Application for the assessment of ELREXFIO® (elranatamab) indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information

Contact information

Contact information	
Name	**Daniel Sloth Hauberg / Pfizer**
Title	Senior Market Access Manager
Phone number	0045 26709423
E-mail	Daniesloth.hauberg@pfizer.com

Table of contents

Tables and Figures

List of Tables:

List of Figures:

Abbreviations

AE	Adverse event
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematologic
BCMA	B-cell maturation antigen
BIC	Bayesian information criterion
CI	Confidence interval
CD38	Cluster of differentiation 38
CR	Complete response
CRAB	Calcium elevation, renal failure, anemia and lytic bone lesions
CRD	Centre for Review and Dissemination
CRS	Cytokine release syndrome
CT	Computed tomography
DLT	Dose limiting toxicities
DMC	Danish Medicines Council
DMSG	Danish Myeloma Study Group
DoCR	Duration of complete response
DoR	Duration of response
DRG	Diagnosis-related group
DSA	Deterministic sensitivity analysis
ECOG PS	Eastern Cooperative Oncology Group performance status
EHA	European Hematologic Association
EMA	European Medicines Agency
EORTC QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 item
EQ-5D	EuroQol 5 Dimension
ESMO	European Society for Medical Oncology
ESS	Effective sample size
FISH	Fluorescence in situ hybridization
FLC	Free light chains
HBV	Hepatitis B virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICER	Incremental cost-effectiveness ratio
IMiD	Immune-mediated inflammatory disease
IMWG	International Myeloma Working Group
ISS	International Staging System
ITC	Indirect treatment comparison
KM	Kaplan Meier
LoT	Lines of treatment
mAbs	Monoclonal antibodies
MAH	Market Authorization Holder

MAIC	Matching-adjusted indirect comparison
MeSH	Medical subject headings
MM	Multiple myeloma
MOA	Mode of action
MR	Minimal response
MRD	Minimal residual disease
M-protein	Monoclonal protein
NDMM	Newly diagnosed multiple myeloma
NE	Not estimable
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PGIC	Patient Global Impression of Change
PH	Proportional hazard
PI	Proteasome inhibitor
PICO	Population, Intervention, Comparison and Outcomes
PPP	Pharmacy purchasing price
PPS	Post Progression Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	Patient Reported Outcomes
QALY	Quality adjusted life year
QLQ-MY20	Multiple Myeloma module quality of life (QoL) questionnaire
Q2W	Once every 2 weeks
RCT	Randomised controlled trial
RDI	Relative dose intensity
RRMM	Relapsed/refractory multiple myeloma
SC	Subcutaneous
SmPC	Summary of product characteristics
TCE	Triple-class exposed
TCR	Triple-class refractory
TNF	Tumor necrosis factor
TTD	Time to treatment discontinuation

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Elrexfio®
Generic name	Elranatamab
Therapeutic indication as defined by EMA	Elranatamab is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM), who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.
Marketing authorization holder in Denmark	Pfizer
ATC code	L01FX32
Combination therapy and/or co-medication	Recommended pre-treatment medicinal products. The following pre-treatment medicinal products should be administered approximately 1 hour prior to the first three doses of elranatamab, which includes step-up dose 1, step-up dose 2, and the first full treatment dose: • paracetamol 500 mg orally (or equivalent) • dexamethasone 20 mg orally or intravenously (or equivalent) • diphenhydramine 25 mg orally (or equivalent) • Prophylactic antimicrobials and anti-virals should be considered according to local institutional guidelines
(Expected) Date of EC approval	December 8 2023

Overview of the medicine	
Has the medicine received a conditional marketing authorization?	Yes. March 2025. In order to further characterise the duration of response and long-term safety in subjects with multiple myeloma (MM) who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, the market authorization holder (MAH) shall submit the final study report of C1071003, a Phase 2, open-label, multicentre, non-randomised study of elranatamab monotherapy in participants with MM who are refractory to at least one PI, one IMiD, and one anti-CD38 Ab. June 2027. In order to confirm the efficacy and safety of elranatamab indicated as monotherapy for the treatment of adult patients with RRMM, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy, the MAH shall submit the results of study C1071005 a phase 3 randomised study of elranatamab monotherapy and elranatamab + daratumumab versus daratumumab + pomalidomide + dexamethasone in participants with RRMM, who have received at least one prior line of therapy, including lenalidomide and a PI.
Accelerated assessment in the European Medicines Agency (EMA)	N/A
Orphan drug designation (include date)	N/A
Other therapeutic indications approved by EMA	N/A
Other indications that have been evaluated by the DMC (yes/no)	N/A
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Elranatamab 40 mg/mL solution for injection: 2 different volumes available: • One single vial containing 44 mg of elranatamab in 1.1 ml (40 mg/ml) • One single vial containing 76 mg of elranatamab in 1.9 ml (40 mg/ml)

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Elranatamab is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM), who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.
Dosage regiment and administration	Elranatamab 40 mg/mL solution for injection: 2 different volumes available: • Vial containing 44 mg of elranatamab in 1.1 ml (40 mg/ml) • Vial containing 76 mg of elranatamab in 1.9 ml (40 mg/ml)
Choice of comparator	Teclistamab
Prognosis with current treatment (comparator)	Multiple myeloma (MM) is considered an incurable disease, with most patients experiencing multiple relapses that require further treatment (i.e. relapsed or refractory MM (RRMM)) even in those who respond to treatment initially. Efficacy of treatment regimens decreases with relapses leading to reduced duration of response and increased therapy resistance. Patients with MM report impaired health-related quality of life (HRQoL). Moreover, current MM therapies are associated with a number of toxicities that may negatively impact HRQoL.
Type of evidence for the clinical evaluation	Elranatamab: • MagnetisMM-3. Ongoing, multicenter, open-label, single-arm, phase 2 study Teclistamab: • MajesTEC-1. Ongoing, first-in-human, multicenter, open-label, single-arm, phase 1/2 study. Indirect comparative analysis (MAIC) of elranatamab and teclistamab

Summary	
Most important efficacy endpoints (Difference/gain compared to comparator)	**OS** Elranatamab: At 14.7 months OS was not reached, and the Kaplan–Meier estimate at 14.7 months was 56.7% (95% CI: 47.4–65.1). Latest follow-up (data cut-off date September 11 2023; median duration 17.6 months) showed a median OS of 21.9 months. OS not mature yet – study still ongoing. Results from an extended follow up was recently presented at EHA June 2024. Updated results in BCMA-naive patients > 2 years after the last patient was initially dosed in Magnetism MM-3 showed a median OS of 24.6 months (95%CI, 13.4 -not evaluable (NE) months (81). Teclistamab: With a median follow-up of 22 months median OS was 21.91 months (95% CI, 16.0–NE). Indirect comparison: Naïve analysis: OS is equal. MAIC analysis - elranatamab was associated with a numerically longer OS compared with teclistamab (not statistically significant). **PFS** Elranatamab: At the 14.7 months follow-up, 33.3% of patients still received elranatamab and median PFS was not reached. Kaplan–Meier estimate of PFS at 14.7 months was 50.9% (95% CI: 40.9–60.0). Last follow-up (data cut-off date September 11 2023; median duration 17.6 months) showed sustained clinical efficacy with a median PFS of 17.2 months. Teclistamab: Median follow-up of 23 months median PFS was 11.3 months (95% CI, 8.8–16.4). Indirect comparison: Naïve analysis: N/A. MAIC: Elranatamab associated with significantly longer PFS than teclistamab.
Most important serious adverse events for the intervention and comparator	Most important serious adverse events reported for elranatamab in ≥5% of patients (Cohort A) were COVID-19 pneumonia: 17 (13.8%), cytokine release syndrome: 16 (13%), pneumonia: 12 (9.8%). Most common serious adverse events for teclistamab in ≥5% of patients (Cohort A) were COVID 19: 24 (14.5%), pneumonia: 17 (10.3%) and sepsis: 3 (1.5%).
Impact on health-related quality of life	Clinical documentation: Overall, treatment with elranatamab demonstrated improvements in QoL in heavily pre-treated patients with RRMM. Health economic model: N/A (cost-minimization analysis)
Type of economic analysis that is submitted	Cost-minimization model adopting a partitioned survival approach
Data sources used to model the clinical effects	• Elranatamab: MagnetisMM-3 (46,49-52). • Teclistamab: MajesTEC-1 (48,53). • MAIC analysis of elranatamab and teclistamab (64)

Summary	
Data sources used to model the health-related quality of life	N/A (cost-minimisation analysis)
Life years gained	N/A (cost-minimisation analysis)
QALYs gained	N/A (cost-minimisation analysis)
Incremental costs	Base case 1: -346,935 DKK per patient in savings with elranatamab (vs. teclistamab) Base case 2: -775,894 DKK per patient in savings with elranatamab (vs. teclistamab)
ICER (DKK/QALY)	N/A (cost-minimisation analysis)
Uncertainty associated with the ICER estimate	ICER: N/A Incremental costs: TTD, RDI, mean weight and vial sharing
Number of eligible patients in Denmark	Incidence: 60% out of 90 patients (i.e., 54 RRMM patients) Prevalence: 3,500 patients
Budget impact (in year 5)	-17,271,984 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Pathophysiology of Multiple Myeloma

Multiple myeloma (MM) is a plasma cell malignancy characterized by the proliferation of a single clone of plasma cells derived from B cells in the bone marrow, which leads to hypercalcemia, renal impairment, anemia, bone fractures, and susceptibility to infections (1). It is a biologically heterogenous malignancy that appears to arise from the accumulation of chromosomal abnormalities in plasma cells, a type of white blood cell, responsible for the production of antibodies (1). These malignant plasma cells (myeloma cells) migrate and collect in the bone marrow of multiple bones, leaving less space for healthy cells and interfering with the production of other normal blood cells such as red blood cells and platelets. Malignant plasma cells can also be extramedullary or found in the peripheral blood and/or soft tissues and organs, which leads to damage in other anatomic locations (2).

A characteristic feature of myeloma cells is the overexpression and secretion of a high level of a harmful abnormal antibody called monoclonal immunoglobulin or monoclonal protein (M-protein) (2,3). M-proteins accumulate, interfering with organ function and causing damage (2). Roughly 15% to 20% of patients with MM have myeloma cells that produce only part of the immunoglobulin, the free light chains (FLCs), whereas <3% secrete no M-protein. In addition, B-cell maturation antigen (BCMA) expression is a hallmark of myeloma cells. BCMA is a member of the tumor necrosis factor (TNF) receptor family, which enhances both survival and proliferation (4,5).

Clinical symptoms and diagnosis of multiple myeloma

The M-proteins, FLCs, and malignant cells as well as the inflammatory cytokines secrete are responsible for several deleterious effects that lead to organ damage and the symptoms experienced by patients with MM (2). The most common symptoms of MM are related to the underlying pathology of the CRAB features, i.e. calcium elevation, renal failure, anemia, and lytic bone lesions (2). Most patients present with pain, especially bone pain, and fatigue; dyspnea and neurologic symptoms are also common). MM has a heterogeneous progression pathway, with periods of disease control after initial therapy followed by progression, typically with subsequently shorter periods of response and relapse with each successive therapy (6).

MM is diagnosed based on the detection of serum M-protein levels, clonal plasma cell infiltration in bone marrow and assessment of biomarkers and CRAB features. These

criteria have been established by the International Myeloma Working Group (IMWG), and involve assessments of blood tests, urine tests, bone marrow examination, CT scan of the skeleton as well as the assessment of the cytogenetic profile (7). In Denmark, MM is diagnosed based on the nationwide clinical guidelines, developed by the Danish Myeloma Study Group (DMSG) (8,9), which are aligned with the IMWG guidelines.

Prevalence and prognosis in Denmark

MM is the second most common hematologic malignancy in Denmark with a total of approximately 3,500 people living with this disease (10) of which approximately 2,058 require treatment (11). Each year approximately 380 new patients are diagnosed with MM, who require treatment, with a median age around 70 years (12).

The risk of MM increases with age and occurs slightly more frequently in men than in women (13). The prevalence of MM is increasing due to the increasing average life expectancy of the Danish population as well as improved prognosis (13). The latter is due to the introduction of high-dose chemotherapy with stem cell transplant in the early 1990s and the many new treatments that have been introduced since then (13). With the introduction of proteasome inhibitors (PI), immunomodulatory drugs (IMiDs) and particularly monoclonal antibodies (mAbs) the 5-year survival rate has increased more than 10% points over the last 5 years for both younger (i.e. ≤ 70 years of age) and older patients (i.e. >70 years of age) in Denmark (11).

According to the 2021 annual report from the Danish Myeloma Study Group (DMSG) the 3-year survival for Danish patients with MM is 82% for younger patients (<70 years), 58% for older patients (>70 years) and 69% for the entire patient group (11). The 5-year survival for the same patient groups is 69%, 40% and 53% (12).

Despite the advances and availability of multiple therapeutic options, MM is considered an incurable disease, with most patients experiencing multiple relapses that require further treatment (i.e. relapsed or refractory MM, RRMM) even in those who respond to treatment initially (2,14). The efficacy of treatment regimens decreases with each relapse, leading to reduced duration of response (DoR) and increased resistance to available therapies (2). The increasing complexity of tumor genetics, the accumulation of mutations, and the tumor microenvironment all contribute to reduced efficacy of treatments and refractoriness over time and over increasing line(s) of treatment (LoT) (2).

Apart from refractoriness to previous treatment regimens, age and/or frailty, there are also other disease- and patient-related factors that may impact prognosis negatively, such as high-risk cytogenetic features, high tumor burden (i.e., high International Staging System, ISS stage), renal impairment, and extramedullary plasmacytomas (15-17).

Health-Related Quality of Life

Patients with MM experience variable morbidity caused by bone destruction/ fractures, renal dysfunction, bone marrow failure, high infection rates and potential physical disability. The most prevalent symptoms across the disease pattern from diagnosis to advanced MM disease stage are fatigue, pain, insomnia, and peripheral neuropathy

resulting in decreased physical, cognitive and role functioning (18). In addition, a substantial proportion of MM patients report depression, anxiety, and impairment of psychosocial well-being (19). As a result, patients with MM report impaired health-related quality of life (HRQoL). Moreover, current therapies for MM are associated with a number of toxicities that may also negatively impact patients' quality of life (21).

3.2 Patient population

The relevant Danish patient population for this application is adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 antibody and have demonstrated disease progression on the last therapy; in line with the approved EMA indication for elranatamab (Elrexfio®) (21). Relapsed and refractory MM (RRMM) is defined as disease that is nonresponsive on salvage therapy or progresses within 60 days of the last therapy in patients who achieved at least a minimal response (MR) to treatment prior to disease progression (21). With each successive relapse, symptoms return, quality of life worsens, and the chance and duration of response typically decreases. Therefore, there remains a significant and critical unmet need for new therapeutic options with alternative mechanisms of action that can better control the disease; provide deeper, more sustained responses; and yield better long-term outcomes including maintenance of HRQoL.

Patients with RRMM may receive different MM treatment combinations/ regimens with each relapse. RRMM can therefore be divided into distinct subsets, defined by the patient's previous exposure and response to the different types of treatment.
Triple-class exposed (TCE) patients refer to patients who have been treated with a proteasome inhibitor (PI such as bortezomib, carfilzomib and ixazomib), an immuno-modulatory drug (IMiD such as thalidomide, lenalidomide and pomalidomide) and anti-CD38 monoclonal antibody (such as daratumumab and isatuximab). They have typically received one drug from each treatment class in various combinations (22,23). While they may have relapsed, they are not necessarily refractory to these treatments. Triple class refractory (TCR) patients, on the other hand, have been treated with and are refractory to these three main drug classes (PI, IMiD and anti-CD38-mAb) (24,25). Patients are defined as pentarefractory if they are refractory to two IMiDs, two PIs and one anti-CD38 monoclonal antibody (23,26-28).

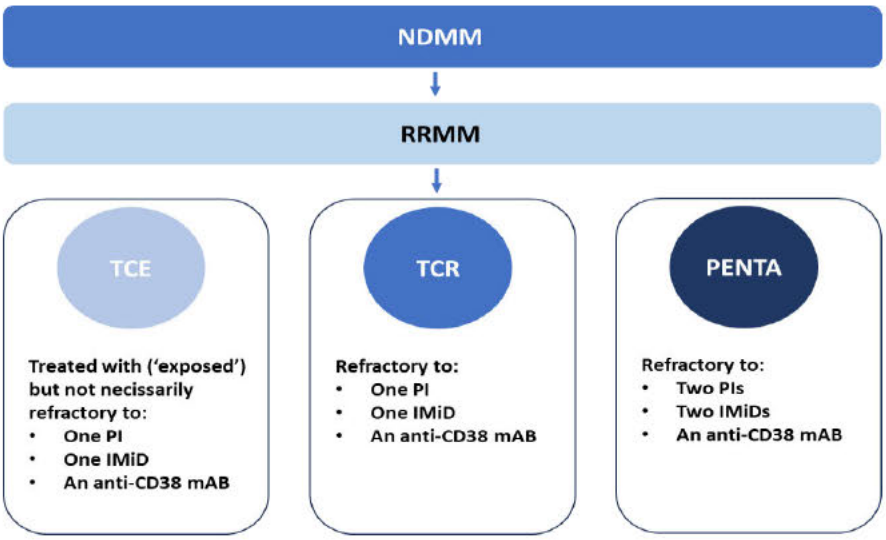


Figure 1 Types of refractory and relapsed MM.
Abbreviations: CD38, cluster of differentiation 38; IMiD, immunomodulatory drug; mAb, monoclonal antibody; NDMM, newly diagnosed multiple myeloma; Penta, penta-refractory; PI, proteasome inhibitor; RRMM, relapsed or refractory multiple myeloma; TCE, triple-class exposed; TCR, triple-class refractor. Source: Adapted from (22,29,30).

The Danish myeloma database does not contain information on the prevalence and incidence of TCE or TCR MM patients. However, the DMC, has estimated the number of patients that reach fourth line treatment and thus are TCE/TCR estimated to be 90 patients per year, and of these approximately 60% (54 patients) would be eligible for treatment with teclistamab (31). As teclistamab has the exact same indication as elranatamab, the eligible patient population for elranatamab is also estimated to 54 patients per year.

Table 1 Incidence and prevalence of MM in Denmark in 2017 -2021.

Year	2017	2018	2019	2020	2021
Incidence in Denmark	537	552	607	564	632
Prevalence in Denmark	2,665	2,852	3,106	3,332	3,577

Source: (10).

Table 2 Estimated number of patients eligible for treatment.

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	54	54	54	54	54

3.3 Current treatment options

The goals of therapy include inducing deep and lasting remissions to prolong both PFS and OS, in addition to relieving disease-related symptoms and preserving HRQoL (32,33). The exact approach depends on a patient's risk classification, health status, age, and prior treatment history.

In Denmark treatment of MM is based on the nationwide clinical guidelines, developed by the Danish Medicines Council and the DMSG (8,9) and consists of a combination of chemotherapy and immunotherapy that is given in different treatment regimens, and as a general rule continuously until disease progression. The disease at some point becomes refractory to the given treatment, and then the patient needs a different type of treatment regimen with a different mode of action (MoA). The various treatment lines/regimens in Danish clinical practice are outlined in the treatment algorithm in Figure 2.

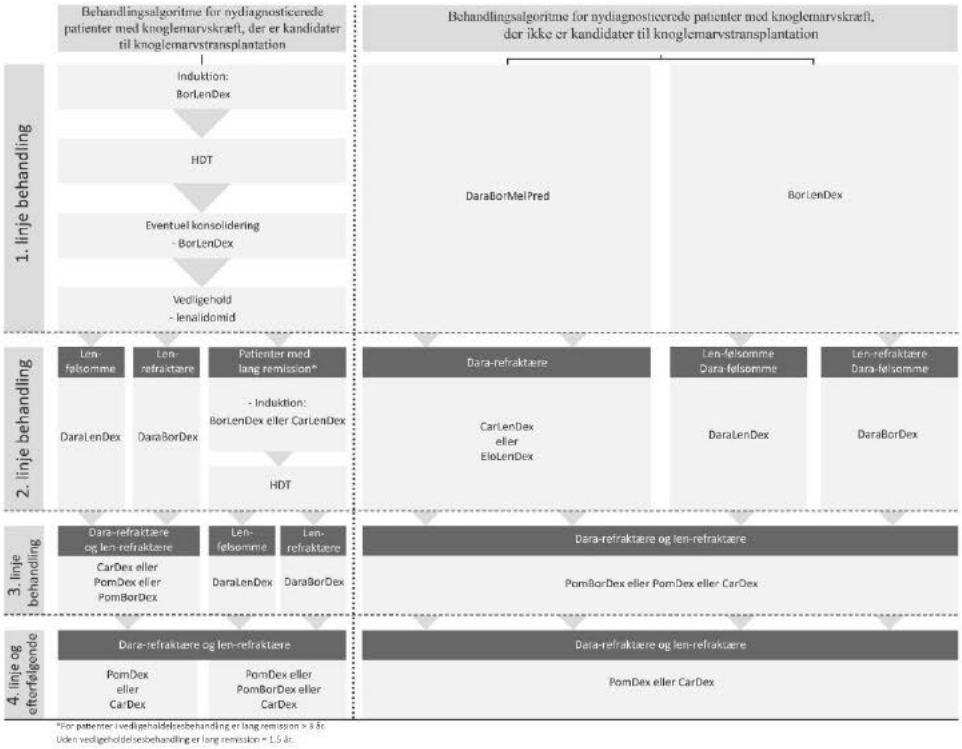


Figure 2 Treatment algorithm for patients with multiple myeloma (MM).

As can be seen from Figure 2, treatment of RRMM is heterogenous and the regimen selected should consider a patient's previous treatments, including response and tolerability, as well as their frailty/performance status, preferences, co-morbidities and patient preferences, including the number of treatment visits.

Carfilzomib- and pomalidomide-containing regimens are the recommended treatment in the 4th and subsequent lines (i.e. can be used for 3rd relapse to patients who have received at least three previous treatments). Carfilzomib and dexamethasone (CarDex), pomalidomide and dexamethasone (PomDex), or pomalidomide, bortezomib and dexamethasone (PomBorDex) are the recommended treatment regimens, while pomalidomid + cyklofosfamid + dexamethason (PomCyDex) can be considered (8).

On February 21 2024, the DMC recommended teclistamab as a treatment option for adult patients with RRMM in 4th or later lines of therapy, as compared to pomalidomide - or carfilzomib-containing treatment regimens the DMC assessed that treatment with teclistamab postpones the time to disease progression and increases patients' survival (31). The recommendation applies to patients who are in good general condition (performance status 0-1) and who have received at least three previous treatments, including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody, and who have had disease progression during the last recent treatment.

Real world studies show that the median OS of TCR patients is approximately 1 year (34,35), and a Danish real-world study, showed that TCE patients who started a pomalidomide-based regimen had a median OS of approximately 1 year (36). At a median follow-up of 14.1 months RRMM patients treated with teclistamab in the MajecTEC-1 trial had a median duration of OS of 18.3 months (95% CI, 15.1 to not estimable) (37).

For patients who experience disease progression during 4th line treatment or who can no longer tolerate the treatment, the treatment options are limited. These patients are generally penta-refractory and retrospective real-world studies show that the median remaining life expectancy is approx. 6 months (27,38). In a recently published RWD study with 123 German patients treated with teclistamab, of which 60% were penta-refractory, the median OS was not reached after a median of 5.5 months of follow-up (39).

3.4 The intervention

Elranatamab is a humanized, off-the-shelf, bispecific antibody that targets BCMA on myeloma cells and CD3 on T-cells (Figure 3) (21). It is comprised of humanized anti-BCMA and anti-CD3ε targeting arms paired on an IgG2a backbone with nullified Fc binding function, which leads to a longer half-life.

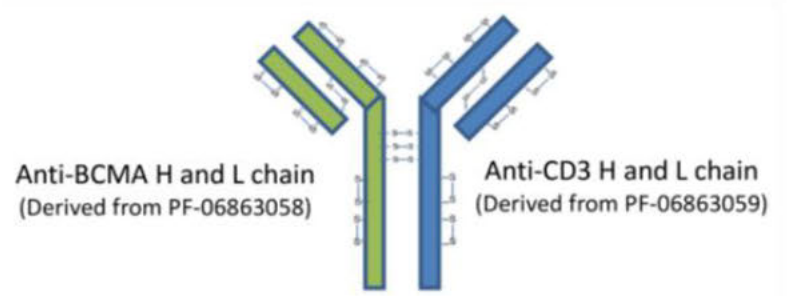


Figure 3 Molecular structure of elranatamab.
Abbreviations: BCMA, B-cell maturation antigen

Elranatamab binds to the BCMA expressed on the surface of myeloma cells (present on 80% to 100% of myeloma cells) and to the CD3 receptor on T-cells, effectively creating a bridge between them (see Figure 4 (40-42).

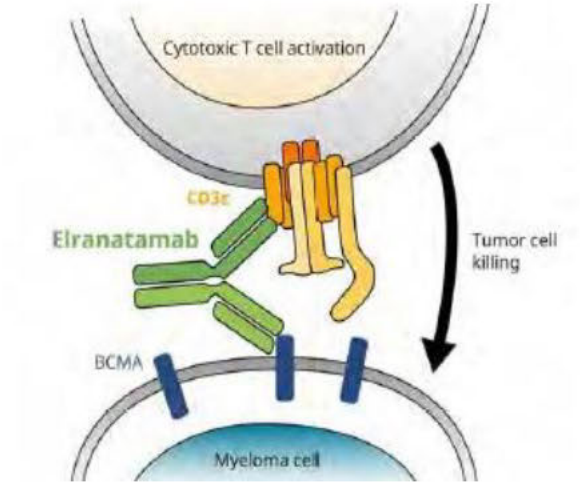


Figure 4 Mechanism of action of elranatamab.
Abbreviations: BCMA, B-cell maturation antigen

Activated T-cells release perforin and granzyme B leading to cytolysis of myeloma cells (40,43-45). Elranatamab-mediated activation of T-cells also leads to cytokine release, enhancing the immune response and recruiting tumor-infiltrating lymphocytes to the myeloma cells (46).

Elranatamab received a conditional marketing authorisation from EMA in December 2023, and pursuant to Article 14-a of Regulation (EC) No 726/2004, the Danish Medicines Agency shall complete within stated timeframes (refer to section 1 for further details).

Overview of intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Elranatamab (Elrexfio®) is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy
Method of administration	Subcutaneous injection. The required dose should be injected into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, it may be injected into the subcutaneous tissue of the thigh.
Dosing	Elranatamab has fixed dosing. The recommended doses are step-up doses of 12 mg on day 1 and 32 mg on day 4, followed by a full treatment dose of 76 mg weekly from week 2 to week 24. For patients who have received at least 24 weeks of treatment and have achieved a response, the dosing interval should transition to an every two-week schedule. Due to the risk of CRS and ICANS, patients should be monitored for signs and symptoms for 48 hours after administration of each of the 2 step-up doses and instructed to remain within proximity of a healthcare facility.

Dosing schedule	Week/day	Dos
Step-up dosing[a,b]	Week 1: day 1	Step-up dose 1
	Week 1: day 4	Step-up dose 2
Weekly dosing[a,c,d]	Week 2-24: day 1	Full treatment dose
Every 2 weeks dosing[d,e]	Week 25 onward: day 1	Full treatment dose

a. Pre-treatment medicinal products should be administered prior to the first three doses of ELREX
b. A minimum of 2 days should be maintained between step-up dose 1 (12 mg) and step-up dose 2
c. A minimum of 3 days should be maintained between step-up dose 2 (32 mg) and the first full tre
d. A minimum of 6 days should be maintained between doses.
e. For patients who have achieved a response.

Dosing in the health economic model (including relative dose intensity)	The dosing of elranatamab in the cost-minimization analysis follows the SmPC (21) as well as the MagnetisMM-3 study (for dose intensity) (47).
Should the medicine be administered with other medicines?	The following pre-treatment medicinal products should be administered approximately 1 hour prior to the first three doses of elranatamab, which includes step-up dose 1, step-up dose 2, and the first full treatment dose to reduce the risk of CRS: • Paracetamol 500 mg orally (or equivalent) • Dexamethasone 20 mg orally or intravenously (or equivalent) • Diphenhydramine 25 mg orally (or equivalent) • Prophylactic antimicrobials and antivirals should be considered according to local institutional guidelines.

Overview of intervention	
Treatment duration / criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity
Necessary monitoring, both during administration and during the treatment period	Due to the risk of CRS and ICANS, patients should be monitored for signs and symptoms for 48 hours after administration of each of the 2 step-up doses and instructed to remain within proximity of a healthcare facility. During treatment patients should be monitored for CRS and ICANS and counselled to seek urgent medical attention should signs or symptoms of CRS or neurologic toxicity occur. Patients should be monitored for signs and symptoms of infection prior to and during treatment with elranatamab and treated appropriately. Complete blood cell counts should be monitored at baseline and periodically during treatment. Immunoglobulin levels should be monitored during treatment. Treatment with subcutaneous or intravenous immunoglobulin (IVIG) should be considered if IgG levels fall below 400 mg/dL and patients should be treated according to local institutional guidelines, including infection precautions and antimicrobial prophylaxis.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	Elranatamab 40 mg/mL solution for injection: 2 different volumes available: • Single vial containing 44 mg of elranatamab in 1.1 ml (40 mg/ml) • Single vial containing 76 mg of elranatamab in 1.9 ml (40 mg/ml)

3.4.1 The intervention in relation to Danish clinical practice

Elranatamab is approved for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy (21).

Most of the MM patients included in the MagnestisMM-3 trial, whose data contributed to the approved indication, were TCR and had ECOG status of ≤2. With the current Danish treatment guidelines this patient population would correspond to patients reaching 4th line therapy (12). Current treatment options for 4th line therapy are carfilzomib- and pomalidomide-containing regimens, and most recently on February 21 2024, the DMC recommended the BCMA-targeted bispecific antibody, teclistamab, as a treatment option for adult patients with RRMM in 4th or later lines of therapy (31).

3.5 Choice of comparator(s)

The recommended treatment regimens in 4th line, according to the current guidelines from the Danish Medicines Council are (8,9):

- PomDex; i.e. pomalidomide plus dexamethasone
- PomBorDex; i.e. pomalidomide plus bortezomib and dexamethasone
- CarDex; i.e. Carfilzomib plus dexamethasone

On February 21 2024, the BCMA-targeted bispecific antibody, teclistamab, has also been recommended by the DMC as a treatment option for adult patients with RRMM and a performance status 0-1, who have received at least three prior therapies, including an IMiD, PI and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy (31).

The most relevant comparator for elranatamab is therefore teclistamab, as elranatamab and teclistamab have an identical mechanism of action and EMA approved indication, while the MagnetisMM-3 and MajesTEC-1 studies also have a similar study design and included comparable patient populations.

Overview of comparator	
Generic name	Teclistamab (Tecvayli®)
ATC code	L01FX24
Mechanism of action	Teclistamab is a full-size, IgG4-PAA bispecific antibody that targets the CD3 receptor expressed on the surface of T cells and B cell maturation antigen (BCMA), which is expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. With its dual binding sites, teclistamab is able to draw CD3+ T cells in close proximity to BCMA+ cells, resulting in T cell activation and subsequent lysis and death of BCMA+ cells, which is mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T cells. This effect occurs without regard to T cell receptor specificity or reliance on major histocompatibility complex (MHC) Class 1 molecules on the surface of antigen presenting cells. The presence of pomalidomide in vitro, substrate proteins aiolos and Ikaros are targeted for ubiquitination and subsequent degradation leading to direct cytotoxic and immunomodulatory effects.
Method of administration	Subcutaneous injection.
Dosing	The recommended dosing schedule for teclistamab is provided in the table below from the SmPC. The recommended doses of teclistamab are 1.5 mg/kg by subcutaneous injection (SC) weekly, preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg. In patients who have a complete response or better for a minimum of 6 months, a reduced dosing frequency of 1.5 mg/kg SC every two weeks may be considered.

Overview of comparator

TECVAYLI dosing schedule

Dosing schedule	Day	Dose[a]	
All patients			
Step-up dosing schedule[b]	Day 1	Step-up dose 1	0.06 mg/kg SC single dose
	Day 3[c]	Step-up dose 2	0.3 mg/kg SC single dose
	Day 5[d]	First maintenance dose	1.5 mg/kg SC single dose
Weekly dosing schedule[b]	One week after first maintenance dose and weekly thereafter[e]	Subsequent maintenance doses	1.5 mg/kg SC once weekly
Patients who have a complete response or better for a minimum of 6 months			
Biweekly (every two weeks) dosing schedule[b]	Consider reducing the dosing frequency to 1.5 mg/kg SC every two weeks		

[a] Dose is based on actual body weight and should be administered subcutaneously.
[b] See Table 2 for recommendations on restarting TECVAYLI after dose delays.
[c] Step-up dose 2 may be given between two to seven days after Step-up dose 1.
[d] First maintenance dose may be given between two to seven days after Step-up dose 2. This is the first full maintenance dose (1.5 mg/kg).
[e] Maintain a minimum of five days between weekly maintenance doses.

Dosing in the health economic model (including relative dose intensity)	The dosing of teclistamab in the cost-minimization analysis follows the SmPC (48) as well as the MagnetisMM-3 study (for relative dose intensity) [redacted].
Should the medicine be administered with other medicines?	**Pre-treatment medicinal products** The following pre-treatment medicinal products must be administered 1 to 3 hours before each dose of the teclistamab step-up dosing schedule (see table above from the SmPC) to reduce the risk of cytokine release syndrome. • Corticosteroid (oral or intravenous dexamethasone 16 mg) • Antihistamine (oral or intravenous diphenhydramine 50 mg, or equivalent) • Antipyretics (oral or intravenous acetaminophen 650 to 1 000 mg, or equivalent. Administration of pre-treatment medicinal products may also be required prior to administration of subsequent doses of teclistamab for the following patients: • Patients who repeat doses within the teclistamab step-up dosing schedule due to dose delays, or • Patients who experienced CRS following the previous dose • Prevention of herpes zoster reactivation Prior to starting treatment with teclistamab, antiviral prophylaxis should be considered for the prevention of herpes zoster virus reactivation, per local institutional guidelines
Treatment duration/ criteria for end of treatment	Patients should be treated with teclistamab until disease progression or unacceptable toxicity.

Overview of comparator	
Need for diagnostics or other tests (i.e. companion diagnostics)	Patients with evidence of positive hepatitis B virus (HBV) serology should be monitored for clinical and laboratory signs of HBV reactivation while receiving teclistamab, and for at least six months following the end of teclistamab treatment. Immunoglobulin levels should be monitored during treatment with teclistamab. Patients should be treated according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement. Complete blood cell counts should be monitored at baseline and periodically during treatment. Supportive care should be provided per local institutional guidelines.
Package size(s)	Teclistamab 10 mg/mL solution for injection (only for priming dose) One 3 mL vial contains 30 mg of teclistamab (10 mg/mL). Teclistamab 90 mg/mL solution for injection One 1.7 mL vial contains 153 mg of teclistamab (90 mg/mL).

3.6 Cost-effectiveness of the comparator(s)

Teclistamab has been evaluated by the DMC and was February 21 2024 recommended for adult patients with relapsed and refractory multiple myeloma who have received at least three previous treatments, including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody, and who have had disease progression during the most recent treatment. The recommendation applies to patients who are in good general condition (performance status 0-1) (31).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In the evaluation of teclistamab, the DMC states that OS, PFS and HRQoL are sufficient for evaluation of efficacy (31). Although Janssen provided other efficacy parameters such as, ORR, VGPR, DOR, MRD negativity, these were not included in the DMC's efficacy evaluation of teclistamab (31). In this application for elranatamab, we therefore only focus on OS, PFS and HRQoL (Table 3).

Table 3 Efficacy outcome measures relevant for the application.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall Survival (OS)			
MagnetisMM-3 Latest data cut-off date (Source: 52)	Data cut-off: September 11 2023 (median duration of follow-up: 17.6 months)	[redacted]	[redacted]
MagnetisMM-3 (Sources: 47, 51)	Data cut-off: March 14 2023 (median duration of follow-up: 14.7 months)		OS was summarized using Kaplan-Meier method and displayed graphically. Median OS and 2-sided 95% CI was provided.
MajesTEC-1 (Sources: 37,53)	Clinical cut-off date: March 16 2022 (median duration of follow-up: 14.1 months) and January 4 2023 (median duration of follow-up: 23 months)	Time from date of first dose of study drug to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive	The efficacy population for this analysis included all patients who had received at least one dose of teclistamab at the recommended phase 2 dose in phase 1 or phase 2 as of September 7, 2021. Kaplan–Meier methods were used to estimate time-to-event end points (progression-free survival and overall survival).
Progression-Free Survival (PFS)			
MagnetisMM-3 Latest data cut-off date (Source: 52)	Data cut-off: September 11 2023 (median duration of follow-up: 17.6 months)	[redacted]	[redacted]

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
MagnetisMM-3 (Sources: 47[redacted] 51)	Data cut-off: March 14 2023 (median duration of follow-up: 14.7 months)		[redacted] PFS was summarized using Kaplan-Meier method and displayed graphically. Median PFS and 2-sided 95% CI will be provided. [redacted]
MajesTEC-1 (Sources: 37,53)	Clinical cut-off date: March 16 2022 (median duration of follow-up: 14.1 months) and January 4 2023 (median duration of follow-up: 23 months)	Time from the date of first dose of study drug to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause, whichever occurs first.	For subjects who had not progressed and are alive, data was censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. PFS was summarized using Kaplan-Meier method and displayed graphically.
Health-Related Quality of Life (HRQoL)			
MagnetisMM-3 (Source: 54)	Data cut-off: March 14 2023 (median follow up: 14.7 months)	*European Organisation for the Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-30)* The EORTC QLQ-	All Patient Reported Outcomes (PRO) measures were administered electronically on D1 and D15 of the first three cycles (C) and D1 of each subsequent cycle through C12. The PRO analysis dataset for each cohort included all patients in the safety analysis dataset who completed a baseline (last PRO assessment prior to

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		C30 is a validated cancer-specific questionnaire across five functional scales (physical, role, cognitive, emotional and social), one global health status scale, three symptom scales (pain, fatigue, and nausea or vomiting) and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). Better health is indicated by higher scores on the five functional scales and the global health status scale. Conversely, higher scores on the symptom scale indicate a greater degree of symptom severity (55,56). *EuroQoL-5D-5L (EQ-5D-5L)* The EQ-5D-5L health questionnaire is a measure of health status assessing five domains (mobility, self-care, usual activities, pain, and anxiety or depression) and includes a visual analogue scale	or on the first dose of study treatment) and ≥1 post-baseline PRO assessment. EORTC QLQ-C30 contains 30 questions organized into 5 multi-item functional scales, 3 multi-item symptom scales, a global health/quality of life scale, and 6 single item symptom scales. For each of the 15 scales, the results will be summarized using descriptive statistics including mean, standard deviation, 95% CI, median, minimum, maximum at each timepoint. This will be done based on the observed values as well as change from baseline values. Analysis of the EQ-5D index and EQ-VAS will consist of descriptive statistics based on observed values and, separately, based on change from baseline. The EORTC QLQ-MY20 contains 20 questions organized into 2 functional scales and 2 symptom scales (57). As with the QLQ-C30, the analysis of the QLQ-MY20 scales will be summarized using descriptive statistics including mean, standard deviation, 95% CI, median, minimum, maximum at each timepoint. This will be done based on the observed values as well as change from baseline values. Like for the other PROs, data on PGIC was summarized using descriptive statistics at each time point, and the relative changes from baseline were calculated as the change in the least square means (LSM).

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		(VAS) wherein respondents rate their overall health on that day on a scale of 0 to 100 (where 0 and 100 are worst and best possible health, resp.). *Multiple Myeloma module quality of life (QoL) questionnaire (QLQ-MY20)* A myeloma-specific questionnaire to assess disease symptoms, side effects of treatment, future perspectives and body image (30). Decreases in disease symptom and side-effect domain scores and increases in future perspective and body image domain scores indicate improvement (58). *Patient Global Impression of Change (PGIC)* The PGIC were collected to assess the patient's overall sense of a change in their disease since starting treatment or a perception of their disease severity at a given point in time respectively.	

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
MajesTEC-1 (Source: 59)	Clinical cut-off date: March 16 2022	EORTC QLQ-C30 and EQ-5D-5L (see above for definitions)	Patients enrolled in Phase 2 part of the trial completed both PRO assessments during site visits through use of on-site tablets at screening and on day 1 of every other treatment cycle (28 days/cycle). Change from baseline in patient-reported overall symptoms, functioning, and HRQoL were secondary endpoints of the phase II part of the study. No imputation of missing data. No adjustments for multiplicity were made, as these analyses were not part of the statistical hierarchy, and no P - values were presented. Descriptive statistics were used as appropriate: number and percentage were used to report categorical variables, with means, medians, and ranges used to report continuous variables. Compliance rates for completion of PROs were calculated as the number of assessments received divided by the number of assessments expected (number of patients on treatment) at each time point. Changes from baseline in the EORTC QLQ-C30 scales and the EQ-5D-5L VAS were fitted to a mixed-effects repeated measures model that included patient as a random effect, and baseline PRO value and time as fixed effects. Post hoc analyses based on depth of patient response to teclistamab (complete response or better [≥CR], very good partial response [VGPR], and partial response [PR]) were also conducted. Results are presented as LS means with 95% CIs. The proportions of patients with clinically meaningful improvement or worsening at any time on study treatment were calculated using thresholds that were defined a priori and based on the published literature: change ≥10 points for the EORTC QLQC-30 scales (60,61) and ≥7

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			points for the EQ-5D-5L VAS (62). Median time to meaningful worsening was calculated using the Kaplan-Meier method; for this analysis, worsening was defined using a distribution-based meaningful change threshold defined as at least one half of 1 standard deviation from baseline. Death due to disease progression was included as worsening. Patients who had not met the definition of worsening were censored at the last PRO assessment.

* Time point for data collection used in analysis (follow-up time for time-to-event measures)

Validity of outcomes

The DMC considered the following outcomes OS, HRQoL and PFS sufficient for the evaluation of the effect of teclistamab and ciltacabtagene autoleucelfor the treatment of adult patients with RRMM, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy (31). Therefore, this application for elranatamab also only focusses on these efficacy parameters.

4. Health economic analysis

The health economics analysis was a cost-minimisation analysis of elranatamab compared to teclistamab in RRMM patients who had received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and had demonstrated disease progression on the last therapy. A cost-minimization analysis was chosen, as it was expected that the efficacy and safety profiles of elranatamab and teclistamab are comparable and similar. Uncertainty in the parameters included in the analysis was assessed with deterministic one-way sensitivity analyses (DSAs) and scenario analyses. A budget impact analysis was conducted to assess the budgetary impact of recommending elranatamab for RRMM patients.

Two base case analyses were presented in the present application. The two base cases differed in terms of the curves applied for OS and PFS. The modelling of PFS and OS in base case 1 and base case 2 is described in section 8. The rationale for presenting two base case analyses was showing the impact of assuming equal effect in terms of OS and PFS based on elranatamab data with a median follow-up of 14.7 months (from MagnetisMM-3) and based on teclistamab data with a median follow-up of 22.8 months (from MajesTEC-1).

4.1 Model structure

Even though the analysis was a cost-minimization analysis, the model adopted a partitioned survival approach to account for the progressive nature and increased mortality of patients with multiple myeloma. The model comprised three mutually exclusive health states: PFS, progressed and death. All patients entered the model in the progression-free state and either moved to a post-progression-free state according to IMWG criteria as the disease progressed or died. Death was an absorbing state. The model structure is illustrated in Figure 5:

- PFS was the starting health state and defined as the time from the date of first dose until confirmed progressed disease per IMWG criteria
- Progressed state encompassed time after the first progression until death
- Death

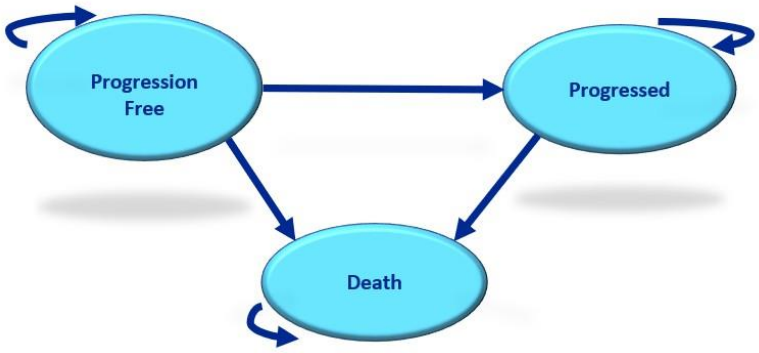


Figure 5 Model structure.

The model estimated the proportion of patients in each health state at each time point. The probability of patients residing in each health state for any given time point was calculated by the methods explained below:

- PFS: probability a patient has not yet progressed and is still alive, calculated from the PFS curve
- Progressed state: (probability a patient is alive, as calculated from the OS curve) – (probability a patient has not yet progressed and is still alive, as calculated from the PFS curve)
- Death: 1 – (probability a patient is alive, as calculated from the OS curve)

As the analysis was a cost-minimization analysis, PFS and OS in the model were assumed to be similar for elranatamab and teclistamab based on the 14.7-month data from cohort A in MagnetisMM-3 on elranatamab or the 22.8-month data from MajesTEC-1. The OS curve was applied to estimate the proportion of the cohort being alive over time and was extrapolated beyond the currently available data to meet the requirement of modelling over the selected time horizon. The area under the extrapolated OS curve provided an estimate of mean life expectancy. TTD was also included to model how much of the time patients are on active treatment while in the PFS state. In addition, for each health state, a specific cost was assigned within each period to calculate the cumulative costs over model time horizon.

4.2 Model features

Table 4 presents a summary of the model features.

Table 4 Features of the economic model.

Model features	Description	Justification
Patient population	Adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, with an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. The patient population included in the model was cohort A from MagnetisMM-3, i.e., a population with no prior BCMA-directed therapy	Based on the full EMA indication. The rationale for selecting a population with no prior BCMA-directed therapy (cohort A in MagnetisMM-3) was that this population corresponds to the population in the DMC evaluation of teclistamab.
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime, 32 years in the base case	Capture all health benefits and costs in line with DMC guidelines and based on median age in Denmark, which according to the DMC's evaluation of teclistamab is 68 years (31)
Cycle length	1 week	To sufficiently account for the changes in the health states of the model or treatment strategies. This is the majority choice of the previous HTA submissions in RRMM, such as NICE TA658 (isatuximab), NICE TA510 (daratumumab), NICE TA505 (ixazomib) and NICE TA427 (pomalidomide).
Half-cycle correction	Yes	To estimate the costs more accurately across model cycles.
Discount rate	3.5%	A discount rate of 3.5% for all years was applied in accordance with 2024 guidelines from the Ministry of Finance (63).
Intervention	Elranatamab in a dosing regimen with step-up doses of 12 mg on day 1 and 32 mg on day 4, followed by a full	The dosing regimen is in accordance with the SmPC on

Model features	Description	Justification
	treatment dose of 76 mg weekly (week 2 - week 24). Patients who have received at least 24 weeks of treatment and have achieved a response, the dosing interval transition to an every-2-week schedule (21).	elranatamab (21).
Comparator	Teclistamab in a dosing regimen of 1.5 mg/kg by SC injection weekly, preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg. In patients who have a complete response or better for a minimum of 6 months, a reduced dosing frequency of 1.5 mg/kg SC every 2 weeks may be considered (48).	Teclistamab was recently recommended by the DMC as standard treatment for patients in the same indication as elranatamab (31). Therefore, teclistamab was regarded as the relevant comparator for elranatamab. Dosing regimen in accordance with the SmPC.
Outcomes	OS, PFS, TTD and safety	OS and PFS were applied in the model to account for increased mortality and progressive nature of multiple myeloma. TTD was applied to model time patients are on active treatment. Safety was applied to assess increment-tal cost associated with mana-ging AEs in elranatamab and teclistamab.

5. Overview of literature

A systematic literature search was conducted for the present application, as no head-to-head studies between elranatamab and teclistamab exist. In the systematic search, relevant search terms for the condition (relapsed and/or refractory multiple myeloma), intervention (elranatamab) and comparator (teclistamab) were applied as well as filters to identify RCTs and a filter to exclude irrelevant publication types and study designs. In addition, the time period was set to 2015 and onwards. The literature search was conducted in the databases Medline (via PubMed) and CENTRAL (via Cochrane Library) on March 5 2024 and is described in detail in Appendix H. In addition, conference materials, clinicaltrials.gov, EMA's webpage and the DMC's webpage were searched for relevant information.

5.1 Literature used for the clinical assessment

The aim of the systematic literature search was to identify studies assessing the efficacy, HRQoL and safety of elranatamab and teclistamab. The MagnetisMM-3 trial (NCT04649359) (47) was used to demonstrate efficacy and safety of elranatamab, whereas the efficacy and safety of teclistamab was demonstrated using the MajesTEC-1 trial (NCT03145181 and NCT04557098) (37). The studies were used for indirect comparative analyses of elranatamab and teclistamab in an unanchored MAIC published in Mol et al. 2024 (64). In Table 5 we present an overview of the studies and literature used in the present application. In addition to the studies on elranatamab and teclistamab, the SmPC and public assessment report on elranatamab and teclistamab were identified on EMA's webpage and included in order to inform the present application (21,48,51,53). The DMC evaluation of teclistamab was also included (31).

Table 5 Relevant literature included in the assessment of efficacy and safety.

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (from clinicaltrials.gov)	Used in comparison of
Lesokhin AM, Tomasson MH, Arnulf B, Bahlis NJ, Miles Prince H, Niesvizky R, Rodríguez-Otero P, Martinez-Lopez J, Koehne G, Touzeau C, Jethava Y, Quach H, Depaus J, Yokoyama H, Gabayan AE, Stevens DA, Nooka AK, Manier S, Raje N, Iida S, Raab MS, Searle E, Leip E, Sullivan ST, Conte U, Elmeliegy M, Czibere A, Viqueira A, Mohty M. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med. 2023 Sep;29(9):2259-2267. doi: 10.1038/s41591-023-02528-9. Epub 2023 Aug 15. PMID: 37582952; PMCID: PMC10504075. (47) Mohty M, Bahlis NJ, Nooka AK, DiBonaventura M, Ren J, Conte U. Impact of elranatamab on quality of life: Patient-reported outcomes from MagnetisMM-3. Br J Haematol. 2024 Feb 29. doi: 10.1111/bjh.19346. Epub ahead of print. PMID: 38420657. (54) Conference materials: Tomasson M, Shinsuke L, Niesvizky R, Mohty M, Bahlis NJ, Martinez-Lopez J, Koehne G, Rodriguez Otero P, Miles Prince H, Viqueira A, Leip E, Conte U, T Sullivan S, Lesokhin A. Long-Term Efficacy and Safety of Elranatamab Monotherapy in the Phase 2 MagnetisMM-3 Trial in Relapsed or Refractory Multiple Myeloma. Presented at the 65th American Society of Hematology (ASH) Annual Meeting · December 9-12, 2023 · San Diego, CA, USA. doi: 10.1182/blood-2023-182130. (52)	MagnetisMM-3	NCT04649359	Start: February 2 2021 Primary completion (actual): June 17 2022 Study completion (estimated): December 31 2025 Data cut-off: [redacted] Lesokhin et al. 2023 (47): Data cut-off for efficacy and safety was March 14 2023, except for CRS and ICANS data, which was based on January 12 2023. Tomasson et al. 2023 (52): September 11 2023 Future data cut-offs: Dates for future data cut-offs are currently unknown.	Elranatamab vs. teclistamab
Moreau P, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, Nooka AK, Martin T, Rosinol L, Chari A, Karlin L, Benboubker L, Mateos MV, Bahlis N, Popat R, Besemer B, Martínez-López J, Sidana S, Delforge M, Pei L, Trancucci D, Verona R, Girgis S, Lin SXW, Olyslager Y, Jaffe M, Uhlar C,	MajesTEC-1	Phase 1: NCT03145181 Phase 2:	Phase 1 Start (actual): May 16 2017	Elranatamab vs. teclistamab

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (from clinicaltrials.gov)	Used in comparison of
Stephenson T, Van Rampelbergh R, Banerjee A, Goldberg JD, Kobos R, Krishnan A, Usmani SZ. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med. 2022 Aug 11;387(6):495-505. doi: 10.1056/NEJMoa2203478. Epub 2022 Jun 5. PMID: 35661166; PMCID: PMC10587778. (37) Martin TG, Moreau P, Usmani SZ, Garfall A, Mateos MV, San-Miguel JF, Oriol A, Nooka AK, Rosinol L, Chari A, Karlin L, Krishnan A, Bahlis N, Popat R, Besemer B, Martínez-López J, Delforge M, Trancucci D, Pei L, Kobos R, Fastenau J, Gries KS, van de Donk NWCJ. Teclistamab improves patient-reported symptoms and health-related quality of life in relapsed or refractory multiple myeloma: Results from the phase II MajesTEC-1 Study. Clin Lymphoma Myeloma Leuk. 2024 Mar;24(3):194-202. doi: 10.1016/j.clml.2023.11.001. Epub 2023 Nov 2023. PMID: 38052709. (59) Conference materials: Sidana S, Moreau P, Garfall A, Bhutani M, Oriol A, Nooka A, Martin T, Rosiñol Dachs L, Mateos MV, Bahlis NJ, Popat R, Besemer B, Martinez-Lopez J, Krishnan A, Delforge M, Trancucci D, Verona R, Stephenson T, Chastain K, van de Donk NWCJ. P879: Long-term follow-up from MajesTEC-1 of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM). Hemasphere. 2023 Aug 8;7(Suppl):e62475d0. doi: 10.1097/01.HS9.0000970420.62475.d0. PMCID: PMC10431083. (66)		NCT04557098	Primary completion (actual): November 9 2021 Study completion (estimated): July 22 2026 Data cut-off: March 29 2021 (Source: 65) Phase 2 Start: September 17 2020 Primary Completion (estimated): March 13 2025 Study Completion (estimated): September 25 2025 Data cut-off: January 4 2023 (Source: 66)	
Mol I, Hu Y, LeBlanc TW, Cappelleri JC, Chu H, Nador G, Aydin D, Schepart A, Hlavacek P. A matching-adjusted indirect comparison of the efficacy of elranatamab versus teclistamab in patients with triple-class exposed/refractory multiple myeloma. Leuk Lymphoma. 2024 Feb 12:1-9. doi: 10.1080/10428194.2024.2313628. Epub ahead of print. PMID: 38347747. (64)	MAIC Indirect comparison	N/A	N/A	Elranatamab vs teclistamab

5.2 Literature used for the assessment of health-related quality of life

Not applicable as a cost-utility analysis was not conducted, i.e., no utilities were necessary for the analysis. HRQoL outcomes were included in the search for efficacy and safety on elranatamab and teclistamab.

Table 6 Relevant literature included for (documentation of) health-related quality of life *(Table 6 is Not Applicable)*

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
N/A	N/A	N/A

5.3 Literature used for inputs for the health economics model

Not applicable.

Table 7 Relevant literature used for input to the health economic model (Table 7 is Not Applicable)

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

6.1 Efficacy of elranatamab compared to teclistamab in patients with triple-class exposed/refractory multiple myeloma

6.1.1 Relevant studies

Table 8 Overview of study design for studies included in the comparison.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
MagnetisMM-3 NCT04649359. Lesokhin et al. (Source: 47) Tomasson et al. (Source: 52) Mohty et al. (Source: 54)	Ongoing, multicenter, open-label, single-arm, phase 2 study	Cohort A (BCMA-naïve patients) had a median length of follow-up of 14,7 months (range: 0.2–25.1 months) (47); 17.6 months (range: 0.2-31.1 months)	Adult patients with multiple myeloma refractory to at least one proteasome inhibitor, one immunomodulatory drug and one anti-CD38 antibody, and disease relapsed or refractory to their last antimyeloma regimen on the last therapy. Not previously treated with BCMA-directed therapy. Eligible patients had a score of ≤2 on the Eastern Cooperative Oncology Group performance-status scale	Subcutaneous elranatamab 76 mg once weekly in 28-d cycles after two step-up priming doses of 12 mg and 32 mg given on day 1 and day 4 of cycle 1. After six cycles, persistent responders (partial response (PR) or better lasting at least 2 months) switched to a dosing interval of once every 2 weeks (Q2W). Number of patients switching to Q2W dosing: 50.	N/A	Outcomes were measured at data cut-off March 14 2023 - median follow-up of 14.7 months (0.2 to 25.1) and data cut-off September 11 2023 – median duration of follow-up of 17.6 months (0.2-31.1) – OS not mature yet Primary Endpoint: • Objective response rate (ORR) by blinded independent central review (BICR) per IMWG criteria. Secondary Endpoints: • ORR by BICR baseline extramedullary disease status, ORR by investigator, complete response (CR) rate (defined as CR or better), time to response (TTR), duration of response (DOR), duration of CR or better (DOCR), minimal residual disease (MRD) negativity rate, PFS, OS, safety, pharmacokinetics and immunogenicity. Adverse events (AEs) and laboratory abnormalities.
MajesTEC-1, NCT03145181 Moreau et al. (Source: 37) Sidana et al.	Ongoing, first-in-human, multicenter, open-label, single-arm,	Cohort A (i.e. patients who received ≥3 prior MM treatment lines of treatment and	Patients were ≥18 years of age, had a documented diagnosis of relapsed or refractory myeloma according to the criteria of the International Myeloma Working Group. Patients must have previously received at least three lines	Teclistamab. Dose: 1.5 mg/kg, subcutaneously Dosing schedule: Step-up doses of 0.06 and 0.3 mg/kg were administered, followed by 1.5 mg/kg.	N/A	Outcomes were measured at data cut-off March 16 2022 - median duration of follow-up of 14.1 month (0.3 to 24.4) and data cut-off: January 4 2023 – median duration of follow-up of 23 months:

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
(Source: 66) Martin et al. (Source: 59)	phase 1/2 study.	previously received an IMiD, PI and anti-CD38 mAb) median duration of follow-up: 14,1 month (range 0.3 to 24.4) (data cut-off: March 16 2022); 23 months (data cut-off: January 4 2023)	of therapy (including an IMiD, a PI, and an anti-CD38 antibody) and have had progressive, measurable disease at screening. Previous treatment with a BCMA-targeted therapy was not allowed. Eligible patients had a score of 0 or 1 on the Eastern Cooperative Oncology Group performance-status scale.	The step-up doses were separated by 2 to 4 days and were completed 2 to 4 days before the administration of the first full teclistamab dose (1.5 mg/kg) Timing of switch to Q2W dosing: 11.3 months Number of patients switching to Q2W dosing: 63		Primary Endpoint: • ORR (PR or better) as defined by IMWG criteria Secondary Endpoints: • PFS; OS; DOR; VGPR or better/CR or better/sCR as defined by IMWG response criteria; TTR; MRD negativity status; occurrence and severity of adverse events, serious adverse events and laboratory values; pharmacokinetic parameters; presence and activity of teclistamab antibodies; change from baseline in overall HRQoL; symptoms and functioning; ORR in patients with high-risk molecular features

6.1.2 Comparability of studies

MagnetisMM-3 was an open label, phase 2 study and MajesTEC-1 was an open label phase1/2 study. Overall, the inclusion and exclusion criteria of the trials were similar; however, MajesTEC-1 excluded patients with Eastern Cooperative Oncology Group performance status (ECOG PS) >1, whereas MagnetisMM-3 allowed enrollment of patients with an ECOG PS of 2. As such, patients with ECOG PS = 2 in the MagnetisMM-3 trial were removed from the analysis (resulting N = 116).

In the MajesTEC-1 trial, extra-medullary disease was defined as the presence of one or more extramedullary soft-tissue lesions. This definition was slightly different from the definition in theMagnetisMM-3 trial where it was defined as the presence of any plasmacytoma (extramedullary and/or paramedullary) with a soft-tissue component. Therefore, a new variable for extramedullary plasmacytomas was created for elranatamab using the MagnetisMM-3 IPD. This variable more closely follows the definition of extramedullary disease in MajesTEC-1 and was used in the MAIC.

6.1.2.1 Comparability of patients across studies

Table 9 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety.

	MagnetisMM3	MajesTEC-1
	elranatamab n=123 (sources: 47,49-52)	teclistamab n=165 (sources: 37,53)
Median age (range) years	68.0 (36–89)	64.0 (33–84)
Gender Male n, (%)	68 (55.3)	96 (58.2)
Race, n (%)		
White	72 (58.5)	134 (81.2)
Asian	16 (13.0)	3 (1.8)
Black or African American	9 (7.3)	21 (12.7)
Not reported or unknown[a]	26 (21.1)	N/A
Other	N/A	7 (4.2)
Geographical region, n (%)		N/A
North America	58 (47.2)	
Europe	45 (36.6)	
Asia	12 (9.8)	
Other	8 (6.5)	
Median time since diagnosis (range)	72.9 months ((16-228 months)[b]	84 months (10–272 months)
[ECOG performance status, n (%)]		
0	45 (36.6)	55 (33.3)
1	71 (57.7)	110 (66.7)

	MagnetisMM3	MajesTEC-1
	elranatamab n=123 (sources: 47,49-52)	teclistamab n=165 (sources: 37,53)
2	7 (5.7)	N/A
Type of myeloma, n (%)		N/A
IgG	65 (52.8)	
Non-IgG	21 (17.1)	
IgA	20 (16.3)	
IgD	1 (0.8)	
Light chain	24 (19.5)	
Unknown	13 (10.6)	
[R-ISS disease stage, n (%) characteristic]		n=162
I	28 (22.8)	85 (52.5)
II	68 (55.3)	57 (35.2)
III	19 (15.4)	20 (12.3)
Unknown	8 (6.5)	N/A
Cytogenetic risk, n (%)		
Standard	83 (67.5)	N/A
High[c]	31 (25.2)	38/148 (25.7)[d]
Missing	9 (7.3)	N/A
Extramedullary disease by BICR, n (%)[e]	39 (31.7)	N/A
≥1 Extra-medullary plasmacytoma — no. (%)[f]	N/A	28 (17.0)
Bone marrow plasma cells, n (%)		
<50%	89 (72.4)	N/A
≥50%	26 (21.1)	N/A
≥60%	N/A	18/160 (11.2)
Missing	8 (6.5)	N/A
≥1 poor prognosis feature[g]	94 (76.4)	N/A
Prior stem cell transplant, n (%)	87 (70.7)	135 (81.8)
Number of prior lines		
2	5(4%)	N/A
3	21 (17%)	N/A
4	33 (27%)	N/A
≥5	64 (52%)	N/A
Median (range)	5 (2-22)	5 (2–14)
Exposure status n (%)		
triple class	123 (100)	165 (100.0)

	MagnetisMM3	MajesTEC-1
	elranatamab n=123 (sources: 47,49-52)	teclistamab n=165 (sources: 37,53)
penta-drug	87 (70.7)	116 (70.3)
Refractory status n (%)		
triple class[h]	119 (96.7)	128 (77.6)
penta-drug[i]	52 (42.3)	50 (30.3)
Refractory to last line of therapy, n (%)	118 (95.9)	148 (89.7)

a. Includes patients recruited in countries where the collection of races is prohibited.
[redacted] Date of Initial Diagnosis to date of first dose comes from [redacted]
c. Includes t(4;14), t(14;16) and del(17p) chromosomal abnormalities
d. del(17p): 23/148 (15.5%); t(4:14): 16/148 (10.8%) and t(14;16): 4/148 (2.7%)
e. Extramedullary disease was defined as the presence of any plasmacytoma (extramedullary and/or paramedullary with a soft-tissue component).
f. Included in this category are patients with soft-tissue plasmacytomas that were not associated with bone.
g. Poor prognosis feature refers to at least one of the following: ECOG performance status of 2, R-ISS stage III, high cytogenetic risk, extramedullary disease at baseline, bone marrow plasma cells ≥50% or penta-refractory disease
h. Triple-class refers to at least one proteasome inhibitor, one immunomodulatory drug and one anti-CD38 antibody
i. Penta-drug refers to at least two proteasome inhibitors, two immunomodulatory drugs and one anti-CD38 antibody

MagnetisMM-3 had a higher proportion of patients with ISS stage III and a lower proportion of patients who were ISS stage I compared with MajesTEC-1. In addition, there was a higher proportion of patients with extramedullary disease and TCR or penta-drug refractory status in MagnestisMM-3 versus MajesTEC-1. After adjustment in the MAIC, the key prognostic variables and effect modifiers (i.e., age, sex (for OS endpoint only) median time since diagnosis, ISS stage, high-risk cytogenetics, extramedullary disease, number of prior lines of therapy, ECOG performance status, and penta-drug exposed and penta-drug refractory status) were comparable between patients who received elranatamab and those who received teclistamab.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Unfortunately, the Danish Myeloma Database does not provide information on patients who are TCE/TCR. However, a study by Szabo et al. looking at the use patterns and efficacy of pomalidomide in Danish patients with RRMM, including outcomes in patients who had previously been exposed to a PI, IMiD and the anti-CD38 Mab, daratumumab, showed that median age in this latter group was 71.4 years (36). Time from diagnosis to becoming TCE was 4.2 years, and the median prior lines of therapy was 4 (36). According to the DMC most patients reaching 4th line of therapy have an ECOG >1, and their median age is around 68 (31).

Table 10 Characteristics in the relevant Danish population and in the health economic model.

	Value in Danish population (Sources: 12,31,36)
Age (median)	71.4
Gender	N/A
Time from diagnosis to t0; years; median (IQR)	4.2 (2.8–7.0)
Prior lines of therapy (median)	4
High risk FISH	26%

t0 = The date of initiation of the index regimen with pomalidomide
FISH, Fluorescence in situ hybridization; high-risk FISH, at least one of *t*(4;14), *t*(14;16) or del17p

6.1.4 Efficacy – results per MagnetisMM-3

In the data read-out in Lesokhin et al. (2023) with the cut-off date of March 14 2023 - reflecting a median duration of follow-up of 14.7 months (range: 0.2–25.1 months) - 33.3% of patients were still receiving elranatamab (47).
The median duration of treatment was 5.6 months (range: 0.03–24.4 months), 48.0% were treated for at least 6 months and 35.8% for at least 12 months. The median relative dose intensity for all treatment cycles was 78.4% (range: 8.9–101.3%). The most common primary reasons for permanent treatment discontinuation were progressive disease (PD)/lack of efficacy (41.5%) and AEs (13.8%) (47).

The last data read-out from the MagnetisMM-2 study have been presented at the ASH conference by Tomasson et al. (2023) with a data cut-off date of September 11 2023 reflecting a median duration of follow-up of 17.6 months (range: 0.2-31.1 months) (52). At this data cut-off 26.8% of the patients were still receiving elranatamab treatment and still with a median duration of treatment of 5.6 months.

In the presentation of the PFS and OS efficacy outcomes below results for both data cut-off dates are presented.

In addition updated results were presented at EHA June 2024 last week and we include the long term survival results from Magnetsism MM-3 in the section below. Elranatamab continued to demonstrate deep and durable responses in heavily pretreated patients, BCMA-naive patients with RRMM. With extended follow up, ORR per BICR remained at 61%.

Progression Free Survival
The median PFS was not reached (95% CI: 9.9 months to not estimable), with 70 (56.9%) patients censored at data cut-off, and the Kaplan–Meier estimate of PFS at 14.7 months was 50.9% (95% CI: 40.9–60.0; Figure 6). For patients in ≥CR, the Kaplan–Meier estimates of PFS at 14.7 months was 89.5% (95% CI: 74.3–95.9).

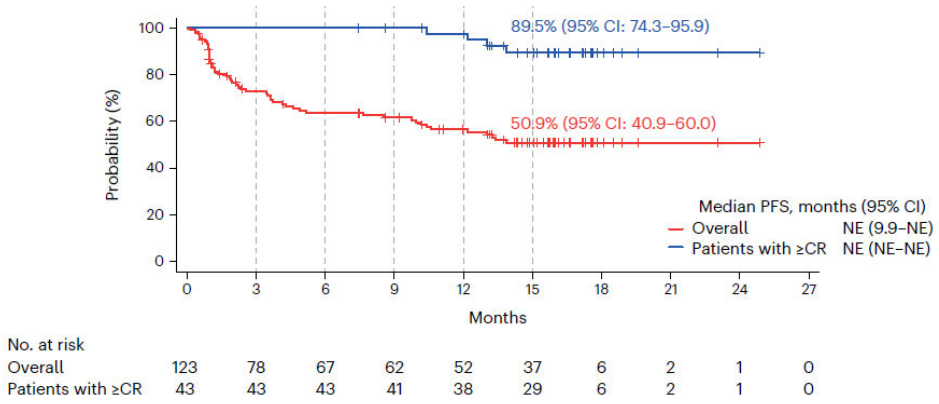


Figure 6 PFS assessed by BICR per IMWG criteria in the overall population (red line) and in 43 patients who had ≥CR (blue line). Source: (47).

Tick marks indicate censored data. NE, not estimable.

At the latest follow-up from the ongoing phase 2 MagnetisMM-3 trial of elranatamab with a median duration of follow-up of 17.6 months (range: 0.2-31.1 months; data cut-off: September 11, 2023) demonstrated sustained clinical efficacy (52). The probability of maintaining a response at 18 months was 68.8% and the Kaplan–Meier median PFS was 17.2 months (Figure 7).

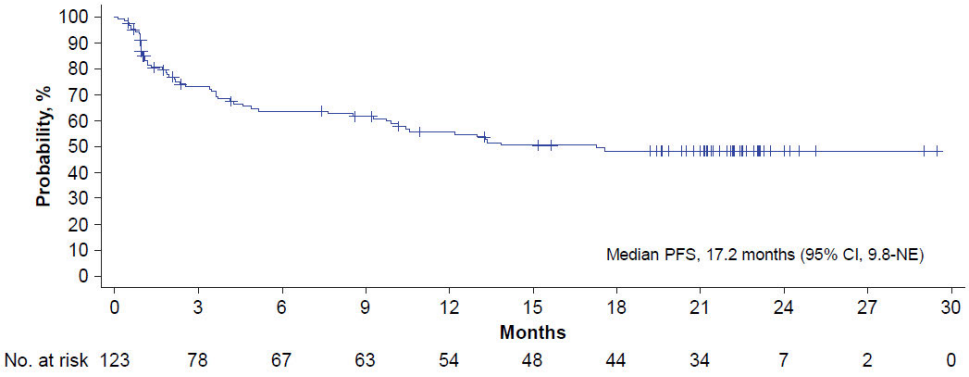


Figure 7 PFS after 17.6 months of follow-up (data cut-off date of September 11 2023) Source: (52).

Tick marks indicate censored data. NE, not estimable.

Overall survival

The median duration of OS was not reached (95% CI: 13.9 months to not estimable), and the Kaplan–Meier estimate at 14.7 months was 56.7% (95% CI: 47.4–65.1; Figure 8). For patients in ≥CR, the Kaplan–Meier estimates of OS at 14.7 months was 92.6% (95% CI: 78.7–97.6) (Figure 8).

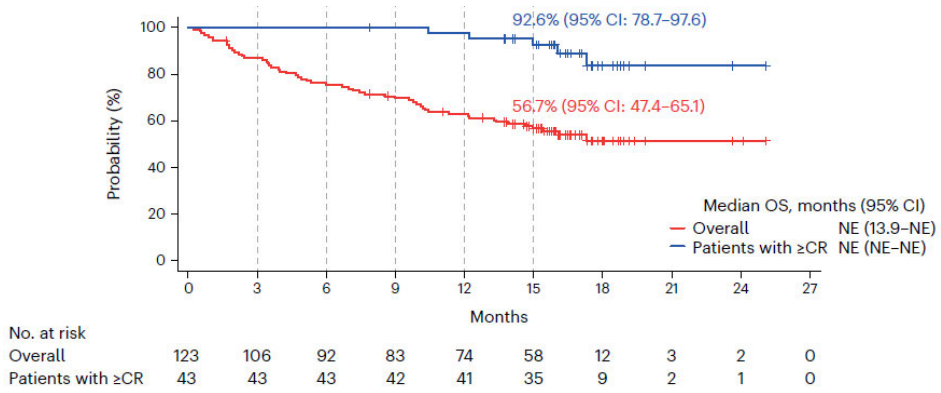


Figure 8 OS in the overall population (red line) and in 43 patients who had ≥CR (blue line). Source: (47).
Tick marks indicate censored data. NE, not estimable.

The latest follow-up with a data cut-off date of September 11 2023 (median duration of follow-up of 17.6 months (range: 0.2-31.1 months) showed that the Kaplan-Meier median OS was 21.9 months (Figure 9) (52). Though OS is not mature yet.

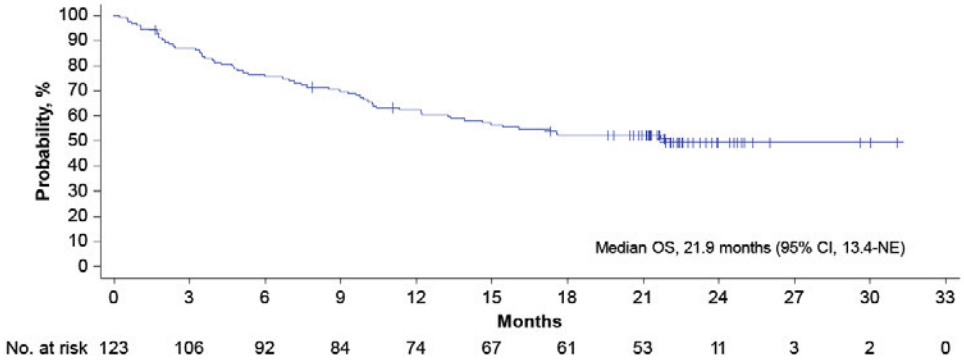


Figure 9 OS after 17.6 months of follow-up (data cut-off date of September 11 2023) Source: (52).
Tick marks indicate censored data. NE, not estimable.

Results from an extended follow up was recently presented at EHA June 2024. Updated results in BCMA-naive patients > 2 years after the last patient was initially dosed in Magnetism MM-3 showed a median OS of 24.6 months (95%CI, 13.4 -not evaluable (NE) months (81).

HRQoL

Patient reported outcomes (PRO) in terms of HRQoL were an exploratory endpoint of the MagnetisMM-3 study.

The PRO analysis dataset included all patients in the safety analysis dataset who completed a baseline (last PRO assessment prior to or on the first dose of study treatment) and ≥1 post-baseline PRO assessment (54). [redacted]

QLQ-30

Based on their QLQ-30 scores, BCMA-naïve patients (cohort A) showed a transient worsening in the mean global health status score relative to baseline through C2D15 (LSM change [95% CI], −5.9 [−10.7 to −1.1]), followed by an improvement back to baseline levels at C3D1 that was maintained through C12D1 [redacted]. Furthermore, they had significant (i.e. 95% CI did not cross zero) reductions in pain, starting at C4D1 (−6.7 [−13.0 to −0.4]), which were maintained through C12D1 (Figure 10).

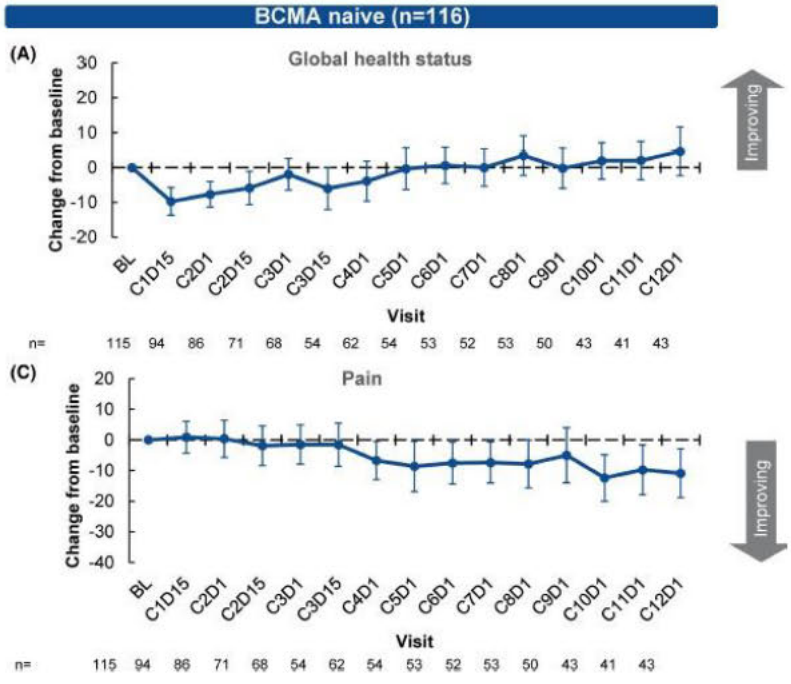


Figure 10 Change from baseline in QLQ-C30.

QLQ-MY20

Results from the myeloma-specific QLQ-MY20 questionnaire revealed that BCMA-naïve patients (Cohort A) had significant reductions in disease symptoms starting at C5D1 (−6.9 [−10.6 to −3.1]), which were maintained through C12D1. On the other hand, in the side effects domain there was a transient worsening in the score relative to baseline through C2D15 (4.3 [1.4–7.2]), followed by an improvement back to baseline levels at C3D1 that was maintained through C12D1.

There was little change in the body image domain for patients over treatment cycles, whereas significant improvements in the future perspectives' domain scores were observed as early as C1D15 (5.2 [1.1–9.2], which continued to improve or were maintained through C12D1 (Figure 11).

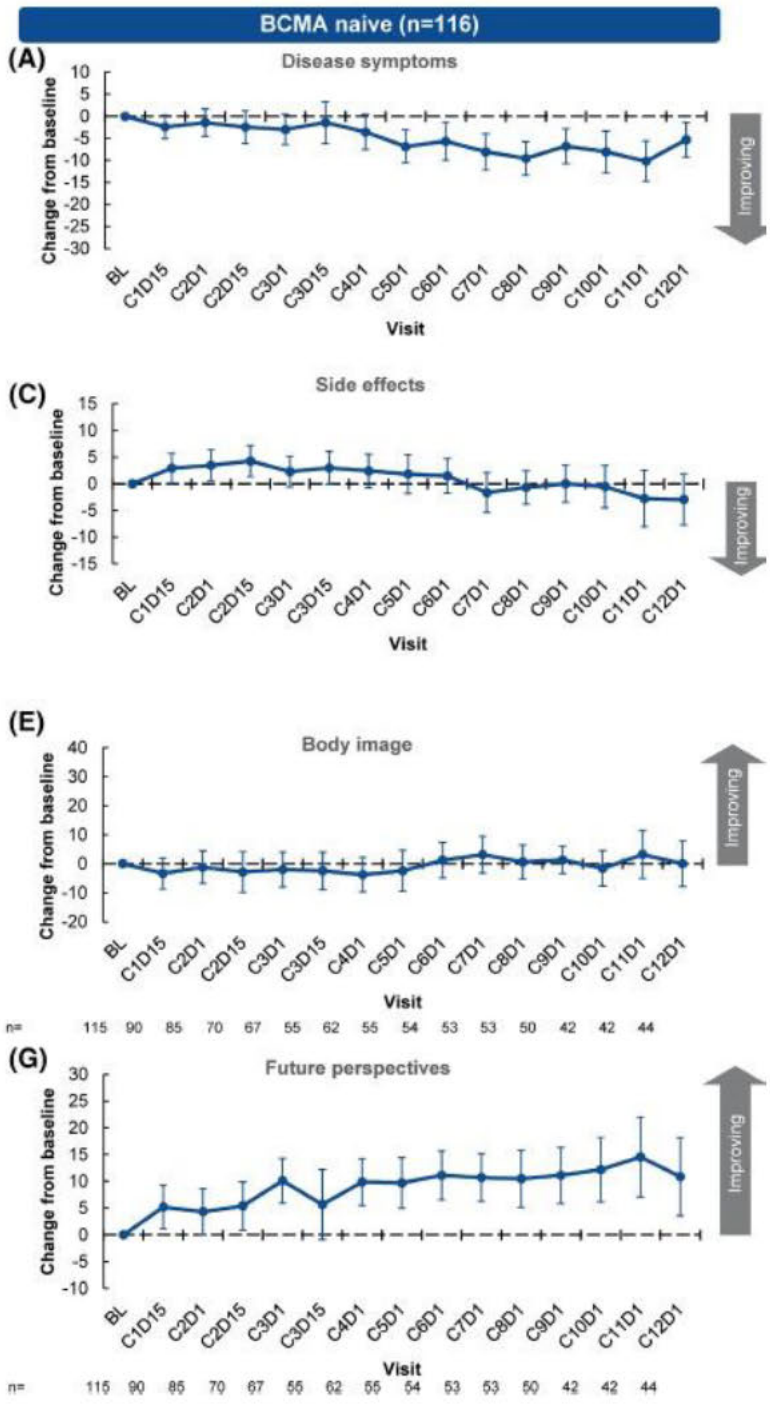


Figure 11 Change from baseline in QLQ-MY20.

EQ-5D

In cohort A, overall QOL assessed by EQ-5D remained at baseline levels until C11D1, when a slight improvement was observed and then maintained through C12D1 (Figure 12). The EQ-5D VAS scores followed a trend similar to the EQ-5D index scores, with a transient decrease from baseline followed by an increase in scores over time starting at C6D1, reflecting an improvement in general HRQoL.

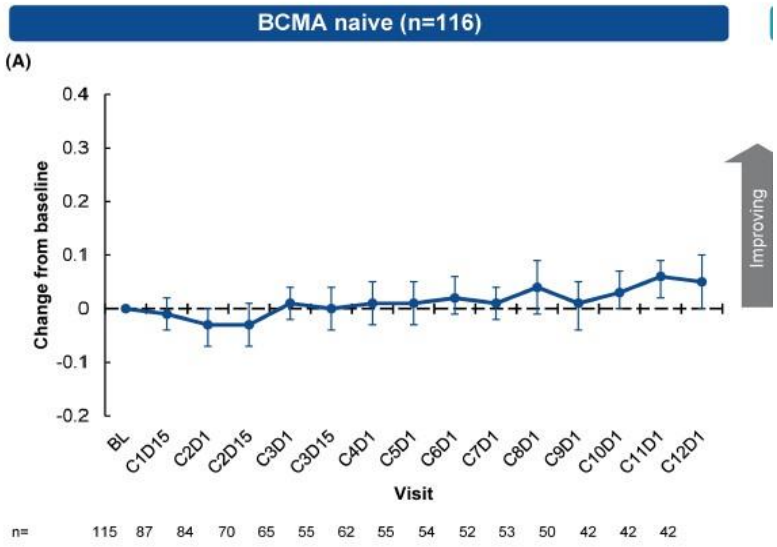


Figure 12 Change from baseline in EQ-5D index score. BL, baseline; C, cycle; D, day.

PGIC

By the first PGIC assessment (C1D15), 40.2% of BCMA-naïve patients (Cohort A) were reporting an improvement in the disease symptoms (either 'a little better' or 'much better'). These improvements continued through C5D1 for BCMA-naïve patients and C2D15 for BCMA-exposed patients and were maintained in both groups through C12D1 (Figure 13).

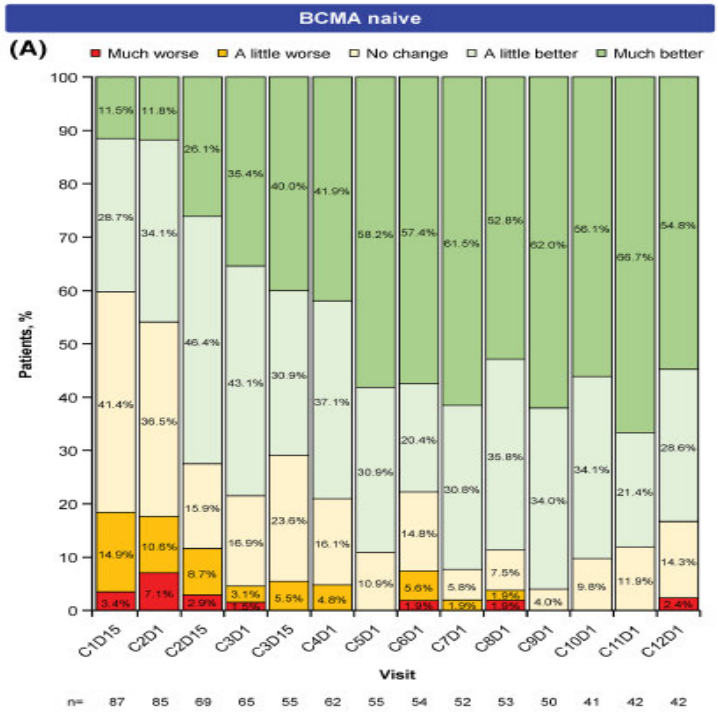


Figure 13 Impression of change in disease with elranatamab. C, cycle; D, day.

6.1.5 Efficacy – results per MajesTEC-1

As of March 16 2022, after a median follow-up of 14.1 months (range, 0.3 to 24.4), 70 patients (42.4%) were continuing to receive treatment, with a median treatment duration of 8.5 months (range: 0.2-24.4 months) (37). A total of 98 patients (59.4%) received at least 6 months of teclistamab treatment, and 79 patients (47.9%) received at least 9 months of treatment. The median relative dose intensity (the ratio of the dose administered to the planned dose) for all treatment cycles, including step-up doses, was 93.7%.

Progression free survival

The median duration of progression-free survival was 11.3 months (95% CI, 8.8 to 17.1).

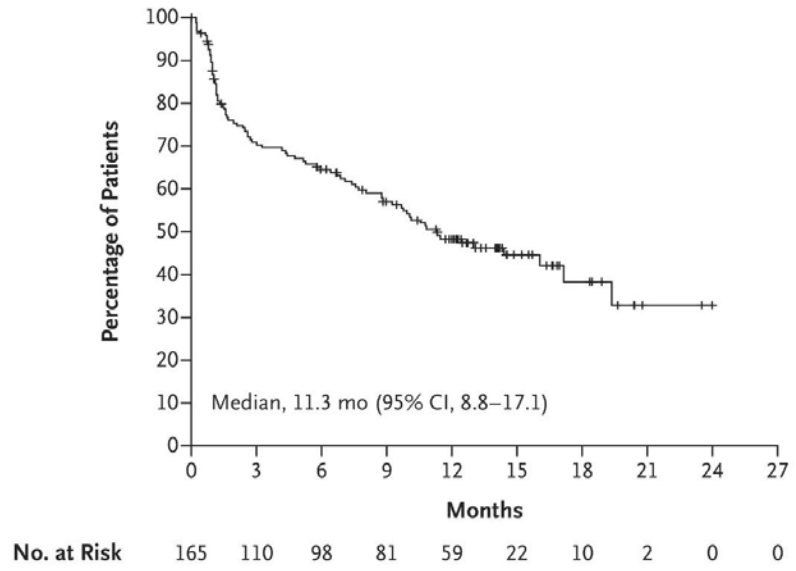


Figure 14 Progression-free survival in the overall population at data cut-off March 16 2022. Source: (48).

Sidana et al presented updated results from the MajesTEC-1 study with extended follow-up at EHA 2023. After a median follow-up of 23 months (data cut-off January 4, 2023) median PFS was 11.3 months (95% CI, 8.8–16.4) (66).

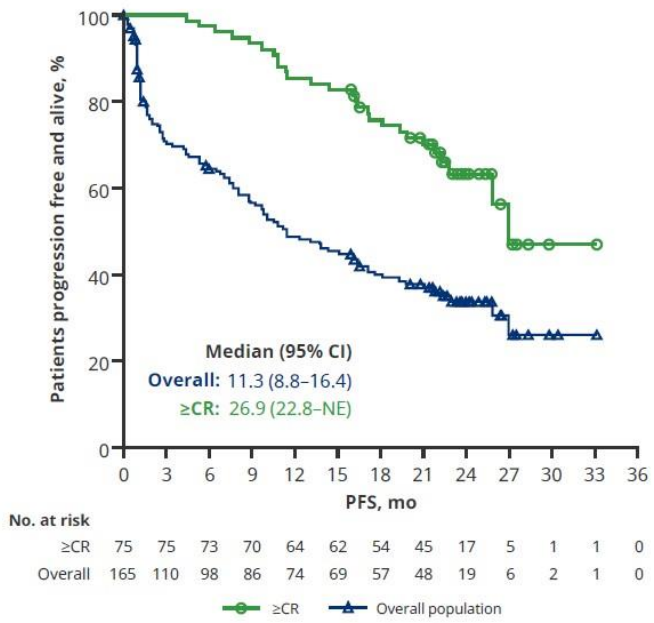


Figure 15 Progression- free survival in the overall population and patients ≥CR at data cut-off January 4, 2023. Source: (66).

Overall survival

The median duration of overall survival was 18.3 months (95% CI, 15.1 to not estimable) and was not mature after censoring of data for 97 patients (58.8%) at data cut-off March 16 2022.

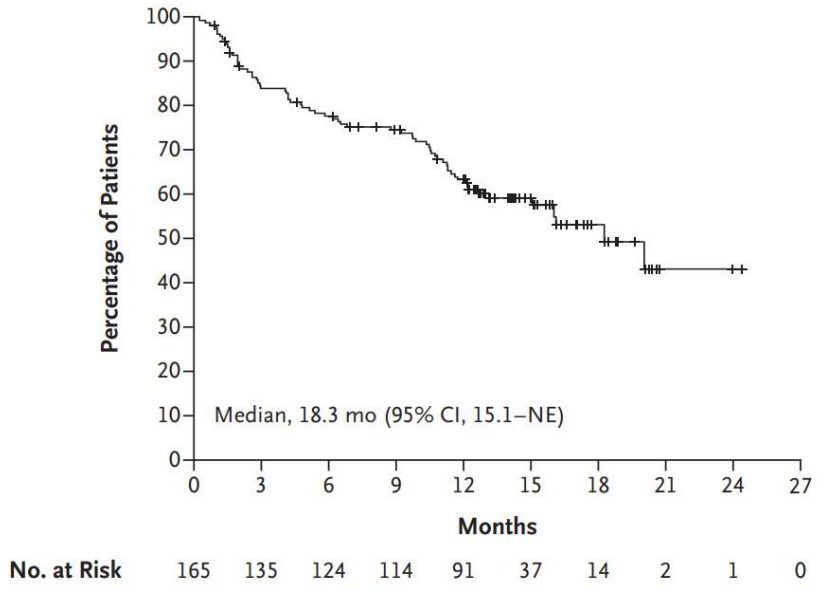


Figure 16 Overall survival for 165 patients at data cut-off March 16 2022. Source: (48).

Sidana et al did also report updated OS results from the MajesTEC-1 study at EHA 2023. After a median follow-up of 22 months median OS was 21.9 months (95% CI, 16.0–NE) (66).

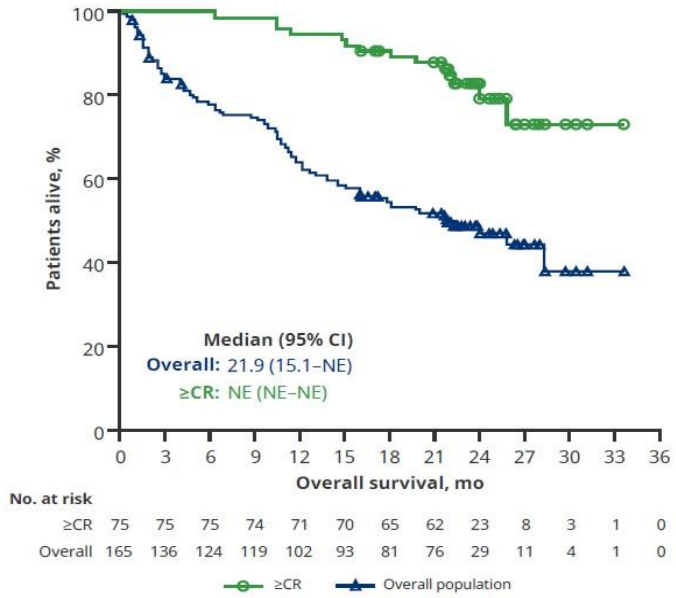


Figure 17 Overall survival for all 165 patients and those with ≥CR at data cut-off January 4, 2023. Source: (66).

CR = complete response

HRQoL

Change from baseline in patient-reported overall symptoms, functioning, and HRQoL were secondary endpoints of the phase II part of the MajesTEC-1 study. All 125 patients enrolled in phase II provided PRO data for analyses. Compliance rates for all patients who provided PRO assessments (n = 125) were 83% at baseline for the EORTC QLQ-C30 and 77% for the EQ-5D-5L and were similar through cycle 8 (≥77%). There was no imputation of missing data and no adjustments for multiplicity were made, as these analyses were not part of the statistical hierarchy, and no *P* -values are presented (59).

EORTC QLQ-C30

Treatment with teclistamab was associated with a reduction in symptoms and a sustained improvement in overall HRQoL. Pain scores improved as early as cycle 2 and showed meaningful improvement (95% CIs for LS mean change did not include 0) at cycles 4 through 12 (Figure 18 A). Fatigue initially worsened but returned to near-baseline levels for cycles 4, 6, and 8 before showing a trend toward improvement for cycles 10 and 12 (Figure 18 B). Symptoms of nausea and vomiting worsened from baseline at cycle 2 but showed little change from baseline from cycle 4 onward (Figure 18 C). Average EORTC QLQ-30 GHS scores improved from baseline at cycles 4, 6, 8, 10, and 12 (Figure 18 D). LS mean change in EQ-5D-5L VAS showed improvement from cycle 4 through cycle 12 (Figure 18 E).

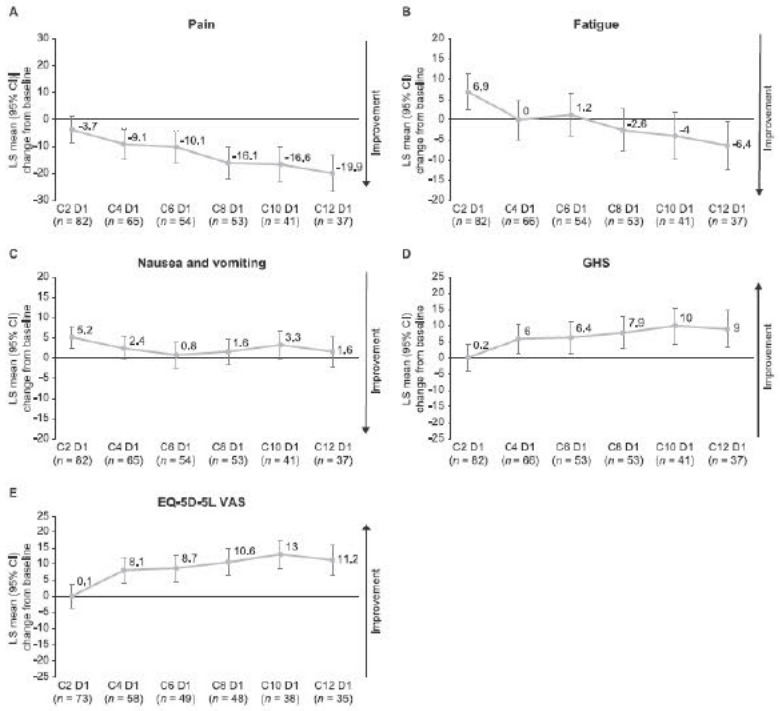


Figure 18 Change from baseline in EORTC QLQ-C30 (A) pain, (B) fatigue, (C) nausea and vomiting, (D) GHS, and (E) EQ-5D-5L VAS scores.

Values are LS mean changes from a mixed-effects model for repeated measures. C = cycle; D = day; EQ-5D-5L VAS = EuroQol 5 Dimension 5 Level visual analogue scale; GHS = global health status; LS = least squares

The proportion of patients reporting clinically meaningful improvements generally increased over time for all scales of EORTC QLQ-C30 and EQ-5D-5L VAS score (Figure 19).

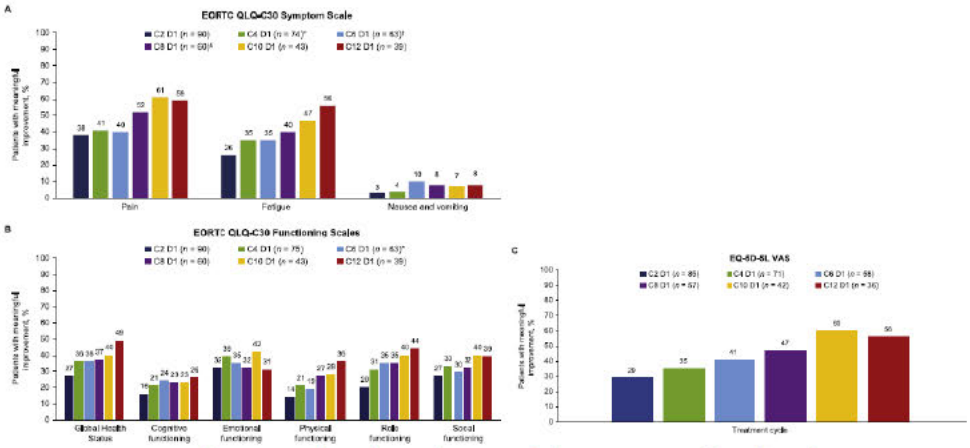


Figure 19 Percentage of patients who achieved meaningful improvement from baseline in EORTC QLQ-C30 (A) symptom, (B) functioning scales, and (C) EQ-5D-5L VAS based on a literature-defined threshold.

Meaningful improvement was defined as a ≥10-point decrease from baseline for symptom scales and ≥10-point increase from baseline for functioning scales and ≥7 points for the EQ-5D-5L VAS. C = cycle; D = day; EQ-5D-5L VAS = EuroQol 5 Dimension 5 Level visual analogue scale. (A)a n = 75 for fatigue.b n = 62 for pain.c n = 58 for pain. (B)a n = 62 for global health status.

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

The focus of the present comparative analysis presented in this application is on OS and PFS of elranatamab and teclistamab. There was no difference in the definition of these outcomes in the MagnetisMM-3 study and the MajesTEC-1 study. In both studies OS was defined as *time from date of first dose until death (all-cause) or study completion, whichever occurred first*. Similarly, PFS was in the two studies defined as *time from the date of initial dose until progressive disease per IMWG criteria, or death due to any cause*.

Furthermore, both studies did also use two of the same PRO instruments to measure changes in patients HRQoL: the EORTC QLQ-C30 and the EuroQol 5D-5L questionnaires.

7.1.2 Method of synthesis

As there is no head-to-head randomized controlled trial comparing elranatamab to teclistamab, an indirect treatment comparison was made. Indirect treatment comparison methods can be used, when patient data at individual level are available from one trial, but only summary data are available from another trial. A commonly used method for indirect treatment comparison is the Matching-Adjusted Indirect treatment Comparison (MAIC) method. MAIC is a statistical method trying to account for cross-trial differences by applying propensity score weighting to balance covariate distributions across populations in the trials. The MAIC method can be anchored or unanchored. The unanchored MAIC is usually chosen in cases, where there is no connected network between the trials compared, which is the case dealing with single-arm trial, e.g. like MagnetisMM-3 and MajesTEC-1 trials. The unanchored MAIC was therefore chosen as the method for indirect treatment comparison to evaluate the comparative effectiveness of elranatamab in relation to teclistamab with the focus upon OS and PFS outcomes (64).

Data Sources

For elranatamab, individual patient data (IPD) from MagnetisMM-3 (Cohort A (BCMA-naïve); *N* = 123) were used (47[redacted]). Published summary data from MajesTEC-1 (*N* = 165) reported in Sidana et al. were used for PFS and OS for teclistamab (66). Furthermore, baseline characteristics and response outcome data for the MajesTEC-1 study were obtained from Moreau et al. (37). Length of follow-up was 14.7 months for elranatamab from the MagnetisMM-3 trial following the data cut-off date of March 14 2023 as reported in Lesokhin et al. (47) and 14.1 months for teclistamab from the MajesTEC-1 trial as reported in Moreau et al. (37) and for ~23 months for Sidana et al. (66).

The latest data cut-off date of September 11 2023 for elranatamab – median duration of follow-up of 17.6 months – as reported in Tomasson et al. (52) was not included in the MAIC (64). However, Tomasson et al.'s results demonstrated sustained clinical efficacy of elranatamab, why this supports the results found in the MAIC (64).

Matching-Adjusted Indirect Comparison (MAIC)

To adjust for cross-trial differences, patients from MagnetisMM-3 were reweighted to match the selected key baseline characteristics of patients who received teclistamab in the MajesTEC-1 study as reported by Moreau et al. (37). Weights were determined using a propensity score-type logistic regression via the method of moments (67) based on age, median time since diagnosis, International Staging System (ISS) disease stage, high-risk cytogenetics as defined by the presence of one of t(4;14), t(14;16), or del17p, extramedullary disease, number of prior lines of therapy, Eastern Cooperative Oncology Group performance status (ECOG PS), penta-drug exposed and penta-drug refractory status (64). The complete list of prognostic variables (PVs) and effect modifiers (EMs) was derived from an SLR conducted on clinical and RWE studies in relapsed refractory multiple myeloma (RRMM) with a focus on PVs/EMs, a review of previous indirect treatment comparison (ITC) studies in triple class exposed/refractory (TCE/R) MM, and clinical opinions. The only difference in the list of PVs/EMs for the endpoints of OS and PFS is gender. Gender was identified as a PV/EM for OS in the SLR. Therefore, it was only included in the adjustment for OS.

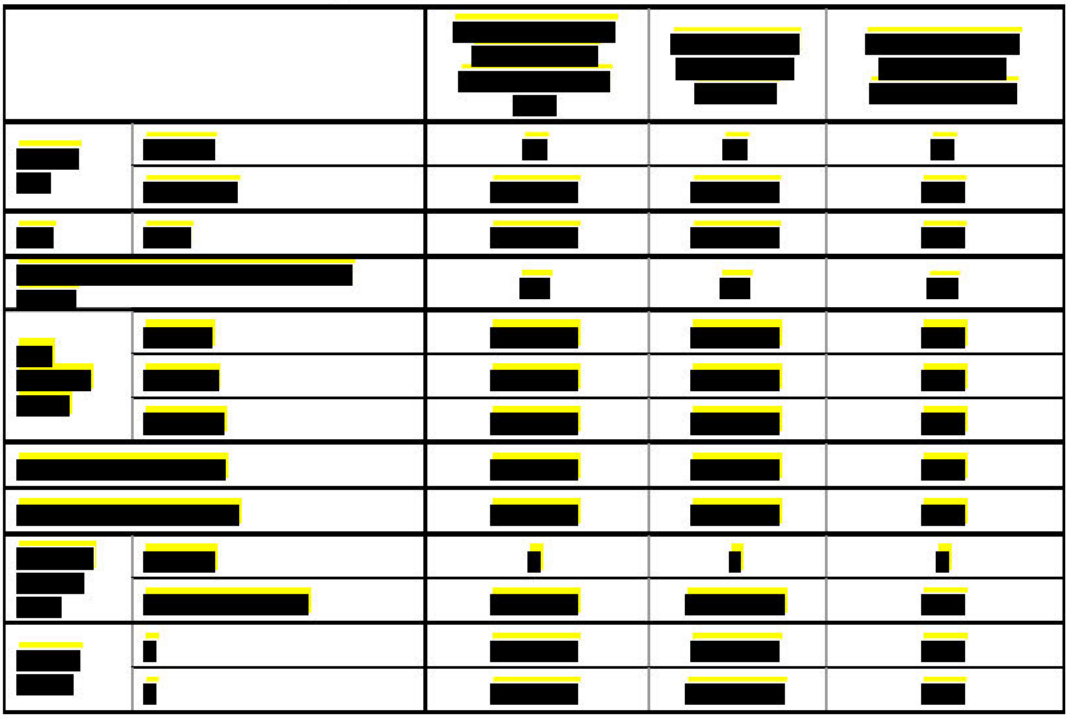
The distribution of weights for elranatamab vs. teclistamab are presented in Figure 20 and Figure 21 below for the two outcome measures OS and PFS.

Figure 20 Distribution of weights: Elranatamab vs Teclistamab – overall survival (OS)
Source: Data on file (64)

Figure 21 Distribution of weights: Elranatamab vs Teclistamab – progression-free survival (PFS)
Source: Data on file (64)

Table 11 presents the baseline characteristics for cohort A from the MagnetisMM-3 study post-matching (weighting). In addition, the table also shows unweighted baseline characteristics from both the MagnetisMM-3 (elranatamab) (first column) and the MajesTEC-1 (teclistamab) study (second column).

Table 11 Pre- and Post-matching baseline characteristics: Elranatamab vs. Teclistamab



[redacted]

Only PFS and OS were adjusted as KM curves for TTD were not available.
In MagnetisMM-3, certain adjusted baseline characteristics contained missing values. To potentially increase the sample size, variables in the elranatamab individual patient level data that contained missing data were imputed in the sensitivity analysis. This means that a random sample of the observed data was used to run the imputation.

Table 12 presents the two baseline variables with missing values, [redacted], respectively, including the percentage of data that were missing and therefore imputed in the sensitivity analysis.

Table 12 Overview of variables with missing values from the elranatamab individual patient level data

[redacted]

Table 13 summarizes the base case settings and scenario analyses.

Table 13 Overview of base case settings and scenario analyses for MAIC (64).

Scenario	Settings
Naïve comparison	Unadjusted comparison of elranatamab and comparator
Base case	Adjusting for: age, median time since diagnosis, ISS disease stage, high-risk cytogenetics as defined by the presence of one of t(4;14), t(14;16), or del17p, extramedullary disease, number of prior lines of therapy, ECOG PS, penta-drug exposed and penta-drug refractory status. Sex was included in the analysis for OS.
Sensitivity analysis	Using imputed data for variables in MagnetisMM-3 data where there were missing data (imputed based on a random sample of the observed data)

To assess time-to-event endpoints, Kaplan–Meier's curves from MajesTEC-1 were digitized following the methodology outlined by Guyot et al. (67). Subsequently, a

weighted (based on the weights assigned for the adjustment of baseline characteristics) Cox proportional hazards model was employed to estimate each hazard ratio (HR) and its respective 95% CI. Conclusions regarding significantly better or worse outcomes were drawn based on whether the 95% CI excluded 1 (for odds ratio/HR) or 0 (for rate difference). Numeric conclusions are based on the HR/odds ratio value. Effective sample size (ESS) was assessed after conducting the MAIC. The ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate (68). The ESS is one key statistic which shows the statistical power of a MAIC analysis. A small ESS is indicative of large differences in patient populations between the comparators.

Comparability assessment

As MajesTEC-1 excluded patients with ECOG PS >1, whereas MagnetisMM-3 allowed enrolment of patients with an ECOG PS of ≤2, patients with an ECOG PS of 2 in MagnetisMM-3 trial were removed from the analysis (resulting in N=116).
In the MajesTEC-1 trial, extramedullary disease was defined as the presence of one or more extramedullary soft-tissue lesion. This definition was slightly different from the definition in the MagnetisMM-3 trial where it was defined as the presence of any plasmacytoma (extramedullary and/or paramedullary) with a soft-tissue component. Therefore, a new variable for extramedullary plasmacytomas was created for elranatamab using the MagnetisMM-3 IPD. This variable more closely follows the definition of extramedullary disease in MajesTEC-1 and was used in the present MAIC analysis.

Between the two trials, median age, proportion of male patients, median time since diagnosis, and proportion with high cytogenetic risk were similar. MagnetisMM-3 had a higher proportion of patients with ISS stage III and a lower proportion of patients who were ISS stage I compared with MajesTEC-1. In addition, there was a higher proportion of patients with extramedullary disease and TCR or penta-drug refractory status in MagnestisMM-3 versus MajesTEC-1. After adjustment in the MAIC, the key prognostic variables and effect modifiers (i.e. age, gender (for OS endpoint only), median time since diagnosis, ISS stage, high-risk cytogenetics, extramedullary disease, number of prior lines of therapy, ECOG performance status, and penta-drug exposed and penta-drug refractory status) were comparable between patients who received elranatamab and those who received teclistamab.

7.1.3 Results from the comparative analysis

In Table 14 below the overall results of the MAIC analysis (64) are presented. Again, be aware of that the latest data cut-off date of September 11 2023 for elranatamab by Tomasson et al. (52) was not included in this comparison. But efficacy results of elranatamab demonstrated sustainability. Further, it has to be remembered that OS results of elranatamab is not mature yet, as the trial is still ongoing.

Table 14 Results from the comparative analysis of elranatamab vs. teclistamab for patients with triple-class exposed/refractory multiple myeloma. Source: (64).§

Multiple myeloma Outcome measure	Elranatamab (N=116)	Teclistamab (N=165)	Result
OS, time point	Median: Not estimable at median FU 14,7 months	Median: 21.9 months (95% CI, 16.0–NE) at ~23 months FU	Unweighted HR (95% CI): 1.05 (0.74, 1.50) Weighted HR, base-case (95% CI): 0.66 (0.42, 1.03) Weighted HR, sensitivity (95% CI): 0.79 (0.52, 1.18)
PFS, time point	Median: Not estimable at median FU 14,7 months	Median: 11.3 months (95% CI: 8.8, 16.4) at ~23 months FU	Unweighted HR (95% CI): 0.86 (0.61, 1.21) Weighted HR, base-case (95% CI): 0.59 (0.39, 0.89) Weighted HR, sensitivity (95% CI): 0.65 (0.44, 0.95)

§. Data for Quality of Life is not included as no MAIC was performed on this outcome.

7.1.4 Efficacy – results per OS

In the naïve analysis, the OS of elranatamab was similar to teclistamab (Table 15). Following MAIC adjustment, the HR improved and elranatamab was associated with a numerically longer OS compared with teclistamab, yet results were not statistically significant. The HR of elranatamab compared with teclistamab was 1.053 (0.738,1.502) before weighting and 0.660 (0.423, 1.030) after weighting. Like the base case, the OS of elranatamab was in the sensitivity analysis numerically longer than teclistamab following MAIC adjustment, yet the results were not statistically significant (Table 15).

Table 15 Hazard ratios of OS: elranatamab vs. teclistamab. Source: (64).

Scenario	ESS	HR (95% CI)	p-value
Naïve comparison	116	1.053 (0.738, 1.502)	0.777
Base case*	73	0.660 (0.423, 1.030)	0.067
Sensitivity analysis# (imputation)	87	0.785 (0.520, 1.183)	0.247

Abbreviations: CI = confidence interval; ESS = effective sample size; HR = hazard ratio; OS = overall survival
* adjusted for age, sex, median time since diagnosis, ISS stage, high-risk cytogenetics, extramedullary disease, number of prior lines of therapy, ECOG performance status, and penta-drug exposed and penta-drug refractory status
# using imputed data for variables in MagnetisMM-3 data where there were missing data (imputed based on a random sample of the observed data)

Figure 22 shows the Kaplan Meier curves for OS for elranatamab (unweighted and weighted) and teclistamab.

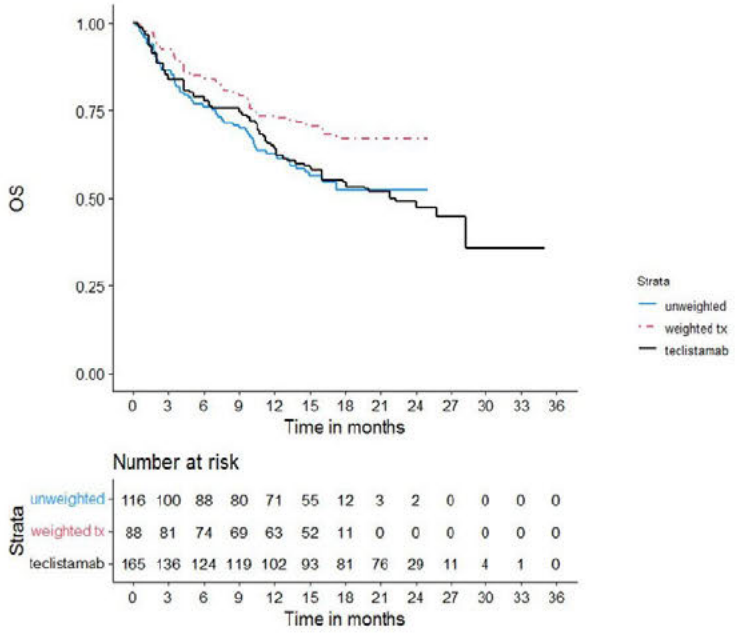


Figure 22 OS results for elranatamab in MagnetisMM-3 versus teclistamab in MajesTEC-1 (64). Source: (64).

CI: confidence interval; HR: hazard ratio; NE: not estimable; OS: overall survival

Table 16 provides the OS-rates at 6, 12 and 15 months for both the unadjusted (MagnetisMM-3) cohort A population and the MAIC population. Both estimates are based on the March 14, 2023, data cut of MagnetisMM-3, which represented a median follow-up of 14.7 months. Due to this follow-up period it isn't possible to provide OS rates for time periods exceeding 15 months.

Table 16: OS rates at 6, 12 & 15 months: Unadjusted and MAIC adjusted for elranatamab.

	Median OS follow up		
[redacted]		[redacted]	
	OS % (95% CI)		
Probability of being event-free at month	6	12	15
[redacted]			

Source: Data on file (50), Data on file (64)

7.1.5 Efficacy – results per PFS

In the MAIC analysis elranatamab was associated with significantly longer PFS than teclistamab. The PFS HR compared with teclistamab was 0.856 (0.608, 1.205) before weighting and 0.586 (0.386, 0.889) after weighting (Table 17). The sensitivity analysis results were consistent with the base case.

Table 17 Hazard ratios of PFS: elranatamab vs. teclistamab. Source: (64).

Scenario	ESS	HR (95% CI)	p-value
Naïve comparison	116	0.856 (0.608, 1.205)	0.373
Base case*	73	0.586 (0.386, 0.889)	0.012
Sensitivity analysis# (imputation)	87	0.646 (0.439, 0.949)	0.026

Abbreviations: CI = confidence interval; ESS = effective sample size; HR = hazard ratio; OS = overall survival
* adjustied for age, median time since diagnosis, ISS stage, high-risk cytogenetics, extramedullary disease, number of prior lines of therapy, ECOG performance status, and penta-drug exposed and penta-drug refractory status
# using imputed data for variables in MagnetisMM-3 data where there were missing data (imputed based on a random sample of the observed data)

Figure 23 shows the Kaplan Meier curves for PFS for elranatamab (unweighted and weighted) and teclistamab.

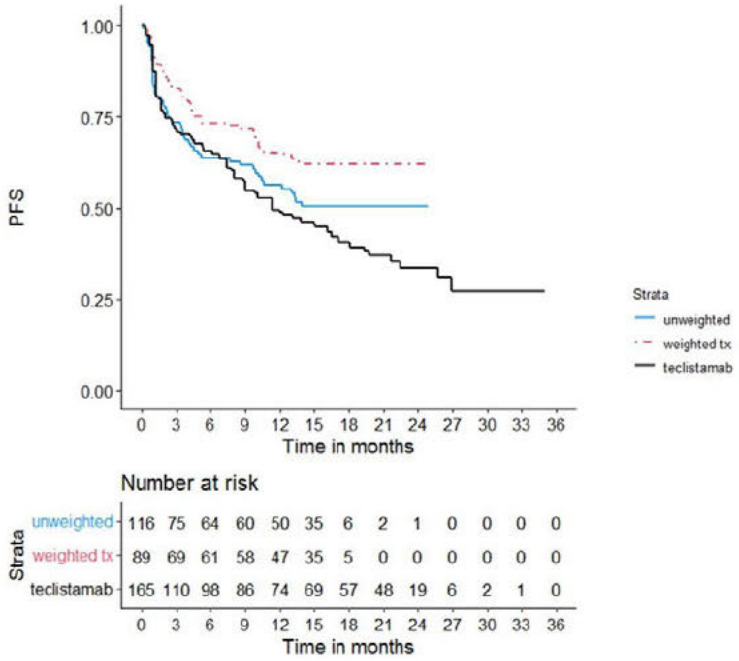


Figure 23 PFS results for elranatamab in cohort A of MagnetisMM-3 vs. teclistamab in MajesTEC-1. Source: (64).
CI: confidence interval, HR: hazard ratio; NE_ not estimable; PFS: progression-free survival

Table 18 provides the PFS-rates at 6, 12 and 15 months for both the unadjusted (MagnetisMM-3) cohort A population and the MAIC adjusted population. Both estimates are based on the March 14, 2023, data cut of MagnetisMM-3, which represented a median follow-up of 14.7 months. Due to this follow-up period it isn't possible to provide PFS rates for time periods exceeding 15 months.

Table 18: PFS rates at 6, 12 & 15 months: Unadjusted and MAIC adjusted for elranatamab.

	Median PFS follow up		
[redacted]		[redacted]	
	PFS % (95% CI)		
Probability of being event-free at month	6	12	15
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Source: Data on file (50), Data on file (64)

7.1.6 Efficacy – results per HRQoL

To contextualize the patient-reported outcome (PRO) benefit derived from elranatamab, a comparison with published teclistamab results was performed. Data for elranatamab were obtained from the March 14 2023 data cut of MagnetisMM-3, which represented a median follow-up of 14.7 months and was the source of a recent publication on the elranatamab PRO data (Mohty et al 2024). Data from both Cohort A and B were combined in this analysis.

Data for teclistamab were obtained from Martin et al (2024) which summarized the PROs from the MajesTEC-1 trial after 14.1 months of follow-up (results from 22.8 months of follow-up are referenced in the article as part of a sensitivity analysis but were not reported; the authors indicated there was no change to the overall results with this additional follow-up).

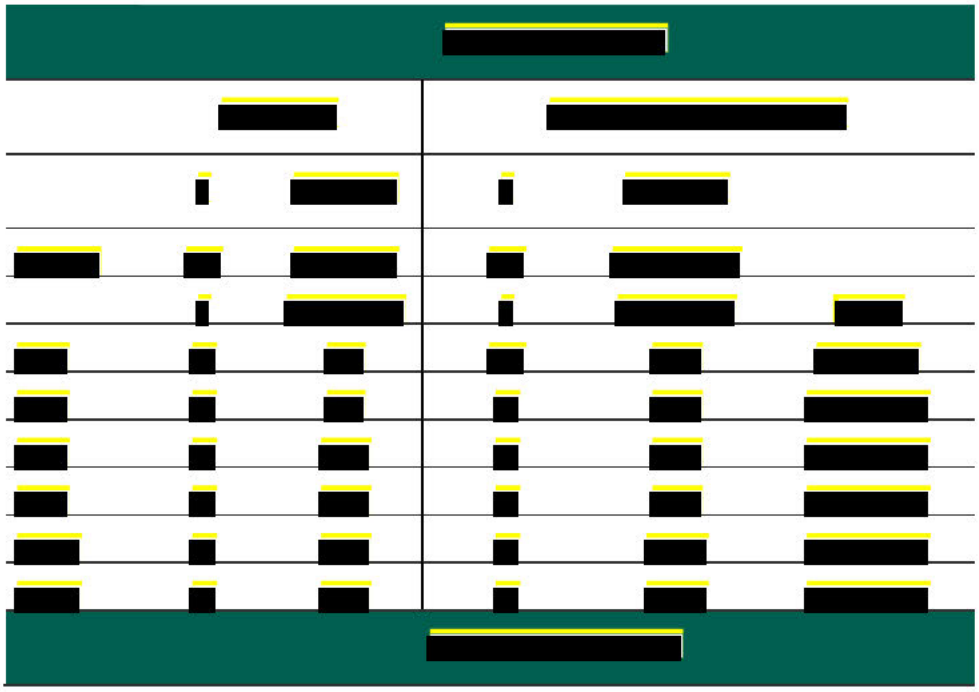
No matching-adjusted indirect treatment comparison (MAIC) was employed to evaluate the comparative effectiveness of elranatamab in relation to teclistamab with regards to HRQoL. It should be noted, that any naïve comparisons across trials are subject to several biases and this comparison is no exception, with a few additional challenges. First, the set of measures are not the same across trials. We were only able to contextualize the specific PROs at the specific time points as reported by Martin et al (2024). This was limited to select EORTC-QLQ C30 domain scores (pain, fatigue, nausea and vomiting, and the general health score [GHS]) and the visual analog scale (VAS) of the EQ-5D. We cannot determine how changes in other patient-relevant measures (eg, disease symptoms from the EORTC-QLQ MY20 or patient global impression of change [PGIC]) would differ across trials or how changes would compare at different timepoints not included in Martin et al (2024). Additionally, although 95% confidence intervals are reported visually in Martin et al (2024) they are not reported numerically, which makes any reliable statistical comparison impossible.

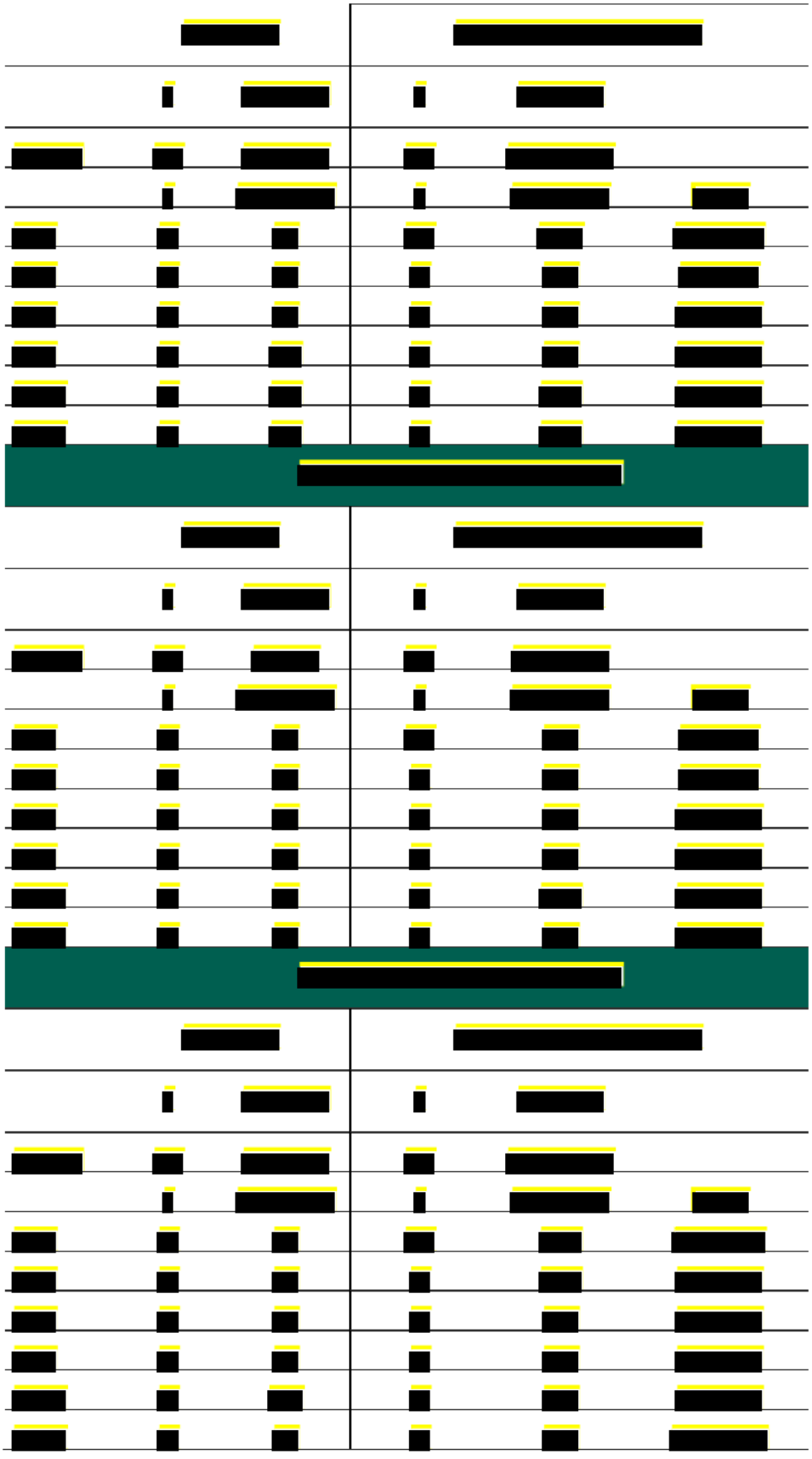
Aside from these challenges, the typical limitations also apply. The specific methods of administering the PRO measures across trials could differ (e.g., instructions given to the patient, when the administrations took place in relation to other study procedures, etc.), which would introduce measurement bias. Similarly, the geographic footprint of the two trials varied so different proportions of different language versions of the PRO measures

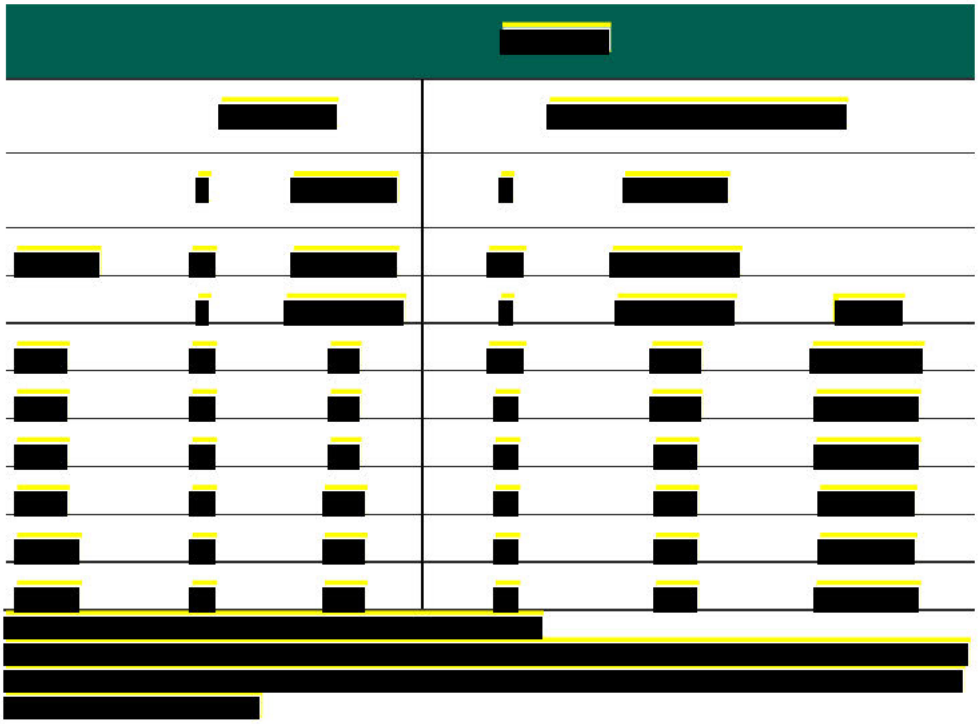
were administered. Across both trials, such versions would be linguistically validated but it is not clear the extent to which the quantitative properties (such as the sensitivity to detect change) of these different language versions would equate to one another. Lastly, the patient populations of these two trials differ. For example, MagnetisMM-3 included patients with an ECOG performance score of 2, while MajesTEC-1 did not. Proportions of patients with extramedullary disease, triple-class refractoriness, and other characteristics all varied and it is not clear the extent to which these factors could affect PROs and changes over time. The baseline values of these PRO measures were also different between the two trials, and it is not clear the degree to which changes from baseline would be influenced by the baseline value itself.

With these limitations in mind, the least square mean (LSM) changes from baseline for elranatamab from MagnetisMM-3 and for teclistamab from MajesTEC-1 are reported in Table 19. The results are broadly similar. A naïve comparison between elranatamab and teclistamab would suggest similar trajectories of both pain and fatigue over the specific time points included in Martin et al (2024). Although the decreases of both symptoms were numerically larger in MajesTEC-1 for some time points, the baseline values were also higher and patients across both trials ultimately had nearly identical scores by C12D1 (ie, approximately [redacted] for pain and fatigue, respectively). The reverse was true for nausea and vomiting in which case the decreases were numerically larger in MagnetisMM-3 but patients also had higher baseline values with the scores being nearly identical by C12D1 (ie, approximately [redacted]). For both the general health score (GHS) and the EQ-5D-5L VAS, numerically higher baseline scores were observed in MagnetisMM-3 and, at select time points, numerically higher improvements in MajesTEC-1. Ultimately, similar scores across both trials were observed by C12D1 (ie, [redacted] for GHS and [redacted] for EQ-5D VAS).

Table 19: Patient-reported outcome changes from baseline for elranatamab in MagnetisMM-3 and teclistamab in MajesTEC-1.







Especially considering the limitations of such a comparison, which is associated with significant sources of bias and uncertainty, the results would suggest an equivalent benefit of both teclistamab and elranatamab with respect to changes in PROs while on treatment.

7.1.7 Overall assessment of the indirect comparison of elranatamab and teclistamab in terms of OS and PFS

The results from the MAIC analyses showed that - after adjusting for cross-trial differences with elranatamab patients (MagnetisMM-3) being reweighted to match the selected key baseline characteristics of teclistamab patients (MajesTEC-1) - elranatamab had an OS similar to teclistamab (although numerically higher), as well as a significantly longer PFS compared with teclistamab (64).

However, the MAIC method has the limitation that it is only possible to adjust baseline variables that are mutually reported in the trials, which is not always the case in trials with slightly different design. What is not possible with MAIC is to address the potential unmeasurable differences between the trials. Although the underlying MAIC approach was thorough and based on extensive literature reviews, differences cannot be ruled out. Furthermore, it was possible in the MAIC analysis to adjust for the notable difference in proportion of patients with TCR multiple myeloma in the MagnetisMM-3 trial (97%) versus the MajesTEC-1 trial (78%) due to the resulting reduction in effective sample size (ESS) of the elranatamab patients primarily. This is, however, likely to be conservative as patients with TCR multiple myeloma tend to have poorer outcomes than those who are simply TCE and thus not being an advantage for elranatamab. Finally, it has to be noted that the efficacy results of elranatamab from the latest data cut-off date of September 11 2023 was not included in the MAIC analysis, but that these efficacy

results – both PFS and OS – would have reassured the sustainability of the elranatamab results. Adding to this also that the OS results of elranatamab is not mature yet, since the MagnetisMM-3 trial is still ongoing.

It should be noted, that updated results of a matching-adjusted indirect comparison of elranatamab were recently presented at EHA June 2024. These results show that indirect comparison of elranatamab versus teclistamab in patients with triple-class exposed/refractory multiple myeloma, in some of the presented analyses, shows a statistically significant longer OS and PFS and a numerically longer DOR than teclistamab. (82). At the time of application, it has not been possible to include these results in the assessment.

With this indirect comparison of elranatamab versus teclistamab (64) focusing on OS and PFS it can though conservatively be concluded that the two treatment options at least have similar outcomes. This supports the decision to undertake a cost-minimization analysis in the health economic part of the application for elranatamab.

8. Modelling of efficacy in the health economics analysis

Even though a cost-minimisation analysis was conducted, it was necessary to include OS and PFS as parameters in the model in order to model survival and progression of the RRMM patients. TTD was also included to model discontinuation of treatment in patients on elranatamab and teclistamab.

In the base case 1 analysis, to be consistent with the comparative analysis of elranatamab versus teclistamab in the MAIC (Section 7) the efficacy results (OS, PFS and TTD) used for elranatamab in the cost-minimisation analysis was those with a data cut-off date March 14 2023 and a median duration of follow-up of 14.7 months as presented by Lesokhin et al. (47). In base case 2, OS and PFS for elranatamab and teclistamab were modelled based on the data-cut from 4 January 2023 in MajesTEC-1.

8.1 Presentation of efficacy data from the clinical documentation used in the model

In base case 1, MagnetisMM-3 data on OS and PFS was applied for both elranatamab and teclistamab based on the assumption that the efficacy of the two treatment options is comparable; hence the feasibility of a cost-minimization analysis (see section 7 above). TTD data on elranatamab came from MagnetisMM-3 and included patients with an ECOG PS of 2. OS and PFS (and TTD) in the health economic model are based on the non-weighted KM curves from MagnetisMM-3. As mentioned in section 7.1.2 it is not possible to present a weighted TTD as KM curves for TTD were not available and there is therefore consistency between the chosen methods for generating both OS, PFS and TTD. TTD for teclistamab was obtained from *Figure 16* in the DMC's evaluation of teclistamab, which was based on data from MajesTEC-1 (31). OS, PFS and TTD were extrapolated beyond the time periods of the trials.

In the base case 2 analysis, the OS curve and PFS curve for teclistamab from *Figure 5* and *Figure 10,* respectively, in the DMC evaluation of teclistamab were applied. The curves were from the MajesTEC-1 trial on teclistamab with a median duration of 22.8 months (4 January 2023, Sidana et al. 2023). Based on these curves, we have estimated the relevant extrapolation parameters and entered them into the model. The extrapolation parameters have been estimated based on more than 400 data points from each of the two curves. If the Danish Medicines Council wishes to prepare calculations based on the exact parameters used in the health economic analysis of teclistamab, these can be inserted in the Survival sheet in cells Y1695:Y1696 for OS and cells Y3379:Y3380 for PFS. In base case 2, the OS and PFS curves from the DMC evaluation of teclistamab were applied to both teclistamab and elranatamab. TTD in base case 2 was based on *Figure 16* for teclistamab and data from MagnetisMM-3 for elranatamab.

In the following sections, the extrapolation of OS, PFS and TTD in the model is described.

8.1.1 Extrapolation of efficacy data

Standard parametric fits (i.e., Weibull, log-normal, exponential, log-logistic, Gompertz, generalised gamma and gamma) were used on the Kaplan-Meier (KM) curves based on either 14.7-month data from cohort A in the MagnetisMM-3 or 22.8-months data from MajesTEC-1. The best parametric fits were decided based on both the visual checks and Akaike information criterion (AIC)/Bayesian information criterion (BIC) statistics.

8.1.1.1 Extrapolation of overall survival

In both base cases, life tables from the Danish general population from Statistics Denmark were included in the model to ensure that the risk of death in the model was not lower than the risk of death of the general population. The exponential parametric curve was selected based on clinical plausibility and statistical fit. See Appendix D for a justification for selecting this curve.

Table 20 Summary of assumptions associated with extrapolation of OS.

Method/approach	Description/assumption
Data input	MagnetisMM-3 and MajesTEC-1
Model	Parametric survival model
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	Base case 1: Log-normal Base case 2: N/A
Function with best BIC fit	Base case 1: Exponential Base case 2: N/A
Function with best visual fit	Base case 1: Weibull, exponential and gamma Base case 2: N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	[redacted]

Method/approach	Description/assumption
	[redacted]
Function with the best fit according to external evidence	Not assessed due to missing evidence
Selected parametric function in base case analysis	Base case 1: Exponential Base case 2: N/A
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/crossover	No
Assumptions of waning effect	No
Assumptions of cure point	No

[redacted]

Figure 24 [redacted]

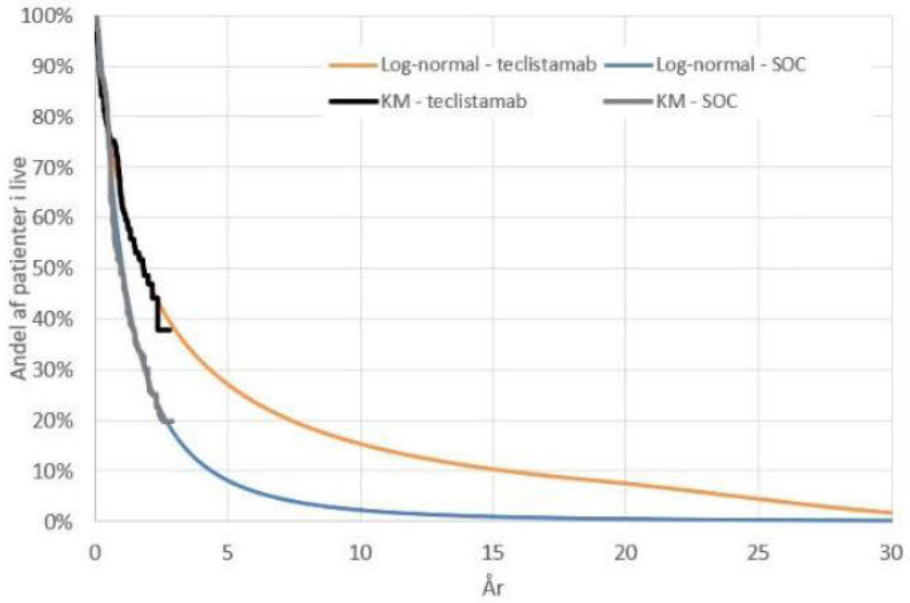


Figure 25 Base case 2: Observed and extrapolated OS curves for teclistamab from MajesTEC-1. Source: Figure 5 from DMC teclistamab evaluation.

8.1.1.2 Extrapolation of progression-free survival

PFS was also extrapolated based on individual parametric fits. The fitted PFS curves were capped by the fitted OS curves so that the PFS curves were never higher than the OS curves.

Table 21 Summary of assumptions associated with extrapolation of PFS.

Method/approach	Description/assumption
Data input	MagnetisMM-3 and MajesTEC-1
Model	Parametric survival model
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	Base case 1: Log-normal Base case 2: N/A
Function with best BIC fit	Base case 1: Generalized gamma Base case 2: N/A
Function with best visual fit	Base case 1: Exponential, gamma and Weibull

Method/approach	Description/assumption
	Base case 2: N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	Not assessed due to missing evidence
Function with the best fit according to external evidence	Not assessed due to missing evidence
Selected parametric function in base case analysis	Base case 1: Weibull Base case 2: Log-normal
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/crossover	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 26 [redacted]

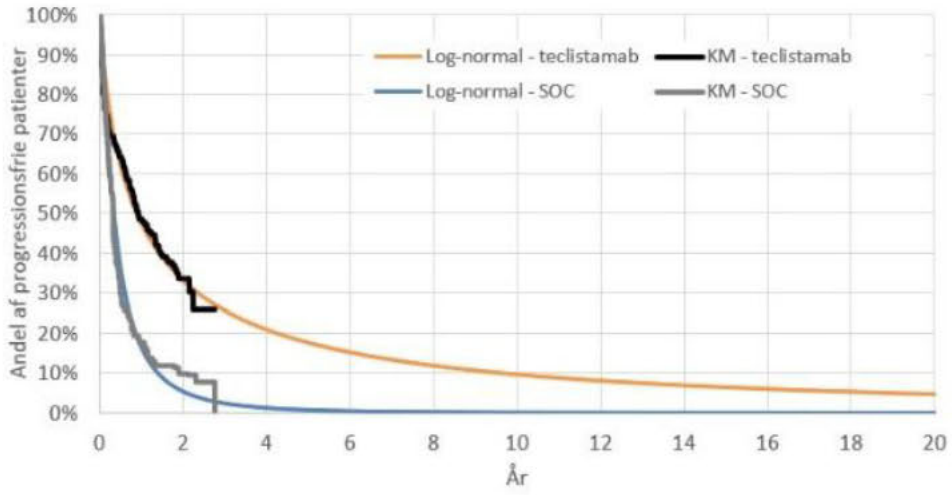


Figure 27 Observed and extrapolated PFS curves for teclistamab from MajesTEC-1. Source: Figure 10 from DMC teclistamab evaluation.

8.1.1.3 Extrapolation of time to treatment discontinuation

Patients with multiple myeloma may discontinue treatment for different reasons, such as AEs, disease progression, investigator-determined or patient preference. Therefore, TTD curves were fitted to account for the time spent on the treatment within the PFS state, and patients were partitioned into on and off treatment while remaining progression-free. In both base cases, for elranatamab, TTD was based on data from MagnetisMM-3 and extrapolated beyond the follow-up period with the standard parametric models. For teclistamab, the extrapolation of TTD was based on *Figure 16* from the DMC's evaluation of teclistamab (31) that shows both the observed and the extrapolated TTD curve for patients treated with teclistamab. The method applied is described in more details in Appendix D.

Table 22 Summary of assumptions associated with extrapolation of TTD in both base cases.

Method/approach	Description/assumption
Data input	MagnetisMM-3 and MajesTEC-1
Model	Standard parametric models
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	Elranatamab: log-normal Teclistamab: N/A
Function with best BIC fit	Elranatamab: log-normal Teclistamab: N/A

Method/approach	Description/assumption
Function with best visual fit	Elranatamab: exponential, Weibull and gamma Teclistamab: N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	Not assessed due to missing evidence
Function with the best fit according to external evidence	Not assessed due to missing evidence
Selected parametric function in base case analysis	Elranatamab: Weibull Teclistamab: log-normal
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/crossover	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 28 [redacted]

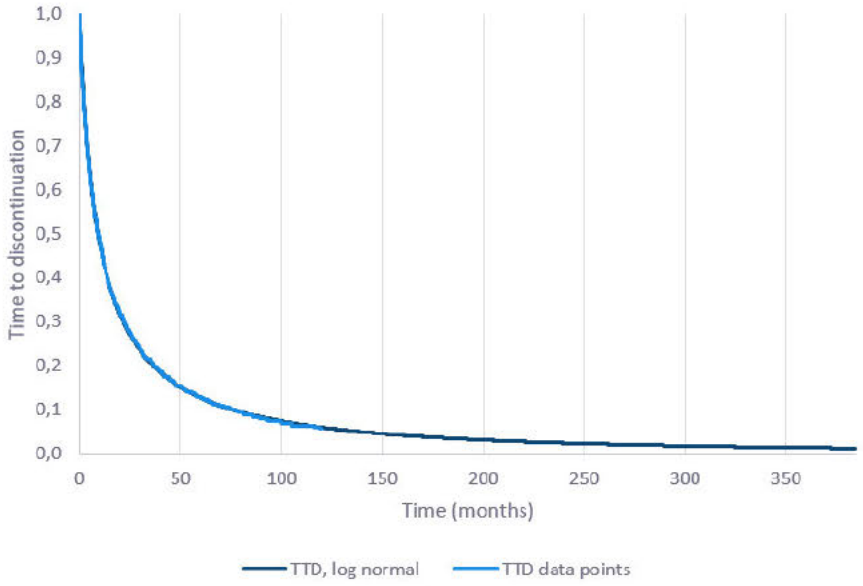


Figure 29 TTD for teclistamab. Source: (31).

8.1.2 Calculation of transition probabilities

Not applicable.

Table 23 Transitions in the health economic model *(Table 23 is Not Applicable)*

Health state (from)	Health state (to)	Description of method	Reference
N/A	N/A	N/A	N/A

8.2 Presentation of efficacy data from additional documentation

No other data than data from MagnetisMM-3 and MajesTEC-1 was included in the present application.

8.3 Modelling effects of subsequent treatments

Subsequent treatment was included in the model. There was no difference in terms of which treatments patients would subsequently receiver after treatment with elranatamab and teclistamab. The included subsequent treatments were based on the DMC evaluation of teclistamab, where the DMC stated that patients would receive PomDex or CarDex in a 50/50 split (31). Only the costs of subsequent treatments were included; no effects were included, as the present analysis was a cost-minimisztion analysis. Please see section 11.6 for an explanation of how the costs of subsequent treatments were accounted for in the model.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

In this application, a cost-minimisation analysis was conducted. The cost-minimisation analysis was built on the premise that elranatamab and teclistamab exhibit equivalent efficacy and safety profiles as supported by evidence presented in the previous sections 6 and 7, and the later section 9. The model incorporates distinct TTD curves for elranatamab and teclistamab following the section 8.1.1.3 above. The argument for differentiating the TTD-curves is based on the observation that although elranatamab and teclistamab are evaluated to have equivalent efficacy outcomes, these results are obtained with varying durations of treatment. Specifically, the median treatment duration for elranatamab was 5.6 months (range: 0.03–24.4 months) in MagnetisMM-3 and 9.3 months (range: 0.2–33.6 months) for teclistamab in MajesTEC-1. Therefore, we regarded it as justifiable to incorporate this anticipated difference in treatment duration into the cost-minimisation model. To assess the impact of the assumption of different TTD between elranatamab and teclistamab, respectively, a scenario analysis has been included. Via the drop-down menu in cell O39 in the 'Survival curves' tab, it is possible to assume the same TTD for both treatments.

Table 24 to Table 26 below present estimates for the modelled average and modelled median of OS, PFS and TTD predicted by the extrapolation models (undiscounted estimates with no half-cycle correction). In addition, the medians from the trials are presented. It should be noted that it isn't possible to calculate the average duration of treatment from the study, as not all patients in the study have discontinued treatment at the specified data cut.

Table 24 OS estimates in the model.

	Modelled average for OS (reference to source Excel sheet)	Modelled median for OS (reference to source Excel sheet)	Observed OS median from relevant study
Elranatamab	Base case 1: 26.52 ('Survival curves' sheet) Base case 2: 62.04	Base case 1: 18.17 ('Survival curves' sheet) Base case 2: 20.01	Median duration of OS was not reached before data cut-off on March 14 2023 (95% CI: 13.9; NE) (47)
Teclistamab	Base case 1: 26.52 ('Survival curves' sheet) Base case 2: 62.04	Base case 1: 18.17 ('Survival curves' sheet) Base case 2: 20.01	21.9 months (96% CI: 16,0; NE) (66)

Note: OS is identical for elranatamab and teclistamab due to the assumption of similar efficacy based on the evidence from the MAIC (64). Equal eficacy is the rationale for choosing a cost-minimization approach. Data is based on data from MagnetisMM-3.

Table 25 PFS estimates in the model.

	Modelled average for PFS (reference to source Excel)	Modelled median for PFS (reference to source Excel)	Observed PFS median from relevant study
Elranatamab	Base case 1: 24.87 ('Survival curves' sheet) Base case 2: 42.19	Base case 1: 15.41 ('Survival curves' sheet) Base case 2: 10.35	Median PFS was not reached before data cut-off on March 14 2023 (95% CI: 9.9; NE) (47)
Teclistamab	24.87 ('Survival curves' sheet) Base case 2: 42.19	15.41 ('Survival curves' sheet) Base case 2: 10.35	11.3 months (96% CI: 8.8; 16.4) (38)

Note: OS is identical for elranatamab and teclistamab due to the assumption of similar efficacy based on the evidence from the MAIC (64). Equal efficacy is the rationale for choosing a cost-minimisation approach. Data is based on data from MagnetisMM-3 and Majestec-1.

Table 26 TTD estimates in the model.

	Modelled average for TTD (reference to source Excel)	Modelled median for TTD (reference to source Excel)	Observed TTD median from relevant study
Elranatamab	Base case 1: 15.53 ('Survival curves' sheet) Base case 2: 15.64	Base case 1: 6.67 ('Survival curves' sheet) Base case 2: 6.67	Median duration of treatment was 5.6 months (range: 0.03–24.4) from data cut-off on March 14 2023 (47)
Teclistamab	Base case 1: 21.05 ('Survival curves' sheet) Base case 2: 30.43	Base case 1: 8.97 ('Survival curves' sheet) Base case 2: 8.97	Median treatment duration was 9.3 months (range: 0.2–33.6) from data cut-off on January 2023 per DMC evaluation (31)

Note: the difference in the modelled average and median TTD between elranatamab and teclistamab is because the difference in TTD between elranatamab and teclistamab was accounted for in the model.

Table 27 presents the modelled average treatment length and time in the model health states.

Table 27 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half-cycle correction.

Treatment	Modelled average treatment length (months)	PFS (months)	PPS (months)	Death (months)
Base case 1				
Elranatamab	15.53	24.87	1.65	357.54
Teclistamab	21.05	24.87	1.65	357.54
Base case 2				
Elranatamab	15.64	42.19	19.84	322.03
Teclistamab	30.43	42.19	19.84	322.03

Note: the time in the model health states is identical for elranatamab and teclistamab due to the expectation of similar OS and PFS between elranatamab and teclistamab. PPS = Post Progression Survival.

9. Safety

9.1 Safety data from the clinical documentation

The MagnetisMM-3 study consisted of cohort A (N = 123) and Cohort B (N= 64) (46,[redacted]). Patients in Cohort A did not receive prior BCMA-directed therapy. Cohort B consisted of patients previously exposed to BCMA-directed ADC and/or CAR T-cell therapies, hence not relevant for this comparison. The safety findings were generally consistent between Cohort A and Cohort B. As in the rest of the application presenting efficacy and costs results of elranatamab the particular focus of the safety data for elranatamab will be on the Cohort A. This patient population did not receive prior BCMA-directed therapy (N=123) and is therefore of relevance for the use of elranatamab and for the comparison with teclistamab. Generally, safety findings were consistent between Cohort A and Cohort B.

The safety data in this application has the same cut-off date (March 14 2023) (46), as the efficacy results. [redacted]. In addition, a later data cut-off (September 11 2023 with a follow-up of 17.6 months) (52) will also be included to show the safety data.

Safety data on *adverse events* (defined as treatment-emergent adverse events, all causalities) and *adverse reactions* (defined as treatment-emergent adverse events which were treatment related) for Cohort A are shown in Table 28 below.

Similar to the DMC evaluation of teclistamab (31) the safety populations for teclistamab presented here included all patients who had received at least one dose of teclistamab either in the phase 1 study (only included patients with the same dose as in phase 2 study) or in the phase 2 study (31,48). The data cut-off date was March 16 2022.

Given that safety data of the two comparators comes from two individual single-arm phase 2 studies with uncertainty due to cross-trial differences no comparative assessment of safety have been made except a visual comparison from the safety results presented in the tables below for elranatamab and teclistamab, respectively. Overall, though, the safety profile and evidence found for elranatamab seems to be comparable to that of teclistamab.

Table 28 Overview of safety events.

	Elranatamab (N=123) (Source: 47) Cohort A. Median follow-up: 14.7 months	Teclistamab (N=165) (Source: 37) Median follow-up: 14.1 months	Difference, % (95 % CI)
Number of adverse events, n	[redacted][@]	N/A	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	123 (100.0)	165 (100.00)	N/A
Number of serious adverse events*, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	[redacted][@]	113 (68.5)[&]	N/A
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	[redacted][@]	156 (94.5)[%]	N/A
Number of adverse reactions, n	[redacted][$]	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted][$]	154 (93.3)[&]	N/A
Number and proportion of patients who had a dose reduction, n (%)[§]	[redacted][@]	123 (74.5)[++]	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted][@]	95 (57.6)[+]	N/A
Number and proportion of patients who dis-continue treatment due to adverse events, n (%)	[redacted][@,Ω]	63 (38.2)[+,Ø, Ω]	N/A
Number and proportion of patients with a serious adverse reaction, n (%)	39 (31.7)	48 (29.1)[+++]	N/A

	Elranatamab (N=123) (Source: 47) Cohort A. Median follow-up: 14.7 months	Teclistamab (N=165) (Source: 37) Median follow-up: 14.1 months	Difference, % (95 % CI)
Number and proportion of patients who died while on the study, n (%)	55 (44.7)	68 (41.2)	N/A
Death due to disease progression, n (%)	37 (30.1%)	41 (24.8)	N/A
Deaths considered related to treatment, n (%)	4 (3.25¤)#	5 (3.0)¥	N/A

@Source: [redacted]
& Source: 31 (Source table 17, page 33).
% Source: 31.
¤ Number has been calculated by Pfizer.
§ Due to differences in reporting for elranatamab and teclistamab this contains both data regarding dose reduction, discontinuation/skip and delay. And for both comparators this is due to adverse events.
* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (https://database.ich.org/sites/default/files/E2A_Guideline.pdf).
$ Source: [redacted]
+ Source: 53 (Source table 28).
++ Source: 53 (Source page 120).
+++ Source: 53 (Source table 29).
Ø Based on 61 patients discontinue due to treatment progression and 2 due to adverse events.
One patient with adenoviral hepatitis, one with adenovirus infection and pneumonia adenoviral, one with pneumonia pseudomonal and one with failure to thrive
¥ One patient who had discontinued teclistamab due to progressive multifocal leukoencephalopathy, two patients who had contracted Covid-19, one patient who had hepatic failure, and one patient who had streptococcal pneumonia
Ω Participants with permanent discontinuation of study drug due to adverse events.

Extended follow-up from the ongoing phase 2 MagnetisMM-3 trial of elranatamab was recently presented at a conference (data cut-off: Sep 11 2023: follow-up 17.6 months) (52). The poster showed sustained clinical efficacy and no new safety signals. All patients in Cohort A had at least one AE and 71.5% experienced grade 3/4 AEs. Safety findings in Cohort A were generally consistent with results from the 14.7 month follow-up with no new safety signals observed. CRS was the most common AE (any grade) and no grade 3/4 events CRS or ICANS events were reported. Death due to TEAEs occurred in 20.3% of patients in Cohort A; disease progression was the cause of death reported in 8.9% of patients and infection in 6.5%. Disease progression was the most common reason for treatment discontinuation (39.8%) (52).

The safety profile of elranatamab across all four elranatamab studies (1003 (MagnetisMM-3), 1001, 1002 and 1009) including 265 patients, was consistent (51). Most patients developed at least one TEAE during the study, and the most commonly affected system organ classes (SOCs) for both any grade TEAEs and Grade 3/4 TEAEs were Blood and lymphatic system disorders, Immune system disorders and Infections and infestations.

9.1.1 Serious adverse events

Table 29 below, presents the serious adverse events reported in ≥5% of patients in the safety population. For both comparators serious adverse event data is presented for Cohort A. Overall numbers of adverse events per type were not available. For elranatamab, [redacted]. These two are the only grade 5 AEs in Table 29 of our application.

Disease progression is listed as an AE because per protocol disease progression with a fatal outcome within the active collection period (during the on-treatment period) of the study should be reported as an SAE. The protocol states: 'Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study, the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 if it occurs during the active collection period'. Plasma cell myeloma are patients who were progressing and died of myeloma.

Table 29 Serious adverse events reported in ≥ 5% of patients in the safety population.

Adverse events	Elranatamab (N=123) (data on file) Median follow-up: 14.7 months		Teclistamab (N=165) (37 (Appendix Table S8)) Median follow-up: 14.1 months	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	[redacted]	[redacted]	107 (64.8)	N/A
COVID-19 pneumonia	[redacted]	[redacted]	N/A	N/A
Cytokine release syndrome	[redacted]	[redacted]	14 (8.5)	N/A
Pneumonia	[redacted]	[redacted]	17 (10.3)	N/A
Disease progression	[redacted]	[redacted]	N/A	N/A
Sepsis	[redacted]	[redacted]	3 (1.8)*	N/A
COVID-19	[redacted]	[redacted]	24 (14.5)	N/A
Plasma cell myeloma	[redacted]	[redacted]	N/A	N/A

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

The selected serious adverse events reported in ≥ 5% of patients follows the findings among the elranatamab patients, as this is only reported as ≥ 2% of patients for teclistamab. However, the number and proportions reported for teclistamab in the table are correct.
[5]@Source: [redacted]
§ Data on file. [redacted]
& Data on file. [redacted]
+ Source: 53 (Source table 32).

All serious adverse events observed in the MagnetisMM-3 study – both for all causalities and for treatment related only – are listed in Appendix E.

9.1.2 Efficacy and safety of elranatamab in a patient population in poorer general condition

We note that in section 2.3.1 of the Danish Medicines Council's 'Anbefaling og vurdering' regarding teclistamab it is stated that the Danish patient population will generally be older and with poorer general condition in the 4th line compared to study populations. Therefore, in the assessment of teclistmab, the Danish Medicines Council adjusts the median age and instead assumes it to be 68 years. The median age of cohort A in MagnetisMM-3 study is 68 years, c.f. Table 9.

To further evaluate the effect of elranatamab in a patient population in poorer general condition we also refer to data presented at European Hematology Association (EHA). These data report the efficacy and safety of elranatamab monotherapy in the real- word setting in relapsed-refractory multiple myeloma (RRMM) from the French compassionate use program. Here 101 patients with a median age of 68 years were treated as part of the program. Data shows that despite the advanced disease stage including a significant proportion of patients with prior anti-BCMA directed therapy, extra-medullary disease, adverse prognostic features e.g., severe kidney dysfunction and poor ECOG-PS, these results demonstrate a good safety profile and efficacy of elranatamab in patients with RRMM treated in a real-world setting (83).

9.1.3 DRS, ICANS and deaths related to adverse events

Table 30 and Table 31 presents study participants evaluable for CRS and ICANS, respectively. In cohort A, [redacted] patients experience a grade 1 CRS AE, and [redacted] patients experience a grade 2 CRS AE. For ICANS, [redacted] patients in cohort A, experience grade 1 and 2 ICANS. [redacted]

Table 30 Patients Evaluable for Adverse Event CRS

Source: Data on file (data cut-off of March 14, 2023)

Table 31 Patients Evaluable for Adverse Event ICANS

Source: Data on file (data cut-off of March 14, 2023)

At the 14 March 2023 cut-off a total of [redacted] study participants had died, c.f. Table 32. Of these, [redacted] died of Treatment-Emergent Adverse Events, i.e., deaths during the on-treatment period, c.f. Table 32.

Table 32 Summary of Death (Safety Analysis Set)

Number (%) of Participants	Elranatamab, Cohort A (N=123) n (%) Median follow-up: 14.7 months
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]

Number (%) of Participants	Elranatamab, Cohort A (N=123) n (%) Median follow-up: 14.7 months
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

Table 33 Summary of Treatment-Emergent Adverse Events Leading to Death

Number (%) of Participants	Elranatamab, Cohort A (N=123) n (%) Median follow-up: 14.7 months
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Number (%) of Participants	Elranatamab, Cohort A (N=123) n (%) Median follow-up: 14.7 months
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

9.1.4 Adverse events in the health economic model

The health economic model (cost-minimization) includes the costs of managing adverse events with the two comparators. Evidence on grade 3/4 adverse events for elranatamab (MagnetisMM-3 study) and for teclistamab (MajesTEC-1 study) were used in the model. This was done to include the costs of managing adverse events with the two comparators. Adverse events with grade 1/2 (except for CRS) or with a frequency lower than 5% were excluded as these would have no impact on the economic analysis and its result. In addition, no comparative analysis on the safety data have been conducted. Given the relatively small impact safety data, both on cost and utility decrement, has on the ICER we don't anticipate weighted safety data will have a significant impact on the results. Below in Table 34 is the included adverse events shown.

Table 34 Adverse events used in the health economic model - most common (≥5%) Grade 3/4 AEs from MagnetisMM-3 (data cut-off March 14 2023) and MajesTEC-1.

Adverse events	Elranatamab (N=123), Cohort A	Teclistamab (N=165)		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Anaemia	37.4%	37.6%	Elranatamab: (47) Teclistamab: (31)	Grade 3/4 and ≥5%
CRS (grade 1-2)	57.7%	71.5%	Elranatamab: (47) Teclistamab: (31)	Grade 3/4 and ≥5%
Hypertension	[redacted]	6.1%	Elranatamab: ([redacted]) Teclistamab: (31)	Grade 3/4 and ≥5%
Hypophosphatemia	[redacted]	6.7%	Elranatamab: § Teclistamab: (31)	Grade 3/4 and ≥5% (for teclistamab)
Leukopenia	[redacted]	9.1%	Elranatamab: ([redacted]) Teclistamab: (31)	Grade 3/4 and ≥5%
Lymphopenia	25.2%	34.5%	Elranatamab: (47) Teclistamab: (31)	Grade 3/4 and ≥5%
Neutropenia	48.8%	65.5%	Elranatamab: (47) Teclistamab: (31)	Grade 3/4 and ≥5%
Pneumonia (and COVID-19 pneumonia for elranatamab)	[redacted]	13.3%	Elranatamab: (47,[redacted]) Teclistamab: (31)	Grade 3/4 and ≥5%
Thrombocytopenia	23.6%	22.4%	Elranatamab: (47) Teclistamab: (31)	Grade 3/4 and ≥5%
Hypokalaemia	10.6%	4.8%	Elranatamab: (47) Teclistamab: (37,70,[redacted])	Grade 3/4 and ≥5% (for elranatamab)

§ Data on file.
*For elranatamab, pneumonia also included COVID-19 pneumonia. 11.4% in Cohort A reported COVID-19 pneumonia, which was added to the 8.1% who reported pneumonia. COVID-19 pneumonia was not reported for teclistamab.

9.2 Safety data from external literature applied in the health economic model

Not applicable as no external sources have been used for adverse events in the cost-minimisation model.

Table 35 Adverse events that appear in more than X % of patients *(*Table 35 *is Not Applicable)*

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

Not applicable – this includes related tables. This section is not relevant with the analysis being a cost-minimization analysis. The decision about choosing a cost-minimization analysis is based on the comparable and equal efficacy and safety profiles of elranatamab and teclistamab, respectively, as presented above in Section 7 and 9.

11. Resource use and associated costs

All costs related to treating RRMM patients with elranatamab and teclistamab were considered to be included in the model. To estimate the resource use and identify unit costs, the SmPCs of elranatamab and teclistamab, data from the trials, information from the DMC evaluation of teclistamab, and assumptions were applied. Below, descriptions of each cost element and how the element was valued in the health economics analysis, are presented.

11.1 Medicine costs – elranatamab and teclistamab

All drug costs included in the model were based on the pharmacy purchasing price (PPP) obtained in March 2024. The PPPs of the available packages of elranatamab and teclistamab are presented in Table 39.

11.1.1 Elranatamab medicine costs

Patients in the elranatamab arm received elranatamab according to the posology described in the SmPC (21). The dosing schedule for elranatamab is presented in Table 36. As seen in the table, after 24 weeks of treatment, patients can switch to a once every 2-week dosing regimen (Q2W) if they have achieved a response. In the model, patients in cohort A who were still on treatment after 24 weeks could switch to the Q2W regimen (i.e., discontinuation was accounted for). In MagnetisMM-3, 50 of the 123 patients in cohort A who had not discontinued treatment after 24 weeks switched to the Q2W dosing regimen, i.e., 75.67% (see calculation in 'Treatment' sheet in the Excel model). According to the SmPC, patients should receive treatment with elranatamab until disease progression or unacceptable toxicity (21).

Table 36 Elranatamab dosing schedule. Source: (21).

Dosing schedule	Week/day	Dose	
Step-up dosing[a,b]	Week 1: day 1	Step-up dose 1	12 mg
	Week 1: day 4	Step-up dose 2	32 mg
Weekly dosing[a,c,d]	Weeks 2-24: day 1	Full treatment dose	76 mg once weekly
Every 2 weeks dosing (Q2W)[d,e]	Week 25 onwards: day 1	Full treatment dose	76 mg once every 2 weeks

a. Pre-treatment medicinal products should be administered prior to the first three doses of elranatamab.
b. A minimum of 2 days should be maintained between step-up dose 1 (12 mg) and step-up dose 2 (32 mg).
c. A minimum of 3 days should be maintained between step-up dose 2 (32 mg) and the first full treatment (76 mg) dose.
d. A minimum of 6 days should be maintained between doses.
e. For patients who have achieved a response.

11.1.2 Teclistamab medicine costs

Patients in the teclistamab arm received teclistamab according to the posology described in the SmPC (48). The dosing schedule for teclistamab is presented in Table 37.

Patients on teclistamab could also switch to a Q2W dosing regimen as per the SmPC, if they achieved a complete response or better. In MajesTEC-1, 63 out of the 165 patients (85.26%) who had not discontinued treatment switched to the Q2W dosing regimen (see calculation in the 'Treatment' sheet in the Excel model). The time point for when the switch occurred in the model was based on the median time to switching dosing regimen from MajesTEC-1 stated in the DMC evaluation of teclistamab, which was 11.3 months (49 weeks) and was also used in the DMC evaluation of teclistamab (31).

Table 37 Teclistamab dosing schedule. Source: (48).

Dosing schedule	Day	Dose[a]	
All patients			
Step-up dosing schedule	Day 1	Step-up dose 1	0.06 mg/kg SC single dose
	Day 3[b]	Step-up dose 2	0.3 mg/kg SC single dose
	Day 5[c]	First maintenance dose	1.5 mg/kg SC single dose
Weekly dosing schedule	1 week after first maintenance dose and weekly thereafter[d]	Subsequent maintenance doses	1.5 mg/kg SC once weekly
Patients who have a complete response or better for a minimum of 6 months			
Biweekly (every 2 weeks, Q2W) dosing schedule	Consider reducing the dosing frequency to 1.5 mg/kg SC every 2 weeks		

a. Dose is based on actual body weight and should be administered subcutaneously.
b. Step-up dose 2 may be given between 2 and 7 days after step-up dose 1.
c. First maintenance dose may be given between 2 and 7 days after step-up dose 2. This is the first full maintenance dose (1.5 mg/kg).
d. Maintain a minimum of 5 days between weekly maintenance doses.

11.1.3 Relative dose intensity in the model

Relative dose intensity (RDI) measures the proportion of the administrated dose in relation to the planned dose, from treatment initiation to discontinuation. RDI was included in the model because 100% treatment adherence is not expected in a real-world setting. The RDI rates of elranatamab were obtained directly from the MagnetisMM-3 trial. In the MagnetisMM-3 trial, RDI was defined as the ratio of the delivered dose intensity (mg/week) to the planned dose intensity (mg/week) for elranatamab. The dose intensity and planned dose intensity were calculated from the

actual treatment duration, actual total cumulative dose, and the planned treatment duration and total planned dose. The difference between the overall dose intensity and the planned dose intensity was due to dose interruptions and dose reductions.

The RDI calculation thus accounts for the planned dose change resulting from the Q2W switch starting from cycle 7, as per the trial protocol to ensure there was no double counting in the treatment cost calculation regarding the Q2W switch in the model. Below example calculations on the total planned dose for a given cycle is provided:

Cycle 1:
Planned dose (mg/cycle) = 12mg+32mg + (76mg × 3)

After Cycle 1:
If the participant is on QW dosing schedule for the cycle:
Planned dose (mg/cycle) = 76mg × 4

If the participant is on Q2W dosing schedule for the cycle (possible from week 25 onwards):
Planned dose (mg/cycle) = 76mg × 2

In the MagnetisMM-3 trial, the RDI was 78.35%. The dose intensity and planned dose intensity were calculated from the actual treatment duration, actual total cumulative dose, and the planned treatment duration and total planned dose. The difference between the overall dose intensity and the planned dose intensity was due to dose interruptions and dose reductions. In MajesTEC-1, the median RDI for all treatment cycles, including step-up doses, was 93.7% (37).

In the model base case, the RDIs were multiplied by the drug costs, the administration costs and the cost of patient time use and transportation per planned dose to derive the cost incurred by the actual dose. The median RDIs for elranatamab and teclistamab are presented in Table 38.

Table 38 Medicine information used in the model.

Medicine	Dose	Relative dose intensity (median)	Frequency	Vial sharing
Elranatamab	Step-up doses of 12 mg SC on day 1 and 32 mg SC on day 4, followed by a full treatment dose of 76 mg SC weekly from week 2 to week 24	78.35%	For patients who have received at least 24 weeks of treatment and have achieved a response, the dosing interval should transition to an every-2 week schedule (21,47)	Yes
Teclistamab	1.5 mg/kg SC	93.70%	A reduced dosing	Yes

Medicine	Dose	Relative dose intensity (median)	Frequency	Vial sharing
	weekly, preceded by step-up doses of 0.06 mg/kg SC and 0.3 mg/kg SC		frequency of every 2 weeks may be considered for patients who have a complete response or better for a minimum of 6 months (37,48)	

Table 39 Package information on elranatamab and teclistamab (March 26 2024).

Pharmaceutical	Strength	Package size	PPP (DKK)
Elranatamab	44 mg	1.1 ml	22,982.38
	76 mg	1.9 ml	39,700.96
Teclistamab	10 mg/ml	3 ml	6,571.53
	90 mg/ml	1.7 ml	33,217.67

11.1.4 Wastage in the model

Wastage was included in the model, and the analysis was based on the same assumptions and rationale as applied in the teclistamab DMC evaluation (31). In the DMC evaluation of teclistamab, wastage was assumed to be reduced through vial sharing and administering treatment to multiple patients on the same day, as both elranatamab and teclistamab are administered at the hospital. In the base case, vial sharing was assumed for 50% of elranatamab and teclistamab administrations in accordance with the teclistamab DMC evaluation (31). Vial sharing was included in the DSA, and a scenario analysis was conducted with no vial sharing to assess the impact of this parameter on the base case result.

11.2 Medicine costs – co-administration

Not applicable. According to the SmPCs, pre-treatment with medical products should be administered prior to treatment with both elranatamab and teclistamab (21,48). Medicine costs associated with pre-treatment were not included in the model due to the minimal impact of these costs on the analysis and the similarity of the pre-treatments associated with elranatamab and teclistamab (21,48).

11.3 Administration costs

Administration costs were included for treatments administered subcutaneously and intravenously at the hospital (Table 40). Orally administered treatments were not ascribed an administration cost, as patients can administer these at home. A macro-costing approach was applied in the present model. For both subcutaneous and intravenous administration, the DRG 2024 tariff 17MA98 of DKK 1,989 was applied based on the tariffs provided with interactive DRG when combining the diagnosis code DC900 with the procedure code BWAA6 and the procedure code BWAA3. The same approach was applied in the teclistamab application, which was accepted by the DMC (31).

The SmPCs for both teclistamab and elranatamab state that patients should remain within proximity of a healthcare facility after each dose in the step-up dosing schedule (21,48). In the DMC evaluation of teclistamab, it was expected that patients were admitted to the hospital for 48 hours for each dose in the step-up dosing schedule (31). Thus, 6 admission days were included for teclistamab (48 hours for step-up dose 1, 48 hours for step-up dose 2 and 48 hours for the first maintenance dose), and 4 days were included for elranatamab (48 hours for step-up dose 1 and 48 hours for step-up dose 2).

The DRG 2024 tariff 16MA11 of DKK 60,906 was applied for admissions associated with administration of the step-up doses of teclistamab and elranatamab. The tariff was divided by 16 (the trim point for the tariff) to get the cost per day, which was estimated to be 3,807 DKK per day. This approach was applied to ensure consistency with the approach applied in the DMC's evaluation of teclistamab (31).

Table 40 Administration costs used in the model.

Administration type	Frequency	Unit cost (DKK)	DRG code	Reference
Subcutaneous administration	Weekly or once every 2 weeks	1,989 per administration	17MA98	DRG 2024 tariff
Hospital admission associated with administering the first two doses of teclistamab and elranatamab	Teclistamab: 48 hours for step-up dose 1, 48 hours for step-up dose 2 and 48 hours for first maintenance dose Elranatamab: 48 hours for step-up dose 1 and 48 hours for step-up dose 2	3,807 per admission day	16MA11 (divided by 16 days)	Admission: (31,21,48) Unit cost: DRG 2024 tariff
Intravenous administration of carfilzomib (subsequent treatment option)	Cycle 1: administration on day 1, day 2, and on days 8, 9, 15 and 16 in a 28-day cycle Cycle 2+:	1,989 per administration	17MA98	DRG 2024 tariff

Administration type	Frequency	Unit cost (DKK)	DRG code	Reference
	administration on days 1, 2, 8, 9, 15 and 16 on 28-day cycles			

11.4 Disease management costs

It was assumed that patients on elranatamab would have their disease managed and monitored to the same extent as patients on teclistamab. Therefore, the estimation of disease management costs was based on the DMC evaluation of teclistamab. In the teclistamab evaluation, a monthly monitoring visit at the haematologic department was included; thus, one monitoring visit per month was included in the model for both elranatamab and teclistamab. The unit cost of a monitoring visit was based on the DRG 2024 tariff 17MA98 (Table 41).

Table 41 Disease management costs used in the model.

Activity	Frequency	Unit cost (DKK)	DRG code	Reference
Monitoring visit at the haematologic department	Monthly	1,989	17MA98	DRG 2024 tariff and (31)

11.5 Costs associated with management of adverse events

Costs for managing AEs were included in the model, and the included AEs are presented in Table 42. The included AEs were the grade 3/4 AEs from the BCMA-naive patient population from the MajesTEC-1 trial that in the DMC evaluation of teclistamab were listed as being treatment requiring. The corresponding rates for each AE for elranatamab came from the MagnetisMM-3 trial. In addition, the other grade 3/4 AEs from MagnetisMM-3 with a frequency of ≥5% were also included, which included hypokalaemia and COVID-19 pneumonia. The resource use (one time cost) associated with managing each AE listed in Table 42 was also based on the DMC evaluation of teclistamab. According to the DMC (31), all AEs except neutropenia and pneumonia can be managed at an outpatient visit, whereas neutropenia and pneumonia require hospital admission. Unit costs of managing AEs were based on DRG 2024 tariffs (Table 43).

Table 42 Most common (≥5%) Grade 3/4 AEs from MagnetisMM-3 (data cut-off March 14 2023) and MajesTEC-1.

AE	Elranatamab (N=123), cohort A	Teclistamab (N=165)	Reference

AE	Elranatamab (N=123), cohort A	Teclistamab (N=165)	Reference
Anaemia	37.4%	37.6%	Elranatamab: (47) Teclistamab: (31)
CRS (grades 1-2)	57.7%	71.5%	Elranatamab: (47) Teclistamab: (31)
Hypertension	[redacted]	6.1%	Elranatamab: ([redacted]) Teclistamab: (31)
Hypophosphatemia	[redacted]	6.7%	Elranatamab: Data on file Teclistamab: (31)
Leukopenia	[redacted]	9.1%	Elranatamab: ([redacted]) Teclistamab: (31)
Lymphopenia	25.2%	34.5%	Elranatamab: (47) Teclistamab: (31)
Neutropenia	48.8%	65.5%	Elranatamab: (47) Teclistamab: (31)
Pneumonia (+ COVID-19 pneumonia in elranatamab)	[redacted]	13.3%	Elranatamab: (47[redacted]) Teclistamab: (31)
Thrombocytopenia	23.6%	22.4%	Elranatamab: (47) Teclistamab: (31)
Hypokalaemia	10.6%	4.8%	Elranatamab: (47) Teclistamab: (37,70[redacted])

*For elranatamab, pneumonia included COVID-19 pneumonia. [redacted] (47[redacted]). COVID-19 pneumonia was not reported for teclistamab.

Table 43 Resource use and unit costs associated with included AEs.

	Resource use	DRG code	Unit cost (DKK)
Anaemia	Managed at outpatient visit	17MA98	1,989
CRS	Managed at outpatient visit	17MA98	1,989
Hypertension	Managed at outpatient visit	17MA98	1,989
Hypophosphatemia	Managed at outpatient visit	17MA98	1,989

	Resource use	DRG code	Unit cost (DKK)
Leukopenia	Managed at outpatient visit	17MA98	1,989
Lymphopenia	Managed at outpatient visit	17MA98	1,989
Neutropenia	Requires admission	49PR07	20,330
Pneumonia (and COVID-19 pneumonia for elranatamab)	Requires admission	04MA13	43,907
Thrombocytopenia	Managed at outpatient visit	17MA98	1,989
Hypokalaemia	Managed at outpatient visit	17MA98	1,989

11.6 Subsequent treatment costs

Subsequent treatment was included in the model for both elranatamab and teclistamab. When patients progressed on elranatamab and teclistamab, they would discontinue elranatamab treatment or teclistamab treatment and start the subsequent treatment. The types of subsequent treatments were based on the subsequent treatments that the DMC regarded as possible standard clinical practice for RRMM patients after progressing on teclistamab in their evaluation of teclistamab. According to the DMC, the choice of subsequent treatment is dependent on the treatments that the individual patient has received in previous lines. Most patients will receive subsequent treatment with pomalidomide in combination with dexamethasone (PomDex) or carfilzomib in combination with dexamethasone (CarDex). Based on this, these two subsequent treatment options were included in the model in a 50/50 split.

In the model, one-off subsequent treatment costs and one-off administration costs (for carfilzomib) were calculated based on the average weekly cost and median treatment duration of the subsequent treatments. The one-off costs were applied to the newly progressed patients at the time of progression. Of these newly progressed patients, subsequent treatment was applied to 63.9% of patients in the elranatamab arm based on data from MagnetisMM-3 and 65.8% in the teclistamab arm based on data from the MajesTEC-1 trial. The median duration of subsequent treatment was capped by the estimated duration of PPS calculated from the model, making sure that the subsequent treatment duration was not longer than the PPS duration. The median subsequent treatment duration for cohort A in MagnetisMM-3 was 7.98 months (35 weeks) and applied for both elranatamab and teclistamab due to the assumption of equality between elranatamab and teclistamab.

Information on the included subsequent treatments is presented in Table 44. The cheapest packages were included in the model if more packages were available.

Table 44 Medicine costs of subsequent treatments. Source: www.medicinpriser.dk (March 26 2024).

Medicine	Strength	Package size	PPP (DKK)	Relative dose intensity	Average duration of treatment
Pomalidomide (Imnovid)	4 mg	21 blisters	51,674.20	Not reported	7.98 months (median)
Dexamethasone (2care4)	4 mg	100 tablets	600.00	Not reported	7.98 months (median)
Carfilzomib (Kyprolis)	60 mg	1 vial	7,549.57	Not reported	7.98 months (median)

11.7 Patient costs

In accordance with DMC guidelines (72) and similar to the DMC evaluation of teclistamab (31), patient-related time use and costs and transportation costs were included in the model. No caregiver time or costs were included in the model. The patient time associated with elranatamab and teclistamab was based on the time spent on treatment-related activities and traveling to and from the hospital. Based on the DMC guideline (72), a cost of DKK 203 per patient hour was applied.

In terms of transportation, a distance of 20 km to and from the hospital (40 km in total per visit) was assumed, and a unit cost per km of DKK 3.73 was applied in accordance with DMC guidelines (72). Thus, a transportation cost of DKK 149 was applied for each hospital visit. It was assumed that patients spend 30 minutes on transportation to and from the hospital, i.e., 60 minutes per visit. The activities to which patient time use and transportation were ascribed, and the time spent by the patient on each activity, are presented in Table 45. Each activity was ascribed a transportation cost of DKK 149.

Table 45 Patient costs used in the model.

Activity	Time spent (hours)*	Source
Subcutaneous administrations at the hospital	4 hours	DMC teclistamab evaluation (31)
IV administration of carfilzomib at the hospital	4 hours	DMC teclistamab evaluation (31)
Hospital admission	24 hours per admission day	DMC teclistamab evaluation (31)

Activity	Time spent (hours)*	Source
Disease management visit	4 hours	DMC teclistamab evaluation (31)

*The time spent includes 1 hour of transportation associated with each visit to the hospital.

11.8 Other costs (e.g., costs for home care nurses, outpatient rehabilitation and palliative care)

No other costs were included.

12. Results

12.1 Base case overview

Table 46 provides an overview of the settings applied in the two base case analyses of the cost-minimisation analysis.

Table 46 Base case overview.

Feature	Description
Comparator	Teclistamab
Type of model	Cost-minimisation model adopting a partitioned survival approach
Time horizon	32 years (lifetime)
Treatment line	Fourth line: patients should have received at least three prior therapies, with an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody
Inclusion of subsequent treatment	Yes, 50% PomDex and 50% CarDex
Costs included	Medicine costs Administration costs Subsequent treatment costs Disease management costs Costs of managing AEs Patient costs Transportation costs
Dosage of medicines	Based on weight (teclistamab) and BSA (carfilzomib)
Average time on treatment	Elranatamab: 15.53 months Teclistamab: 21.05 months
Parametric function for PFS	Weibull
Parametric function for OS	Exponential
Parametric function for TTD	Elranatamab: Weibull Teclistamab: log-normal
Inclusion of waste	Yes, 50% in each alternative following DMC (31)

12.1.1 Base case results

In the base case 1 analysis, the incremental cost per patient for elranatamab compared to teclistamab was DKK -346,935 over a time horizon of 32 years. Table 47 and Figure 30 present an overview of the base case results.

Table 47 Base case 1 results, discounted estimates (DKK).

	Elranatamab (DKK)	Teclistamab (DKK)	Difference (DKK)
Medicine costs	1,439,383	1,700,975	-261,591
Medicine costs – co-administration	0	0	0
Administration	85,139	136,942	-51,803
Disease management costs	54,133	54,133	0
Costs associated with management of adverse events	21,865	22,889	-1,024
Subsequent treatment costs	47,020	48,418	-1,398
Patient costs	71,457	99,092	-27,635
Transportation costs	9,949	13,431	-3,482
Total costs	**1,728,946**	**2,075,881**	**-346,935**
Incremental costs per life year gained		**N/A ***	
Incremental cost per QALY gained (ICER)		**N/A ***	

* Due to being a cost-minimisation analysis.

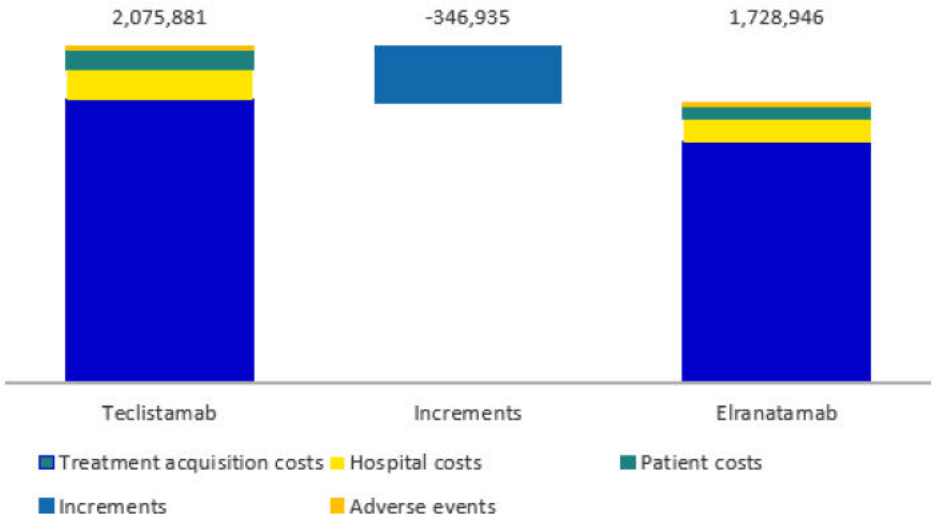


Figure 30 Result of the base case 1 analysis (DKK).

In the base case 1 analysis, the incremental cost per patient for elranatamab compared to teclistamab was DKK -775,894 over a time horizon of 32 years.

Table 48 Base case 2 results, discounted estimates (DKK).

	Elranatamab (DKK)	Teclistamab (DKK)	Difference (DKK)
Medicine costs	1,444,357	2,093,116	-648,759
Medicine costs – co-administration	0	0	0
Administration	85,388	164,279	-78,891
Disease management costs	104,652	104,652	0
Costs associated with management of adverse events	21,892	22,918	-1,026
Subsequent treatment costs	90,573	93,266	-2,693
Patient costs	93,846	132,869	-39,023
Transportation costs	14,058	19,560	-5,502
Total costs	**1,854,765**	**2,630,660**	**-775,894**

	Elranatamab (DKK)	Teclistamab (DKK)	Difference (DKK)
Incremental costs per life year gained		N/A *	
Incremental cost per QALY gained (ICER)		N/A *	

* Due to being a cost-minimisation analysis.

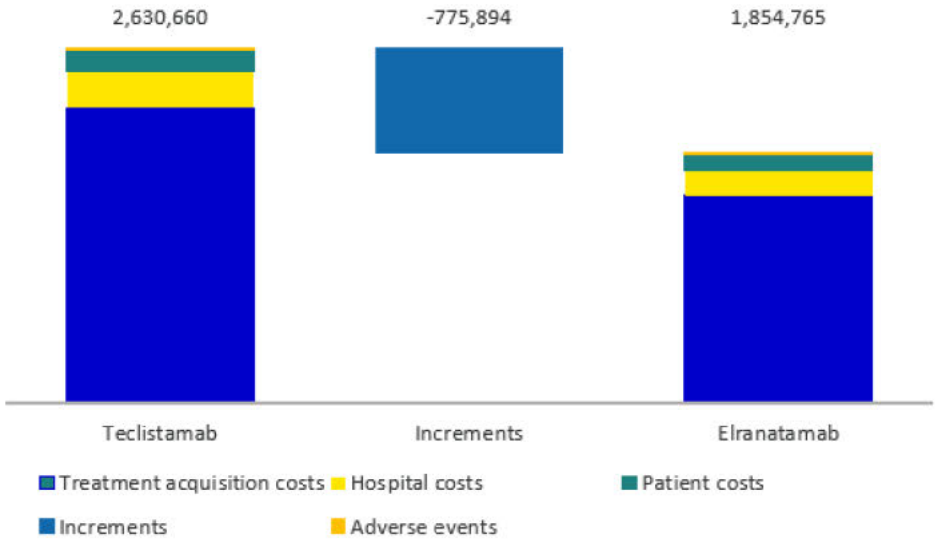


Figure 31 Result of the base case 2 analysis (DKK).

12.2 Sensitivity analyses

Uncertainty in the input parameters in the model has been explored through various sensitivity and scenario analyses, which are presented in this section. The sensitivity analyses were conducted based on base case 1.

12.2.1 Deterministic sensitivity analyses

The DSAs included in the present application are presented in Table 49. The parameters included in the DSA were RDI for elranatamab and teclistamab, the mean weight, vial sharing, and the PPP on elranatamab and teclistamab, as these parameters were identified as potentially having the largest impact on the result of the base case. In addition to the performed DSAs, scenario analyses were also performed and are presented in the next section.

As seen in Figure 32, the parameters with the largest impact on the base case result were the RDI of teclistamab and elranatamab.

Table 49 One-way sensitivity analyses results (DKK).

	Change	Reason/ Rationale/ Source	Incremental cost (DKK)		Incre-mental benefit (QALYs)	ICER (DKK/QALY)
			Low	High		
Base case 1 result	-	-	-346,935		N/A	N/A
RDI, teclistamab	Low: 50% High: 100%	Included as RDI is expected to have a large impact on the medicine costs	508,796	-470,301	N/A	N/A
RDI, elranatamab	Low: 50% High: 100%	Included as RDI is expected to have a large impact on the medicine costs	-893,529	70,481	N/A	N/A
Mean weight	Low: -20% High: +20%	To assess the impact of changing this parameter	-202,996	-490,874	N/A	N/A
Vial sharing	Low: 30% High: 70%	To assess the impact of changing this parameter	-447,134	-246,737	N/A	N/A
PPPs	Low: -20% High: +20%	Included in accordance with DMC guidelines	-294,617	-399,253	N/A	N/A

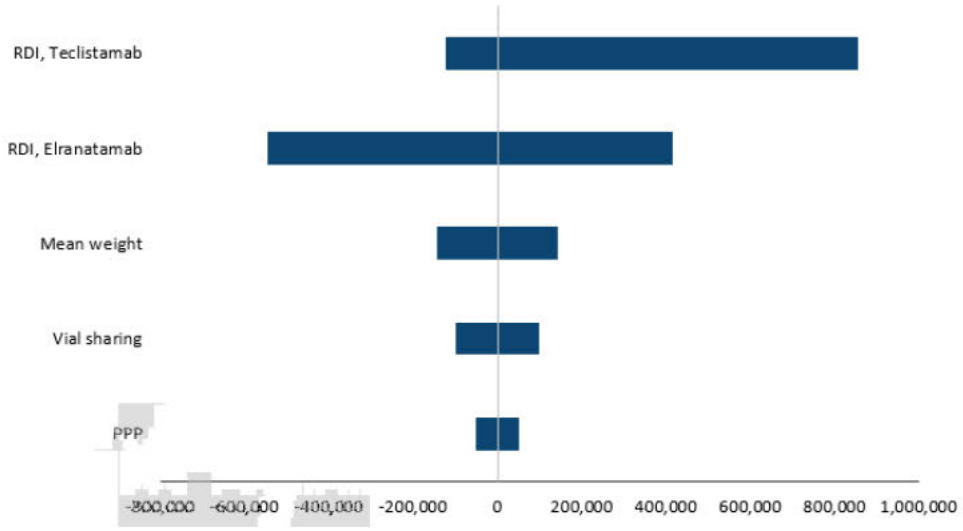


Figure 32 Tornado diagram from the DSA (DKK).

12.2.1.1 Scenario analyses

Scenario analyses were performed to assess the impact of alternative model choices on the result of the base case. The performed scenario analyses can be seen in Table 50. Selecting the same average modelled TTD for both elranatamab and teclistamab was the scenario analysis where the incremental cost was changed the most compared to the base case. Reducing the time horizon to 1 year and applying a median RDI of 100% for both elranatamab and teclistamab did also have large impact on the base case result. In addition, excluding vial sharing from the analysis, selecting the Weibull curve for OS, the exponential curve for PFS and the exponential curve for TTD also resulted in incremental costs that were significantly different from the base case result. However, all scenarios resulted in elranatamab being a cost-saving alternative compared to teclistamab.

Table 50 Scenario analyses results (DKK).

	Change	Reason/ Rationale/ Source	Incremental cost (DKK)	Incre-mental benefit (QALYs)	ICER (DKK / QALY)
Base case 1 result	-	-	-346,935	N/A	N/A
No difference in RDI between elranatamab and teclistamab	Median RDI for both alternatives increased to 100%	Included as RDI is expected to have a large impact on the medicine costs	-52,885	N/A	N/A
No difference in average modelled TTD between	The modelled average TTD was set to 15.53 months for both	Included to assess the impact of applying different TTD estimates for	155,218	N/A	N/A

	Change	Reason/ Rationale/ Source	Incremental cost (DKK)	Incre-mental benefit (QALYs)	ICER (DKK / QALY)
elranatamab and teclistamab	elranatamab and teclistamab	elranatamab and teclistamab			
Time horizon of 1 year	Reducing the time horizon from 32 years to 1 year	In accordance with DMC guidelines	-163,620	N/A	N/A
Time horizon of 10 years	Reducing the time horizon from 32 years to 10 years	In accordance with DMC guidelines	-349,332	N/A	N/A
Time horizon of 20 years	Reducing the time horizon from 32 years to 20 years	In accordance with DMC guidelines	-346,959	N/A	N/A
OS parametric function: Weibull	Selecting the Weibull curve to extrapolate OS instead of exponential	In accordance with DMC guidelines	-481,933	N/A	N/A
OS parametric function: gamma	Selecting the gamma curve to extrapolate OS instead of exponential	In accordance with DMC guidelines	-422,322	N/A	N/A
PFS parametric function: gamma	Selecting the gamma curve to extrapolate PFS instead of Weibull	In accordance with DMC guidelines	-347,545	N/A	N/A
PFS parametric function: exponential	Selecting the exponential curve to extrapolate PFS instead of Weibull	In accordance with DMC guidelines	-200,194	N/A	N/A
TTD parametric function: exponential	Selecting the exponential curve to extrapolate TTD instead of Weibull	In accordance with DMC guidelines	-594,430	N/A	N/A
TTD parametric function: gamma	Selecting the gamma curve to extrapolate TTD instead of Weibull	In accordance with DMC guidelines	-452,191	N/A	N/A
No vial sharing	From 50% to 0%	To assess the	-597,431	N/A	N/A

	Change	Reason/ Rationale/ Source	Incremental cost (DKK)	Incre-mental benefit (QALYs)	ICER (DKK / QALY)
included	vial sharing	impact of this parameter in the result			

12.2.2 Probabilistic sensitivity analyses

Not applicable since only a cost-minimisation analysis and model were used.

13. Budget impact analysis

The purpose of the budget impact analysis was to estimate the budgetary impact of recommending elranatamab as standard treatment for patients with RRMM. The budget impact was estimated per year in the first 5 years after the recommendation of elranatamab. The budget impact analysis compares the expenditures in the scenario where elranatamab is recommended as a possible standard treatment and the scenario where elranatamab is not recommended as a possible standard treatment. The total budget impact per year is the difference between the two scenarios. The budget impact analysis was based on the base case 1 analysis.

Number of patients (including assumptions of market share)

The number of patients was based on the number of new patients estimated by the myeloma expert committee in the DMC evaluation of teclistamab (31). As stated in the evaluation, the population of patients with multiple myeloma eligible for fourth line treatment is expected to be 100 patients per year. Furthermore, it is expected that around 10% of these will not receive an active treatment, i.e., 90 patients will be eligible for active fourth line treatment each year. Among the 90 patients, the expert committee in the DMC evaluation of teclistamab (31) expect that 40% will prefer a peroral regimen, i.e., 60% (54 patients) will receive either elranatamab or teclistamab. If elranatamab is recommended as a possible standard treatment, it is therefore expected that all 54 patients (with a market share of 100%) will receive elranatamab, as the choice of treatment will be based on the lowest net price due to the similar effect and side effects and route of administration between the two medicines.

The number of patients expected to receive elranatamab and teclistamab, respectively, in the first 5 years after the recommendation is presented in Table 51.

Table 51 Number of new patients expected to be treated over the next 5-year period if elranatamab is recommended (adjusted for market share).

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Elranatamab	54	54	54	54	54
Teclistamab	0	0	0	0	0
			No recommendation		
Elranatamab	0	0	0	0	0
Teclistamab	54	54	54	54	54

Budget impact

An overview of the results of the budget impact analysis is presented in Table 52. A graphic presentation of the results is presented in Figure 33. Over all 5 years in the budget impact analysis, the budget impact is DKK -62,425,411.

Table 52 Expected budget impact of recommending elranatamab for the indication (DKK).

	Year 1	Year 2	Year 3	Year 4	Year 5
Elranatamab is recommended	51,288,043	68,065,842	77,871,665	84,006,744	88,007,182
Elranatamab is NOT recommended	60,190,835	77,737,784	89,748,482	98,708,622	105,279,165
Budget impact of the recommendation	-8,902,791	-9,671,942	-11,876,817	-14,701,877	-17,271,984

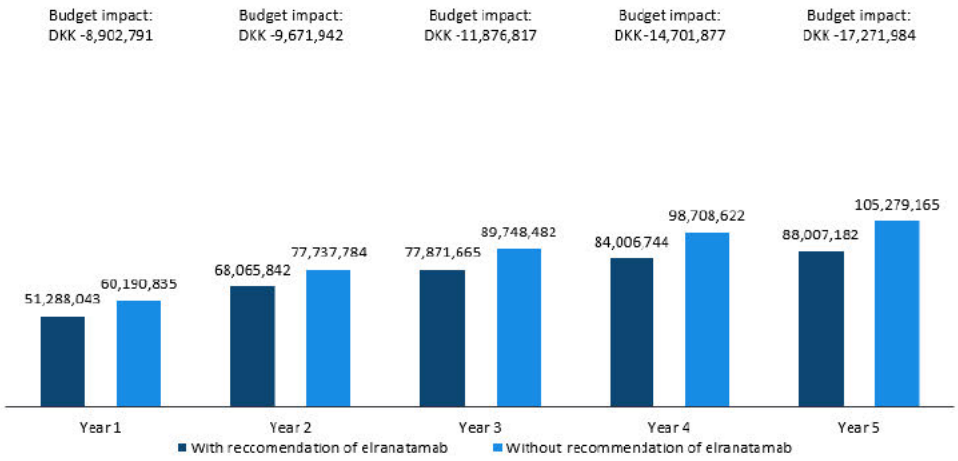


Figure 33 Budget impact of recommending elranatamab for RRMM patients (DKK).

14. List of experts

Not applicable as no external experts were consulted.

15. References

1. Rajkumar SV, Kumar S. Multiple Myeloma: Diagnosis and Treatment. Mayo Clin Proc 2016;91:101–19.
2. Kumar SK, Rajkumar V, Kyle RA, van Duin M, Sonneveld P, Mateos MV, Gay F, Anderson KC. Multiple myeloma. Nat Rev Dis Primer 2017;3:17046.
3. American Cancer Society, 2018c. What is multiple myeloma? https://www.cancer.org/cancer/multiple-myeloma/about/what-is-multiple-myeloma.html.
4. Carpenter RO, Evbuomwan MO, Pittaluga S, Rose JJ, Raffeld M, Yang S, Gress RE, Hakim FT, Kochenderfer JN. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Clin Cancer Res Off J Am Assoc Cancer Res 2013;192048–60.
5. Shah N, Chari A, Scott E, Mezzi K, Usmani SZ. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. Leukemia 2020;34:985–1005.
6. Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, Hajek R, Dimopoulos MA, Ludwig H, Einsele H, Zweegman S, Facon T, Cavo M, Terpos E, Goldschmidt H, Attal M, Buske C. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28: iv52–iv61.
7. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O, Paiva B, Dispenzieri A, Weiss B, LeLeu X, Zweegman S, Lonial S, Rosinol L, Zamagni E, Jagannath S, Sezer O, Kristinsson SY, Caers J, Usmani SZ, Lahuerta JJ, Johnsen HE, Beksac M, Cavo M, Goldschmidt H, Terpos E, Kyle RA, Anderson KC, Durie BG, Miguel JF. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e538-48.
8. Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (myelomatose). Version 1.11. 26 Sept 2023.
9. DMSG. Myelomatose – relapsbehandling. Version 2.1. 9 Januar 2024.
10. Factsheet multiple myelomas from NORDCAN database downloaded from multiple_myelomer-380-danmark-208.pdf (www.iarc.fr).
11. Dansk Myelomatose Database - National årsrapport 2021.
12. Medicinrådets anbefaling vedr. ciltacabtagene autoleucel til behandling af patienter med knoglemarvskræft, som har fået mindst tre tidligere terapier eller DMSG Klinisk Retningslinje Diagnostik og opfølgning af myelomatose. Version 2.0. Godkendt 22 Januar 2024.
13. DMSG Klinisk Retningslinje Diagnostik og opfølgning af myelomatose. Version 2.0. Godkendt 22 Januar 2024.
14. Szabo AG, Iversen KF, Möller S, Plesner T. The Clinical Course of Multiple Myeloma in the Era of Novel Agents: A Retrospective, Single-Center, Real-World Study. Clin Hematol Int 2019;1(4):220-8.
15. Chen X, Luo X, Zu Y, Issa HA, Li L, Ye H, Yang T, Hu J, Wei L. Severe renal impairment as an adverse prognostic factor for survival in newly diagnosed multiple myeloma patients. J Clin Lab Anal 2020;34:e23416.
16. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol 2022;97:1086–107.

17. Terebelo HR, Abonour R, Gasparetto CJ, Toomey K, Durie BG, Hardin JW, Jagannath S, Wagner L, Narang M, Flick ED. Development of a prognostic model for overall survival in multiple myeloma using the Connect® MM Patient Registry. Br J Haematol 2019;187:602–6.
18. Nielsen LK, Larsen RF, Jarlbaek L, Möller S, Jespersen E. Health-related quality of life in patients with multiple myeloma participating in a multidisciplinary rehabilitation program. Ann Hematol 2021;100(9):2311-2323.
19. Zaleta A.K, Miller MF, Olson JS, Yuen EYN, LeBlanc TW, Cole CE, McManus S, Buzaglo JS. Symptom Burden, Perceived Control, and Quality of Life Among Patients Living With Multiple Myeloma. J Natl Compr Canc Netw 2020;18:1087–95.
20. Colson K. Treatment-related symptom management in patients with multiple myeloma: a review. Support Care Cancer 2015;23:1431–45.
21. European Medicines Agency. Summary of product characteristics: elranatamab https://www.ema.europa.eu/en/documents/product-information/tecvayli-epar-product-information_en.pdf.
22. Madduri D, Hagiwara M, Parikh K, Pelletier C, Delea T, Kee A, Chari A. Real-world treatment patterns, healthcare use and costs in triple-class exposed relapsed and refractory multiple myeloma patients in the USA. Future Oncol 2021;17:503–15
23. Varughese P, Smith R, Xue M, Dorrow N, Hogea C, Maiese EM, Buckingham T. Real-world treatment patterns and outcomes of triple-class treated patients with multiple myeloma in the United States. Expert Rev Hematol 2023;16:1–10.
24. Lee HC, Ramasamy K, Weisel K, Abonour R, Hardin JW, Rifkin RM, Ailawadhi S, Terebelo HR, Durie BGM, Tang D, Joshi P, Liu L, Jou YM, Che M, Hernandez G, Narang M, Toomey K, Gasparetto C, Wagner LI, Jagannath S. Treatment Patterns, Survival, Quality of Life, and Healthcare Resource Use Among Patients With Triple-Class Refractory Multiple Myeloma in US Clinical Practice: Findings From the Connect MM Disease Registry. Clin Lymphoma Myeloma Leuk 2023;23:112–22.
25. Wang PF, Yee CW, Gorsh B, Zichlin ML, Paka P, Bhak RH, Boytsov N, Khanal A, Noman A, DerSarkissian M, Ferrante S, Duh MS. Treatment patterns and overall survival of patients with double-class and triple-class refractory multiple myeloma: a US electronic health record database study. Leuk. Lymphoma 2023;64:398-406.
26. Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, Gupta R, Varnado W, Fiala MA, Chhabra S, Malek E, Mansour J, Paul B, Barnstead A, Kodali S, Neppalli A, Liedtke M, Narayana S, Godby KN, Kang Y, Kansagra A, Umyarova E, Scott EC, Hari P, Vij R, Usmani SZ, Callander NS, Kumar SK, Costa LJ. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia 2019;33:2266–75. (2019a).
27. Gill SK, Unawane R, Wang S, Ahn J, Aleman A, Siegel DS, Vesole DH, Parmar H, Phull P, Biran N. I-Open: Inferior Outcomes of Patients with Quad and Penta-Refractory Multiple Myeloma (MM) Compared to Those of Patients Who Have Been Quad and Penta Exposed. Blood Cancer Journal 2022;12:138.
28. Goldsmith SR, Fiala MA, Wang B, Schroeder MA, Wildes TM, Ghobadi A, Stockerl-Goldstein K, Vij R. DCEP and bendamustine/prednisone as salvage therapy for quad- and penta-refractory multiple myeloma. Ann Hematol 2020;99:1041–48.

29. Dhanasiri S, Hollier-Hann G, Stothard C, Dhanda DS, Davies FE, Rodriguez-Otero P. Treatment Patterns and Outcomes in Triple-Class Exposed Patients With Relapsed and Refractory Multiple Myeloma: Findings From the Multinational ITEMISE Study. Clin Ther 2021;43:1983-96.
30. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, Munshi N, Lonial S, Bladé J, Mateos MV, Dimopoulos M, Kastritis E, Boccadoro M, Orlowski R, Goldschmidt H, Spencer A, Hou J, Chng WJ, Usmani SZ, Zamagni E, Shimizu K, Jagannath S, Johnsen HE, Terpos E, Reiman A, Kyle RA, Sonneveld P, Richardson PG, McCarthy P, Ludwig H, Chen W, Cavo M, Harousseau JL, Lentzsch S, Hillengass J, Palumbo A, Orfao A, Rajkumar SV, Miguel JS, Avet-Loiseau H. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17:e328–e346.
31. Medicinrådet. Medicinrådets anbefaling vedr. teclistamab til behandling af patienter med knoglemarvskræft, som har fået mindst tre tidligere behandlingslinjer - herunder et immunmodulerende middel, en proteasomhæmmer og et anti-CD38- antistof, og som har udvist sygdomsprogression under den sidste behandlingslinje. Februar 2024. https://medicinraadet-classic.azureedge.net/media/2plk3ijp/medicinradets-anbefaling-vedr-teclistamab-til-knoglemarvskraeft-vers-1-0x.pdf.
32. Bylund CL, Eggly S, LeBlanc TW, Kurtin S, Gandee M, Medhekar R, Fu A, Khurana M, Delaney K, Divita A, McNamara M, Baile WF. Survey of patients and physicians on shared decision-making in treatment selection in relapsed/refractory multiple myeloma. Transl Behav Med 2023: ibac099.
33. Sonneveld P. Management of multiple myeloma in the relapsed/refractory patient. Hematol Am Soc Hematol Educ Program 2017:508–517.
34. Zanwar S, Ho m, Kapoor P, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Hayman SR, Dingli D, Kourelis T, Fonder A, Hobbs M, Hwa Y, Gonsalves W, Warsame R, Muchtar E, Leung N, Kyle RA, Rajkumar SV, Kumar S. Outcomes of triple class (proteasome inhibitor, IMiDs and monoclonal antibody) refractory patients with multiple myeloma. Leukemia 2022;36:873-6.
35. Mateos MV, Weisel K, De Stefano V, Goldschmidt H, Delforge M, Mohty M, Cavo M, Vij R, Lindsey-Hill J, Dytfeld D, Angelucci E, Perrot A, Benjamin R, van de Donk NWCJ, Ocio EM, Scheid C, Gay F, Roeloffzen W, Rodriguez-Otero P, Broijl A, Potamianou A, Sakabedoyan C, Semerjian M, Keim S, Strulev V, Schecter JM, Vogel M, Wapenaar R, Nesheiwat T, San-Miguel J, Sonneveld P, Einsele H, Moreau P. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia 2022;36:1371–6. (2022a).
36. Szabo AG, Thorsen J, Iversen KF, Levring MB, Helleberg C, Hermansen E, Bønløkke ST, Nielsen K, Teodorescu EM, Kurt E, Strandholdt CN, Vangsted AJ. The real-world use and efficacy of pomalidomide for relapsed and refractory multiple myeloma in the era of CD38 antibodies. EJHaem 2023;4:1006-12.
37. Moreau P, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, Nooka AK, Martin T, Rosinol L, Chari A, Karlin L, Benboubker L, Mateos MV, Bahlis N, Popat R, Besemer B, Martínez-López J, Sidana S, Delforge M, Pei L, Trancucci D, Verona R, Girgis S, Lin SXW, Olyslager Y, Jaffe M, Uhlar C, Stephenson T, Van Rampelbergh R, Banerjee A, Goldberg JD, Kobos R, Krishnan A, Usmani SZ.

Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med 2022;387:495–505.
38. Atrash S, Mammadzadeh A, Peng F, Alkharabsheh O, Afrough A, Cui W, Mahmoudjafari Z, Abdallah AO, Hashmi H. Outcomes of Penta-Refractory Multiple Myeloma Patients Treated with or without BCMA-Directed Therapy. Cancers (Basel) 2023;15:2891.
39. Riedhammer C, Bassermann F, Besemer B, Bewarder M, Brunner F, Carpinteiro A, Einsele H, Faltin J, Frenking J, Gezer D, Goldman-Mazur S, Hänel M, Hoegner M, Kortuem KM, Krönke J, Kull M, Leitner T, Mann C, Mecklenbrauck R, Merz M, Morgner A, Nogai A, Raab MS, Teipel R, Wäsch R, Rasche L. Real-world analysis of teclistamab in 123 RRMM patients from Germany. Leukemia 2024;38:365-71.
40. Abramson HN. B-Cell Maturation Antigen (BCMA) as a Target for New Drug Development in Relapsed and/or Refractory Multiple Myeloma. Int J Mol Sci 2020;21.
41. Lesokhin AM, Levy MY, Dalovisio AP, Bahlis NJ, Solh M, Sebag M, Jakubowiak A, Jethava YS, Costello CL, Chu MP, Savona MR, Gasparetto C, Trudel S, Chou J, Udata C, Basu C, Krupka HI, Raje NS. Preliminary Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Subcutaneously (SC) Administered PF-06863135, a B-Cell Maturation Antigen (BCMA)-CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). Blood 2020;136:8–9.
42. Yu B, Jiang T, Liu D. BCMA-targeted immunotherapy for multiple myeloma. J Hematol Oncol 2020;13:125.
43. Karwacz K, Hooper A, Chang CPB, Krupka H, Chou J, Lam V, Djuretic IM, Chaparro-Riggers J, Sapra P. BCMA-CD3 bispecific antibody PF-06863135: Preclinical rationale for therapeutic combinations. 2020.
44. Panowski SH, Kuo TC, Zhang Y, Chen A, Geng T, Aschenbrenner L, Kamperschroer C, Pascua E, Chen W, Delaria K, Farias S, Bateman M, Dushin RG, Chin SM, Van Blarcom TJ, Yeung YA, Lindquist KC, Chunyk AG, Kuang B, Han B, Mirsky M, Pardo I, Buetow B, Martin TG, Wolf JL, Shelton D, Rajpal A, Strop P, Chaparro-Riggers J, Sasu BJ. Preclinical Efficacy and Safety Comparison of CD3 Bispecific and ADC Modalities Targeting BCMA for the Treatment of Multiple Myeloma. Mol Cancer Ther 2019;18:2008–20.
45. Udata C, Wei D, Jiang S, Forgie A, Hooper A, Qiao W, Musante C, Yin D. Abstract 5508: BCMA-CD3 bispecific antibodies: A modeling framework to characterize kinetics of bispecific antibody, T cell, cytokines, and serum M-protein. Cancer Res 2020;80:5508.

46. Jakubowiak AJ, Bahlis NJ, Raje NS, Costello C, Dholaria BR, Solh MM, Levy MY, Tomasson MH, Dube H, Damore MA, Jiang S, Basu C, Skoura A, Chan EM, Trudel S, Chu MP, Gasparetto CJ, Dalovisio AP, Sebag M, Lesokhin AM. Elranatamab, a BCMA-targeted T-cell redirecting immunotherapy, for patients with relapsed or refractory multiple myeloma: Updated results from MagnetisMM-1. J Clin Oncol 2022:8014.
47. Lesokhin AM, Tomasson MH, Arnulf B, Bahlis NJ, Miles Prince H, Niesvizky R, Rodríguez-Otero P, Martinez-Lopez J, Koehne G, Touzeau C, Jethava Y, Quach H, Depaus J, Yokoyama H, Gabayan AE, Stevens DA, Nooka AK, Manier S, Raje N, Iida S, Raab MS, Searle E, Leip E, Sullivan ST, Conte U, Elmeliegy M, Czibere A, Viqueira A, Mohty M. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med 2023;29:2259–67.
48. European Medicines Agency. Summary of product characteristics: Tecvayli https://www.ema.europa.eu/en/documents/product-information/tecvayli-epar-product-information_en.pdf.
49. [redacted]
51. Assessment report (EPAR) Elrexfio. 12 October 2023. EMA/544323/2023. Committee for Medicinal Products for Human Use (CHMP).
52. Tomasson M, Iida S, Niesvizky R, Mohty M, Bahlis NJ, Martinez-Lopez J, Koehne G, Rodríguez-Otero P, Prince HM, Viqueira A, Leip E, Conte U, Sullivan ST, Lesokhin AM. Long-Term Efficacy and Safety of Elranatamab Monotherapy in the Phase 2 Magnetismm-3 Trial in Relapsed or Refractory Multiple Myeloma (RRMM). Blood. 2023 Nov 28;142(Supplement 1):3385. Presented at the 65th American Society of Hematology (ASH) Annual Meeting, December 9-12, 2023, San Diego, CA, USA.
53. Assessment report (EPAR) Tecvayli. 21 July 2022. EMA/789141/2022. Committee for Medicinal Products for Human Use (CHMP).
54. Mohty M, Bahlis NJ, Nooka AK, DiBonaventura M, Ren J, Conte U. Impact of elranatamab on quality of life: Patient-reported outcomes from MagnetisMM-3. Br J Haematol 2024.
55. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.
56. Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual (3rd edition) . Brussels, Belgium: European Organisation for Research and Treatment of Cancer; 2001 .
57. Forde K, Cocks K, Wells JR, McMillan I, Kyriakou C. Use of the European Organisation for Research and Treatment of Cancer multiple myeloma module (EORTC QLQ-MY20): a review of the literature 25 years after development. Blood Cancer J 2023;13:79.

58. Martin T, Lin Y, Agha M, Cohen AD, Htut M, Stewart AK, Hari P, Berdeja JG, Usmani SZ, Yeh TM, Olyslager Y, Goldberg JD, Schecter JM, Madduri D, Jackson CC, Deraedt W, Gries KS, Fastenau JM, Trudeau JJ, Akram M, Pacaud L, Jakubowiak A, Jagannath S. Health-related quality of life in patients given ciltacabtagene autoleucel for relapsed or refractory multiple myeloma (CARTITUDE-1): A phase 1b-2, open-label study. Lancet Haematol 2022;9:e897–e905.
59. Martin TG, Moreau P, Usmani SZ, Garfall A, Mateos MV, San-Miguel JF, Oriol A, Nooka AK, Rosinol L, Chari A, Karlin L, Krishnan A, Bahlis N, Popat R, Besemer B, Martínez-López J, Delforge M, Trancucci D, Pei L, Kobos R, Fastenau J, Gries KS, van de Donk NWCJ. Teclistamab Improves Patient-Reported Symptoms and Health-Related Quality of Life in Relapsed or Refractory Multiple Myeloma: Results From the Phase II MajesTEC-1 Study. Clin Lymphoma Myeloma Leuk. 2024;24:194–202.
60. Cocks K, King MT, Velikova G, Fayers PM, Brown JM. Quality, interpretation and presentation of European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 data in randomised controlled trials. Eur J Cancer 2008;44:1793–8.
61. Osoba D. Health-related quality of life and cancer clinical trials. Ther Adv Med Oncol 2011;3:57–71.
62. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:70.
63. Finansministeriet. Notat: Nøgletalskatalog. https://fm.dk/media/27419/noegletalskatalog_februar-2024.pdf
64. Mol I, Hu Y, LeBlanc TW, Cappelleri JC, Chu H, Nador G, et al. A matching-adjusted indirect comparison of the efficacy of elranatamab versus teclistamab in patients with triple-class exposed/refractory multiple myeloma. Leuk Lymphoma 2024:1–9.
65. Usmani SZ, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, Rosinol L, Chari A, Bhutani M, Karlin L, Benboubker L, Pei L, Verona R, Girgis S, Stephenson T, Elsayed Y, Infante J, Goldberg JD, Banerjee A, Mateos MV, Krishnan A. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Lancet 2021;398:665–74.
66. Sidana S, Moreau P, Garfall A, Bhutani M, Oriol A, Nooka A, Martin T, Rosiñol Dachs L, Mateos MV, Bahlis NJ, Popat R, Besemer B, Martinez-Lopez J, Krishnan A, Delforge M, Trancucci D, Verona R, Stephenson T, Chastain K, van de Donk NWCJ. P879: Long-term follow-up from MajesTEC-1 of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM). Hemasphere 2023;7(Suppl):e62475d0.
67. Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.
68. Phillippo D, Ades T, Dias S, et al. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE. NICE Decision Support Unit. Sheffield: University of Sheffield; 2016. p. 82.

69. National Institute for Health Care and Excellence. Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma. Technology appraisal guidance. Reference number: TA658. https://www.nice.org.uk/guidance/ta658
70. van de Donk NWCJ, Moreau P, Garfall AL, Bhutani M, Oriol A, Nooka AK, et al. Long-term follow-up from MajesTEC-1 of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM). J Clin Oncol 2023 Jun 1;41(16_suppl):8011.
71. [redacted]
72. Medicinrådet. Medicinrådets metodevejledning for vurdering af nye lægemidler (Version 1.2) Februar 2021. https://medicinraadet.dk/media/hciai0yz/medicinr%C3%A5dets_metodevejledning_for_vurdering_af_nye_l%C3%A6gemidler-vers-_1-2_adlegacy.pdf
73. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics 1982;38:29-41.
[redacted]
75. Beinfeld M, Lee S, McQueen B, Fluetsch N, Pearson SD, Ollendorf DA. Anti B-cell maturation antigen CAR T-cell and antibody drug conjugate therapy for heavily pretreated relapsed and refractory multiple myeloma: A summary from the Institute for Clinical and Economic Review's Midwest Comparative Effectiveness Public Advisory Council. J Manag Care Spec Pharm 2021;27:1315–20.
76. Lee SJ MR, Beinfeld M, Fluetsch N, Whittington MD, Pearson SD, Ollendorf DA. Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma; Final Evidence Report. Institute for Clinical And Economic Review. 2021. https://icer.org/assessment/multiple-myeloma-2021/#timeline.
77. Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2021;21:111.
78. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd; 2019. https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119536604.fmatter
79. Tacconelli E. Systematic reviews: CRD's guidance for undertaking reviews in health care. Lancet Infect Dis 2010;10:226.
80. National Institute for Health and Care Excellende (NICE). The guidelines manual: Process and methods. 2012.
81. Mohty M, Lida S, Bahlis N, Sullivan S, Conte U, Leip E, Viqueira A. Long-Term Survival After Elranatamab Monotherapy in Patients With Relapsed or Refractory Multiple Myeloma: MagnetisMM-3. Presented at EHA conference, June 2024, Madrid
82. Mol I, Hu Y, Leblanc T, Capelleri J, Chu H, Nador G, Aydin D, Cruz I, Hlavacek p. Updated Results of a Matching-Adjusted Indirect Comparison of Elranatamab Vs Teclistamab in Patients With Triple-Class Exposed/Refractory Multiple Myeloma. Presented at EHA conference, June 2024, Madrid
83. Malard F, Bobin A, Labopin M, Karlin L, Frenzel L, Roussel M, Vignon M, Godet S, Chalopin T, Moyer P, Chalayer E, Piocelle F O, Mariette C, Croizier C, Claudine S, Dib M, CALLOCH R L, Ali-Ammar N, Loirat M, Benbrahim O, Payssot A, Trebouet A, Perrot A, Leleu X; Mohty M. EFFICACY AND SAFETY OF ELRANATAMAB

MONOTHERAPY IN THE REALWORD SETTING IN RELAPSED-REFRACTORY MULTIPLE MYELOMA (RRMM): RESULTS OF THE FRENCH COMPASSIONATE USE PROGRAM ON BEHALF OF THE IFM. Abstract 906 presented at EHA conference, June 2024, Madrid

Appendix A. Main characteristics of studies included

Table 53 Main characteristic of studies included.

Trial name: MagnetisMM-3	NCT number: NCT04649359
Objective	Evaluate the efficacy and safety of elranatamab monotherapy in patients with relapsed or refractory multiple myeloma who are refractory to at least one PI, one IMiD and one anti-CD38 mAb.
Publications – title, author, journal, year	Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Alexander M. Lesokhin et al. Nature Medicine 2023 (47) Long-Term Efficacy and Safety of Elranatamab Monotherapy in the Phase 2 Magnetismm-3 Trial in Relapsed or Refractory Multiple Myeloma (RRMM). Tomasson et al. Blood 2023 (52) Impact of elranatamab on quality of life: Patient-reported outcomes from MagnetisMM-3. Mohty M et al., Br J Haematol. 2024;00:1–10. (54)
Study type and design	Ongoing, multicenter, open-label, single-arm, phase 2 study
Sample size (n)	123

Trial name: MagnetisMM-3	NCT number: NCT04649359
Main inclusion criteria	• Male or female participants age ≥18 years. • Prior diagnosis of MM as defined according to IMWG criteria (7). • Measurable disease based on IMWG criteria as defined by at least 1 of the following: a) Serum M-protein ≥0.5 g/dL by SPEP b) Urinary M-protein excretion ≥200 mg/24 hours by UPEP c) Serum immunoglobulin FLC ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (1.65) • Refractory to at least one IMiD • Refractory to at least one PI • Refractory to at least one anti-CD38 antibody • Relapsed or refractory to last anti-MM regimen. Note: Refractory is defined as having disease progression while on therapy or within 60 days of last dose in any line, regardless of response. • Has not received prior BCMA-directed therapy. • ECOG performance status ≤2 • LVEF ≥40% as determined by a MUGA scan or ECHO • Adequate hepatic function characterized by the following: a) Total bilirubin ≤2 x ULN (≤3 x ULN if documented Gilbert's syndrome); b) AST ≤2.5 x ULN; and c) ALT ≤2.5 x ULN • Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min (according to the Cockcroft Gault formula, by 24-hour urine collection for creatinine clearance, or according to local institutional standard method). • Adequate BM function characterized by the following: a) ANC ≥1.0 × 109/L (use of granulocyte-colony stimulating factors is permitted if completed at least 7 days prior to planned start of dosing); b) Platelets ≥25 × 109/L (transfusion support is permitted if completed at least 7 days prior to planned start of dosing); and c) Haemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 7 days prior to planned start of dosing). • Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1

Trial name: MagnetisMM-3		NCT number: NCT04649359
Main exclusion criteria	• Smoldering MM. • Active plasma cell leukemia. • Amyloidosis. • POEMS syndrome • Stem cell transplant within 12 weeks prior to enrolment or active GVHD. • Ongoing Grade ≥2 peripheral sensory or motor neuropathy. • History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy. • Active HBV, HCV, SARS-CoV2, HIV, or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 14 days prior to enrolment. • Previous treatment with an anti-BCMA bispecific antibody.	
Intervention	123 enrolled participants received SC elranatamab with a 2 step-up priming regimen of 12 mg on C1D1 and 32 mg on C1D4 followed by the first full dose (76 mg) of elranatamab on C1D8 and QW thereafter, except for the first 4 participants that received 1 step-up priming dose of 44 mg on C1D1 followed by the first full dose (76 mg) on C1D8. Premedication with dexamethasone, acetaminophen and diphenhydramine prior to administration of the step-up priming dose(s) and first full dose of elranatamab was required. If a participant received QW dosing for at least 6 cycles and achieved an IMWG response category of PR or better persisting for at least 2 months, the dose interval was to be changed from QW to Q2W (e.g., beginning C7D1). If the participant subsequently began to have an increase of disease burden not yet qualifying as PD according to IMWG criteria, dose intervals were to return to weekly dosing.	
Comparator(s)	Not applicable	
Follow-up time	Median follow-up of 14.7 months (range: 0.2–25.1 months) (47) Latest median follow-up of 17.6 months (range: 0.2-31.1 months) (52)	
Is the study used in the health economic model?	Yes, used in cost-minimization analysis	

Trial name: MagnetisMM-3	NCT number: NCT04649359
Primary, secondary and exploratory endpoints	Primary Endpoint: • ORR by BICR per IMWG, where objective response was defined as having a best overall response (BOR) of confirmed sCR, CR, VGPR or PR per IMWG criteria Secondary Endpoints: • ORR by BICR baseline EMD status per IMWG • DOR by BICR and investigator per IMWG • CRR by BICR and investigator per IMWG • ORR by investigator per IMWG • DOCR by BICR and investigator per IMWG • PFS by BICR and investigator per IMWG • OS • TTR by BICR and investigator per IMWG • MRD negativity rate (central lab) per IMWGORR in patients with high-risk molecular features • AEs and laboratory abnormalities as graded by NCI CTCAE v5.0. • Severity of CRS and ICANS assessed according to ASTCT criteria • Pre- and postdose concentrations of elranatamab • ADAs and NAbs against elranatamab Exploratory endpoints: • Measurements of biomarkers (DNA, RNA, protein or defined cell types) resulting from analyses of peripheral blood, saliva and/or BM biospecimens • Selected PK, efficacy, safety and biomarker endpoints • EORTC QLQ-C30 and MY20 • EORTC QLQ CIPN20 • EQ-5D • PGI-S and PGI-C • Hospitalizations, including length of stay, ICU admissions, transfusions, infections and outpatient visits **Endpoints included in this application:** PFS and OS
Method of analysis	All efficacy analyses were intention-to-treat analyses. We used the Kaplan–Meier method to estimate rates of progression-free survival and overall survival.
Subgroup analyses	Subgroup analyses are not presented in this application
Other relevant information	Not applicable

Trial name: MajesTEC-1	NCT number: NCT03145181 (Phase 1) NCT04557098 (Phase 2)
Objective	Part 1 (Dose Escalation): To identify the proposed RP2D(s) and schedule assessed to be safe for teclistamab Part 2 (Dose Expansion): To characterize the safety and tolerability of teclistamab at the proposed RP2D(s) Part 3 (Phase 2): To evaluate the efficacy of teclistamab at RP2D
Publications – title, author, journal, year	Teclistamab in relapsed or refractory multiple myeloma. Moreau P, Garfall AL, van de Donk N, et al. N Engl J Med. 2022;387(6):495–505. (37) Long-term follow-up from MajesTEC-1 of teclistamab, a B-cell maturation antigen (BCMA) × CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM) Sidana S et al. Presented at EHA 2023 Hybrid Congress: June8-11, 2023. (66) Teclistamab Improves Patient-Reported Symptoms and Health-Related Quality of Life in Relapsed or Refractory Multiple Myeloma: Results From the Phase II MajesTEC-1 Study. Martin TG et al. Clinical Lymphoma, Myeloma and Leukemia, 2024; Vol. 24, No. 3, 194–202. (59)
Study type and design	Ongoing, multicenter, open-label, single-arm, phase 1-2 study
Sample size (n)	165
Main inclusion criteria	• Age ≥18 years with documented diagnosis of MM according to IMWG diagnostic criteria. • Relapsed or refractory measurable multiple myeloma following prior treatment with ≥3 prior MM treatment lines that included an ImiD, a PI, and anti-CD38 mAb. • Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1. • Measurable disease: MM must be measurable by central laboratory assessment: - Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or - Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain (FLC} ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio - If central laboratory assessments are not available, relevant local laboratory measurements must exceed the minimum required level by at least 25%. • Pretreatment clinical laboratory values meeting minimal thresholds defined by the protocol*.

Main exclusion criteria

- Treatment with any therapy that is targeted to BCMA or any other CD3-redirecting drug.
- Prior antitumor therapy including: chemotherapy, targeted therapy, immunotherapy, radiotherapy or treatment with an investigational drug or used an invasive investigational medical device within 3 weeks or at least 5 half-lives prior to the first dose of study drug, whichever is less.
- Toxicities from previous anticancer therapies should have resolved to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy.
- Received a cumulative dose of corticosteroids equivalent to ≥140 mg of prednisone within the 14-day period before the first dose of study drug.
- Stem cell transplant:
  - Allogenic stem cell transplant ≤6 months before the first dose of study drug.
    Subjects with allogenic stem cell transplant should not have any symptoms of acute or chronic graft versus host disease.
  - Autologous stem cell transplant ≤12 weeks before the first dose of study drug.
- Known active CNS involvement or exhibits clinical signs of meningeal involvement of multiple myeloma.
- Plasma cell leukemia (>2.0 x 109/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or amyloidosis.
- Known to be seropositive for human immunodeficiency virus or acquired immune deficiency syndrome.
- Hepatitis B infection as defined according to the American Society of Clinical Oncology guidelines. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status Hepatitis C (anti-hepatitis C virus [HCV] antibody positive or HCV-RNA quantitation positive) or known to have a history of hepatitis C. If positive, further testing of quantitative levels to rule out positivity is required.
- Pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation.
- Known allergies, hypersensitivity, or intolerance to JNJ-64007957 or its excipients.
- Any serious underlying medical condition, such as:
  - Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection
  - Active autoimmune disease or a documented history of autoimmune disease
  - Psychiatric conditions (e.g, alcohol or drug abuse), dementia, or altered mental status
  - Any other issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

- Pregnant or breast-feeding or planning to become pregnant while enrolled in this study or within 90 days after receiving the last dose of study drug.

Trial name: MajesTEC-1	NCT number: NCT03145181 (Phase 1) NCT04557098 (Phase 2)
Intervention	165 patients received once-weekly subcutaneous teclistamab at a dose of 1.5 mg per kilogram, which had been preceded by step-up doses of 0.06 and 0.3 mg per kilogram. The step-up doses were separated by 2 to 4 days and were completed 2 to 4 days before the administration of the first full teclistamab dose. Hospitalization and premedication with dexamethasone (16 mg), acetaminophen, and diphenhydramine were required for each step-up dose and for the first full dose of teclistamab. The cycle duration was 21 days in phase 1 and 28 days in phase 2. Patients continued to receive teclistamab until the occurrence of disease progression, unacceptable toxicity, withdrawal of consent, death, or the end of the study (defined as 2 years after the administration of the first dose of teclistamab in the last enrolled patient).
Comparator(s)	Not applicable
Follow-up time	At data cut-off March 16 2022, the median follow-up was 14.1 months (range: 0.3–24.4 months) (37). At data cut-off January 4 2023, the median follow-up was 23 months (66).
Is the study used in the health economic model?	Yes, used in cost-minimization analysis.

Trial name: MajesTEC-1	NCT number: NCT03145181 (Phase 1) NCT04557098 (Phase 2)
Primary, secondary and exploratory endpoints	Primary Endpoint: • ORR (PR or better) as defined by the IMWG criteria as assessed by the independent review committee Secondary Endpoints: • DOR • VGPR or better/CR or better/sCR as defined by the IMWG response criteria • TTR • PFS • OS • MRD negativity status • Occurrence and severity of adverse events, serious adverse events, and laboratory values • Pharmacokinetic parameters • Presence and activity of anti-teclistamab antibodies • Change from baseline in overall HRQoL, symptoms, and functioning. • ORR in patients with high-risk molecular features Exploratory endpoint: • To explore the relationships between pharmacokinetics, pharmacodynamics, adverse event profile, and clinical activity of teclistamab • To investigate predictive biomarkers of response or resistance to teclistamab • To investigate pharmacodynamic markers • To investigate immunoregulatory activity of teclistamab • To evaluate MRU • To assess TTNT **Endpoints included in this application:** PFS, OS and safety were included in this application
Method of analysis	All efficacy analyses were intention-to-treat analyses. The Kaplan–Meier method was used to estimate rates of progression-free survival and overall survival.
Subgroup analyses	Not applicable
Other relevant information	** These thresholds are defined in the full inclusion/exclusion criteria.*

Appendix B. Efficacy results per study

Results per study

Table 54 Results per study.

Results of MagnetisMM 3 (NCT04649359)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS	Elranatamab	123	Not reached (95%CI: 9.9 months to not estimable), with 70 (56.9%) patients censored at data cut-off, and the Kaplan-Meier estimate of PFS at 14.7 months was 50.9% (95%CI 40.9-60.0) (47). Latest follow-up – 17.6 months median follow-up (data cut-off:	N/A		N/A	N/A	N/A	N/A	The median PFS is based on the Kaplan-Meier (KM) estimate [redacted]	(47[redacted],52)

Results of MagnetisMM 3 (NCT04649359)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
			September 11 2023) Kaplan–Meier median PFS was 17.2 months (95%CI 9.8-NE) (52).								
Median Overall survival (@median follow-up of 14.7 months)	elranatamab	123	Not reached (95% CI: 13.9 months to not estimable), and Kaplan-Meier estimate at 14.7 months was 56.7% (95% CI:47.4 – 65.1) (47). Latest follow-up – 17.6 months median follow-up (data cut-off: September 11 2023) Kaplan–Meier median OS was 21.9	N/A	N/A	N/A	N/A	N/A	N/A	[redacted]	(47[redacted],52)

Results of MagnetisMM 3 (NCT04649359)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
			months (95%CI 13.4-NE) (52).								
HRQoL	Elranatamab	123	See section 6.1.4	N/A	N/A	N/A	N/A	N/A	N/A	See section 6.1.4	(54)

Results of MajesTEC-1 (NCT03145181 and NCT04557098)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median PFS (data cut-off March 16, 2022, i.e. median follow-up	Teclistamab	165	11.3 months (95% CI: 8.8 to 17.1) (37). Later follow-up: 22 months (data cut-off January	N/A	N/A	N/A	N/A	N/A	N/A	The median PFS is based on the Kaplan-Meier (KM) estimate	(37,66)

Results of MajesTEC-1 (NCT03145181 and NCT04557098)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
of 14.1 months)			4, 2023) median PFS was 11.3 months (95% CI, 8.8–16.4) (66).								
Median Overall survival (data cut-off March 16, 2022, i.e. median follow-up of 14.1 months)	Teclistamab	165	18.3 months (95% CI: 15.1 to not estimable) and was not mature after censoring of data for 97 patients (58.8%) (37). Later follow-up: 22 months (data cut-off January 4, 2023) median OS was 21.9 months (95% CI, 16.0–NE) (66).	N/A	N/A	N/A	N/A	N/A	N/A	The median survival is based on the KM estimate	(37,66)
HRQoL	Teclistamab	125	See section 6.1.5	N/A	N/A	N/A	N/A	N/A	N/A	See section 6.1.5	(59)

Appendix C. Comparative analysis of efficacy

The objective of this matching-adjusted indirect treatment comparison (MAIC) was to evaluate the comparative effectiveness of elranatamab in relation to teclistamab (also see Section 7). The latest data cut-off date of September 11 2023 for elranatamab – median duration of follow-up of 17.6 months – as reported in Tomasson et al. (52) was not included in the MAIC (64). However, Tomasson et al.'s results demonstrated sustained clinical efficacy of elranatamab, why this supports the results found in the MAIC (64).

To adjust for cross-trial differences, patients from MagenetisMM-3 were reweighted to match the selected key baseline characteristics of patients who received teclistamab in MajesTEC-1 as reported by Moreau et al. (48). Weights were determined using a propensity score-type logistic regression via the method of moments (67) based on age, median time since diagnosis, International Staging System (ISS) disease stage, high-risk cytogenetics as defined by the presence of one of t(4;14), t(14;16), or del17p, extramedullary disease, number of prior lines of therapy, Eastern Cooperative Oncology Group performance status (ECOG PS), penta-drug exposed and penta-drug refractory status. Sex was included in the analysis for OS. Effective sample size (ESS) was assessed after conducting the MAIC. The ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate (68). The ESS is one key statistic which shows the statistical power of the MAIC analysis. A small ESS is indicative of large differences in patient populations between the comparators.

In MagnetisMM-3, certain adjusted baseline characteristics contained missing values. To potentially enhance the ESS, a sensitivity analysis was conducted. This involved imputing the missing values for the adjusted baseline characteristics of elranatamab using a random sample of observations from MagnetisMM-3.
Unanchored MAIC analyses were conducted in R studio 12.0 (R version 4.2.2) following the code provided in the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) 18 by Phillippo et al. (68). In the MAICs, adjusted OS and PFS after 14.7 months of follow-up for elranatamab were compared with teclistamab.
To assess time-to-event endpoints, Kaplan–Meier's curves from MajesTEC-1 were digitized following the methodology outlined by Guyot et al. (67). Subsequently, a weighted (based on the weights assigned for the adjustment of baseline characteristics) Cox proportional hazards model was employed to estimate each hazard ratio (HR) and its respective 95% CI. Conclusions regarding significantly better or worse outcomes were drawn based on whether the 95% CI excluded 1 (for odds ratio/HR) or 0 (for rate difference). Numeric conclusions are based on the HR/odds ratio value.

Table 55 below, provides the HRs for OS and PFS.

In the naïve analysis, the OS of elranatamab was similar to teclistamab. Following MAIC adjustment, the HR improved and elranatamab was associated with a numerically longer

OS compared with teclistamab, yet results were not statistically significant. The HR of elranatamab compared with teclistamab was 1.053 (0.738,1.502) before weighting and 0.660 (0.423, 1.030) after weighting. Similar to the base case, in the sensitivity analysis, the OS of elranatamab was numerically longer than teclistamab following MAIC adjustment, yet the results were not statistically significant.

The PFS of elranatamab was significantly longer than teclistamab in the MAIC adjustment. The PFS HR compared with teclistamab was 0.856 (0.608, 1.205) before weighting and 0.586 (0.386, 0.889) after weighting. The sensitivity analysis results were consistent with the base case.

Table 55 Hazard ratios of OS and PFS: elranatamab vs. teclistamab.

Outcome	Scenario	ESS	HR (95% CI)	p-value
OS	Naïve comparison	116	1.053 (0.738, 1.052)	0.777
	Base Case	73	0.660 (0.423, 1.030)	0.067
	Sesitivity analysis (imputation)	87	0.785 (0.520, 1.183)	0.247
PFS	Naïve comparison	116	0.856 (0.608, 1.205)	0.373
	Base Case	75	0.586 (0.386, 0.889)	0.012
	Sensitivity analysis (imputation)	89	0.646 (0.439, 0.949)	0.026

Appendix D. Extrapolation

Standard parametric fits (i.e., Weibull, log-normal, exponential, log-logistic, Gompertz, generalised gamma and gamma) were used on the KM curves based on 14.7-month data from MagnetisMM-3 for OS and PFS for both elranatamab and teclistamab based on the assumption that the OS and PFS of these two treatments are comparable and similar. The best parametric fits were decided based on both the visual checks and AIC/BIC statistics.

D.1 Extrapolation of overall survival

D.1.1 Data input

In the base case, OS was derived based on cohort A of MagnetisMM-3 (14.7-month data).

D.1.2 Model

Parametric survival model.

D.1.3 Proportional hazards

Not applicable.

D.1.4 Evaluation of statistical fit (AIC and BIC)

The AIC and BIC statistics for OS are presented in Table 56 along with a ranking of the best statistical fit. As seen, log-normal had the best statistical fit based on the lowest mean value of AIC/BIC.

Table 56 [redacted]

Parametric model	AIC	BIC	Mean	Rank
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

D.1.5 Evaluation of visual fit

The standard parametric fits for OS, the KM curve from MagnetisMM-3 and the survival curve for the general Danish population are presented in Figure 34.

Figure 34

D.1.6 Evaluation of hazard functions

Not applicable.

D.1.7 Validation and discussion of extrapolated curves

Due to missing long-term external data on OS in the relevant population, the choice of parametric model was based on statistical fit and a visual check of each curve.

D.1.8 Adjustment of background mortality

Life tables from the Danish general population from Statistics Denmark were included in the model to ensure that the risk of death in the model was not lower than the risk of death of the general population. The DMC template was used to adjust for background mortality.

D.1.9 Adjustment for treatment switching/crossover

Not applicable.

D.1.10 Waning effect

Not applicable.

D.1.11 Cure-point

Not applicable.

D.2 Extrapolation of progression-free survival

D.2.1 Data input

PFS was derived based on cohort A (14.7-month data) from MagnetisMM-3 (46).

D.2.2 Model

Parametric survival model.

D.2.3 Proportional hazards

Not applicable.

D.2.4 Evaluation of statistical fit (AIC and BIC)

The AIC and BIC statistics for PFS are presented in Table 57 along with a ranking of the best statistical fit. [redacted]

Table 57 [redacted]

Parametric model	AIC	BIC	Mean	Rank
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

D.2.5 Evaluation of visual fit

[redacted]

Figure 35 [redacted]

D.2.6 Evaluation of hazard functions

Not applicable.

D.2.7 Validation and discussion of extrapolated curves

Due to missing long-term external data on PFS in the relevant population, the choice of parametric model was based on statistical fit and a visual check of each curve.

D.2.8 Adjustment of background mortality

Not applicable.

D.2.9 Adjustment for treatment switching/crossover

Not applicable.

D.2.10 Waning effect

Not applicable.

D.2.11 Cure-point

Not applicable.

D.3 Extrapolation of time to treatment discontinuation

D.3.1 Data input

TTD for elranatamab was based on data from the MagnetisMM-3 trial and extrapolated beyond the trial follow-up period with standard parametric fits models. The extrapolation of TTD for teclistamab for the health economics model was based on *Figure 16* from the DMC evaluation of teclistamab (31). This figure portrays both the observed and the extrapolated TTD curve for patients treated with teclistamab.

As we did not have access to patient data for TTD of teclistamab, we extracted data points from the extrapolated TTD curve (log-normal curve) in *Figure 16* (31). This was carried out by applying a tool established in Liu et al. (77) and can be found in the 'Survival' sheet in the Excel model starting from row 6744. To ensure accuracy and reliability of the data extracted, we undertook three independent extractions of data points from the graph, resulting in a sample size of 267 data points. The collected data points were applied to estimate the parameters for the log-normal distribution, which was the chosen parametric distribution in the previously mentioned assessment of teclistamab.

Following this method, we estimated the mean log (meanlog) of the distribution to be 2.21 and the standard deviation log (sdlog) to be 0.50. The extrapolation of the TTD

curve for teclistamab, together with the extracted data points from *Figure 16* in (31), are presented in Figure 37 below together with the Figure 36 for elranatamab.

D.3.2 Model

Standard parametric models for elranatamab.

D.3.3 Proportional hazards

Not applicable.

D.3.4 Evaluation of statistical fit (AIC and BIC)

The AIC/BIC information is presented in Table 58. As seen, log-normal provided the best statistical fit.

Table 58 [redacted]

Parametric model	AIC	BIC	Average	Rank
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

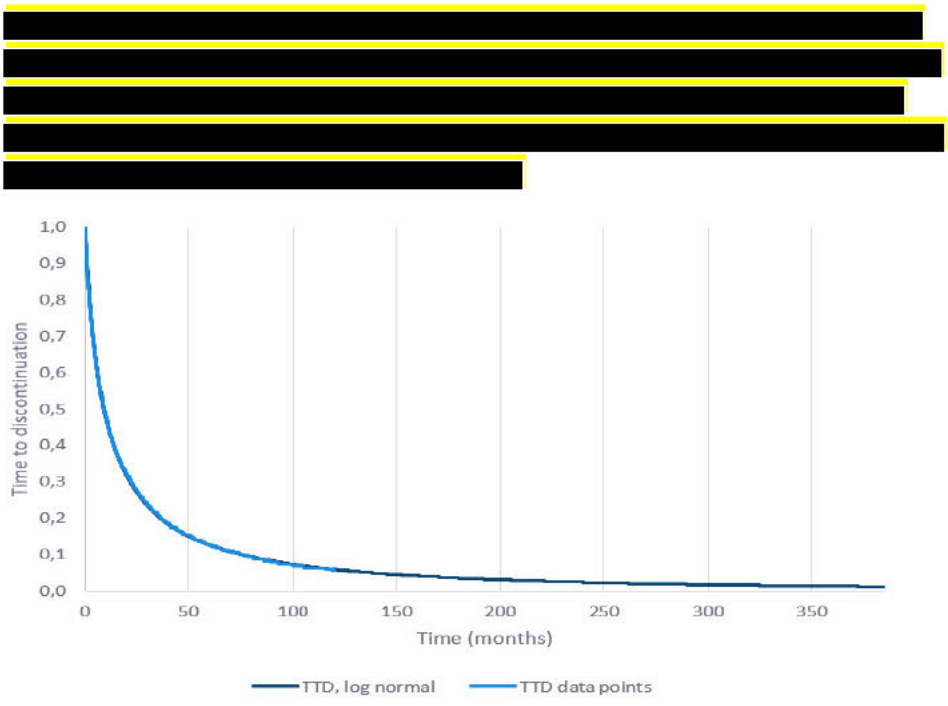


Figure 37 Log-normal curve for teclistamab and TTD data points from Figure 16 in the DMC evaluation of teclistamab. Source: (31).

D.3.6 Evaluation of hazard functions

Not applicable.

D.3.7 Validation and discussion of extrapolated curves

Due to missing long-term external data on TTD in the relevant population, the choice of parametric model was based on statistical fit and a visual check of each curve.

D.3.8 Adjustment of background mortality

Not applicable.

D.3.9 Adjustment for treatment switching/crossover

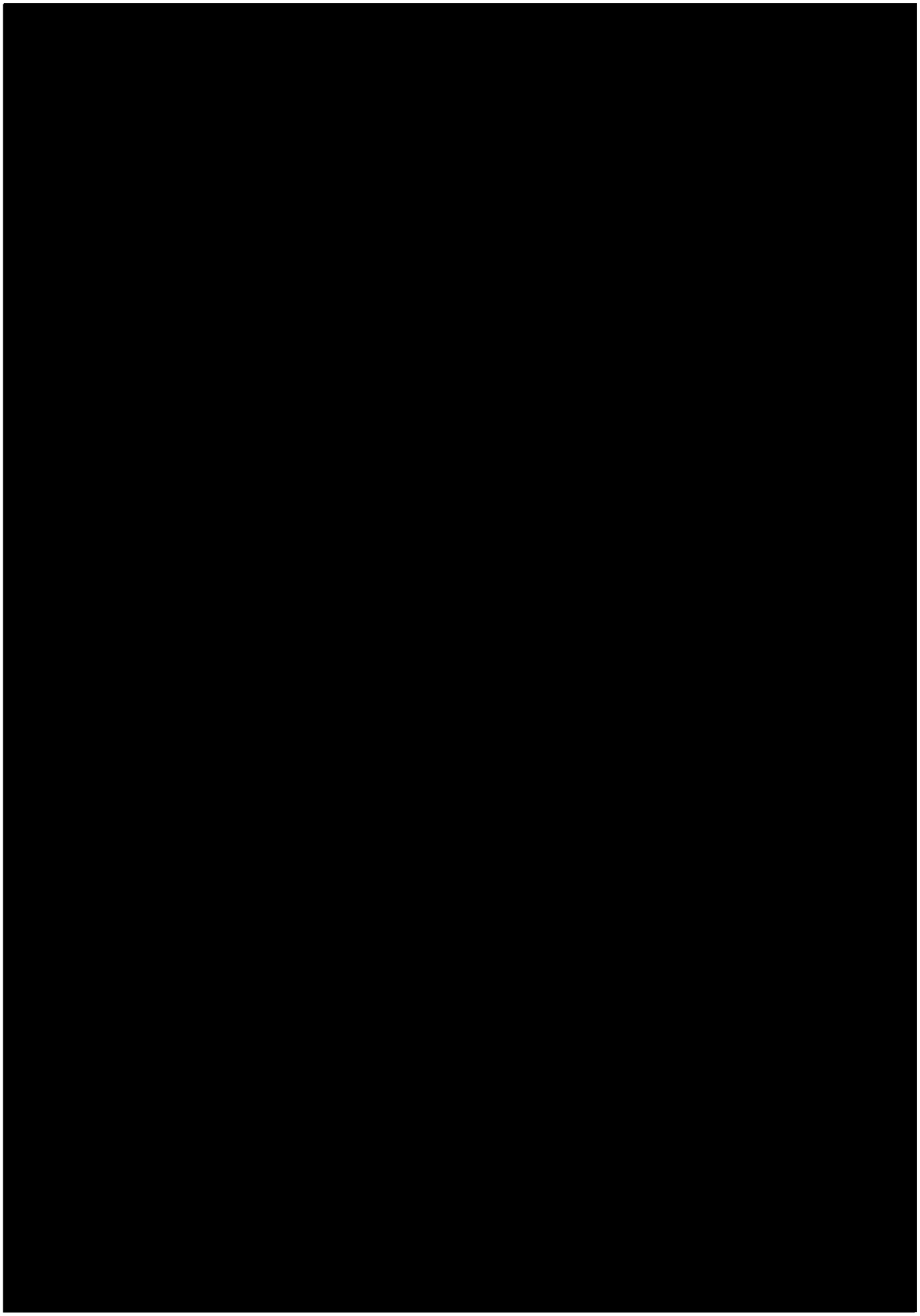
Not applicable.

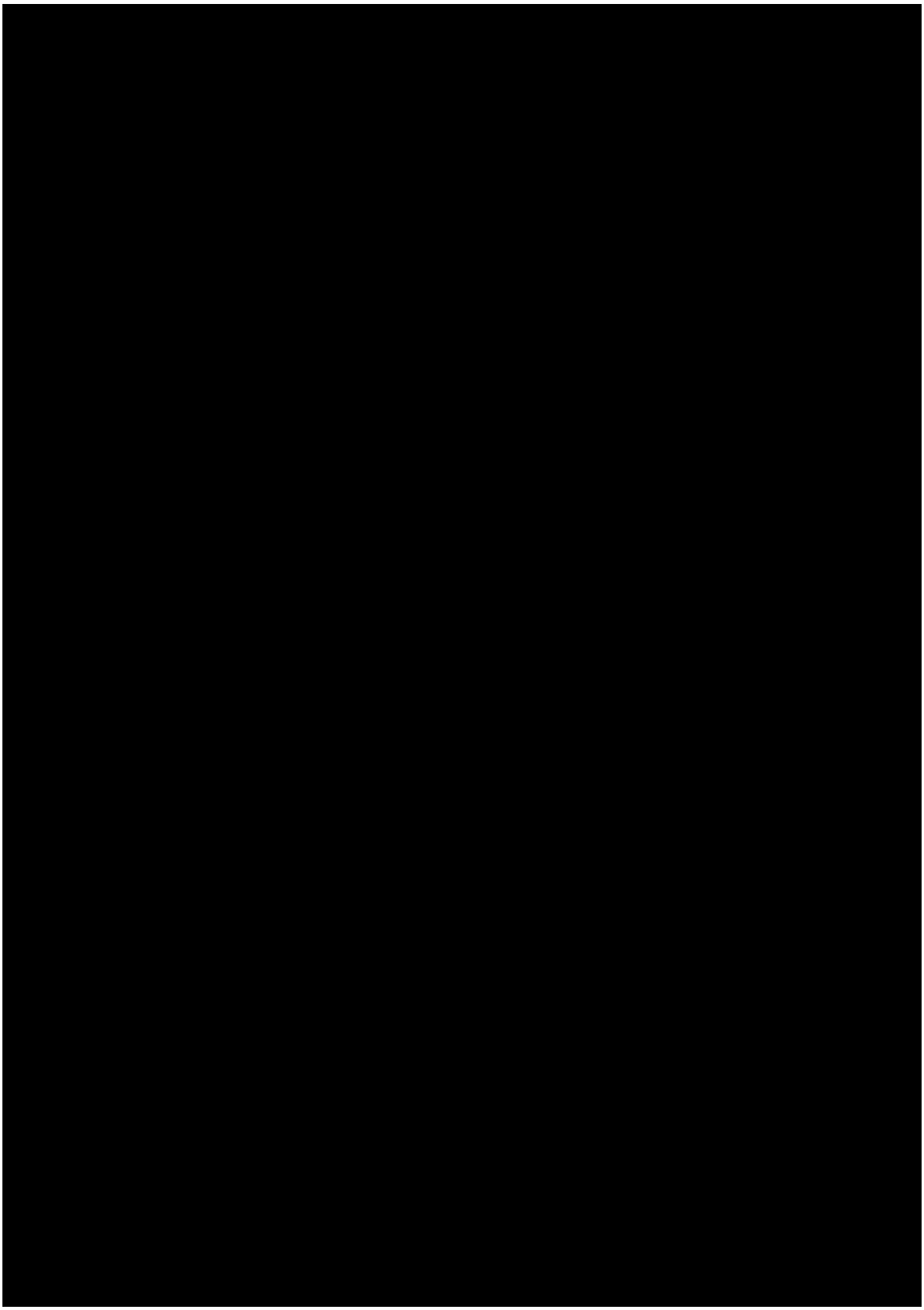
D.3.10 Waning effect

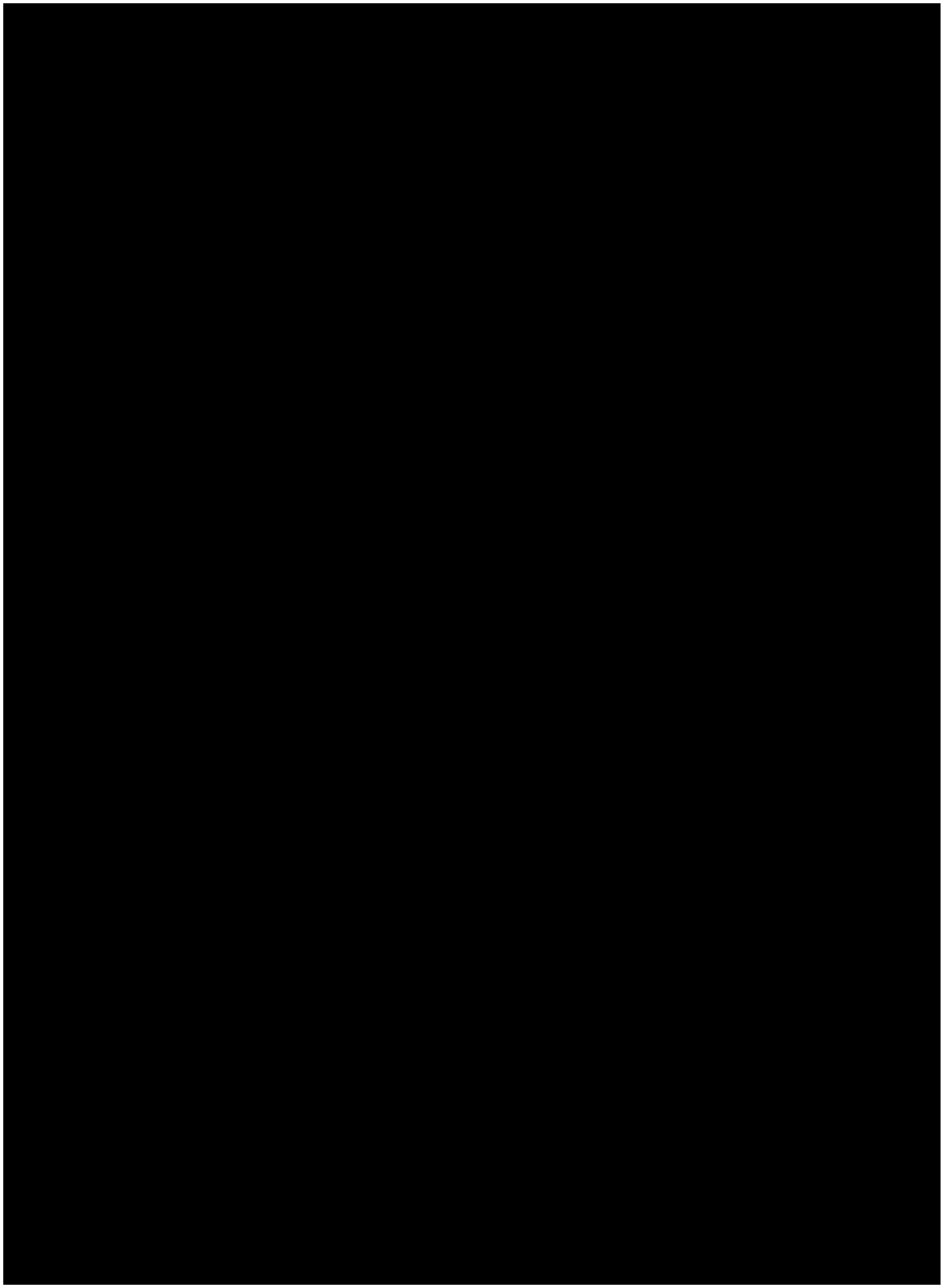
Not applicable.

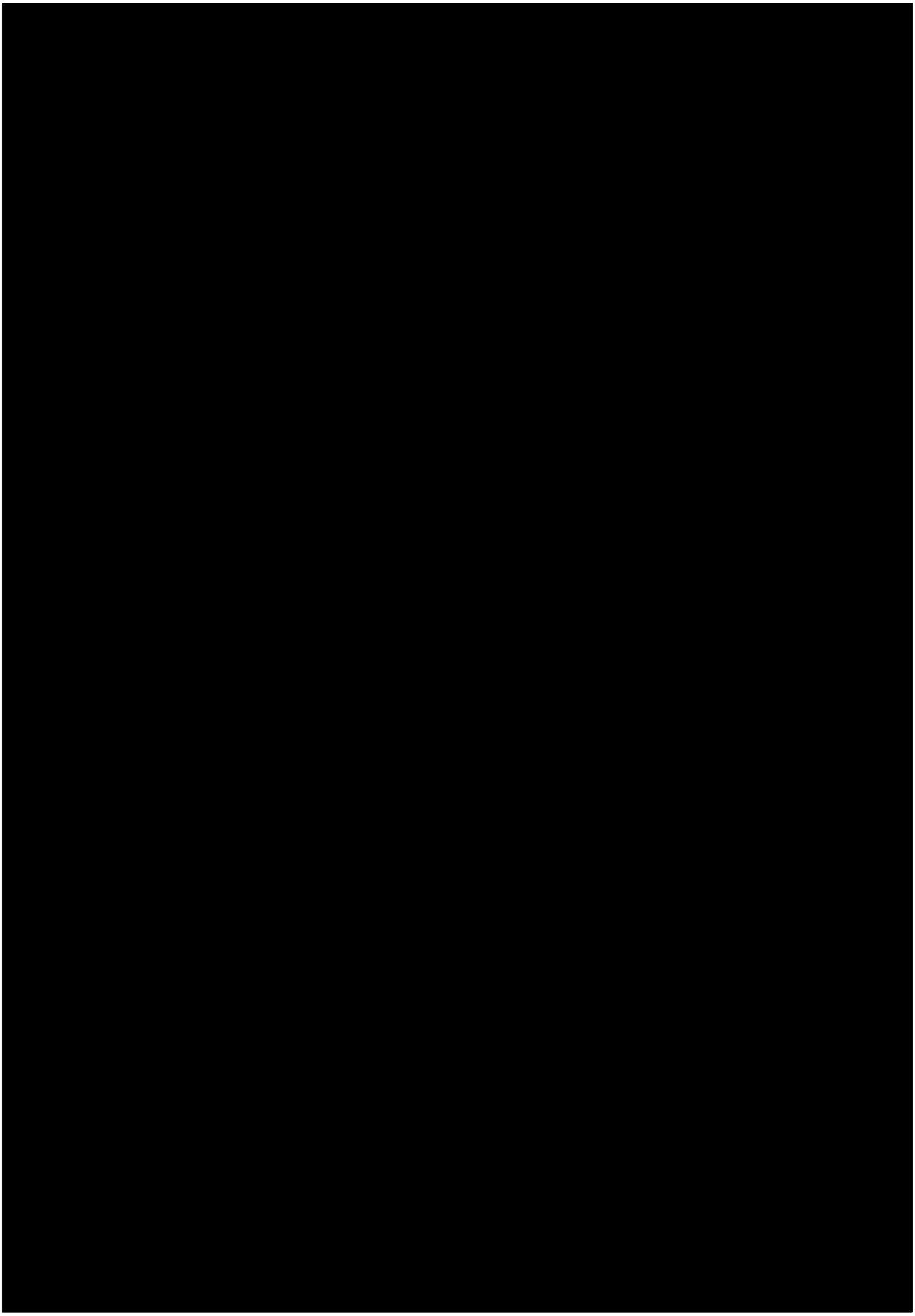
D.3.11 Cure-point

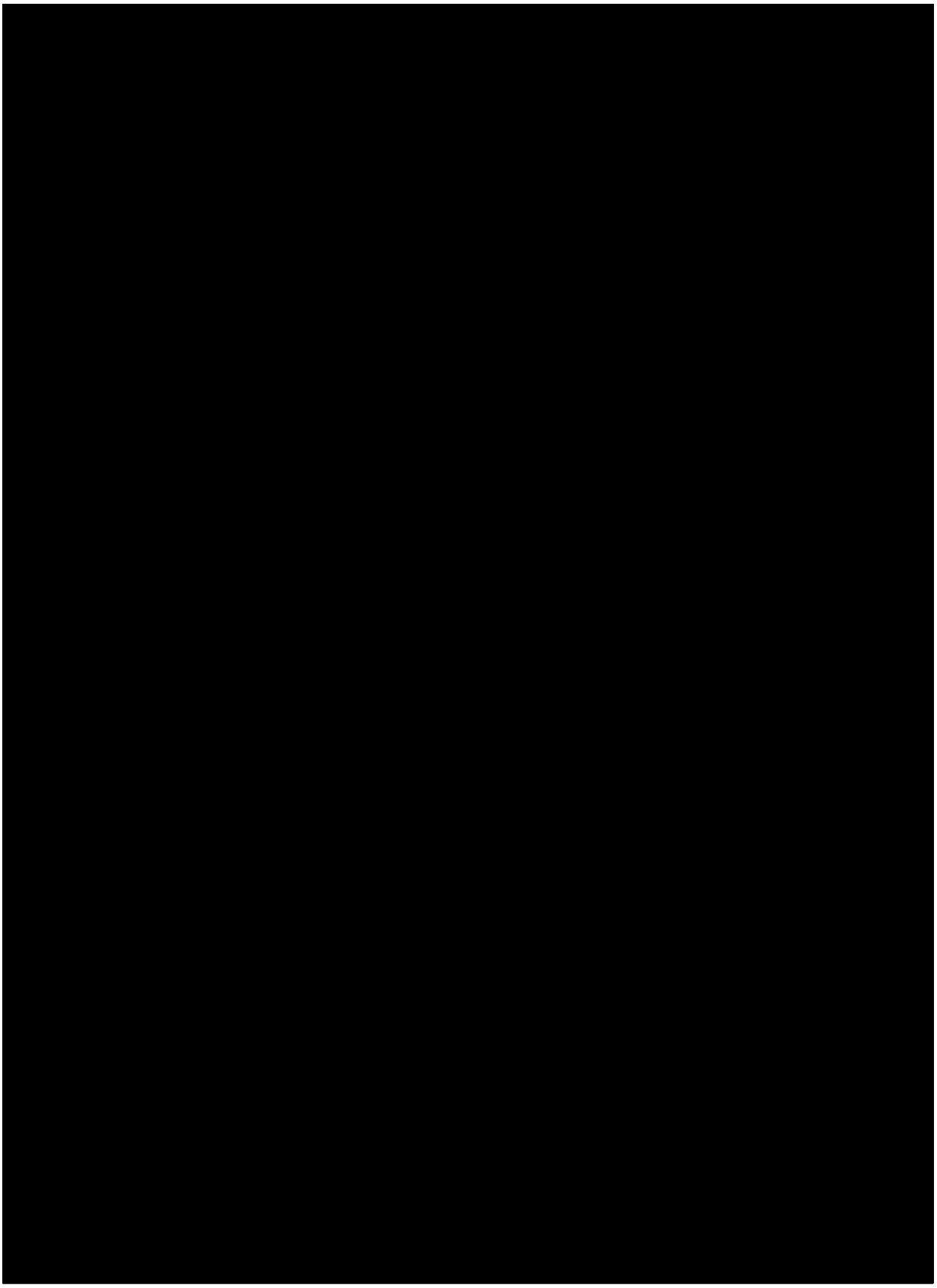
Not applicable.

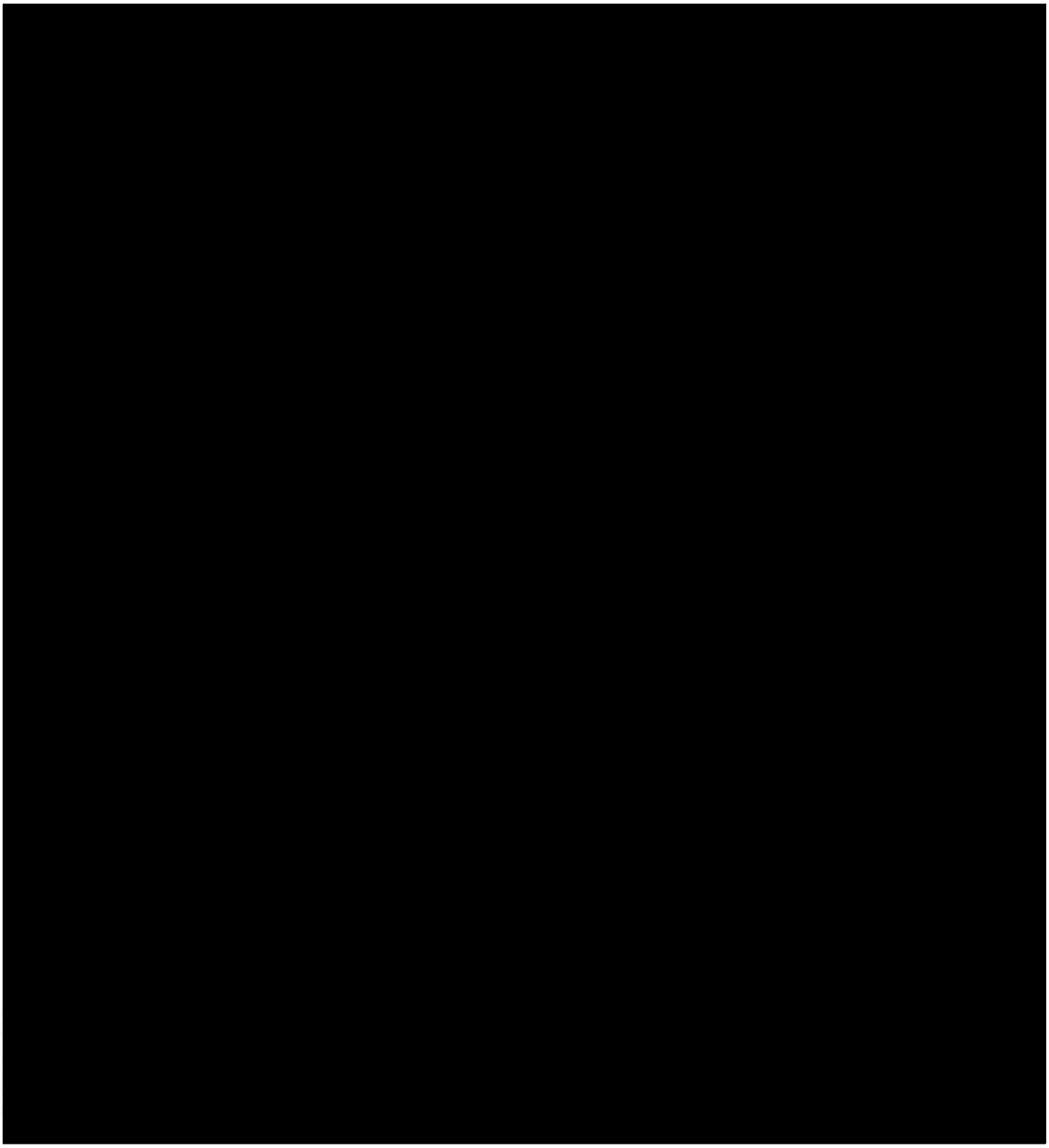












Appendix F. Health-related quality of life

Not applicable, as the health economic model is based on a cost-minimization analysis.

Appendix G. Probabilistic sensitivity analyses

Not applicable – including related tables – since only a cost-minimization analysis and model were used.

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

A systematic literature search was performed. The objective of the search was to assess the efficacy and safety of elranatamab and teclistamab in patients with relapsed and/or refractory multiple myeloma.

The literature search was conducted in the databases Medline (via PubMed) and CENTRAL (via Cochrane Library) on March 5 2024 (Table 61). The databases were searched for relevant literature to identify studies published from 2015 onwards. The time period started at 2015 based on when the elranatamab and teclistamab studies were conducted. Moreover, we searched the Clinical Trials Register (clinicaltrials.gov) to identify relevant ongoing clinical trials that include patients with relapsed and/or refractory multiple myeloma, where elranatamab and/or teclistamab were included as an intervention and/or a comparator (Table 62).
Additionally, conference proceedings were manually searched for abstracts using keywords such as 'multiple myeloma', 'elranatamab' and 'teclistamab' (

Table 63). We also searched EMA's webpage to identify relevant material on elranatamab and teclistamab and the DMC's webpage to identify documents on their recent evaluation of teclistamab.

As it was expected that we would identify sufficient material from the search described above, we did not search other databases or other HTA agency webpages.

Table 61 Bibliographic databases included in the literature search.

Database	Platform/source	Relevant period for the search	Date of search completion
Medline	PubMed	2015-2024	March 5 2024
CENTRAL	The Cochrane library	2015-2024	March 5 2024

Table 62 Other sources included in the literature search.

Source name	Location/source	Search strategy	Date of search
EMA's webpage	https://ema.europa.eu	Searched for elranatamab and teclistamab documents	March 5 2024
Clinicaltrials.gov	https://clinicaltrials.gov	Searched to identify ongoing clinical trials	March 5 2024
The DMC's webpage	www.medicinraadet.dk	Searched to identify the DMC's recent evaluation of teclistamab	March 5 2024

Table 63 Conference materials included in the literature search.

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Hematology (ASH)	https://hematology.org	Manually searched	Multiple myeloma, elranatamab, teclistamab	March 5 2024
European Hematology Association (EHA)	https://ehaweb.org	Manually searched	Multiple myeloma, elranatamab, teclistamab	March 5 2024
International Myeloma Working Group (IMWG)	https://myeloma.org	Manually searched	Multiple myeloma, elranatamab, teclistamab	March 5 2024
American Society of Clinical Oncology (ASCO)	https://asco.org	Manually searched	Multiple myeloma, elranatamab, teclistamab	March 5 2024
European Society for Medical Oncology (ESMO)	https://esmo.org	Manually searched	Multiple myeloma, elranatamab, teclistamab	March 5 2024

H.1.1 Search strategies

The search strategy was based on the PICO-T (patient population, intervention, comparators, outcomes and time period) elements with reference to systematic searching best practices recommendations of the Cochrane Handbook for Systematic Reviews of Intervention, Centre for Review and Dissemination (CRD) Guidance for Undertaking Reviews in Health Care (78,79), and NICE guidance for literature searching and evidence submission (80).

Search results were merged using the reference management software Rayyan to remove duplicate records. All titles and abstracts were reviewed for information that clearly met the inclusion and exclusion criteria stated in Table 66. The full text of studies that passed the first level of screening was retrieved and reviewed using the same inclusion/exclusion criteria. Multiple publications from the same study were identified and linked. The search terms constituted the following three topics:

- Terms to capture the study population
- Terms to capture the relevant interventions
- Terms to capture relevant study designs

Search terms included key words (free text) and subject headings (e.g., medical subject headings [MeSH]). Table 64 and Table 65 present the search strategy applied in the databases and results obtained on March 5 2024.

Table 64 Search string for MEDLINE (via PubMed).

No.	Query	Results
#1	"multiple myeloma"[MeSH Terms] OR ("multiple"[All Fields] AND "myeloma"[All Fields]) OR "multiple myeloma"[All Fields] OR "myeloma"[All Fields] OR "myelomas"[All Fields] OR "myeloma's"[All Fields]	77,763
#2	"refractory*"[Title/Abstract] OR "relapsed*"[Title/Abstract] OR "recurrent*"[Title/Abstract] OR "refractory or relapsed"[Title/Abstract] OR "relapsed or refractory"[Title/Abstract] OR "triple-class"[Title/Abstract] OR "relapsed and/or refractory"[Title/Abstract]	532,281
#3	#1 AND #2	7,977
#4	"Elranatamab"[All Fields] OR "PF-06863135"[All Fields]	24
#5	"Teclistamab"[All Fields] OR "Tecvayli"[All Fields]	77
#6	#4 OR #5	89
#7	#3 AND #6	61
#8	"Editorial"[Publication Type] OR "Historical Article"[Publication Type] OR "Case Reports"[Publication Type] OR "Comment"[Publication Type] OR "Interview"[Publication Type]	4,265,496
#9	#7 NOT #8	55

Table 65 Search string for CENTRAL (via the Cochrane library).

No.	Query	Results
#1	Multiple Myeloma	6,484
#2	Myeloma:ti,ab	6,371
#3	MeSH descriptor: [Multiple Myeloma] explode all trees	2,428
#4	("multiple myeloma"):ti,ab,kw	6,318
#5	(Kahler disease):ti,ab,kw	7
#6	("plasma cell myeloma"):ti,ab	21
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	6,886
#8	("refractory"):ti,ab	22,594
#9	("relapse"):ti,ab	31,334
#10	(recurrent):ti,ab	36,600
#11	(triple-class):ti,ab	69
#12	(relapsed or refractory):ti,ab	28,283
#13	(refractory or relapsed):ti,ab	28,283
#14	#8 OR #9 OR #10 OR #11 OR #12 OR #13	88,890
#15	#7 AND #14	2,417
#16	(elranatamab):ti,ab,kw	15
#17	PF-06863135	9
#18	#16 OR #17	15
#19	(Teclistamab):ti,ab,kw	21
#20	(Tecvayli):ti,ab,kw	1
#21	#19 OR #20	21
#22	#18 OR #21	36
#23	#15 AND #22	23

No.	Query	Results

H.1.2 Systematic selection of studies

Study selection was undertaken on two levels. The detailed inclusion/exclusion criteria provided in Table 66 were used as a guideline for the study selection to ensure that all decisions regarding the inclusion and exclusion of studies were consistent.

H.1.2.1 Level 1 screening based on title and abstract

Citations from the databases were imported to the reference management software Rayyan and duplicates were removed. First, the screening was done based on title and abstract. The screening was conducted by two researchers independently and in parallel based on the pre-defined inclusion and exclusion criteria. Any disagreement was resolved by discussion or involvement by an independent third reviewer. Citations that did not match the criteria stated in Table 66 were excluded at this level.

For all studies meeting the inclusion criteria based on title and abstract screening, the full text was obtained. If a determination to include or exclude could not be made based solely on the title and abstract, the full text was obtained for level 2 screening.

H.1.2.2 Level 2 screening based on full text of publication

The full text of publications selected for inclusion at level 1 were again screened by two reviewers independently and in parallel in level 2. Any disagreement was again resolved by discussion or involvement by an independent third reviewer. Full-text articles were reviewed to determine relevance based on the same inclusion and exclusion criteria used for level 1 screening.

Table 66 Inclusion and exclusion criteria used for assessment of studies.

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Relapsed and/or refractory multiple myeloma (triple-class-exposed: proteasome inhibitors, immunomodulatory drugs, and anti-CD38 antibodies)	- Newly diagnosed multiple myeloma - Patients with multiple myeloma who are not triple-class exposed
Intervention	Elranatamab and/or teclistamab	Any other treatment regimen or treatment combination
Comparators	-	-
Outcomes	Studies reporting at least one of the outcomes regarded as relevant for the present	Studies that do not report any of the outcomes in the inclusion criteria

	application: - OS - PFS - HRQoL - Safety	
Study design/publication type	- RCTs - Systematic reviews of RCTs - Non-randomised clinical trials (phase 1, phase 2, phase 3, phase 4) - Observational studies (retrospective studies, prospective studies)	- Editorial articles - Historical articles - Comments - Interviews
Time period	2015 and onwards	Hits older than 2015
Language	English	Languages other than English

The study selection process is reported in the PRISMA diagram below (Figure 38). 55 records were identified through Medline (via PubMed), and 23 records were identified through CENTRAL (via the Cochrane library). A total of 71 records were identified and assessed for eligibility after duplicates were removed. Of these, 54 records were excluded based on title and abstract screening (level 1), leaving 17 studies eligible for full-text screening (level 2). At the end of the full-text review, 12 studies were excluded, due to reasons listed in Table 67. This resulted in the inclusion of five articles. One abstract (66) and one poster (52) were identified through the search for conference materials, and the SmPCs and public assessment reports on elranatamab and teclistamab were identified through the EMA webpage. On the DMC webpage, we identified the DMC evaluation of teclistamab and the associated application. Thus, 8 additional records were identified through other sources.

Table 67 List of excluded articles and reasons for exclusion after full-text assessment.

Reference	Reason for exclusion
Usmani et al. 2021: Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study	Excluded as no relevant endpoint for the relevant dose was reported
Moreau et al. 2023: Comparative Efficacy of Teclistamab Versus Current Treatments in Real-World Clinical Practice in the Prospective	Comparative analyses of teclistamab and LocoMMotion based on teclistamab data from MajesTEC-1

LocoMMotion Study in Patients with Triple-Class-Exposed Relapsed and/or Refractory Multiple Myeloma	
Krishnan et al. 2023: Teclistamab versus real-world physician's choice of therapy in triple-class-exposed relapsed/refractory multiple myeloma	Study based on data from MajesTEC-1, where teclistamab data from MajesTEC-1 is compared to other treatments used in real-world clinical practice
Khanam et al. 2023: The Role of Bispecific Antibodies in Relapsed Refractory Multiple Myeloma: A Systematic Review	Excluded as it included data from older data cut-offs
Miao et al. 2023: Population Pharmacokinetics and Exposure-Response with Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma: Results From MajesTEC-1	Population pharmacokinetic study and analysis of exposure–response relationships from MajesTEC-1 study
Nooka et al. 2023: Incidence, timing and management of infections in patients receiving teclistamab for the treatment of relapsed/refractory multiple myeloma in the MajesTEC-1 study	Analysis of MajesTEC-1 data to provide recommendations for prevention and management of potential infections during teclistamab treatment
Moreau et al. 2023: Comparative Effectiveness of Teclistamab Versus Real-World Physician's Choice of Therapy in LocoMMotion and MoMMent in Triple-Class-Exposed Relapsed/Refractory Multiple Myeloma	Comparative analyses of teclistamab and LocoMMotion based on teclistamab data from MajesTEC-1
Costa et al. 2024: Elranatamab efficacy in MagnetisMM-3 compared with real-world control arms in triple-class refractory multiple myeloma	Study based on data from MagnetisMM-3, where elranatamab data from MagnetisMM-3 is compared to other treatments used in real-world clinical practice
Mol et al. 2024: A matching-adjusted indirect comparison of the efficacy of elranatamab versus physician's choice of treatment in patients with triple-class-exposed/refractory multiple myeloma	Indirect comparative analysis of irrelevant comparator
Grosicki et al. 2022: MagnetisMM-5: an open-label, multicenter, randomised phase 3 study of elranatamab as monotherapy and in combination with daratumumab in patients with relapsed/refractory multiple myeloma	Only ASCO abstract available; no results posted
Touzeau et al. 2023: MajesTEC-9: a randomised phase 3 study of teclistamab versus pomalidomide, bortezomib, and dexamethasone or carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma	Only ASCO abstract available; no results posted
Bahlis et al. 2023: Elranatamab in relapsed or refractory multiple myeloma: the MagnetisMM-1	Excluded as no relevant endpoint for the relevant dose was reported

phase 1 trial

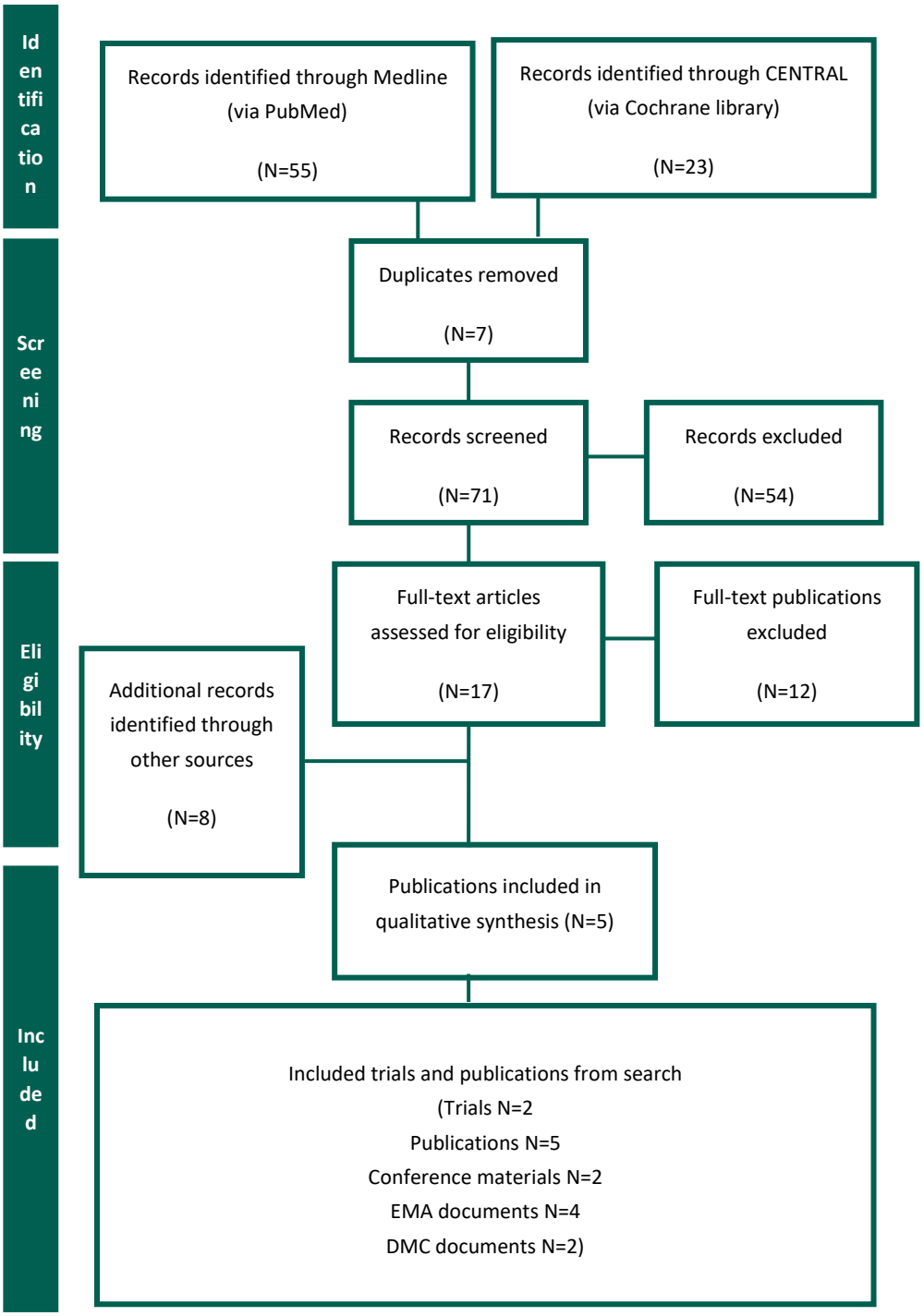


Figure 38 The PRISMA flow diagram showing study selection

Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis, EMA: European Medicines Agency, DMC: Danish Medicines Council.

Table 68 below present the included studies and their design.

Table 68 Overview of study design for trials included in the analyses

Study (ID)	Aim	Study design	Patient population	Intervention and comparator (sample size (N))	Primary outcome and follow-up period	Secondary outcome and follow-up period
MagnetisMM-3 (NCT04649359) (Sources: 47, 52)	To evaluate safety and efficacy of elranatamab in patients with relapsed/refractory multiple myeloma	Phase 2, open-label, multicentre, non-randomised trial	Adult patients (≥18 years) with multiple myeloma who have disease refractory to at least one IMiD, one PI and one anti-CD38 antibody	Total: 187 The study enrolled participants into two independent and parallel cohorts: Cohort A: Patients naïve to BCMA-directed therapies, N=123 Cohort B: Patients with previous exposure to BCMA-directed therapy, N=64	Objective response rate by blinded independent central review according to International Myeloma Working Group response criteria The median follow-up period was 14.7 months (47) and the latest follow-up period of 17.6 months (52).	Objective response rate by blinded independent central review baseline extramedullary disease status Objective response rate by investigator CR rate TTR DoR DOCR MRD negativity rate PFS OS Safety, pharmacokinetics and immunogenicity

Study (ID)	Aim	Study design	Patient population	Intervention and comparator (sample size (N))	Primary outcome and follow-up period	Secondary outcome and follow-up period
MajesTEC-1 (NCT03145181 and NCT04557098) (Sources: 37,66)	To identify the recommended phase 2 dose of teclistamab and evaluate safety and tolerability as well as evaluate the efficacy of the recommended phase 2 dose in patients with relapsed/refractory multiple myeloma	Phase 1-2, first-in-human, open-label, dose escalation study	Adult patients (≥18 years) with relapsed or refractory multiple myeloma, who have previously received at least three lines of therapy (IMiD, PI and anti-CD38 antibody). Eligible patients had a performance score of 0 or 1.	In the phase 1 study, 157 patients were enrolled and received at least one dose of teclistamab, either as an intravenous (IV) infusion (N=84) or as a subcutaneous (SC) injection (N=73). 40 patients were administered the recommended phase 2 dose. In the phase 2 study, 165 patients were enrolled to receive teclistamab at the recommended phase 2 dose	Phase 1: Median follow-up was 16.6 months across IV cohorts and 8.8 months across SC cohorts - Frequency and type of DLTs - Incidence and severity of AEs Phase 2: Median follow-up was 14.1 months (37) and a later follow-up at 23 months (66). - Overall response rate	Phase 1: - Overall response rate, DoR and TTR - Pharmacokinetic parameters, pharmacodynamic markers and anti-teclistamab antibodies Phase 2: - DoR, TTR, PFS and OS - Safety, pharmacokinetics and immunogenicity
MAIC **(Source: 64)**	To evaluate the effectiveness of elranatamab in relation to teclistamab	A matching-adjusted indirect comparison	The study population was the population of MagnetisMM-3 and MajesTEC-1:	For elranatamab, individual patient data from MagnetisMM-3, cohort A (N=123) were	ORR, ≥CR rate and DoR (length of follow-up was 14.7 months for MagnetisMM-3 and 14.1	No secondary outcomes measured

Study (ID)	Aim	Study design	Patient population	Intervention and comparator (sample size (N))	Primary outcome and follow-up period	Secondary outcome and follow-up period
			Adult patients (≥18 years) with multiple myeloma who have previously received at least three lines of therapy (IMiD, PI and anti-CD38 antibody) and with disease relapsed or refractory to their last antimyeloma regimen on the last therapy	used Published summary data from MajesTEC-1 (N=165) were used for teclistamab	months for MajesTEC-1) PFS and OS (length of follow-up was 14.7 months for MagnetisMM-3 and around 23 months for MajesTEC-1)	

H.1.3 Quality assessment

The literature search that was performed has a number of strengths. The search was conducted in the two databases, Medline and CENTRAL, as requested by the DMC, to identify relevant literature to address the objective of the literature search. The PICO and the inclusion and exclusion criteria were defined prior to the literature search, and relevant search terms were applied. The screening of literature and selection of studies were conducted by two researchers independently and in parallel based on the pre-defined inclusion and exclusion criteria. Any disagreements were resolved by discussion or involvement of a third independent reviewer. Because there is an inherent variability and potential for human error in decision-making associated with literature reviews, we used two researchers in the screening and selection process and a third independent adjudicator to alleviate this concern to the extent possible. Additionally, the search was restricted to the English language and to studies published from 2015 onwards, which raises the possibility that relevant trials published in other languages or prior to 2015 were missed, but this is unlikely given the search topic.

H.1.4 Unpublished data

Data from the clinical study report have been applied in the present application. No additional unpublished data have been presented in the present application.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

Not applicable – including related tables.

I.1.1 Quality assessment and generalisability of estimates

Not applicable.

I.1.2 Unpublished data

Not applicable.

Appendix J. Literature searches for input to the health economic model

Not applicable – including related tables.

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk