Janssen-Cilag Farmacêutica, Lda.

Observational Study - Protocol

Characterize infections and outcomes developed in relapsed/refractory multiple myeloma (RRMM) patients treated with Teclistamab.

SPOT study

Protocol 64007957MMY4011

TECVAYLI® (Teclistamab)

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Compliance: This study will be conducted in compliance with the protocol and applicable regulatory requirements.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADR	Adverse Drug Reaction
BsAbs	Bispecific Antibodies
CI	Confidence Interval
CP	Clopper Pearson
CRF	Case Report Form
DoR	Duration of Response
eDC	Electronic Data Capture
ECOG	Eastern Cooperative Oncology Group
FOIA	Freedom of Information Act
FPI	First Patient In
HSCT	Hematopoietic Stem Cell Transplantation
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Units
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IRB	Institutional Review Board
ISS	International Staging System
KM	Kaplan Meier
LPI	Last Patient In
LPO	Last Patient Out
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
OS	Overall Survival
PFS	Progression Free Survival
PQC	Product Quality Complaint
ROC	Receiver Operating Characteristic
RRMM	Relapsed or Refractory Multiple Myeloma
SAP	Statistical Analysis Plan

2. RESPONSIBLE PARTIES

Sponsor's Responsible Physician	PPD Head of Medical Affairs Hematology, Johnson & Johnson Innovative Medicine Portugal
Principal Participating Physician:	Rui Bergantim, Study National Coordinator
Sponsor's contact for this protocol:	PPD Head of Medical Affairs Hematology, Johnson & Johnson Innovative Medicine Portugal

3. SYNOPSIS

Protocol Title: Characterize infections and outcomes developed in relapsed/refractory multiple myeloma (RRMM) patients treated with Teclistamab. (v1.0, 30 July 2024)

Sponsor's Responsible Medical Officer: PPD Study Responsible Scientist (Main Author)

NOTE: The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

Background and Rationale

Bispecific antibodies are emerging as an important novel class of immunotherapeutic agents for the treatment of multiple myeloma (MM). Particularly, Teclistamab offers a new option for patients with relapsed or refractory MM (RRMM) who have exhausted established therapies, the triple class-exposed patients (patients exposed to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies).

Although patients with MM are generally at increased risk of infection due to the disease process and resulting treatments, the mode of action and targets of this new class of drugs may increase the risk even further compared to conventional MM treatment regimens, such as immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies.

The first few months after treatment initiation often represent a critical phase in disease management. Concerning Teclistamab, 28.8% of the RRMM patients from a real-world Portuguese study reported infections, of which 40% were respiratory and 20% associated with the COVID-19. In particular, grade 3/4 infections were more frequent within 2 months of starting treatment. Although infections occur throughout treatment, capturing data in the first three months can provide critical information about the initial infection trend and the need for proactive intervention strategies. Still, there is limited real-world data on the infectious complications following this treatment approach in RRMM patients, considering the incidence, outcomes, prophylaxis and management of infections.

Therefore, this study aims to characterize the infections developed by triple class-exposed RRMM patients and their outcomes during treatment with Teclistamab, the prophylaxis and infection management protocols in Portuguese clinical practice, the overall response to treatment, and the baseline characteristics of patients with and without infections. This real-world data is crucial to build on the knowledge of the spectrum of infections and their management protocols in Portugal in relation to recently published consensus and recommendations on the management of infections with bispecifics. Moreover, it will provide healthcare professionals with an understanding of the safety and effectiveness of emerging treatments in clinical practice and inform on areas of unmet medical need and settings where better education is needed.

Research Question and Objectives

Primary Objective

1. To describe the incidence, severity, timing, management, and outcomes of infection experienced by patients under Teclistamab treatment in the first 3 months outside of clinical trials.

Secondary Objectives

1. To describe the incidence, severity, timing, management, and outcomes of infection experienced by patients under Teclistamab treatment in the first 6 months outside of clinical trials;
2. To describe the prophylaxis and infections management protocols used in the Portuguese clinical practice;
3. To describe the differences in baseline characteristics between MM triple-class exposed patients who experienced infections within the first 3 or 6 months of Teclistamab and those who did not;
4. To describe the overall response rate (partial response or better) and the best response.

Study Design

This is a retrospective, multicenter, observational study to primarily characterize the infections developed by triple class-exposed RRMM patients and their outcomes during Teclistamab treatment, in the Portuguese clinical practice.

Data will be collected from the medical records of patients treated with commercial Teclistamab, in accordance with routine clinical practice. The date of treatment initiation (day 0) is between 01 June 2023 and 3 months before this study enrollment. Data collection will be considered complete for a participating patient if data available in medical records have been recorded in the case report form. Only data available within routine clinical practice will be collected in this study.

Demographic, disease, infections related data (incidence, type, grade, timing, management, and outcomes) and prophylactic measures from the first 3 and 6 months of treatment will be collected.

The end of the study will be the last data collection timepoint for the last patient participating in the study. The overall duration of the study is expected to be, approximately, 12 months.

Setting and Study Population

Participating sites will be hospitals with hematology units specialized in treating and managing patients with RRMM in Portugal. The final number and locations of sites will be based on feasibility assessments, but the inclusion of at least 8 sites is expected.

At each site, the participating physician will determine the eligibility of patients for data collection based on the inclusion and exclusion criteria. To avoid potential selection bias, all eligible patients should be enrolled consecutively in the study when they come for their regular visits.

Where allowed, no informed consent will be collected from deceased patients prior to data collection within the study, due to the retrospective nature of this study. All the data will be collected in one visit and will be based on the information available in clinical records.

Inclusion criteria

1. Aged at least 18 years;
2. Has a documented diagnosis of MM;

3. Patient treated with Teclistamab with at least 3 months of data/follow-up, with date of treatment initiation (day 0) between 01 June 2023 and 3 months before enrollment in the study;

4. Patient in the 4th or 5th line of treatment previously treated with a proteasome inhibitor, an immunomodulator, and an anti-CD38 monoclonal antibody;

5. For living patients, signature of an Informed Consent Form allowing source data verification by the patient or a legally acceptable representative. For deceased patients at the time of data collection, a waiver of the ICF by the ethics committee (IEC/IRB) will apply when allowed.

Exclusion criteria

1. Enrolled in any Teclistamab clinical trial between 01 June 2023 and 3 months before enrollment in the study.

Variables

Where available, the following items are to be collected in one visit (study visit) and documented in the CRF.

Infections:

- Type;
- Grade;
- Time to onset (start and end date of infection);
- Anatomic location or organ system infected;
- Outcome (Hospital admission, duration of hospitalization, intensive care unit, treatment discontinuation or interruption, dose delay or dose reduction, infection resolved, death);
- Concomitant, prophylactic and preemptive medications:
- Supportive therapy;
- Number and grade of infections reported in the 3 months before starting Teclistamab therapy.

Patient and Disease Characteristics:

- Age at treatment initiation;
- Sex;
- Eastern Cooperative Oncology Group Performance status at treatment initiation;
- Comorbidities of clinical interest at treatment initiation;
- Date of initial diagnosis;
- Type of Myeloma;
- ISS Stage at treatment initiation;
- Cytogenetic evaluation at treatment initiation;
- Presence and type of soft tissue plasmacytoma at treatment initiation;
- Presence of hypogammaglobulinemia, Beta 2 microglobulin, albumin, percentage of bone marrow myeloma plasma cells, lactate dehydrogenase levels, hemodialysis requirement, measurable disease and CRAB criteria ('C' denotes increased blood calcium, 'R' signifies kidney damage, 'A' indicates anemia, and 'B' represents bone damage) at treatment initiation.

Evaluation of Effectiveness/Clinical Response

The following data on prior MM therapies will be documented:

- Number and type of previous lines of treatment;
- Type of previous treatment to which the patient has become refractory to;
- Previous Hematopoietic stem cell transplantation;

The following data regarding Teclistamab treatment will be documented:

- Treatment start date;
- Dosing schedule and total number of cycles and doses;
- Treatment hold and reason;
- Stop date and reason for discontinuation;
- First response and best response;
- Disease progression.

Survival data

- Death date and reason of death;
- Date of the last follow-up visit for alive patients.

Evaluation of Safety

Safety evaluation will be based on the collection of data regarding infections and other adverse drug reactions (ADRs).

All infectious events (regardless of causality) as per the data collection plan, other ADRs and special situations documented in the source data following exposure to Teclistamab are to be recorded in the CRF for the protocol-defined data collection period, regardless of seriousness. All ADR (including causal related infections and other ADR) should be collected from the first documented use of Teclistamab until 90 days after the last documented use within the protocol-defined data collection period.

Data Sources

The primary data source for this study will be the medical records of each patient. Source documentation should be available in patients' medical records for all data entered into the CRF.

Study Size

Given this is an exploratory retrospective study, there is no formal statistical hypothesis. The sample will be a convenience sample of patients who fulfill all eligibility criteria and are/were being treated at one of the participating sites. As the study main objective is descriptive, the inclusion of approximately 50 patients treated with Teclistamab for at least 3 months is expected. This sample size is based on feasibility, i.e., available medical records of patients who initiated treatment with Teclistamab between 01 June 2023 and 3 months before study enrollment in any of the participating hematology outpatient sites.

Data Analysis

Statistical analyses will be descriptive. The study is not intended to test pre-defined formal statistical hypotheses. Categorical, continuous and time to event variables will be summarized as:

- Categorical variables, e.g., incidence of ADRs, severity, etc.: number of participants [n] within each category and percentage [%] with 95% Clopper Pearson confidence interval (CI). The denominator will be the total number of participants within each category. Number of missing values will be displayed, if applicable.
- Continuous variable: number of participants [n], mean, standard deviation, median, minimum, and maximum. Number of missing values will be displayed, if applicable.
- Time-to-event variables (time to first dose adjustment, first interruption, discontinuation, duration of response, first response, best response, progression, and death): Kaplan-Meier method and displayed graphically where appropriate, median time event with, corresponding 95% CI, 25th, 75th percentile, and the range (minimum and maximum) will be displayed. Event free survival at month 3, 6, and 12 will be presented.

All statistics (estimates) will be presented with corresponding 95% CI and interpretation will be based on 95% CI. To investigate which covariates might influence infection rate (Yes/No), the exact logistic model will be applied with the following covariates: demographic, clinical outcomes. Infection rate might be adjusted for the treatment exposure and presented with 95% CI, if data allow. Handling of missing data, if there are less than 30% missing per variable, the single imputation, e.g., median, or multiple and/or single (e.g., median) imputation will be applied first, then these variables will be used in the model.

A Statistical Analysis Plan will be developed.

Milestones

The planned dates for key milestones in this study are:

Milestone:	**Planned Date:**
Start of data collection – First Patient In	14 February 2025
Interim report	*To be defined* [a]
End of data collection – Last Patient In	14 February 2026
Database lock	14 February 2026
Final report of study results	14 November 2026
Manuscript	14 February 2027

[a] If scientific relevant, an interim analysis is expected to be held when approximately 50% (n=25) of the planned sample size has been enrolled.

DATA COLLECTION OVERVIEW

Table 1: Data Collection Overview.

	Study Visit/Data Collection
Demographics and patients' characteristics	
Patient consent [a]	X
Selection (eligibility) criteria	X
Age at treatment initiation	X
Sex	X
Comorbidities of clinical interest	X
ECOG performance status	X
Survival Status	
Death date	X
Reason of death	X
Date of the last follow-up visit for alive patients	X
Multiple Myeloma Characteristics	
Date of diagnosis of multiple Myeloma	X
Type of Myeloma	X
ISS Stage	X
Cytogenetic assessment [b]	X
Soft tissue plasmacytoma assessment [b]	X
Presence of hypogammaglobulinemia, Beta 2 microglobulin level, albumin, percentage of bone marrow myeloma plasma cells, Lactate dehydrogenase levels, hemodialysis requirement, CRAB criteria and measurable disease.	X
Multiple Myeloma Therapy	
Prior history of MM therapies (previous agents; HSCT; number, type and grade of reported infections in previous 3 months)	X
MM current therapy (start/stop dates and reason for discontinuation, dosing schedule, treatment hold and reason for treatment hold, number of cycles and doses, first and best responses, disease progression)	X
Infection Characterization [c]	
Type of infection	X
Grade (≥ 3/ <3)	X
Time to onset (start and end of infection)	X

	Study Visit/Data Collection
Anatomic location or organ system infected (respiratory tract, urinary tract, skin-soft tissue, gastrointestinal, other)	X
Outcome (hospital admission, days of hospitalization, intensive care unit requirement, treatment discontinuation, dose adjustment and survival/death)	X
Prophylaxis (vaccination status, grow factors, antibacterial, antiviral, antifungal, immunoglobulins supplementation and other prophylaxis including start/stop dates, dosing schedule)	X
Management (treatment interruptions; interruption duration; treatment restart; supportive therapies)	X
Adverse drug reactions [d]	X
Effectiveness of treatment	
First response	X
Best response	X
Disease progression	X

[a] Prior to data collection, all patients or their legal representative must sign an Informed Consent Form (ICF) allowing source data verification in accordance with local requirements and sponsor policy. Where allowed by the local ethics committee, a waiver of informed consent will be requested for patients deceased at the time of data collection, due to the retrospective nature of this study. Non-inclusion of these patients may compromise the study objectives. All the data will be collected in one visit and will be based on the information available in clinical records.

[b] In case of missing data at study visit, the data from the closest available date will be collected.

[c] All infections events during the first 3 and 6 months of exposure to Teclistamab are to be recorded in the CRF, regardless of seriousness or causality.

[d] All adverse drug reactions and special situations following exposure to Teclistamab are to be recorded in the CRF, regardless of seriousness. Adverse drug reactions should be collected from the first documented use of Teclistamab until 90 days after the last documented use within the protocol-defined data collection period

ADR: Adverse Drug Reaction; ECOG: Eastern Cooperative Oncology Group; HSCT: Hematopoietic Stem Cell Transplantation ISS: International Staging System

4. AMENDMENTS AND UPDATES

Version	Date	Rationale
1.	30 July 2024	Initial protocol.

5. MILESTONES

The planned dates for key milestones in this study are outlined in the table below.

Table 2: Study Milestones

Milestone:	**Planned Date:**
Start of data collection – First patient In	14 February 2025
Interim report	*To be defined* [a]
End of data collection – Last Patient In	14 February 2026
Database lock	14 February 2026
Final report of study results	14 November 2026
Manuscript	14 February 2027

[a] If scientific relevant, an interim analysis is expected to be held when approximately 50% (n=25) of the planned sample size has been enrolled.

6. RATIONALE AND BACKGROUND

6.1. Background

Multiple myeloma (MM) is a malignant disorder characterized by the proliferation of plasma cells in the bone marrow (1). This disease typically affects older adults, aged between 65 and 70 years at diagnosis (2). MM can manifest as symptomatic (active MM) or asymptomatic (smoldering MM) and is categorized between stage 1 and 3. Symptoms vary among individuals but typically include bone pain, anemia, fatigue, kidney dysfunction and recurrent infections (1). In addition, a significant proportion of patients suffer from comorbidities that further increase the disease burden and the risk of death. The most common are cardiovascular disease, secondary malignancies, diabetes mellitus and renal disease (3, 4).

MM is the third most prevalent hematologic malignancy in adults worldwide, with 187,952 new cases and 121,388 deaths in 2022 (5). These numbers are rising, mainly due to an ageing population, improved diagnosis and sociodemographic factors (6). In Portugal, there were 994 new MM cases and 689 annual deaths in the same year, showing an escalating trend similar to other developed countries (5, 7).

MM patients have weakened immune systems, rendering them more susceptible to infection, which represent a major cause of death in this population (8, 9). This susceptibility is further exacerbated by the immunosuppressive nature of the drug therapy used to treat the disease (10, 11). Other factors also increase the risk of infection in these patients, such as female sex, advanced stage of the disease, poor general health and the presence of catheters (12). Studies have reported a higher incidence of severe (grade 3/4) infections compared to milder (grade 1/2) ones, with a notable concentration of the former occurring early in the treatment period (13, 14). Infections in the urinary tract are the most frequent in MM patients, followed by septicemia and respiratory tract infections. They are strongly associated with high disease burden, relapsed disease, and treatment with high-dose chemotherapy (9).

In fact, and despite the range of therapeutic options that offer long-term efficacy, most MM patients experience disease relapse. With each relapse, the likelihood and duration of the response to treatment decreases, accompanied by a return of symptoms and a subsequent decrease in quality of life. These demand for alternative treatments that maintain long-term outcomes, prevent recurrent relapses and improve patients' quality of life (15).

6.2. Current Treatments

Bispecific antibodies (BsAbs) like Teclistamab are an emerging novel class of immunotherapeutic agents for the treatment of MM (16). Teclistamab targets the B-cell maturation antigen on MM cells and redirects T cells to eliminate them, offering a new option for patients with relapsed or refractory MM (RRMM) who have exhausted established therapies, the triple class-exposed patients [patients exposed to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies (mAB)] (15, 17).

Despite its proven efficacy, the mechanism of action and targets of Teclistamab further increase the risk of infection in MM patients (18). In the MajesTEC-1 study, Teclistamab was associated with a high incidence of infections in RRMM triple class-exposed patients (80.0%) who had previously received at least three therapy lines, in particular grade 3/4 infections (55.2%) (14). A single-center study reported a 55% infection rate after Teclistamab in 22 relapsed patients previously treated with a B-cell maturation antigen-targeted therapy, who were excluded from the MajesTEC-1 study (19).

A recent real-world Portuguese analysis evaluating the safety and effectiveness of Teclistamab in 19 patients from 7 hospitals reported an infection rate of 28.8% (20). Of those, 40% were respiratory and 20% associated with the COVID-19. In fact, grade 3/4 infections were more frequent within the first two months of treatment, which often represent a critical phase in disease management (14). In the same Portuguese study, 52.6% of patients had hypogammaglobulinemia and received intravenous immunoglobulin therapy replacement, highlighting the local adoption of the latest recommendations for prophylaxis and management of infections (20).

Although infections occur throughout treatment, capturing data in the first three months can provide critical information about the initial infection trend and the need for proactive intervention strategies.

6.3. Overall Rationale for the Study

Teclistamab is the first bispecific mAb approved for the treatment of patients with RRMM and has shown promising results in triple class-exposed patients. Managing these patients poses a challenge due to the limited treatment options and the severe nature of the disease. However, there is limited real-world data available on the infectious complications following this treatment approach in patients with RRMM (16).

Recently, the CONNECT MM registry reported that up to 40% of patients treated in routine care would not meet the strict eligibility criteria for participation in randomized controlled trials in newly diagnosed MM (21). However, knowing these patients is crucial to build on recently published consensus and recommendations on managing infections with BsAbs. Therefore, the current study primarily aims to characterize the infections developed by triple class-exposed RRMM patients and their outcomes during Teclistamab treatment, in the Portuguese clinical practice. Additionally, it intends to describe the baseline characteristics of patients with and without infections, the prophylaxis and infection management protocols, as well as the overall response to treatment.

This real-world data will build on the knowledge of the spectrum of infections and their management protocols in triple class-exposed MM patients in Portugal in relation to recently published consensus and recommendations on the management of infections after BsAbs treatment. Moreover, it will provide healthcare professionals with an understanding of the safety and effectiveness of emerging treatments in clinical practice and inform on areas of unmet medical need and settings where better education is needed.

7. RESEARCH QUESTION AND OBJECTIVES

The **primary objective** is to describe the incidence, severity, timing, management, and outcomes of infection experienced by patients under Teclistamab treatment in the first 3 months outside of clinical trials. **Table 3** lists the associated primary outcomes of interest.

Table 3: Primary outcomes of this study.

Primary Objective	Primary Outcomes	
Describe the incidence, severity, timing, management, and outcomes of infection experienced by patients under Teclistamab treatment in the first 3 months outside of clinical trials	1	Incidence • Among all patients, number of infections reported in the first 3 months of Teclistamab therapy.
	2	Severity and type • Among all infections, number and proportion of infections grade reported in the first 3 months of therapy; • Among all patients, number and proportion of at least one infection grade ≥3 in the first 3 months of therapy; • Among all infections, number and proportion of each type of infections; • Among all infections, number and proportion of each anatomic location or organ system infected.
	3	Infections timing • Among all infections, mean and median time of infection duration (days); • Among all patients, mean and median time of total infections duration (days); • Among all patients, time between Teclistamab start date and first infection date, or last contact date/death date (if no infection has occurred).
	4	Management • Among all patients, number and proportion dosing schedule and frequency Teclistamab treatment; • Mean and median of Teclistamab treatment cycles[a] that the patient received in total; • Mean and median of total doses that patient received during treatment with Teclistamab (excluding Step-up phase); • Among all patients, number and proportion of patients who interrupted treatment at least one time;

[a] 28 days cycles. The Teclistamab treatment first cycle involves an initial phase with two step-up doses and 1full treatment dose.

		• Among all patients, number and proportion of the number of treatment interruptions that have occurred; • Among all interruptions, mean and median of interruptions duration (days); • Among all patients, mean and median time of total interruptions duration (days); • Among all patients who interrupted treatment at least one time, number and proportion of patients with treatment restart; • Among all interruptions, number and proportion of treatment restart; • Among all patients, number and proportion of patient that adjusted dose (dose delay and dose reduction) at least one time; • Among all patients, number and proportion of the number of dose adjustment that have occurred; • Among all dose adjustments, number and proportion of each reason for dose delay and/or dose reduction; • Among all patients, time until first Teclistamab dose adjustment (in days) - time from treatment initiation to first dose adjustment; • Among all patients, mean and median final dose, after all dose adjustments occurred; • Among all infections, number and proportion of each supportive therapies/ medication (Antibacterial, Antiviral, Antifungal, Other) – at least one; • Among all patients, number and proportion of each supportive therapies/ medication (Antibacterial, Antiviral, Antifungal, Other) – at least one; • For each supportive therapy/ medication, mean and median of treatment duration and dose.
	5	Outcomes • Number and proportion of patients with at least one hospitalization due to infections; • Mean and median time of number of hospitalization per patient; • Mean and median time of total hospitalization days; • Number and proportion of patients with at least one intensive care unit (ICU) requirement; • Mean and median time of total ICU days; • Evaluate treatment exposure (in days) to Teclistamab - time from treatment initiation to treatment discontinuation; • Number and proportion of each reason for discontinuation;

		• Among all infections, number and proportion of infections resolved; • Number and proportion of patients survival/death; • Duration of response (DoR) defined as the time of the first response (PR or better) to the date of the first evidence of progressive disease; • Overall survival (OS) defined as the time from the date of treatment initiation with Teclistamab until death; • Progression free survival (PFS) defined as the time from the date of treatment initiation with Teclistamab to the date of the first documented disease progression or death due to any case, whichever occurs first.
	6	Infections in the 3 months before Teclistamab initiation • Among all patients, number and proportion of infections reported; • Among all infections, number and proportion of each infection grade; • Among all patients, number and proportion of at least one infection grade ≥3 in the 3 months before therapy; • Among all infections, number and proportion of each pathogen type.

The **secondary objectives** are:

1. To describe the incidence, severity, timing, management, and outcomes of infection experienced by patients under Teclistamab treatment in the first 6 months outside of clinical trials;

2. To describe the prophylaxis and infections management protocols used in the Portuguese clinical practice;

3. To describe the differences in baseline characteristics between MM triple-class exposed patients who experienced infections within the first 3 or 6 months of Teclistamab and those who did not;

4. To describe the overall response rate (partial response or better) and the best response.

The associated secondary outcomes of interest are listed in **Table 4**.

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Table 4: Secondary outcomes of this study.

Secondary Objectives		Secondary Outcomes	
1	Describe the incidence, severity, timing, management, and outcomes of infection experienced by patients under Teclistamab treatment in the first 6 months outside of clinical trials	1	Incidence • Among all patients, number of infections reported in the first 6 months of Teclistamab therapy.
		2	Severity and type • Among all infections, number and proportion of infections grade reported in the first 6 months of therapy; • Among all patients, number and proportion of patients with at least one infection grade ≥3 in the first 6 months of therapy; • Among all infections, number and proportion of each type of infection, by pathogen; • Among all infections, number and proportion of each anatomic location or organ system infected.
		3	Infections timing • Among all infections, mean and median time of infection duration (days); • Among all patients, mean and median time of total infections duration (days); • Among all patients, time between Teclistamab start date and first infection date, or last contact date/death date (if no infection has occurred).
		4	Management • Among all patients, number and proportion dosing schedule and frequency Teclistamab treatment; • Mean and median of Teclistamab treatment cycles that the patient received in total; • Mean and median of total doses that patient received during treatment with Teclistamab (excluding Step-up phase); • Among all patients, number and proportion of patients who interrupted treatment at least one time; • Among all patients, number and proportion of the number of treatment interruptions that have occurred; • Among all interruptions, mean and median of interruptions duration (days); • Among all patients, mean and median time of total interruptions duration (days); • Among all patients who interrupted treatment at least one time, number and proportion of treatment restart;

			• Among all interruptions, number and proportion of treatment restart; • Among all patients, number and proportion of patient that adjusted dose (dose delay and dose reduction) at least one time; • Among all patients, number and proportion of the number of dose adjustment that have occurred; • Among all dose adjustments, number and proportion of each reason for dose delay and/or dose reduction; • Among all patients, time until first Teclistamab dose adjustment (in days) - time from treatment initiation to first dose adjustment; • Among all patients, mean and median final dose, after all dose adjustments occurred; • Among all infections, number and proportion of each supportive therapies/ medication (Antibacterial, Antiviral, Antifungal, Other) – at least one; • Among all patients, number and proportion of each supportive therapies/ medication (Antibacterial, Antiviral, Antifungal, Other) – at least one; • For each supportive therapy/ medication, mean and median of treatment duration and dose.
		5	Outcomes • Number and proportion of patients with at least one hospitalization due to infections; • Mean and median time of number of hospitalizations per patient; • Mean and median time of total hospitalization days; • Number and proportion of patients with at least one ICU requirement; • Mean and median time of total ICU days; • Evaluate treatment exposure (in days) to Teclistamab - time from treatment initiation to treatment discontinuation; • Number and proportion of each reason for discontinuation; • Among all infections, number and proportion of infections resolved; • Number and proportion of patients survival/death; • OS defined as the time from the date of treatment initiation with Teclistamab until death;

			• PFS defined as the time from the date of treatment initiation with Teclistamab to the date of the first documented disease progression or death due to any case, whichever occurs first.
2	Describe the prophylaxis and infections management protocols used in the Portuguese clinical practice	6	• Number and proportion of vaccination status before Teclistamab treatment initiation; • Number and proportion of patients using prophylactic growth factors during Teclistamab treatment (including 28-day period before Teclistamab treatment); • Number and proportion of patients using each prophylactic growth factor during Teclistamab treatment (including 28-day period before Teclistamab treatment); • Within each prophylactic growth factor: mean and median duration (days); • Within each prophylactic growth factor: number and proportion of each type of infection, by pathogen, and by anatomic location or organ system infected; • Number and proportion of patients using medication/therapy as prophylactic treatment for infections during Teclistamab treatment (including 28-day period before Teclistamab treatment); • Number and proportion of patients using each medication/therapy as prophylactic treatment for infections during Teclistamab treatment; • Within each medication/therapy as prophylactic treatment for infections: mean and median duration (days); • Within each medication/therapy as prophylactic treatment for infections: number and proportion of each type of infection, by pathogen, and by anatomic location or organ system infected; • Number and proportion of patients receiving Immunoglobulin G (IgG) supplementation at the start (including 28-days period before Teclistamab treatment) or during treatment with Teclistamab; • Number and proportion of patients receiving IgG supplementation at the start (including 28-days period before Teclistamab treatment) or during treatment with Teclistamab; • Within each IgG supplementation: mean and median duration (days); • Within each IgG supplementation: number and proportion of each type of infection, by pathogen, and by anatomic location or organ system infected;

3	Describe the differences in baseline characteristics between MM triple-class exposed patients who experienced infections within the first 3 or 6 months of Teclistamab and those who did not	7	For both groups: • Mean and median of age at initial diagnosis, and age at Teclistamab treatment start; • Number and proportion of each sex; • Number and proportion of each ECOG performance status at treatment initiation; • Number and proportion of each comorbidity; • Mean and median of time between initial diagnosis and Teclistamab start therapy; • Number and proportion of each Type of Myeloma; • Number and proportion of each International Staging System (ISS) Stage; • Number and proportion of patients that underwent cytogenetic evaluation; • Within patients that underwent cytogenetic evaluation: number and proportion of patients at high and standard risk. Number and proportion of each genetic mutation; • Number and proportion of presence of soft tissue plasmacytoma; • Number and proportion of type of soft tissue plasmacytoma; • Number and proportion of patients with hypogammaglobulinemia. Mean and median IgG level values observed; • Number and proportion of patients who evaluated Beta 2 microglobulin. Mean and median values observed; • Number and proportion of patients who evaluated Albumin. Mean and median values observed; • Number and proportion of patients with CRAB criteria; • Number and proportion of patients with measurable disease; • Number and proportion of patients who performed hemodialysis at the Teclistamab start; • Number and proportion of patients who evaluated Percentage of bone marrow myeloma plasma cells. Mean and median values observed; • Number and proportion of patients who evaluated Lactate dehydrogenase levels. Mean and median values observed; • Mean and median of the number of previous lines of treatment; • Number and proportion of agents which the patient has been exposed to, before Teclistamab treatment;

			• Number and proportion of agents which the patient has become refractory to, before Teclistamab treatment; • Number and proportion of patient who received hematopoietic stem cell transplantation (HSCT) as part of previous treatment; • Number and proportion of patient who received allogenic transplant (and number). Number and proportion of patient who received 1/ 2/ >2; • Number and proportion of patient who received autologous transplant (and number). Number and proportion of patient who received 1/ 2/ >2;
4	Describe the overall response rate (partial response or better) and the best response	8	• Number and proportion of first response; • Time until first response (in days) - time from treatment initiation to first response; • Time until best response (in days) - time from treatment initiation to best response; • DoR defined as the time of the first response (PR or better) to the date of the first evidence of progressive disease or death; • Number and proportion of best response.

Please refer to Section 8.7 for statistical aspects of outcomes or measures of interest.

8. RESEARCH METHODS

8.1. Study Design

This is a retrospective, multicenter, observational study to primarily characterize the infections developed by triple class-exposed RRMM patients and their outcomes during Teclistamab treatment, in the Portuguese clinical practice.

A diagrammatic representation of the study design is presented in Figure 1.

Figure 1

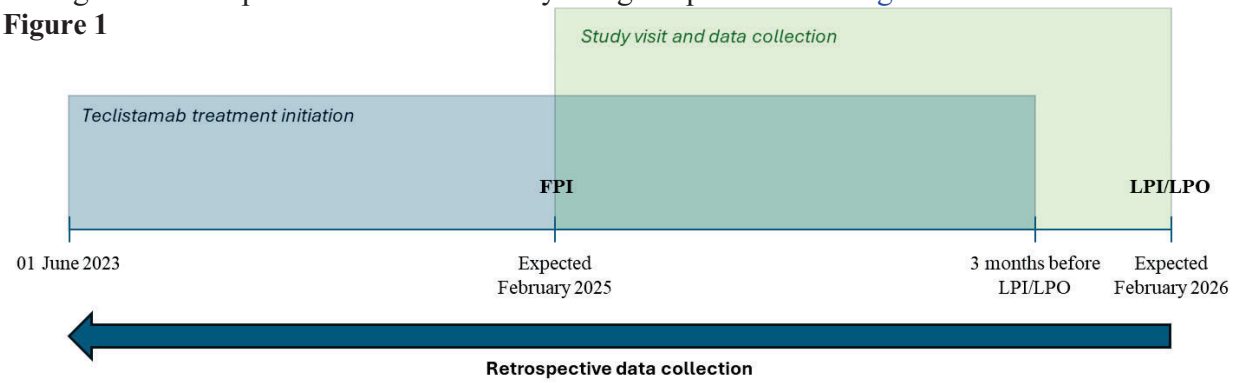

Figure 1: Study Schematic.

FPI: first patient in; LPI: last patient in; LPO: last patient out

Data will be collected from the medical records of patients treated with commercial Teclistamab, in accordance with routine clinical practice. The date of treatment initiation (day 0) is between 01 June 2023 and 3 months before this study enrollment. Data collection will be considered complete for a participating patient if data available in medical records have been recorded in the case report form (CRF). Only data available within routine clinical practice will be collected in this study.

Demographic, disease, infections related data (incidence, type, grade, timing, management, and outcomes) and prophylactic measures from the first 3 and 6 months of treatment will be collected.

The end of the study will be the last data collection timepoint for the last patient participating in the study.

Treatment with Teclistamab will be in accordance with routine clinical practice. Teclistamab and other treatment(s) will not be provided by the sponsor, and patients will not be reimbursed for purchasing any treatments they need to treat their pathology.

Where allowed by the ethics committee [Independent Ethics Committee (IEC)/Institutional Review Board (IRB)], a waiver of informed consent will be requested for patients deceased at the time of data collection, due to the retrospective nature of this study. Non-inclusion of these patients may compromise the study objectives. All the data will be collected in one visit and will be based on the information available in clinical records. The study will start when the first patient who meets all eligibility criteria and signs the informed consent form (ICF) is included in the study and will end when data collection for the last patient is completed. Due to the retrospective nature of the study, data will be collected in one visit. The overall duration of the study is expected to be 12 months.

8.1.1. Rationale for Study Design Elements

In usual clinical practice, physicians adopt more varied prescribing patterns in the treatment of a more heterogeneous patient population. The non-interventional aspect of this study provides an approach to document the selection of treatments and the observation of interventions in a clinical setting, outside interventional trials.

The retrospective observational design enables to collect sufficient quantity of defined variables, where available in clinical practice, to address the study objectives.

8.2. Setting and Study Population

8.2.1. Study Setting

Sites participating in this observational study will be hospitals with hematology units specialized in treating and managing patients with RRMM in routine clinical practice in Portugal. The final number and locations of sites will be based on feasibility assessments, but the inclusion of at least 8 sites is expected.

8.2.2. Patient Selection Criteria

Participating sites will be encouraged to enroll patients consecutively when they come for their regular visits. Additionally, only patients with at least 3 months of data/follow-up will be included. Both methods aim to minimize bias in patient selection. The inclusion of approximately 50 patients is expected during the study period.

At each site, the participating physician will determine the eligibility of patients for data collection in this study based on the inclusion and exclusion criteria described below. If there is a question about any of the selection criteria, the participating physician should consult with the appropriate sponsor representative before enrolling the patient. To avoid potential selection bias, all eligible patients should be offered enrollment for data collection in the study.

Inclusion Criteria

Each patient must satisfy the following criteria to be eligible for data collection in this study:

1. Aged at least 18 years;
2. Has a documented diagnosis of MM;
3. Patient treated with Teclistamab with at least 3 months of data/follow-up, with date of treatment initiation (day 0) between 01 June 2023 and 3 months before enrollment in the study;
4. Patient in the 4^{th} or 5^{th} line of treatment previously treated with a proteasome inhibitor, an immunomodulator, and an anti-CD38 monoclonal antibody;
5. For living patients, signature of an Informed Consent Form allowing source data verification by the patient or a legally acceptable representative. For deceased patients at the time of data collection, a waiver of the ICF by the ethics committee (IEC/IRB) will apply when allowed.

Exclusion Criteria

Patients who meet any of the following criteria will not be eligible for this study:

1. Enrolled in any Teclistamab clinical trial between 01 June 2023 and 3 months before enrollment in the study.

8.2.3. Duration of Study Period(s) and Follow-Up

The retrospective data collection will document data available since the MM diagnosis until the study visit of the last patient in (LPI). The index date (time zero) will be defined as the date of Teclistamab initiation, between 01 June 2023 and 3 months before the study visit of the LPI.

Data will be secondarily collected from the patients' medical records up to the date of informed consent, for patients still under treatment/follow-up, or up to the date of death. Data will refer to at least 3 months of Teclistamab treatment.

A patient may be withdrawn from data collection within the study due to withdrawal of consent. When a patient withdraws consent for data collection within the study, the reason for withdrawal should be documented in the CRF.

Completers will be defined as study participants who died or have at least 3-month data.

8.3. Variables

The Data Collection Overview that follows the abstract summarizes the intended data collection. Only data available from a patient's source medical records will be collected.

The primary data source for this study will be the medical records of each patient. Source documentation should be available in patients' medical records for all data entered into the CRF.

Where available, the following items are to be collected in one visit (study visit) and documented in the CRF:

- Data regarding Infections (see Section 8.3.1)
- Patient and Disease Baseline Characteristics, including demographic data (see Section 8.3.2);
- Effectiveness/clinical response variables (see Section 8.3.3)
- Survival Data (see Section 8.3.4)
- Other Adverse Drug Reactions (ADR) (see Section 8.3.50)
- Medical resource utilization (see Section 8.3.6).

8.3.1. Infections

- Type;
- Grade;
- Time to onset (start and end date of infection);
- Anatomic location or organ system infected;
- Outcomes:
  - Hospital admission;

  - Duration of hospitalization;
  - ICU;
  - Treatment discontinuation;
  - Dose delay or dose reduction;
  - Treatment interruption;
  - Infection resolved;
  - Death;

- Concomitant, prophylactic and preemptive medications:
  - Vaccination status before Teclistamab treatment initiation;
  - Type and date of prophylactic growth factors during Teclistamab;
  - Type and date of prophylactic treatment for infections during Teclistamab;
  - IgG supplementation before and during Teclistamab;

- Supportive therapy;

- Number and grade of infections reported in the 3 months before starting Teclistamab therapy.

8.3.2. Patient and Disease Baseline Characteristics

The baseline value* is defined as the closest non-missing value within 28 days before Teclistamab therapy (Day 1 of treatment). In case of missing data, the data from the closest available date will be collected.

- Age at treatment initiation;
- Sex;
- Eastern Cooperative Oncology Group (ECOG) Performance status at treatment initiation*;
- Comorbidities of clinical interest at treatment initiation*;
- Date of initial diagnosis;
- Type of Myeloma;
- ISS Stage at treatment initiation*;
- Cytogenetic evaluation at treatment initiation*[a];

[a] Patients with mutations t(4,14), t(14,16), del(17p) or amp(1q21) are considered at high risk for infection.

- Presence and type of soft tissue plasmacytoma at treatment initiation*;
- Presence of hypogammaglobulinemia, Beta 2 microglobulin, Albumin, percentage of bone marrow myeloma plasma cells, lactate dehydrogenase levels, hemodialysis requirement, measurable disease and CRAB criteria ('C' denotes increased blood calcium, 'R' signifies kidney damage, 'A' indicates anemia, and 'B' represents bone damage) at treatment initiation*

8.3.3. Evaluation of Effectiveness/Clinical Response

Effectiveness/Clinical Response

Effectiveness and clinical response to MM treatment will be evaluated based on the data collected for both prior MM therapies and Teclistamab treatment.

The following data on prior MM therapies will be documented:

- Number of previous lines of treatment;
- Agents to which the patient has been exposed to;
- Agents to which the patient has become refractory to;
- Hematopoietic Stem Cell Transplantation (HSCT).

The following data regarding **Teclistamab treatment** will be documented:

- Treatment start date;
- Dosing schedule;
- Number of cycles of Teclistamab treatment;
- Number of doses that the patient received during treatment with Teclistamab (excluding Step-up phase);
- Treatment hold and reason; Treatment discontinuation and reason; First response and best response (Specify response status), including dates;
- Disease progression and date.

8.3.4. Survival Data

Survival data will include death date (MM/YYYY) and reason of death, and date of the last follow-up visit for patients who are alive (MM/YYYY).

8.3.5. Evaluation of Safety

In this observational study, Teclistamab (TECVAYLI®) is the Janssen product under study.

Safety evaluation will be based on the collection of data regarding infections and other ADRs.

Adverse Events and Adverse Drug Reactions

All infectious events (regardless of causality) as per the data collection plan, other ADRs and special situations documented in the source data following exposure to Teclistamab are to be recorded in the CRF for the protocol-defined data collection period, regardless of seriousness. All ADR (including causal related infectious and other ADR) should be collected from the first documented use of Teclistamab until 90 days after the last documented use within the protocol-defined data collection period.

8.3.6. Medical Resource Utilization

Medical resource utilization associated with infection episodes will be documented by the participating physician and/or site for all patients throughout the study, as described in section 8.3.1.

8.4. Data Sources

The primary data source for this study will be the medical record of each participating patient. Source documentation should be in patients' records for all data entered into the CRF.

To confirm data collected in the CRF for this study, source documentation should also be available for the following: patient identification, eligibility and study identification; date of signed ICF; date of study completion or withdrawal from the study (if applicable). The author of any entry in the source documents should be identifiable.

The type and level of detail of source data available for a patient should be consistent with that commonly recorded at the participating site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the participating physician before the study.

8.4.1. Data Suitability Assessment

The use of patient clinical records from hospitals provides a robust foundation for an observational retrospective study, thus ensuring data provenance, quality/relevance, and feasibility assessment.

First, patient clinical records in hospitals have a well-established data provenance. They are sourced directly from healthcare providers, ensuring the traceability and reliability of the data.

Second, these records offer high-quality and relevant information for research. They contain comprehensive data on patients' demographics, medical history, treatments, and outcomes. This rich dataset allows researchers to conduct in-depth analyses and draw meaningful conclusions.

Furthermore, the use of patient clinical records is feasible due to their wide availability in hospital databases. With proper permissions and ethical considerations, researchers can access a large pool of retrospective data, saving time and resources compared to primary data collection.

By using clinical records, researchers can overcome the logistical challenges associated with prospective studies, such as recruitment difficulties or long follow-up periods. This enhances the feasibility of the study and facilitates the analysis of results.

8.5. Study Size

This study's primary objective is to describe the incidence, severity, timing, management, and outcomes of infections experienced by patients during Teclistamab treatment in the first 3 months outside of clinical trials.

Given this is an exploratory retrospective study, there is no formal statistical hypothesis. The sample will be a convenience sample of patients who fulfill all eligibility criteria and are/were being treated at one of the participating sites. As the study main objective is descriptive, the inclusion of approximately 50 patients treated with Teclistamab for at least 3 months is expected. This sample size is based on feasibility, i.e., available medical records of patients who initiated treatment with Teclistamab between 01 June 2023 and 3 months before study enrollment in any of the participating hematology outpatient sites.

8.6. Data Collection and Management

Participating sites will enter data into the CRF using electronic data capture (eDC) via an internet browser-based interface. The CRF will direct the site regarding which data are required for collection. Participating sites will be trained in the use of the eDC system. Data collected should be recorded accurately, legibly and promptly for each patient during the study. Further details of CRF completion procedures are presented in Annex 1.8.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a site visit log that will be kept at the participating site. Further details of monitoring procedures are presented in Annex 1.9.

8.7. Data Analysis

Statistical analyses will be descriptive. The study is not intended to test pre-defined formal statistical hypotheses. Statistical analyses will be performed by or under the authority of the sponsor. A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections. Additional details will be provided in the statistical analysis plan (SAP).

8.7.1. Descriptive Analysis

Continuous variables (outcomes of interest) will be summarized using the number of observations, mean, standard deviation, median, percentiles and range (minimum and maximum). Categorical values will be summarized using the number of observations and percentages as appropriate. Corresponding 2-sided 95% Clopper Pearson confidence intervals (CIs) will be presented as appropriate.

Time-to-event data will be summarized by 25th, 50th (median) and 75th percentiles with associated 2-sided 95% CIs, survival (event-free) rates will be displayed at 3, 6 and 12 months, number of events and censored observations and Kaplan-Meier graphical curves.

Patients' demographics and baseline disease characteristics from Section 8.3.2, as well as prior MM therapies from Section 8.3.3, will be summarized as described above.

Variables referent to the index date will be defined as the closest non-missing value within 28 days before the first dose of Teclistamab. In case of missing data, the data from the closest available date will be collected (e.g. cytogenetics, soft tissue plasmacytoma, etc.).

All analysis will be performed for patients with at least one dose of Teclistamab recorded in their medical charts.

The groups of patients, with and without infection, will be characterized. If data allows, the covariates that might influence infection rate (Yes/No) will be investigated, adjusting an exact logistic model. The following covariates will be considered: demographic, clinical outcomes (see Section Variables above). Infection rate might be adjusted for the treatment exposure and presented with 95% CI, if data allow. All statistically and medically relevant variables will be tested as independent variables in the multivariable analysis. For continuous variables it will be performed an analysis to confirm the logit's linearity. If linearity is not present, categorization of the variable is an option, considering medical advice or determining a cut-off using receiver operating characteristic (ROC) curve.

Statistical analysis will be conducted through the software R® version 4.3.1, or later.

The final analysis will be carried out after the last patient completes the study and after the database is clean and closed. The analysis and report will be reviewed by the Clinical Project Manager and Data Manager, and after reviewing them, the report will be sent to the sponsor for approval.

Safety Analyses

Incidence and severity of all grades of infections and ADRs will be summarized as categorical variables during Teclistamab treatment, i.e. the percentage of patients who experience at least 1 occurrence of the given event will be summarized. 95% Clopper-Pearson CIs will also be provided wherever appropriate. This will be presented for the overall study period and during the first 3 and 6 months. Also, a summary of infections before the date of first Teclistamab will be summarized

as a categorical variable. Additionally, the type of infection and respective anatomic location will be considered as categorical variables.

Adjusted event (e.g. for Grade ≥2 infections, ADRs related to Teclistamab) with 95% CIs will be estimated from the Poisson model, including in the model the natural logarithm of Teclistamab exposure time as an offset to account for varying length of patients' time on Teclistamab.

The mean and median time duration of infections will be summarized as a continuous variable.

Survival analysis will be conducted to estimate patient's first infection during Teclistamab treatment from baseline at 3 and 6 months. Survival time will be determined between the first dose of Teclistamab and the occurrence of the first infection. If infection does not occur, the date when the patient ends or withdraws from the study will be considered as censor date.

Kaplan-Meier estimator will be considered to estimate the infection occurrence, and 95% CI for the estimates will be provided. Kaplan-Meier estimates will be represented graphically.

The verbatim terms used by physicians to document ADRs in the CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All documented ADRs will be included in the analysis. For each ADR, the percentage of patients who experience at least one occurrence of the given event will be summarized.

Where appropriate, additional summaries, listings, datasets, or narratives may be provided, as appropriate, for patients who die, who discontinue treatment due to an ADR, or who experience severe ADRs or at least two ADRs.

Effectiveness/Clinical response analyses

The duration of Teclistamab exposure will be summarized as a continuous variable, by means of mean, median and range (minimum and maximum). Number and percentage of patients with Teclistamab interruption periods, dose modifications and early Teclistamab discontinuation will also be summarized considering time-to-event Kaplan-Meier estimates. Reasons for interruption periods, dose modifications and early Teclistamab discontinuation will be described.

Dosing schedule of Teclistamab, dose adjustment, treatment hold, treatment discontinuation, will be summarized as a categorical variable.

Survival analysis will be conducted to estimate the first dose adjustment, first interruption, discontinuation, first response, best response and death for all causes during study period between the index date and the 3, 6 and 12, months. Survival time will be determined between Teclistamab initiation and the occurrence of the first corresponding event.

Time to PFS will be defined as the time from the date of treatment initiation with Teclistamab to the date of the first documented disease progression or death due to any case, whichever occurs first. Duration of response will be defined as the time of the first response (PR or better) to the date

of the first evidence of progressive disease or death. Analysis for time-to-event variables will be performed for all enrolled patients while the analysis for DoR will be calculated among responders (ie, patients with PR or better response).

If dose adjustment, interruption, discontinuation, first response, best response, progression or death does not occur, the date when the patient ends or withdraws from the study will be considered as censor date. Kaplan-Meier estimator will be considered to estimate the event occurrence from the index date until the 3, 6 and 12 months, and 95% CI for those estimates will be provided. Kaplan-Meier estimates will be represented graphically.

Medical resource utilization

Medical resource utilization during Teclistamab administration will be collected and derived from the safety information collected, associated with infection episodes.

The number and the proportion of patients with at least one hospitalization due to infections, and with at least one ICU requirement, will be provided. Additionally, the number of hospitalization days, and number of ICU days will be summarized as continuous variables.

8.7.2. Missing Values

Due to the retrospective nature of this study that will use data from the medical records of patients outside of clinical trials, some missing values might occur. All efforts will be made to prevent missing data during the study conduct.

The missing values will be stated in the corresponding variables in the summary tables.

For handling missing data, if there are less than 30% missing per variable, the single imputation, e.g., median, or multiple and/or single (e.g., median) imputation will be applied first, then these variables will be used in the model.

Regarding time-to-event endpoints no attempts will be made to impute missing values, except for dates of events and censoring dates. Only observed values will be used in the analysis.

8.7.3. Subgroup analysis

The main subgroup will be patients with medical records of infection any time versus patients with medical records of No Infection.

Patient’s demographics and disease characteristics will be summarized also for these 2 subgroups, namely: age at initial diagnosis; age at Teclistamab treatment start; sex; ECOG at treatment initiation; each comorbidity listed; time between initial diagnosis and Teclistamab start therapy; type of Myeloma; ISS stage; cytogenetic evaluation, including the classification in high and standard risk, and the genetic mutation identified; presence of soft tissue plasmacytoma and respective type; presence of hypogammaglobulinemia, beta 2 microglobulin, albumin, percentage of bone marrow myeloma plasma cells, CRAB, lactate dehydrogenase levels; number of previous

lines of treatment; agents which the patient has been exposed to, before Teclistamab treatment; agents which the patient has become refractory to, before Teclistamab treatment; hematopoietic stem cell transplantation (HSCT) as part of previous treatment; allogenic and autologous transplant.

To compare groups of patients, bivariate analysis will be conducted by using Student's t-test (or on-parametric equivalent) for continuous variables and the chi-square test (or Fisher's exact test if the assumptions for chi-squared test are not satisfied) for categorical variables.

All analyses will be tested using two-sided hypotheses at the $\alpha = 0.05$ level.

8.7.4. Interim Analysis

The results might be reported before the final data collection and analyses if scientifically relevant for research purposes, e.g. when approximately data of 25 patients is entered in the database and available. The scope of the interim analysis will be developed and documented in a SAP, if applicable.

8.8. Quality Control

Procedures to ensure the accuracy and reliability of data will include the selection of qualified physicians and appropriate participating sites, review of data collection procedures with the participating physician and site personnel before the study, and periodic monitoring visits and/or remote monitoring by the sponsor (see Section 8.6).

Guidelines for CRF completion will be provided and reviewed by the participating site personnel before the start of the study (see Annex 1.8). The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the participating physician or designee, as appropriate. After uploading the data into the study database, they will be verified for accuracy and consistency with the data sources.

The participating physician and/or site will maintain all CRFs and source documentation that support the data collected for each patient, as well as all study documents specified by the applicable regulatory requirement(s) (see Annex 1.3). The participating physician and/or site will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained for at least 5 years after the completion of the final study report but will be retained for a longer period if required by applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the participating physician and/or site as to when these documents no longer need to be retained. Further details of record retention policies are provided in Annex 1.11.

Representatives of the sponsor may visit the participating site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines

and/or company policy. Similar procedures may also be conducted by a regulatory body. Further details of on-site audit policies are presented in Annex 1.10.

8.9. Strengths and Limitations of the Research Methods

Selection bias in this study will be minimized by the consecutive enrollment of all potentially eligible patients. However, due to the observational nature of this study, non-responders and patients experiencing ADRs, or complications may be lost to follow-up, introducing bias. Residual confounding due to differences in unobserved characteristics cannot be excluded, as in any observational study. Thus, clinical input will be needed to assess these missing clinically relevant variables, and the direction of the related potential bias (if possible).

Although the results of this study cannot be generalized to the whole population of RRMM patients, they are essential to increase the knowledge about these patients. They also complement the information obtained from randomized clinical trials with a broader population with characteristics that potentially make them ineligible for inclusion in clinical trials.

9. PROTECTION OF HUMAN SUBJECTS

Where appropriate, as required by local regulations, this study will be undertaken only after the IEC/IRB has given full approval of the final protocol, any applicable amendments and the ICF, and when the sponsor has received a copy of this approval (see Annex 1.4).

A waiver for the ICF (dependent on approval by IECs, IRBs) may be applicable for deceased patients at the time of data collection. Otherwise, prior to data collection, all patients or their legal representative must sign a ICF allowing source data verification in accordance with local requirements and sponsor policy (see Annex 1.5). Potential participants will be told that their consent to allow collection of information within the context of this non-interventional study is entirely voluntary and may be withdrawn at any time. Patients will be informed of the observational nature of the study, that the sponsor only intends to collect information and follow the course of treatment in the clinical practice setting, and that their participation in the study does not involve invasive procedures outside of the recommendations in the local label.

Data collected from patients enrolled in this study will be limited to those necessary to fulfil the study objectives. It must be collected and processed with adequate precautions and in a codified/pseudoanonimyzed form to ensure confidentiality and compliance with applicable data privacy protection laws and regulations (see Annex 1.7).

10. COLLECTION AND REPORTING OF SAFETY DATA AND COMPLAINTS

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, physicians, and the sponsor, and are mandated by regulatory agencies worldwide. All studies conducted by the sponsor, or its affiliates, will be conducted in accordance with established procedures and regulatory requirements worldwide to ensure appropriate reporting of safety information.

General procedures for the collection and reporting of any ADR, special situations, and product complaints within the study are described in the following sections. Definitions, classifications and related criteria for safety events and complaints are described in Annex 1.14.

10.1. General Procedures

In this observational study, Teclistamab (TECVAYLI ®) is the Janssen product(s) under study. Safety information and Product Quality Complaints (PQCs) for this medicinal product will be collected and reported during the study as described in the following sections.

In addition, if an ADR, a special situation or PQC related to any other Janssen drug is identified during the course of the study, it should be reported as a spontaneous report to the sponsor.

The sponsor will provide appropriate pharmacovigilance training to the participating site personnel. The sponsor assumes responsibility for appropriate reporting of (serious) ADRs and significant safety information originating from the data collected for Janssen medicinal products to the regulatory authorities. All collected infections/ADRs will be summarized in the final study report.

The names (and corresponding contact details) of the individuals who should be contacted regarding product safety issues and/or quality issues are listed on the contact information page(s), which is/are provided separately.

10.1.1. Adverse Events/Drug Reactions

All infectious events (regardless of causality) as per the data collection plan, other ADRs and special situations documented in the source data following exposure to the product under study are to be recorded in the CRF for the protocol-defined data collection period, regardless of seriousness.

For ADRs to be reportable in the CRF, there should be information in the source data and/or retrospective study database confirming that the event is specifically indicated or clearly implied (verbally or documented) to be related to the use of a product under study (see Section 13.14.1). All ADRs (including causal related infections and other ADR) should be collected from the first documented use of a product under study until 90 days after the last documented use within the protocol-defined data collection period.

All serious ADRs (including causal related infections and other ADR) for a Janssen product under study should also be reported directly by the participating physician, within 24 hours of them becoming aware, to the local sponsor using a Serious Adverse Event Report Form (or local equivalent). When necessary, the sponsor will inform the local health authorities following applicable requirements for expedited and aggregated reporting.

Expedited Reporting of Adverse Drug Reactions

Where necessary, the sponsor will report non-serious ADRs to the local health authorities following applicable requirements.

Any event that meets the definition of a serious ADR (see Section 13.14.1) should be reported as a serious ADR according to the requirements in Section 10.1.1.

Additionally, for the Janssen product under study, the following medical concepts require expedited reporting to the sponsor to meet regulatory reporting requirements:

- Lack of Efficacy/Effect

All ADR for a Janssen product under study that fall under these medical concepts should be recorded in the CRF and reported to the local sponsor as soon as possible according to the process for serious adverse event reporting (Section 10.1.1), even though they would not necessarily be considered a serious adverse event.

10.1.2. Pregnancy

Any report of exposure to a product under study during pregnancy which is documented in the source data within the protocol-defined data collection period is to be recorded in the CRF as a special situation.

All reports of pregnancy with an abnormal outcome (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) documented in the source data following exposure to a Janssen product under study must be reported to the sponsor by the participating site personnel within 24 hours of their knowledge of the event using a Serious Adverse Event Form.

10.2. Product Quality Complaints

A PQC may have an impact on the safety and effectiveness of the product.

All initial PQCs involving a Janssen product must be reported to the local sponsor by the participating site personnel within 24 hours after being made aware of the event using the appropriate product quality complaint form.

If the defect for a Janssen product is combined with a serious ADR, the study-site personnel must report both the ADR and the PQC to the sponsor.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a clinical study report generated by the sponsor, which will contain data collected from all study sites that participated in the study. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Patient identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the participating physician) shall be the property of the sponsor as author and owner of copyright in such work.

Further details of publication policies and practices are provided in Annex 1.13.

12. REFERENCES

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13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1. Annex 1.1: List of Standalone Documents

Title	Reference No	Date
None	None	None

13.2. Annex 1.2: Information to be Provided to Participating Physicians

The participating physician will be provided with the following supplies:

- The protocol and amendment(s), if any, signed and dated by the participating physician.
- ICF.
- eCRF Guidelines.

13.3. Annex 1.3: Regulatory Documentation

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities. A study may not be initiated until any applicable local regulatory requirements are met.

Neither the participating physician nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor and will follow the review and approval process in accordance with local regulations.

Required Prestudy Documentation

The following documents must be provided to the sponsor before starting the study:

- Protocol and amendment(s), if any, signed and dated by the participating physician
- Where appropriate, as required by local regulations, a copy of the dated and signed written IEC/IRB approval of the protocol, amendments, ICF, and any recruiting materials.
- Documentation of the qualifications (e.g. curriculum vitae) of the participating physician, where appropriate.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first patient:

- Signed and dated clinical trial agreement, which includes the financial agreement.

13.4. Annex 1.4: Ethics Compliance

Independent Ethics Committee or Institutional Review Board

Before the start of data collection, the participating physician (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, protocol amendments
- Sponsor-approved ICF (and any other written materials to be provided to the patients).
- Participating physician's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB).
- Information regarding name of the sponsor, institutional affiliations, other potential conflicts of interest.
- Any other documents that the IEC/IRB requests to fulfill its obligation.

Where appropriate, as required by local regulations, this study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding those that are purely administrative, with no consequences for data collection) and the ICF, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the participating physician (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding those that are purely administrative, with no consequences for data collection).
- Revision(s) to the ICF and any other written materials to be provided to patients.
- If applicable, new or revised patient recruiting materials approved by the sponsor.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB.
- Reports of ADRs that are serious, unlisted/unexpected, and temporally associated with the product under study.
- New information that may adversely affect the safety of the patients or the conduct of the study.
- Report of deaths of patients under the participating physician's care.
- Notification if a new physician is responsible at the participating site.
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding those that are purely administrative, with no consequences for data collection), the amendment and applicable revisions to the ICF must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At the end of the study, where required by local regulations, the participating physician (or sponsor where required) will notify the IEC/IRB about the study completion.

13.5. Annex 1.5: Patient Consent

A waiver for the ICF (dependent on approval by IECs, IRBs) may be applicable for deceased patients at the time of data collection.

The ICF that is used must be reviewed and approved in accordance with local regulations, applicable regulatory requirements and sponsor policy, and must be in a language that the patient can read and understand. The ICF must be signed before collection of any patient data.

Before enrollment in the study, the participating physician or an authorized member of the participating site personnel must explain to potential participants or their legally acceptable representatives, their involvement in the study and data protection (see Section 9). Patients will be informed that their participation is entirely voluntary and that they may withdraw consent for data collection at any time. They will also be informed that choosing not to participate in this study will not affect the standard of care the patient will receive. Finally, they will be told that the participating physician will maintain a patient identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) or regulations. In this sense, data will be collected and processed with adequate precautions and in a codified/pseudoanonimyzed form to ensure confidentiality. By signing the ICF, the patient or legally acceptable representative is authorizing such access.

The patient or legally acceptable representative will be given sufficient time to read the ICF and will be given the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the patient's or his/her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be provided to the patient.

If the patient is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the patient is obtained.

13.6. Annex 1.6: Patient Identification and Enrollment

The participating physician agrees to complete a patient identification and enrollment log to permit easy identification of each patient during and after the study. This document will be reviewed by the sponsor and participating site contact for completeness. The patient identification and enrollment log will be treated as confidential and will be filed by the participating physician in the study file. To ensure patient confidentiality, no copy will be made. All reports and communications relating to the study will identify patients by patient identification and age at initial informed consent. In cases where the patient is not enrolled for data collection in the study, the date seen and age at initial informed consent will be used.

13.7. Annex 1.7: Patient Data Protection

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study, which must be collected and processed with adequate precautions and in a codified/pseudoanonimyzed form to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of patients confidential.

The ICF obtained from the patient (or his/her legally acceptable representative) includes explicit consent for the processing of personal data and for the participating physician and/or site to allow direct access to his/her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection as appropriate. This consent also addresses the transfer of the data to other entities and other countries. For deceased patients at the time of data collection, an ICF waiver may apply, dependent on approval by IECs, IRBs, and/or local regulations.

The promoter and researcher of the study must guarantee the confidentiality of the participants' data and ensure that it always complies with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.

To this end, each participant recruited for the study is assigned a unique participant identification number. This means that participants' names are not included in the study data sets that are transmitted to the sponsor, and that, in any study documents or materials, participants will not be identified by name, but by an identification number. Any subject related data in this trial are handled confidentially and will be captured in pseudonymized form (subject ID number for the trial – Subject Code-, year of birth) and will only be transmitted to the sponsor and sponsors delegated for scientific and adverse event evaluation.

The patient has the right to request through the participating physician access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

13.8. Annex 1.8: Case Report Form Completion

CRFs are provided for each patient in electronic format.

All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Designated site personnel must complete the CRF as soon as possible after a patient visit.

eDC will be used for this study. The study data will be transcribed from the source documents onto an electronic CRF by personnel at each participating site and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the site. The electronic file will be considered to be the CRF.

The participating physician must verify that all data entries in the CRFs are accurate and correct. All CRF entries, corrections, and alterations must be made by the participating physician or other authorized participating site personnel. If necessary, queries will be generated in the eDC tool. The participating physician or participating site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Personnel at each participating site can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- The manager of the participating site can generate a query for resolution by the personnel at that site.
- Clinical data manager can generate a query for resolution by the participating site personnel.

13.9. Annex 1.9: Monitoring

The sponsor will perform remote monitoring visits as frequently as necessary, as well as at least one on-site monitoring visit. The monitor will record dates of the visits in a site visit log that will be kept at the participating site.

The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and participating site personnel and are accessible for verification by the sponsor/participating-site contact. If electronic records are maintained at the participating site, the method of verification must be discussed with the site personnel.

Direct access to source documentation must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the participating site personnel. The sponsor expects that, during monitoring visits, the relevant participating site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the participating physician on a regular basis during the study to provide feedback on the study conduct.

13.10. Annex 1.10: On-Site Audits

Any audits conducted by the sponsor at a participating site will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected. The participating physician and participating site personnel are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

13.11. Annex 1.11: Record Retention

If the responsible participating physician retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the participating physician relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the participating physician and/or site must permit access to such reports.

13.12. Annex 1.12: Study Completion/Termination

The final data from the participating site will be sent to the sponsor (or designee) after completion of the final data collection time point at that site.

The sponsor reserves the right to close a participating site for data collection or to terminate the study at any time for any reason at the sole discretion of the sponsor.

A participating site is considered closed when all required documents and study specific supplies have been collected and a site closure assessment has been performed.

The participating physician may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a participating site by the sponsor or participating physician may include but are not limited to:

- Failure of the participating physician to comply with the protocol, requirements of the local health authorities, or the sponsor's procedures
- Inadequate recruitment of patients by the participating physician

The participating physician should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

13.13. Annex 1.13: Use of Information and Publication

All information, including but not limited to information regarding Teclistamab or the sponsor's operations (e.g., patent applications, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the participating physician and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The participating physician agrees to maintain this information in confidence, to use this information only to accomplish this study, and not to use it for other purposes without the sponsor's prior written consent.

The participating physician understands that the information obtained in the study will be used by the sponsor in connection with the continued development of Teclistamab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information obtained to be used, the participating physician is obligated to provide the sponsor with all data obtained in the study.

Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the participating physician as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish the primary (multicenter) data and information without approval from the participating physician. The participating physician has the right to publish data specific to the associated participating site after the primary data are published. If a participating physician wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the participating physician will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the participating physician. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary measures of interest of a study have been published. Similarly, participating physicians will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and

interpretation of the data, provided critical review of the paper, and given final approval of the final version.

13.14. Annex 1.14: Definitions and Classifications of Safety Events, Product Complaints, Criteria and Special Situations

13.14.1. Adverse Event Definitions

Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a medicinal product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including an abnormal finding or lack of expected pharmacological action), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to that medicinal product. (Definition based on International Conference on Harmonization [ICH]).

This includes any occurrence that is new in onset or aggravated in severity from the baseline condition, or abnormal results of any diagnostic procedures that are conducted per clinical practice.

Adverse Drug Reaction

An ADR is defined as a response to a medicinal product that is noxious and unintended. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. The phrase "a reasonable possibility" means that there are facts, evidence, or arguments to support a causal association with the medicinal product.

An ADR, in contrast to an adverse event, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All adverse events judged by either the reporting physician or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

Serious Adverse Drug Reaction

A serious adverse drug reaction, based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use, is any adverse drug reaction that at any dose:

- Results in death
- Is life-threatening
  (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

** Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.*

Unexpected Adverse Events

An adverse event is considered unexpected if the nature or severity is not consistent with the applicable product reference safety information. The expectedness of an adverse event will be determined by whether or not it is listed in the applicable reference safety information Product Quality Complaint Definition.

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e. any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

13.14.2. Attribution Definitions

Related

There is a reasonable causal relationship between administration of the the product under study and the adverse event.

Not Related

There is not a reasonable causal relationship between administration of the product under study and the adverse event.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

13.14.3. Severity Criteria

Where applicable, an assessment of severity grade will be made using the following general categorical descriptors:

Mild

Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate

Sufficient discomfort is present to cause interference with normal activity.

Severe

Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The participating physician should use clinical judgment in assessing the severity of events not directly experienced by the patient (e.g. laboratory abnormalities).

13.14.4. Special Situations

Safety events of interest that require reporting and/or safety evaluation by Janssen include, but are not limited to:

- Drug exposure during pregnancy (see Section 10.1.2)
- Exposure to a product from breastfeeding
- Overdose of a product
- Suspected abuse/misuse of a product
- Inadvertent or accidental exposure to a product (e.g. occupational exposure)
- Any failure of expected pharmacological action (i.e. lack of effect) of a product
- Unexpected therapeutic or clinical benefit from use of a product
- Medication error, intercepted medication error, or potential medication error involving a Janssen product (with or without patient exposure to the Janssen product, e.g. product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Suspected transmission of any infectious agent via administration of a product (meets definition of a serious adverse event; see Section 13.14.1)
- Off-label use of a product (only where spontaneously reported by a participating physician)

These safety events may not meet the definition of an adverse event; however, from a policy perspective, they are treated in the same manner as adverse events.

14. ADDITIONAL INFORMATION

NONE.

SPONSOR'S RESPONSIBLE PARTY SIGNATURE AND PARTICIPATING PHYSICIAN AGREEMENT

Sponsor's Responsible Party (Main Author):

Name (typed or printed): PPD

Institution: Janssen-Cilag-Farmacêutica, Lda.

Signature: PPD

Signature: **Email:** PPD

Participating Physician Agreement:

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Coordinating Physician:

Name (typed or printed): Rui Bergantim

Institution and Address: PPD

PPD

PPD

Signature: PPD

Signature: - **Email:** PPD

(Day Month Year)

Principal Participating Physician:

Name (typed or printed):

Institution and Address:

Telephone Number:

Signature: Date:

(Day Month Year)

Note: If the address or telephone number of the participating physician changes during the study, written notification will be provided to the sponsor; a protocol amendment will not be required.

64007957MMY4011_SPOT_Protocol_V1.0_30Jul2024

Final Audit Report 2024-07-31

Created:	2024-07-31
By:	PPD
Status:	Signed
Transaction ID:	CBJCHBCAABAABFSrwijbfdAHLTz_Y8GlAzjcopLft681

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Agreement completed.

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Signature

User	Date	Reason
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Signature

User	Date	Reason
PPD	06-Jan-2025 13:26:17 (GMT)	Document Approval