapy – Overall and by Region
178	14.3.3.8a		x		Drug	Summary of Adverse Events of Interest Leading to a Drug Discontinuation in 4th Line of Therapy – Overall and by Region
179	14.3.3.8b		x		Drug	Summary of Adverse Events of Interest Leading to a Drug Discontinuation in >4th Line of Therapy – Overall and by Region
180	14.3.3.9			x	R-based Regimen	Summary of Drug Action Taken for Administered/Prescribed Therapy by R-based Index Regimen in 2nd Line of Therapy – Overall and by Region
181	14.3.3.10			x	R-based Regimen	Summary of Drug Action Taken for Administered/Prescribed Therapy by R-based Index Regimen in 3rd Line of Therapy – Overall and by Region
182	14.3.3.11			x	R-based Regimen	Summary of Drug Action Taken for Administered/Prescribed Therapy by R-based Index Regimen in >=4th Line of Therapy – Overall and by Region
183	14.3.3.12			x	R-based Regimen	Summary of Adverse Events of Interest Leading to a Drug Discontinuation by R-based Index Regimen in 2nd Line of Therapy – Overall and by Region
184	14.3.3.13			x	R-based Regimen	Summary of Adverse Events of Interest Leading to a Drug Discontinuation by R-based Index Regimen in 3rd Line of Therapy – Overall and by Region
185	14.3.3.14			x	R-based Regimen	Summary of Adverse Events of Interest Leading to a Drug Discontinuation by R-based Index Regimen in >=4th Line of Therapy – Overall and by Region
186	14.4.1.4	x			Regimen	Summary of Historical Treatment Shift Patterns for Relapsed/Refractory Multiple Myeloma Patients by Regimens of Interest – Overall and by Region and Type of Treatment Facility
187	14.4.1.5		x		Drug	Summary of Treatment Shift Patterns for Multiple Myeloma Patients by Drug Classes – Overall, by Region and by

					Class	Type of Treatment Facility
188	14.4.2.1	x			Regimen	Summary of Therapy Plan for Relapsed/Refractory Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
189	14.4.2.1a		x	x	Lines	Summary of Therapy Plan for Relapsed/Refractory Ixazomib Multiple Myeloma Patients - Overall and by Region
190	14.4.2.1b			x	Lines	Summary of Therapy Plan for Relapsed/Refractory IR[D] Multiple Myeloma Patients - Overall and by Region
191	14.4.2.2	x			Regimen	Summary of Therapy Plan for Newly Diagnosed Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
192	14.4.2.6		x		Cohort	Summary of Therapy Plan for Multiple Myeloma Patients – Overall and by Region
193	14.4.3.1				Drug Class	Summary of Supportive Care for 1st Line of Therapy Multiple Myeloma Patients by Treatment Classes of Interest – Overall and by Region
194	14.4.3.2				Drug Class	Summary of Supportive Care for 2nd Line of Therapy Multiple Myeloma Patients by Treatment Classes of Interest – Overall and by Region
195	14.4.3.3				Drug Class	Summary of Supportive Care for 3rd Line of Therapy Multiple Myeloma Patients by Treatment Classes of Interest – Overall and by Region
196	14.4.3.4				Drug Class	Summary of Supportive Care for >=4th Line of Therapy Multiple Myeloma Patients by Treatment Classes of Interest – Overall and by Region
197	14.4.9.1				Drug Class	Summary of Myeloma Related Radiation Therapy for Newly Diagnosed Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
198	14.4.9.2				Drug Class	Summary of Myeloma Related Radiation Therapy for Relapsed/Refractory Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
199	14.4.10.1				Drug Class	Summary of Myeloma Related Surgeries and Other Procedures for Newly Diagnosed Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
200	14.4.10.2				Drug Class	Summary of Myeloma Related Surgeries and Other Procedures for Relapsed/Refractory Multiple Myeloma Patients by Treatment Regimens of Interest – Overall and by Region
201	14.4.11.1	x			Regimen	Summary of Insurance for Relapsed/Refractory Multiple Myeloma Patients by Treatment Regimens of Interest
202	14.4.11.2	x			Regimen	Summary of Insurance for Newly Diagnosed Multiple Myeloma Patients by Treatment Regimens of Interest
203	14.4.12.1	x			Regimen	Summary of Potential Factors for Propensity Score Modeling of Treatment Regimens for 1st Line of Therapy – Overall and by Region
204	14.4.12.2	x			Regimen	Summary of Potential Factors for Propensity Score Modeling of Treatment Regimens for 2nd Line of Therapy – Overall and by Region
205	14.4.12.3				Regimen	Summary of Potential Factors for Propensity Score Modeling of Treatment Regimens for 3rd Line of Therapy – Overall and by Region
206	14.4.12.4				Regimen	Summary of Potential Factors for Propensity Score Modeling of Treatment Regimens for 4th Line of Therapy – Overall and by Region
207	14.4.13.1				Lines	Summary of Patients Advancing in Line of Therapy and Reasons for Not Advancing by Age Group in Newly Diagnosed Multiple Myeloma Patients — Overall and by Region
208	14.4.14.1				R-based Regimen	Summary of Reasons for R-Based Index Regimen Discontinuations and Adverse Events Caused R-Based Index Regimen Discontinuation in 2nd Line of Therapy – Overall and by Region

209	14.4.14.2				R-based Regimen	Summary of Reasons for R-Based Index Regimen Discontinuations and Adverse Events Caused R-Based Index Regimen Discontinuation in 3rd Line of Therapy – Overall and by Region
210	14.4.14.3				R-based Regimen	Summary of Reasons for R-Based Index Regimen Discontinuations and Adverse Events Caused R-Based Index Regimen Discontinuation in >=4th Line of Therapy – Overall and by Region
211	14.4.14.4				Lines	Summary of Reasons for Ixazomib Index Regimen Discontinuations and Adverse Events Caused Ixazomib Index Regimen Discontinuation – Overall and by Region
212	14.4.14.5				Lines	Summary of Reasons for IR[D] Index Regimen Discontinuations and Adverse Events Caused IR[D] Index Regimen Discontinuation – Overall and by Region
213	14.4.15.1				Lines	Summary of Regimens for Patients with Lenalidomide-based Index Regimen in 1st Line of Therapy and at Least 2 Lines of Therapy — Overall and by Region
214	14.4.15.2				Lines	Summary of Regimens for Patients with Lenalidomide-based Index Regimen of 1st Line of Therapy and at Least 3 Lines of Therapy — Overall and by Region
215	14.4.15.3				Lines	Summary of Regimens for Patients with Lenalidomide-based Index Regimen in 2nd Line of Therapy and Non-Lenalidomide Index Regimen in 1st Line and at Least 3 Lines of Therapy — Overall and by Region
216	14.4.16.1				Lines	Summary of Multiple Myeloma Regimen Throughout Study for Patients with Lenalidomide in Maintenance Regimen of 1st Line of Therapy and At Least 2 Lines — Overall and by Region
217	14.4.16.2				Lines	Summary of Multiple Myeloma Regimen Throughout Study for Patients with Lenalidomide in Maintenance Regimen of 1st Line of Therapy and At Least 3 Lines — Overall and by Region
218	14.4.16.3				Lines	Summary of Multiple Myeloma Regimen Throughout Study for Patients with Lenalidomide in Maintenance Regimen of 2nd Line of Therapy and At Least 3 Lines — Overall and by Region
219	14.4.17.1			x	R-based Regimen	Summary of COVID-19 Information – Overall and by Region
Item #	**Figure #**	**IA1**	**IA2**	**IA3**	**Group**	**Description**
1	14.2.1.1			x	Lines	TSQM-9 Effectiveness Over Time by R-based Regimens – Paneled by Line of Therapy
2	14.2.1.2			x	Lines	Change in TSQM-9 Effectiveness Over Time by R-based Regimens – Paneled by Line of Therapy
3	14.2.2.1			x	Lines	TSQM-9 Convenience Over Time by R-based Regimens – Paneled by Line of Therapy
4	14.2.2.2			x	Lines	Change in TSQM-9 Convenience Over Time by R-based Regimens – Paneled by Line of Therapy
5	14.2.3.1			x	Lines	TSQM-9 Global Satisfaction Over Time by R-based Regimens – Paneled by Line of Therapy
6	14.2.3.2			x	Lines	Change in TSQM-9 Global Satisfaction Over Time by R-based Regimens – Paneled by Line of Therapy
7	14.2.3.3			x	Lines	Tingling in Hands or Feet Over Time by R-based Regimens – Paneled by Line of Therapy
8	14.2.3.4			x	Lines	Change in Tingling in Hands or Feet Over Time by R-based Regimens – Paneled by Line of Therapy
9	14.2.4.1			x	Lines	EORTC-QLQ-C30 Global Health Status Over Time in 2nd Line of Therapy
10	14.2.4.2			x	Lines	Change in EORTC-QLQ-C30 Global Health Status Over Time in 2nd Line of Therapy
11	14.2.5.1			x	Covariate	Proportional Hazards Assumption Assessed by Plotting Schoenfeld Residuals versus Event Times for Time to Next Line of Therapy

12	14.2.5.2			x	Covariate	Proportional Hazards Assumption Assessed by Plotting Schoenfeld Residuals versus Event Times for Duration of Therapy
13	14.2.5.3			x	R-based Regimen	Adjusted Survival Functions of Treatment Index Regimen for Time to Next Line of Therapy
14	14.2.5.4			x	R-based Regimen	Adjusted Survival Functions of Treatment Index Regimen for Duration of Therapy
15	14.2.5.5			x	Covariate	Proportional Hazards Assumption Assessed by Plotting Schoenfeld Residuals versus Event Times for Progression-Free Survival
16	14.2.5.6			x	R-based Regimen	Adjusted Survival Functions of Treatment Index Regimen for Progression-Free Suvival
17	14.2.5.7			x	Covariate	Proportional Hazards Assumption Assessed by Plotting Schoenfeld Residuals versus Event Times for Time to Deterioration for Global Health Status/Quality of Life
18	14.2.5.8			x	R-based Regimen	Adjusted Survival Functions of Time to Deterioration for Global Health Status/Quality of Life by R-based Index Regimen
19	14.2.6.1			x	Lines	Kaplan-Meier Plot of Overall Survival (OS) for IR[D] Index Regimen by Lines of Therapy
20	14.2.6.2			x	Lines	Kaplan-Meier Plot of Progression-Free Survival (PFS) for IR[D] Index Regimen by Lines of Therapy
21	14.2.6.3			x	Lines	Kaplan-Meier Plot of Time To Next Line of Therapy (TTNT) for IR[D] Index Regimen by Lines of Therapy
22	14.2.6.4			x	Lines	Kaplan-Meier Plot of Duration of Therapy (DOT) for IR[D] Index Regimen by Lines of Therapy

14.9 EORTC QLQ-C30 Scoring Procedures

General principles of scoring

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
Thus a **high score for a functional scale** represents a *high / healthy level of functioning*,
a **high score for the global health status / QoL** represents a *high QoL*,
but a **high score for a symptom scale / item** represents a *high level of symptomatology / problems*.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the *raw score*.

2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Coding of the scoring procedure is presented in Appendix 3 for three major statistical packages.

Technical Summary

In practical terms, if items $I_1, I_2, \ldots I_n$ are included in a scale, the procedure is as follows:

Raw score
Calculate the raw score
RawScore = $RS = (I_1 + I_2 + ... + I_n)/n$

Linear transformation
Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: $S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$

Symptom scales / items: $S = \{(RS-1)/range\} \times 100$

Global health status / QoL: $S = \{(RS-1)/range\} \times 100$

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range* = 1.

Table 1: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS - 1)/range\} \times 100$$

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$\text{FA } Score = \{(RawScore - 1)/3\} \times 100$$

Missing data

Missing data may be classified as either missing items (one or more missing answers to questions within a questionnaire), or missing forms (the whole questionnaire is missing for a patient). Fayers and Machin (2000) describe methods of analysis for use when data are missing, including imputation techniques.

Missing items

Sometimes a patient will fail to answer a few questions on the QLQ-C30. Our experience to date suggests that less than 2% of patient data will be missing for the QLQ core questionnaire. However, supplementary modules addressing, for example, sexuality issues may have more serious problems with patient compliance. In theory it is important to distinguish between items, which are accidentally missing (commonly described as "missing completely at random"), and items, which are missing for a particular reason. For example, if patients feel very poorly with respect to one item they might wish to avoid answering that question. In practice, however, there is likely to be no way of deciding whether there was a specific reason for the missing values and, in general, it would seem likely that most missing items occur completely at random. In such cases the investigator may wish to calculate the scores based upon those items that were completed, possibly by "imputing" or estimating the missing item.

Various statistical methods exist for imputing values. One might, for example, use multivariate techniques that attempt to estimate the most likely value given information about (a) that patient's previous responses to the same item, (b) other patients' responses at a similar stage in their disease progression and therapy, or (c) the inter-relations and covariance structure with other items.

A simple method for imputing items from multi-item scales, which has been used by many QoL instruments, is the following: if at least half of the items from the scale have been answered, assume that the missing items have values equal to the average of those items which *are* present for that respondent. However, this rule is not always appropriate, and caution should be exercised. Application of this method of imputation is simpler than it perhaps seems; it can be shown that this is algebraically equivalent to using all items, which were completed, and applying the equations already given under "Scoring procedures" for calculating the scale scores; the missing items are simply ignored when making the calculations. Hence the above equations for multi-item scales can be used whenever at least half the items are completed.

Example:

Emotional functioning if Q_{23} is missing (3 items not missing)

$$RawScore = (Q_{21} + Q_{22} + Q_{24})/3$$

$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

For example, role functioning (RF) and cognitive functioning (CF) each contain 2 items, and so these scales can be estimated whenever one of their constituent items is present; physical functioning contains 5 items, and so at least 3 need to have been completed. Using this method, none of the single-item measures can be imputed.

Summary – Missing items

- Have at least half of the items from the scale been answered?
- If *Yes*, use all the items that were completed, and apply the standard equations given on the previous pages for calculating the scale scores; ignore any items with missing values when making the calculations.
- If *No*, set scale score to missing.
- For single-item measures, set score to missing.

14.10 EORTC QLQ-MY20 Scoring Procedures

The myeloma module is meant for use among a wide range of patients with multiple myeloma, varying in disease stage and treatment modality. It was developed according to the EORTC guidelines, and field tested on patients from Norway, Denmark, Sweden, Germany, the Czech Republic, the USA and the UK. The module comprises 20 items assessing disease symptoms, side effects of treatment, body image and future perspective. The module has been translated by the EORTC Quality of Life Unit and is now available in English, Chinese (Taiwan), Czech, Danish, Dutch (formal and informal), French, German, Italian, Norwegian, Spanish and Swedish.

Scoring of the Myeloma Module:

The myeloma module incorporates a single item scale to assess body image, and three multi-item scales assessing disease symptoms, side effects of treatment and future perspective.

The scoring procedure for the myeloma module is identical in principle to that for the function and symptom scales / items of the QLQ-C30[†]. A high score for the symptom scales represents a high level of symptomatology or problems, whilst a high score for the functional scales represents a high level of functioning.

Scale Name	Number of Items	QLQ-MY20 Item Numbers	Item Range*
Symptom Scales			
Disease Symptoms	6	31-36	3
Side Effects of Treatment	10	37-46	3
Functional Scales / Items			
Future Perspective	3	48-50	3
Body Image	1	47	3

* "Item range" is the difference between the possible maximum and the minimum response to individual items.

[†] The Disease Symptoms and Side Effects of Treatment scales use the same algebraic equation as for the QLQ-C30 Symptom scales; whilst the Body Image and Future Perspective scales use the same algebraic equation as for the QLQ-C30 Functional scales.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4

Appendix: Scoring procedure for the EORTC QLQ-MY20

The QLQ MY-20 module includes 20 items, consisting of 3 multi-item scales and 1 single-iter
The following section gives the scoring algorithms for the scales described in a similar fashio
scoring for the EORTC QLQ-C30. *Note: A high score for the symptom scales (DS and SE) repr
high level of symptomatology or problems, whilst a high score for the functional scales / items (
BI) represents a high level of functioning.*

A. Multi-item Scales

DS: Disease Symptoms Scale
SE: Side Effects of Treatment Scale
FP: Future Perspective Scale

DS: Disease Symptoms Scale (items 31–36)

a. Compute the raw score (mean scale score) if at least 3 of the items have a valid score.
   XDS = Mean of (Q31 – Q36)
b. Carry out a linear transformation to convert to a 0-100 scale:
   DS = {(XDS - 1) / 3} * 100
c. If fewer than 3 of the items have a valid score treat the scale as missing.

SE: Side Effects of Treatment Scale (items 37-46)

a. Compute the raw score (mean scale score) if at least 5 of the items have a valid score.
   XSE = Mean of (Q37 – Q46)
b. Carry out a linear transformation to convert to a 0-100 scale:
   SE = {(XSE - 1) / 3} * 100
c. If fewer than 5 of the items have a valid score treat the scale as missing.

FP: Future Perspective Scale (items 48-50)

a. Compute the raw score (mean scale score) if at least 2 of the items have a valid score.
   XFP = Mean of (Q48 – Q50)
b. Carry out a linear transformation to convert to a 0-100 scale:
   FP = {1 - (XFP - 1) / 3} * 100
c. If fewer than 2 of the items have a valid score treat the scale as missing.

B. Single-item Scales

BI: Body Image (item 47)

a. This item is treated individually and should be linearly transformed to a 0-100 scale.
   BI = {1 - (Q47 - 1) / 3} * 100

14.11 TSQM-9 Scoring Procedures

TSQM-9 Scale scores computed by adding the items loading on each factor. The lowest possible score is subtracted from this composite score and divided by the greatest possible score minus the lowest possible score. This provided a transformed score between 0 and 1 that should be multiplied by 100. (see below) *[Note that only one item may be missing from each scale before the subscale should be considered invalid for that respondent]*

EFFECTIVENESS

([(Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100

If one item is missing

([(Sum(Item 1? + Item 2? + Item 3?)) – 2] divided by 12) * 100

CONVENIENCE

([Sum(Item 4 to Item 6) – 3] divided by 18) * 100

If one item is missing

([(Sum(Item4? to Item6?)) – 2] divided by 12) * 100

GLOBAL SATISFACTION

([Sum(Item 7 to Item 9) – 3] divided by 14) * 100

If either Item 7 or 8 is missing

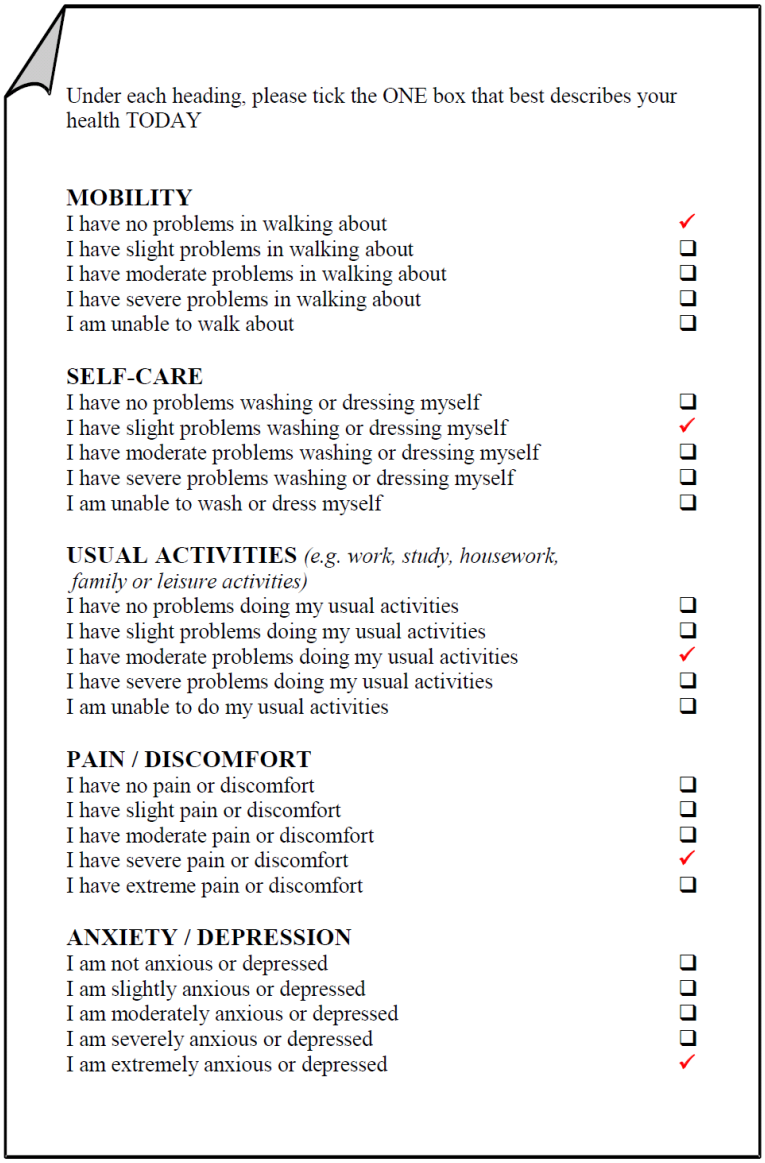
([(Sum(Item7? to Item9?)) – 2] divided by 10) * 100

If Item 9 is missing

([(Sum(Item7 and Item8)) – 2] divided by 8) * 100

14.12 EQ-5D-5L Scoring Procedures

The EQ-5D-5L descriptive system should be scored, for example, as follows:



Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY
- I have no problems in walking about ✓
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE
- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ✓
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ✓
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ✓
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION
- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ✓

Levels of perceived problems are coded as follows:

✓ ☐ ☐ ☐ ☐	Level 1 is coded as a '1'
☐ ✓ ☐ ☐ ☐	Level 2 is coded as a '2'
☐ ☐ ✓ ☐ ☐	Level 3 is coded as a '3'
☐ ☐ ☐ ✓ ☐	Level 4 is coded as a '4'
☐ ☐ ☐ ☐ ✓	Level 5 is coded as a '5'

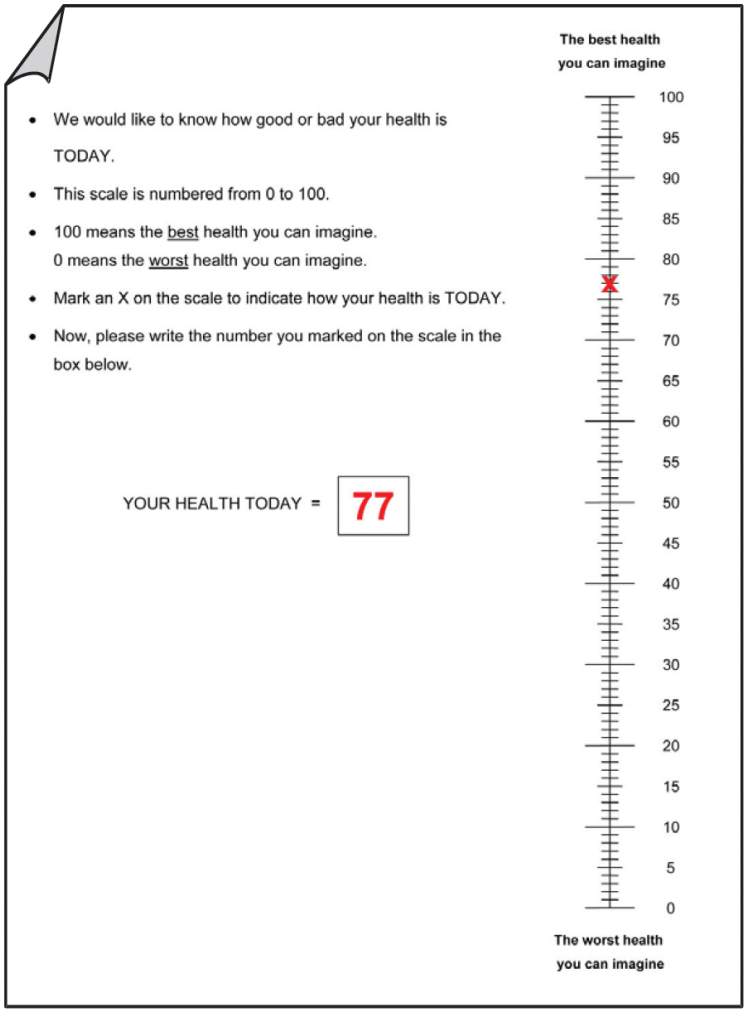
This example identifies the health state '12345'.

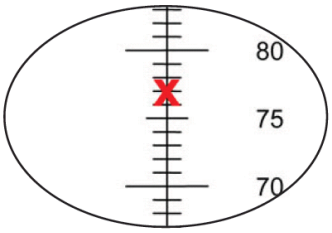
NB: *There should be only ONE response for each dimension*

NB: Missing values *can be coded as '9'.*

NB: Ambiguous values *(e.g. 2 boxes are ticked for a single dimension) should be treated as missing values.*

The EQ VAS should be scored, for example, as follows:





For example this response should be coded as 77

***NB: Missing values** should be coded as '999'.*

***NB:** If there is a discrepancy between where the respondent has placed the X and the number he/she has written in the box, administrators should use the number in the box.*

EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single index value[3]. The index values, presented in country specific value sets, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions. Studies that directly elicit preferences from general population samples to derive value sets for the EQ-5D-5L are under development in a number of countries; however, these studies will take time to complete and for results to be disseminated.

4.1. The EQ-5D-5L Crosswalk Project

In the interim, the EuroQol Group coordinated a study[4] that administered both the 3-level and 5-level versions of the EQ-5D, in order to develop a "crosswalk" between the EQ-5D-3L value sets and the new EQ-5D-5L descriptive system, resulting in crosswalk value sets for the EQ-5D-5L. A total of 3691 respondents completed both the 3L and 5L across 6 countries: Denmark, England, Italy, the Netherlands, Poland and Scotland. Different subgroups were targeted, and in most countries, a screening protocol was implemented to ensure that a broad spectrum of levels of health would be captured across the dimensions of EQ-5D for both the 5L and 3L descriptive systems.

Several methods were consequently tested to optimize the link function between the two descriptive systems. The crosswalk link function resulting from this exercise can be used to calculate index values for EQ-5D-5L, based on the existing value sets for the EQ-5D-3L. Value sets have been derived for EQ-5D-3L in several countries using visual analogue scale (VAS) technique or time trade-off (TTO) valuation techniques. The list of currently available value sets with the number of respondents and valuation technique applied is presented in table 1. Most of the EQ-5D-3L value sets have been obtained using a representative sample of the general population, thereby ensuring that they represent the societal perspective. For anyone working with EQ-5D-3L data, an essential guide to the Group's available value sets can be found in: EuroQol Group Monograph series: Volume 2: EQ-5D value sets: inventory, comparative review and user guide, published by Springer (see section 9.3 for more information).

4.2. Crosswalk value sets for the EQ-5D-5L

EQ-5D-5L value sets are available for each country that performed a valuation study for the EQ-5D-3L (table 1). By using the crosswalk link function and the individual responses to the EQ-5D-5L descriptive system, index values for the EQ-5D-5L can be calculated. Documents containing information on the crosswalk project, tables of values for all 3125 health states and the '**EQ-5D-5L Crosswalk Index Value Calculator'** can be downloaded from the EuroQol website. The SAS and SPSS syntax files can be ordered from the EuroQol Office.

[3] Many different terms are in use for these index values, such as preference weights, preference-based values, utilities, QALY weights, etc. Here, we use the term 'index value'.
[4] Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health.

Table 1: List of available value sets for the EQ-5D-3L (references available on the website)

Country	N	Valuation method
Belgium	722	EQ-5D VAS
Denmark	1686	EQ-5D VAS
Denmark	1332	TTO
Europe	8709	EQ-5D VAS
Finland	1634	EQ-5D VAS
France	443	VAS/TTO
Germany	339	EQ-5D VAS
Germany	339	TTO
Japan	621	TTO
Netherlands	309	TTO
New Zealand	1360	EQ-5D VAS
Slovenia	733	EQ-5D VAS
Spain	300	EQ-5D VAS
Spain	1000	TTO
Thailand	1324	TTO
UK	3395	EQ-5D VAS
UK	3395	TTO
US	4048	TTO
Zimbabwe	2440	TTO

Data collected using EQ-5D-5L can be entered in a database according to the following schema:

Variable name	ID	SEX	AGE	EDU	COUNTRY	YEAR	MOBILITY
Variable description	patient ID number	1=Male 2=Female 9=Missing value	999=Missing value	1=Low 2=Medium 3=High 9=Missing value	Country where data was collected	Year in which data was collected	1=No problems, 2=Slight problems 3=Moderate problems 4=Severe problems 5=Unable to 9=Missing value
Data row 1	1001	1	43	1	UK	2011	4
Data row 2	1002	2	24	2	UK	2011	2

Variable name	SELFCARE	ACTIVITY	PAIN	ANXIETY	STATE	EQ_VAS
Variable description	1=No problems 2=Slight problems 3=Moderate problems 4=Severe problems 5=Unable to 9=Missing value	1=No problems 2=Slight problems 3=Moderate problems 4=Severe problems 5=Unable to 9=Missing value	1=No pain 2=Slight pain 3=Moderate pain 4=Severe pain 5=Extreme pain 9=Missing value	1=Not anxious 2=Slightly anxious 3=Moderately anxious 4=Severely anxious 5=Extremely anxious 9=Missing value	5 digit code for EQ-5D-5L	999=Missing value
Data row 1	1	3	2	5	41325	60
Data row 2	1	1	1	1	21111	90

PRO\crosswalk EQ-5D_Utility score calculation.xlsx

15 References

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