EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2022
EMA/789141/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecvayli

International non-proprietary name: teclistamab

Procedure No. EMEA/H/C/005865/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	anti-drug antibody
ADC	antibody drug conjugate
AE	adverse event
AUC	area under the serum concentration-time curve
AUCtau	area under the concentration-time curve during a dosing interval
B cell	B lymphocyte
BCMA	B cell maturation antigen
BID	twice a day
CAR-T	chimeric antigen receptor T cell
$C_{ave,1stdose}$	predicted average concentration of the first treatment dose
CCS	container closure system
CD3	cluster of differentiation 3
CEX	cation exchange chromatography
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
CNS	central nervous system
CPPs	Critical process parameters
CR	complete response
CRS	cytokine release syndrome
cSDS	Capillary Sodium Dodecyl Sulfate Gel Electrophoresis
C_{trough}	trough serum concentration
$C_{trough,ss}$	predicted steady-state trough serum concentration
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of response
DP	drug product
ECG	electrocardiogram
EC90	90% maximal effective concentration
eCRF	electronic case report form
EEPCB	Extended End of Production Cell Bank
EOI	end of infusion after IV flush

EORTC QLQ-C30 E	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item
EOT	end of treatment
EQ-5D-5L	EuroQol Five Dimension Five Level Questionnaire
E-R	exposure-response
Fab	fragment antigen binding
FAE	Fab-arm exchange
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
FcγR	Fc gamma receptors
FIH	first in human
FLC	free light chain
HC	heavy chains
HILIC	hydrophilic interaction liquid chromatography
HMWS	High molecular weight species
HRQoL	health-related quality of life
ICANS	immune effector cell-associated neurotoxicity syndrome
IE-HPLC	ion exchange High Performance Liquid Chromatography
IL	interleukin
IPCs	in-process controls
GAM	generalised additive modelling
GMP	good manufacturing practice
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRC	independent review committee
ISS	International Staging System
IV	intravenous(ly)
Ka	first-order absorption rate constant
LC	light chains
LMWS	Low molecular weight species
mAB	monoclonal antibody
MAM	Multi-Attribute Monitoring
MCB	Master Cell Bank
MMAEX	multimodal anion exchange chromatography

MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilisation
MSD	Meso Scale Discovery
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next Generation Sequencing
ORR	overall response rate
OS	overall survival
PD1	programmed cell death protein 1
PCR	polymerase chain reaction
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetics
PR	partial response
PRM	primary reference material
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PV	Process validation
Q	inter-compartmental clearance
Q2W	every 2 weeks
QTc	corrected time from ECG Q wave to the end of the T wave corresponding to electrical systole
QW	every week
RRM	Research reference material
RP2D	recommended phase 2 dose
RP-UPLC	reverse phase ultra performance liquid chromatography
sARR	systemic administration-related reaction
SAP	Statistical Analysis Plan
sBCMA	soluble BCMA
SC	subcutaneous(ly)
SCM	stepwise covariate modelling
sCR	stringent complete response
SD	standard deviation
SE-HPLC	Size Exclusion High Performance Liquid Chromatography

SOC	system organ class
SPEP	serum protein electrophoresis
T cell	T lymphocyte
t1/2	half-life
TEAE	treatment-emergent adverse event
Tmax	time to reach the maximum observed serum concentration
T cell	T lymphocyte
Tmax	time to reach the Cmax
TLS	tumour lysis syndrome
TTR	time to response
VGPR	very good partial response
Vss	volume of distribution at steady-state
Vss/F	apparent volume of distribution at steady-state
WBC	white blood cell
WCB	working cell bank
WRM	working reference material

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 31 January 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Tecvayli, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 January 2021.

Tecvayli, was designated as an orphan medicinal product EU/3/20/2331 on 19 October 2020 in the following condition: treatment of multiple myeloma. During the procedure the applicant requested the withdrawal of Tecvayli from the Community Register of orphan medicinal products.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 19 July 2022 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website ema.europa.eu/en/medicines/human/EPAR/tecvayli.

The applicant applied for the following indication: treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior therapies including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision, P/0044/2020 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's requests for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.3. New active substance status

The applicant requested the active substance teclistamab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Teclistamab Janssen-Cilag International was granted eligibility to PRIME on 29 January 2021 in the following indication: treatment of adult patients with relapsed or refractory multiple myeloma, who previously received ≥3 prior lines of therapy.

Eligibility to PRIME was granted at the time in view of the following:

- Despite available treatments, there is still a need for new treatment options for relapsed and refractory multiple myeloma patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody.

- The non-clinical data provided evidence of biological activity and anti-tumour activity in multiple myeloma.

- Preliminary clinical data offers encouraging evidence of a treatment effect in a heavily pre-treated population.

- The mechanism of action, even though similar to CAR-T products in the same indication, offers an alternative route of activation of T-cells, without the manufacturing and administration complications of those products.

Upon granting of eligibility to PRIME, Johanna Lähteenvuo was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 25 May 2021. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

- commercial shelf-life strategy

- changes to the confirmatory study design

- adequacy of the proposed data package, including number of patients treated and amount of follow up data expected to be available at the time of the initial MAA

- strategy to demonstrate significant benefit in the context of orphan maintenance

1.7. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 February 2021	EMA/SA/0000050045	Adriana Andrić and Karri Penttilä
24 June 2021	EMA/SA/0000059258	Jan Sjöberg and Johanna Lähteenvuo
11 November 2021	EMA/SA/0000069104	Johanna Lähteenvuo, Pierre Demolis and Karri Penttilä

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Adequacy of the planned biochemical comparability strategy
- Acceptability of the performed non-clinical toxicology studies to support MAA
- Sufficiency of the development clinical pharmacology data package, including drug-drug interactions and potential for QT prolongation
- Design elements for study 64007957MMY1001 (MajesTEC-1) including inclusion/exclusion criteria, primary endpoint and key secondary endpoints,
- Adequacy of the to-be generated efficacy and safety data to support a conditional MA
- Design elements of the confirmatory MajesTEC-3 study, including: choice of PFS as the primary endpoint, choice of Tec-Dara as the experimental arm and physician's preference for the comparator arm, statistical assumptions, effect size and proposed analyses

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johanna Lähteenvuo   Co-Rapporteur: Armando Genazzani

The application was received by the EMA on	31 January 2022
Accelerated Assessment procedure was agreed-upon by CHMP on	16 December 2021
The procedure started on	17 February 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 April 2022
The CHMP Co-Rapporteur's first Assessment Report (Critique) was circulated to all CHMP and PRAC members on	2 May 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 April 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 May 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 May 2022

The applicant submitted the responses to the CHMP consolidated List of Questions on	17 June 2022
The PRAC Rapporteur's Assessment Report on the responses to the List of Questions was circulated to all PRAC and CHMP members on	1 July 2022
The CHMP Rapporteurs circulated the CHMP on the responses to the List of Questions to all CHMP and PRAC members on	7 July 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 July 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tecvayli on	21July 2022
The CHMP adopted a report on similarity of Tecvayli with Darzalex, Imnovid, Farydak, Kyprolis, Ninlaro, Blenrep, Abecma and Carkykti (see Appendix on similarity)	21 July 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	21 July 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Claimed therapeutic indication

Teclistamab as monotherapy is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior therapies including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

2.1.2. Epidemiology

Multiple Myeloma (MM) is a rare and incurable plasma cell neoplasm which typically affects adults mostly over 60 years of age. The median age at diagnosis is 65–70 years; MM is very rare in patients younger than 40 years old (2% of cases).

MM accounts for 1%-1.8% of all cancers and is the second most common haematological malignancy (after non-Hodgkin's lymphoma [NHL]) with an estimated incidence in Europe of 4.5-6/100 000/year, with approximately 176.404 new MM cases and 117,077 deaths due to MM anticipated in 2020 worldwide (The Global Cancer Observatory 2020).

Multiple Myeloma is characterised by the increased proliferation of malignant monoclonal plasma cells in the bone marrow, with the subsequent bone marrow failure due to replacement of normal bone marrow haematopoiesis, the over-production of monoclonal immunoglobulins (M-protein, either intact immunoglobulins and/or free light chains [FLC]) which could be detected in the serum or urine, and finally the presence of systemic symptoms named as CRAB (hyperCalcemia, Renal impairment, Anaemia and Bone lesions). Increased susceptibility to infections (immunoparesis) and neurological complications are also present (Palumbo 2011).

Based on karyotype, MM is classified as non-hyperdiploid and hyperdiploid, with the latter accounting for 50% to 60% of cases and characterizeised by trisomies in odd-numbered chromosomes. MM has a heterogeneous progression pathway, with multiple relapses over time, whereby several MM cell subclones coexist at baseline and compete for dominance over time, leading to the evolution of drug-resistance clones [Laubach, 2014].

Drug resistance to prior regimens in patients with relapsed/refractory (RR) MM is due to continuous changes in the disease biology, in which a higher proportion of malignant cells are expressing a more aggressive, highly proliferative phenotype over time (Anderson, 2008).

2.1.3. Clinical presentation, diagnosis and stage/prognosis

Multiple myeloma, a malignant disorder of the plasma cells characterised by uncontrolled and progressive proliferation of a plasma cell clone, and accounts for approximately 10% of haematological malignancies (Rodriguez-Abreu 2007; Rajkumar 2011). The proliferation of the malignant clonal plasma cells leads to subsequent replacement of normal bone marrow haematopoietic precursors and overproduction of monoclonal paraproteins (M-proteins). Characteristic hallmarks of multiple myeloma include osteolytic lesions, anaemia, increased susceptibility to infections, hypercalcemia, renal

insufficiency or failure, and neurological complications (Palumbo 2011). Profound intra-tumoral heterogeneity is observed throughout the disease course but is especially problematic after multiple lines of treatment. The coexistence of different tumour subclones displaying different drug sensitivities contributes to both progression of disease and development of drug resistance (Barlogie 2014).

The criteria for diagnosis of MM as defined by the International Myeloma Working Group (IMWG), requires 10% clonal BM plasma cells or biopsy proven bony or extra-medullary plasmacytoma and evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, or biomarkers of malignancy (60% clonal BM plasma cells or involved/uninvolved serum-free light chain ratio >100 or > 1 focal lesion on magnetic resonance imaging studies).

The course of MM is characterised by a period of disease control after initial therapy followed by progression, typically with subsequently shorter periods of response and relapse with each successive therapy (Moreau, 2017). The treatment of MM has notably progressed with the availability of new drugs and its combinations, such way that survival of patients with newly diagnosed MM has increased from approximately 3 years in the years 1985 to 1998 (Kyle 2003) to 6 to 10 years (Moreau 2015) along the last 15 years. Despite the significant improvement in patients' survival over the past 20 years, only 10%-15% of patients achieve or exceed expected survival compared with the matched general population.

The estimated 5-year survival rate for patients with multiple myeloma is approximately 54% (Cancer.net 2020). 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 directed at 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.

Despite advance in therapy, MM remains incurable. Although autologous stem cell transplant (ASCT) has extended survival in newly diagnosed MM, practically all patients eventually relapse, and with each successive relapse, the chance of response and duration of response typically decreases and ultimately the disease becomes refractory and results in cumulative end organ damage (e.g., renal, cytopenias, infections and bone complications).

2.1.4. Management

The treatment landscape for relapsed or refractory multiple myeloma (RRMM) has changed in recent years. Current treatment of MM includes glucocorticoids, chemotherapy, primarily alkylating agents, high dose chemotherapy followed by ASCT, proteasome inhibitors (PIs, such as bortezomib, carfilzomib and ixazomib), immunomodulatory agents (such as thalidomide, lenalidomide and pomalidomide), monoclonal antibodies (mAbs), such as daratumumab, isatuximab and elotuzumab) and the histone deacetylase inhibitor panobinostat. Common standard regimens include either a PI or an IMiD in combination with dexamethasone with or without a monoclonal antibody such as daratumumab. The triplet combination of bortezomib, lenalidomide, and dexamethasone (VRd) is a standard of Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) treatment guidelines (NCCN 2020 and Moreau 2017). Newer classes of medications including XPO1 inhibitors (selinexor) and antibody drug conjugates targeting BCMA (belantamab mafodotin-blmf) have recently been approved by the US food and drug administration (FDA) but have limited therapeutic activity and substantial toxicity.

The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e. clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed).

Despite multiple therapeutic options, MM remains incurable. All patients eventually relapse and become refractory to existing treatments. Median OS in patients who have received at least three prior MM lines of therapy and are refractory to both an IMiD and a PI is only 13 months (Kumar 2017). The reported ORR for approved therapies for the population of heavily pre-treated and refractory patients with MM, is approximately 30% (**Table 1**).

Table 1. Comparison of Efficacy of Therapies for the Treatment of Heavily Pre-treated Relapsed or Refractory Multiple Myeloma

Approved Therapies				
Regimen	ORR	Median PFS (months)	Median DoR (months)	Study Name and Reference
Pomalidomide/low dose dexamethasone[a] (n=302)	31% (POM + LoDex)	4.0 (POM + LoDex)	7.0 (POM + LoDex)	Study MM-003; San Miguel 2013
Carfilzomib[a] (n=157)	19.1%	3.7	7.2	FOCUS; Hajek 2017
Daratumumab (n=106)	29.2%	3.7	7.4	SIRIUS; Lonial 2016
Selinexor/dexamethasone (n=122)	26.2%	3.7	4.4	STORM; Chari 2019
Belantamab mafodotin-blmf (n=97)	32% (2.5 mg/kg cohort)	2.8 (2.5 mg/kg cohort)	11.0 (2.5 mg/kg cohort)	DREAMM-2 Lonial 2020
Therapies Pending Approval				
Regimen	ORR	Median PFS (months)	Median DoR (months)	Study Name and Reference
Idecabtagene vicleucel[b] (n=128) (bb2121)	73%	8.8 (150×10^6 to 450×10^6 CAR+ T cells)	10.7 (150×10^6 to 450×10^6 CAR+ T cells)	KarMMa Munshi 2021
Orvacabtagene autoleucel[c] (n=100)	91%	Not reached (450×10^6 cell and 600×10^6 cell dose groups) 9.3 months (300×10^6 cell dose group)	-	EVOLVE Mailankody 2020

DoR= duration of response; ORR=overall response rate; PFS=progression-free survival; CI = confidence interval

[a] Randomized study; data presented for experimental arm of the study

[b] On 26 March 2021, idecabtagene vicleucel received FDA approval for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapies including an IMiD, a PI, and an anti-CD38 monoclonal antibody.

[c] As of February 2021, the orvacabtagene autoleucel program is no longer being developed by the sponsor (Juno Therapeutics, a Bristol-Myers Squibb company). (Securities and Exchange Commission 2021)

In a recently published chart review, investigators from 14 academic institutions analysed 275 patients to determine the efficacy of subsequent treatments after disease progression on an anti-CD38 monoclonal antibody treatment (Gandhi 2019). This multi-centre, retrospective, observational study investigated the natural history and outcomes of patients with MM refractory to CD38 monoclonal antibodies (MAMMOTH study). Patients were heavily pre-treated with a median of 4 prior lines of therapy (range: 1-16). Regardless of the particular salvage regimen chosen, the observed efficacy of the next treatment after progression on PI, IMiD, and anti-CD38 monoclonal antibody therapy was dismal.

The median OS for the entire cohort was 8.6 months (95% [CI]: 7.5-9.9), ranging from 5.6 months for penta-refractory patients (refractory to anti-CD38 antibody, 2 PIs, and 2 IMiDs) to 11.2 months for patients not simultaneously refractory to an IMiD and PI. Among patients who received ≥1 subsequent treatment after becoming refractory to anti-CD38 antibody therapy (90% of patients in the study), the response rate averaged 31%, with a median PFS and median OS of 3.4 months and 9.3 months, respectively. The median OS for patients who received no further treatment was 1.3 months. The results of the MAMMOTH study were derived from real-world data and support the lack of options for patients who had prior exposure to a PI, IMiD, and anti-CD38 monoclonal antibody therapy. Despite new therapeutic achievements with novel mechanisms of action, MM remains an incurable disease in which all patients eventually relapse. There remains an unmet medical need for new treatment options beyond the current classes of anti-myeloma therapy.

B-cell maturation antigen, also known as CD269 and TNFRSF17, is a 20 kilodalton, type III membrane protein that is part of the tumour necrosis receptor superfamily. BCMA is predominantly expressed in B-lineage cells and plays a critical role in B-cell maturation and subsequent differentiation into plasma cells (Tai 2015). B-cell maturation antigen binds 2 ligands that induce B cell proliferation: a proliferation-inducing ligand ([APRIL]; CD256) and B-cell activating factor (BAFF; CD257) (Avery 2003; Darce 2007; Patel 2004). Binding of BCMA monomers to the APRIL trimer triggers activation and phosphorylation of p38MAPK, ELK, and NF-κB through intracellular tumortumour necrosis factor receptor associated factor molecules leading to pro-survival gene regulation (Bossen 2006; Hsi 2008; Korde 2011). Comparative studies have shown a lack of BCMA in most normal tissues and absence of expression on CD34-positive haematopoietic stem cells (Carpenter 2013; Kimberley 2009). This selective expression and the biological importance for the proliferation and survival of myeloma cells makes BCMA a promising target for the treatment of MM.

Belantamab mafodotin-blmf is a humanised IgG1κ monoclonal antibody conjugated with a cytotoxic agent, maleimidocaproyl monomethyl auristatin F (mcMMAF) that binds to BCMA on myeloma cell surfaces causing cell cycle arrest and inducing antibody-dependent cellular cytotoxicity. Belantamab mafodotin-blmf was recently approved on the basis of the Phase 2, open-label DREAMM-2 study designed to evaluate the efficacy and safety of belantamab mafodotin monotherapy in patients with RRMM who had 4 or more prior lines of treatment, were refractory to a PI, an IMiD, and had failed treatment with an anti-CD38 antibody. The ORR of DREAMM-2 as assessed by IRC was 32% (97.5% CI: 20.8, 42.6). The achieved responses were deep, with more than half of responders (60%) achieving VGPR or better (Lonial 2020).

Chimeric antigen receptor T (CAR-T) cell therapy uses modified autologous T cells that are activated in a major histocompatibility complex independent manner upon binding to their target resulting in the lysis of the targeted cells. Immunotherapy using CAR-T technology to target the BCMA receptor has emerged as a highly promising therapy for patients with advanced MM who have exhausted available therapies such as PI, IMiD, and CD38 monoclonal antibodies.

Early data for idecabtagene vicleucel, a BCMA-directed CAR-T immunotherapy, indicated that BCMA CAR-T therapy could lead to an ORR of approximately 85%, a complete response (CR) rate of 45%, and median PFS of 11.8 months (Raje 2019). Of the 128 subjects who were infused with idecabtagene vicleucel, the ORR was 73.4% for all doses tested and 82% for subjects treated with 450 x 10^6 CAR-positive T cells or higher. The rate of CR/sCR was 31%. The median PFS was 8.6 months. Eighty-four percent of the subjects experienced cytokine release syndrome that was generally mild (Munshi 2020). Most recently, data for idecabtagene vicleucel showed an ORR of approximately 73%, CR rate of 33%, a median PFS of 8.8 months, a median DoR of 10.7 months, and a median OS of 19.4 months (Munshi 2021). On 18 August 2021, idecabtagene vicleucel received EMA conditional approval 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. On 25 May 2022 another BCMA-directed CAR-T immunotherapy ciltacabtagene autoleucel received EMA conditional approval for the same therapeutic indication, based on an ORR of 84.1% in the leukapheresed population and a median DoR of 21.8 months (95%CI 21.8, NE).

Overall, there is an unmet medical need for more treatment options capable of achieving deep and durable responses that afford the opportunity for treatment-free intervals and improved quality of life (QoL) for patients with RR MM who have received ≥ 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 mAb.

2.2. About the product

2.3. Type of application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on a novel mechanism of action, providing an opportunity to treat MM patients refractory to approved medicinal products. Although limited clinical data were available, the ORR and CR rate observed were considered promising. In addition, the off-the shelf availability and less burdensome treatment procedure of teclistamab were considered important benefits from the clinical perspective.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

- It is likely that the applicant will be able to provide comprehensive data.

   The applicant is conducting a randomised phase 3 study, MajesTEC-3, in subjects with multiple myeloma who have been previously treated with 1 to 3 prior lines of therapy, including a PI and lenalidomide. Data from this ongoing Phase 3 study which is expected to be completed by March 2028 will support the conversion of the CMA to a standard marketing authorisation.

- Unmet medical needs will be addressed.

   Teclistamab will provide a novel, targeted option for the treatment of subjects with multiple myeloma, with a mechanism of action that is unique to all other approved therapies. Data from the MajesTEC-1 study, show that teclistamab confers superior efficacy in terms of objective response rates when compared with other available off-the-shelf therapies (belantamab mafodotin and selinexor) for patients with heavily pretreated multiple myeloma who have already exhausted 3 of the most commonly used therapies (a PI, an IMiD, and an anti-CD38 monoclonal antibody).
   Although the CAR-T therapy idecabtagene vicleucel has shown comparable rates of response in this setting, this treatment may not be suitable for all patients due to their potential to cause severe safety events, potential long waits from leukapheresis to treatment and product availability constraints (eg, restricted access and production of the CAR-T cells). Teclistamab therefore offers an alternative therapeutic option that will be readily available to all patients, with a favourable safety profile and superior efficacy in comparison to other off-the-shelf alternatives. Furthermore, preliminary data from Cohort C of the MajesTEC-1 study also suggest that teclistamab provides benefit for patients who have already been treated with a BCMA-targeting ADC or CAR-T therapy, where there are very limited treatment options and is an area of further unmet medical need.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  Based on efficacy, safety, patient eligibility and convenience advantages, teclistamab offers a promising new therapeutic option for patients with heavily pretreated multiple myeloma that will be readily available to all patients and has a favourable safety profile and superior efficacy compared with other off-the-shelf alternatives. Teclistamab also provides an option for patients who are unable to wait for manufacturing of CAR-T cells or unfit for this modality of therapy. Although the pivotal study adopted a Phase 1/2 design that did not utilise randomisation, the applicant considers that a delay to gather further or comparative data would be disproportionate from a public health perspective, as teclistamab addresses an unmet medical need and offers a new therapeutic option for heavily pretreated patients with multiple myeloma, which outweighs the risks due to the immediate need for further data.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as solution for injection containing 10 mg/mL or 90 mg/mL of teclistamab as active substance. Teclistamab should be administered by subcutaneous injection only.

Other ingredients are: EDTA disodium salt dihydrate, Glacial acetic acid, Polysorbate 20, Sodium acetate trihydrate, Sucrose and Water for injection.

The product is available in a Type 1 glass vial with an elastomeric closure and aluminium seal with a flip-off button containing 30 mg of teclistamab (10 mg/mL) or 153 mg of teclistamab (90 mg/mL).

2.4.2. Active substance

General information

Teclistamab (INN) active substance is a humanised immunoglobulin G4 (IgG4) bispecific antibody against B-cell maturation antigen (BCMA) and cluster of differentiation 3 (CD3) receptors. The BCMA targeting arm engages a BCMA presenting malignant B cell, followed by the engagement of an activated T cell by the CD3 binding arm, resulting in malignant cell death due to cell lysis mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T cells.

The molecular mass for the predominant glycoform is 146,261 Da. The active substance consists of 2 heavy chains (HC) and 2 light chains (LC), joined by disulfide bonds. It is prepared by controlled reduction and oxidation of anti-BCMA parental mAb (JNJ-63705473 Protein A eluate) and anti-CD3 parental mAb (JNJ-63483043 Protein A eluate), resulting in an exchange of the Fab arms. The Fab arm exchange was facilitated by amino acid substitutions at positions F410L and R414K in the CH3 domain of the parental JNJ-63483043 HC to enable preferential refolding of the heterodimer.

Manufacture, process controls and characterisation

Janssen Sciences Ireland UC, Ireland (JSI) is the main active substance manufacturing site. The active substance is manufactured, packaged, stability tested and quality-control tested in accordance with good manufacturing practice (GMP).

Description of manufacturing process and process controls

The teclistamab active substance manufacturing process has been adequately described and it encompasses the manufacture of two separate parental monoclonal antibody (mAb) intermediates (protein A eluates: JNJ-63483043, anti-CD3 mAb and JNJ-63705473, anti-BCMA mAb), a Fab arm exchange to produce the bispecific antibody, further purification steps, formulation, filtration and active substance fill. Both parental antibodies are manufactured in separate processes and combined in a subsequent bispecific antibody manufacturing process. The differences in the manufacturing steps between different sites are minor and considered adequately described by the applicant.Parental antibody JNJ-63483043 is manufactured (stages 1-4) at two different manufacturing sites: Biogen, Inc., USA (Biogen) and Janssen Biologics B.V., the Netherlands (JBV).

Parental antibody JNJ-63705473 (stages 1-4) is manufactured at Janssen Sciences Ireland UC, Ireland (JSI). Stages 5-13 of the manufacturing process (purification and formulation of the active substance) are performed at Janssen Sciences Ireland UC, Ireland (JSI). There are minor differences in the manufacturing steps at different sites, however, the parental mAb comparability has been shown.

The manufacturing process of the parental antibodies begins with the thaw of a single Working Cell Banks (WCB) vial corresponding to each parental antibody and serial cell culture expansions leading to one seed bioreactor containing the required viable cell mass and volume for inoculation of the production bioreactor used for the production of each parental antibody. Harvested cell culture is clarified and purified by multiple Protein A cycles per bioreactor harvest. The pooled protein A eluates (parental mAb intermediates) are bottle filled and stored until further processing.

The formation and purification process of the bispecific antibody (teclistamab active substance) starts with the thawing, filtration and individual pooling of sufficient quantities of each parental antibody. The Fab-arm exchange (FAE) is initiated by combining the separately pooled parental Abs (JNJ-63705473 and JNJ-63483043 Protein A eluates), in which half molecules recombine with half molecules from other IgG molecule. The purification of the FAE intermediate includes virus inactivation to inactivate any potentially present lipid-enveloped viral contaminants, two chromatography steps and virus removal filtration. The virus removal filtrate is concentrated, formulated, filtrated, filled into containers and stored.

The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The active substance manufacturing process is considered acceptable.

Reprocessing is not routinely performed as part of the active substance manufacturing process. Protocols have been included in the dossier that adequately describe the reprocessing verification at commercial scale on the first batch that requires reprocessing, for the concerned manufacturing steps. This approach is considered acceptable.

The container closure system (CCS) used for both intermediates (Protein A eluates) and teclistamab active substance storage is a single use, gamma irradiated, pre-sterilised, container with a screw closure. For the active substance, a single use, autoclaved, container with a screw closure is also used. Schematic diagrams of the containers were provided. Container closure integrity of both containers has been demonstrated during freezing, storage, thawing and shipping of materials. The compatibility of

the teclistamab active substance with the containers has been evaluated through stability studies. No incompatibilities between the active substance and container components of the bottles or bags have been observed. The containers were evaluated for potential extractables and leachables in a controlled extraction study and demonstrated low risk of potential leachables to patient safety. The active substance container closure systems are found acceptable.

Control of materials

Anti-CD3 and anti-BCMA substrates producing CHO cells were derived from parental Chinese hamster ovary (CHO) cell line. Information on the source of the cell substrate and analysis of the expression construct to develop the Master Cell Bank (MCB) is described in satisfactory detail.

Selection of single cell clones and production cell lines are adequately described. The adaptation of cell line to serum-free and protein-free media was sufficiently described. The identity of the cell was confirmed to be of hamster origin.

Consistent with ICH Q5D guideline recommendations, a 2-tiered banking system is used to ensure supply of the production cell line to support the manufacture of the active substance. The tiers consist of MCB and WCBs. A new WCB will be generated periodically to ensure a continuous supply for manufacturing. The MCB is expected to last for the life of the product. The MCB and WCB are produced in restricted access laboratories following GMP. Procedures are in place to prevent cross-contamination with other cell lines. A labeling system is used to produce sequentially numbered labels for each vial of the MCB and WCB. Production of MCB and WCB is documented in batch records. The JNJ-63705473 (anti-BCMA) and JNJ-63483043 (anti-CD3) MCBs and WCBs are tested are tested for identity, purity and microbial contamination, in accordance with the ICH Q5A and Q5D guidelines. Additionally, the cell banks are monitored during stability through determination of cell viability and cell growth, following thawing and culture of the cryopreserved cells. Stability analysis of the production clone is also sufficiently performed. Virus testing for the Extended End of Production Cell Bank (EEPCB) was performed according to ICH Q5A.

A complete listing of the compendial and non-compendial raw materials utilised in the manufacture of teclistamab active substance is presented in the dossier. Compendial raw materials will be release tested as per the appropriate compendia. Non-compendial raw materials will be release tested as per the appropriate test methods and have specifications. No animal-derived materials of any kind were used in the creation of the anti-BCMA and anti-CD3 MCBs. Overall, the cell banking system, characterisation and testing are adequately described.

Control of critical steps and intermediates

During the manufacturing processes for parental mAbs and teclistamab active substance, consistent product quality and process performance is ensured through comprehensive control strategy, encompassing release specifications for raw materials and consumables, critical process parameter limits, in-process testing and release and stability specifications for the intermediates and the active substance. The development of the control strategy and, overall, the approach to define criticality of parameters and in-process controls (IPCs) and tests is in line with relevant EMA guidelines. IPCs are an important element in the control strategy for teclistamab active substance and serve to control or confirm product quality and consistency during manufacturing. Three categories of IPCs for the JNJ-63705473, JNJ-63483043 and active substance manufacturing processes have been defined by the applicant: 1) IPC with an acceptance criterion, 2) IPC with an action limit and 3) IPC with a predefined instruction, for which appropriate justification of their acceptance criteria/action limit/predefined instructions has been included in the dossier. Overall, the proposed IPC acceptance criteria, action limits and predefined instructions are supported. Analytical methods used for IPC tests in the

manufacturing of both parental mAb intermediates and teclistamab active substance have been presented. The analytical procedures have been appropriately verified as suitable for use (compendial methods) or validated according to ICHQ2(R1) (non-compendial methods).

The microbial control strategies in place at each site involved in the parental mAbs and active substance manufacture are described in detail. Preparation and control to minimise risks for microbial contamination of facilities, equipment, and materials are considered sufficient.

Intermediates specifications

The release and stability specifications for the parental mAbs are part of an integrated control strategy to ensure product quality. Release and stability specification and batch data for the parental mAbs are provided. The proposed parental antibody specifications include general characteristics (pH), quantity (A280), charge heterogeneity, purity and microbial contaminants (endotoxin, bioburden). Identity tests (dot plot and ion exchange High Performance Liquid Chromatography (IE-HPLC)) are included. Batch analysis data for the parental antibody clinical and process validation batches were provided. Overall, the proposed specifications are considered appropriate for process intermediates.

Process validation

Process validation (PV) for teclistamab active substance has been carried out at commercial scale for manufacturing stages 1-4 at JSI (for parental Ab JNJ-63705473), at Biogen (for parental Ab JNJ-63483043) and at JBV (for parental Ab JNJ-63483043), and for manufacturing stages 5-13 (for teclistamab active substance) at JSI. Validation of the teclistamab active substance manufacturing process was performed and four consecutive batches for each parental antibody (per manufacturing site) and four consecutive teclistamab active substance batches were manufactured and released. For all four active substance PV batches, parental mAb intermediate material from two or three batches was included. Process validation was performed by evaluation of the ability to control process parameters, ability to meet the acceptance criteria for all in-process controls, the ability to meet specification for all routine tests. An extensive set of studies for process validation and process evaluation is presented, along with descriptions of methods and tools. For each process stage, a brief summary, results and conclusions are provided. Except for a few deviations, the PV batches repeatedly met all PV acceptance criteria for the IPCs and process parameters, demonstrating consistent performance, reproducibility and robustness of the manufacturing process. The deviations were acceptably investigated and handled. In conclusion, the teclistamab active substance manufacturing process can be considered adequately validated. In addition, a programme of ongoing process verification is implemented after process validation to ensure the process remains in a state of control.

Process intermediate hold times, active substance shipping and reprocessing have been appropriately validated, although commercial scale verification of reprocessing of several steps is still ongoing and will be performed on the first batch that requires reprocessing. Resin lifetime limits have been determined and will be verified during commercial manufacture. Ultrafiltration membrane, is re-used during multiple manufacturing campaigns. Maximum number of re-uses has not been specified, instead, the performance and acceptability of the ultrafiltration membranes is routinely monitored during manufacturing. This is acceptable and the verification programme is considered suitable.

Manufacturing process development

The commercial teclistamab active substance manufacturing process is the result of development efforts that occurred in parallel with the clinical development programme. Different manufacturing processes include Development process (used to manufacture toxicology batch), Clinical 10 mg/mL

process, Clinical 90 mg/mL process and Clinical and Process Validation 90 mg/mL process. The following significant process changes were made between clinical manufacturing campaigns: active substance change, scale increase, addition of new manufacturing site.

Extensive process and product characterisation were performed at each step to demonstrate comparability and ensure consistent product quality and process performance throughout clinical development. The essential elements of the teclistamab active substance manufacturing process, such as cell culture expansion and modes of chromatographic separation, were retained throughout process development. The development history of the active substance manufacturing process and the process changes made during development have been adequately described and sufficient details for each step has been provided. Production history of all clinical and process validation active substance batches has been presented. Information on manufacturing sites, dates of manufacture, batch size and the use of the batches has been provided.

Four comparability studies are presented in the dossier. The comparability studies encompass comparison of the clinical batch release data, in-process control data, characterisation data, stability data and forced degradation rates (temperature, light). The aspects considered and the panel of tests included in the comparability exercise are considered sufficient and in compliance with ICH Q5E.

Comparability Studies 1 and 2 are small studies, conducted early in process development, comparing one pre-change batch to one post-change batch. Given the stage of the process development where these batches are from and based on the data provided, this approach can be accepted. Based on the results from these two studies, it is agreed that the finished product batches derived from the pre-clinical toxicology and the 10 mg/mL clinical processes, as well as 10 mg/mL and 90 mg/mL finished product batches, are comparable. Similarly, in comparability Study 3, the pre-change 180 mg/vial finished product and the post-change 30 mg/vial and 153 mg/vial finished product batches were considered comparable based on assessments of release and characterisation results and stability data. The differences were small and did not impact the biological activity and are not expected to impact safety. Therefore, no additional non-clinical or clinical testing is deemed necessary.

Based on the presented genealogy of the batches used in clinical development, the commercial scale finished product batches have not been used in clinical trials. Thus, the comparability of scales was regarded as critical for the approval of the commercial scale process. In this study, three sequential pre-change and three sequential post-change active substance batches and one pre-change and two post-change finished product batches of each strength were used for the comparability exercise (except for stability studies). This is considered sufficient, as no changes to the finished product were made. The evaluation included active substance and finished product IPC results, active substance and finished product batch release, characterisation and stability results, active substance degradation rates under heat-stress storage condition and under photo-stress storage conditions. The pre- and post-change active substance batch results met the corresponding IPC, batch release and stability acceptance criteria and were within historical ranges. The differences in these attributes were small, did not impact the biological activity and would not be expected to impact safety. The degradation pathways for the post-change active substance were the same as the pre-change active substance. Based on the data provided, batches from different scales manufacturing processes can be considered comparable. Upon request, the applicant has presented additional data to demonstrate that the sensitivity of comparability shown at active substance and finished product level in comparability study is enough to prove comparability of the parental mAbs that are used to manufacture active substance.

Characterisation

The teclistamab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of an IgG4 bispecific antibody, with Fc Ala/Ala mutations to reduce undesired Fc gamma receptor binding. The

characterisation of teclistamab active substance involved primary structure, carbohydrate structure, disulfide structure and free thiols, intact mass and mass heterogeneity, charge and size heterogeneity, higher order structure and biological characterisation. The analytical results are consistent with the proposed structure. In addition, structure/function relationships have been characterised by forced degradation studies and structural modelling to evaluate the criticality of post-translational modifications for teclistamab. Sufficient data to demonstrate the lack of ADCC activity has been provided. The studies included in the characterisation are considered comprehensive and relevant.

Biological characterisation results indicate that teclistamab has the ability to bind CD3 and BCMA cell surface receptors with high affinity.

Heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. The N-linked oligosaccharide structures of teclistamab have been characterised by hydrophilic interaction liquid chromatography (HILIC) oligosaccharide mapping with MS and MS/MS analysis.

Teclistamab active substance contains cysteine residues, which form disulfide bonds. Peptide map analysis by non-reduced and reduced peptide mapping using reverse phase ultra-performance liquid chromatography (RP-UPLC) with on-line MS analysis demonstrated that teclistamab had the expected disulfide bond structure for a properly folded IgG4-like bispecific antibody.

Size heterogeneity of teclistamab active substance was characterised by AUC, Size Exclusion High Performance Liquid Chromatography (SE-HPLC) and Capillary Sodium Dodecyl Sulfate Gel Electrophoresis (cSDS). The structure and function of HMWS isolated by SE-HPLC were characterised, while the levels of LMWS were very low and not sufficient for isolation and characterisation. The observed level of aggregation in the teclistamab active substance by SE-HPLC was low. The HMWS were a mixture of aggregates All of the LMWS were product related fragments. Protein fragments are likely to have lower bioactivity than the intact protein and are potentially immunogenic.

In summary, the characterisation is considered appropriate for this type of molecule. All product related substances and process related impurities were adequately characterised.

Specification

The active substance specifications comply with the provisions of ICH Q6B and include: general characteristics (color, pH), identity (dot blot), quantity (A280 protein concentration), potency, charge heterogeneity (IE-HPLC), purity (SE-HPLC, cSDS reduced, cSDS non-reduced), process impurities, post-translational modifications (Multi-Attribute Monitoring (MAM) peptide mapping) and microbial contaminants (endotoxin, bioburden).

Demonstration of clearance of process related impurities was performed at commercial scale during process validation and with additional impurity spiking studies at reduced-scale. Based on the demonstrated consistent removal, routine in-process tests or active substance specification for the control of these process-related impurities are not proposed. Some of the process related impurities and product related impurities will be monitored by active substance release testing and an IPC test for the reducing agent is implemented for final active substance. The omission of release testing of excipients sucrose, EDTA and acetate has been justified by process validation studies. The control of excipient Polysorbate 20 is ensured by finished product specification. The overall approach is considered acceptable.

The proposed release test to monitor active substance potency is justified by process development and process development studies.

Acceptance criteria have been established based on evaluation or statistical analysis of release and stability data (including batches used in pivotal clinical studies), product and process knowledge, compendial limits and generally accepted practices for other commercial products. The finished product manufacturing process does not introduce meaningful changes to the product quality and therefore the active substance acceptance criteria are aligned to the finished product specification that controls product-related impurities over the finished product shelf-life.

In summary, the proposed tests panel and acceptance criteria for batch release testing are considered adequate.

Analytical methods

Teclistamab active substance is tested using a combination of compendial and non-compendial analytical tests. Compendial analytical methods used for teclistamab active substance release testing are endotoxin (Kinetic Chromogenic Assay) and bioburden (membrane filtration). The methods are conducted as described by relevant sections of Ph. Eur. and have been verified for use using teclistamab test articles. Results of the verification were provided.

Some non-compendial analytical methods are used for teclistamab active substance batch release. Sufficiently detailed descriptions of the analytical methods including system suitability and test article acceptance criteria were provided, together with a high-level listing of reagents, materials and equipment for the assays were provided. All pre-determined validation acceptance criteria were met. The validation activities covered additionally evaluation of equivalence of the assays between different sites. In general, the methods have been validated according to ICH Q2 (R1). Ph. Eur. 2.6.34 monograph has been considered in the validation of the residual Host cell protein assay.

Description and validation of all other analytical procedures used in routine control of teclistamab active substance (Colour of Solution, pH, Identity by Dot Blot, Protein Concentration by A280, Potency assay , Charge Heterogeneity - IE-HPLC, SE-HPLC, cSDS (Reduced), cSDS (Non-Reduced), and MAM Peptide Mapping) have been discussed in the corresponding finished product section.

Batch analysis

Batch data has been provided for a number of batches including process validation batches and clinical batches manufactured at the proposed commercial scale and at smaller scale, clinical batches with the lower concentration and a toxicology batch. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

Four reference standards used throughout the product development have been described. Research reference material (RRM) was used during developmental phases and a two-tiered reference standard system, involving primary reference material (PRM) and working reference material (WRM), is used for commercial manufacturing.

Two RRMs prepared from two different active substance batches, served as the initial RMs for testing samples during product development. Both RRMs were qualified through a pre-defined release testing and additional characterisation protocol. All pre-set acceptance criteria were met in the qualification.

For commercial manufacturing, an initial PRM and an initial WRM were prepared from a commercial scale active substance batch. The qualification was performed according to a pre-defined release testing and additional characterisation protocol. All pre-set acceptance criteria were met in the qualification. PRM and WRM will be requalified annually using the commercial release test methods. The protocol for the qualification of future PRMs and WRMs is provided.

Overall, the reference standards used throughout the product development have been appropriately described and the protocol for the qualification of new reference standards is acceptable.

Stability

The applicant proposed a shelf-life based on stability data provided for the parental antibodies JNJ-63705473 and JNJ-63483043, as well as for the teclistamab active substance. In addition, results from small-scale freeze/thaw cycling studies (using one batch of parental antibodies and active substance) were presented. The stability samples have been stored in reduced size containers, representative of the commercial scale containers. Information supporting the equivalence of the container type and closure to the container closure system of the commercial batches has been adequately provided. Statistical trending analyses of the real-time stability data were performed as per ICH Q1E. The data from method validation and stressed stability studies show that assays are stability indicating methods.

JNJ-63705473 Protein A eluate (anti-BCMA mAb) shelf-life

Batches of the bottle-filled JNJ-63705473 Protein A eluate have been placed in the stability monitoring programs. At the long-term condition, real-time data is currently available for clinical and PV batches. The studies at long-term conditions are planned to continue for both clinical and PV batches.

No significant trends can be observed in the provided stability data and the proposed commercial release and stability acceptance criteria were met over the proposed shelf-life when stored at the recommended storage condition Therefore, the claimed shelf-life for bottle-filled JNJ-63705473 Protein A eluate (anti-BCMA mAb) when stored at the recommended storage condition can be agreed.

JNJ-63483043 Protein A eluate (anti-CD3 mAb) shelf-life

Clinical batches and PV batches of the bottle-filled JNJ-63483043 Protein A eluate have been placed in the stability monitoring programs. At the long-term condition real-time data is currently available and the studies at long-term conditions are planned to continue.

No significant trends can be observed in the provided stability data and the proposed commercial release and stability acceptance criteria were met over the proposed shelf-life when stored at the recommended storage condition. Therefore, the claimed shelf-life for bottle-filled JNJ-63483043 Protein A eluate (anti-CD3 mAb) when stored at the recommended storage condition can be agreed.

Teclistamab active substance shelf-life

Active substance clinical batches and PV batches were placed in the stability monitoring programs. At the long-term condition real-time data is currently available and the studies at long-term conditions are planned to continue.

No significant trends can be observed in the provided stability data and the proposed commercial release and stability acceptance criteria were met for all active substance batches, at all studied time points, when stored at the recommended storage condition. Therefore, the claimed shelf-life for the active substance when stored at the recommended storage condition is considered acceptable.

Overall, the stability of JNJ-63705473, JNJ-63483043 and teclistamab active substance has been adequately addressed in line with ICH Q5C and ICH Q1A(R2). The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf-life in the proposed container.

The applicant commits to continue the stability studies as described. Confirmed out-of-specification (OOS) results obtained at the recommended storage condition will be reported to the health authority, as appropriate.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is supplied as a sterile liquid in single-use vial presentation for subcutaneous (SC) administration, containing 10 mg/mL or 90 mg/mL of teclistamab as active substance. The final commercial finished product contains 10 mg/ml or 90 mg/mL teclistamab in sodium acetate trihydrate, glacial acetic acid, sucrose, polysorbate 20, EDTA disodium salt dihydrate, at pH 5.2 and stored at 2-8°C.

Each 10 mg/mL vial contains 30 mg of teclistamab in a 3.0 mL nominal fill volume per vial. Each 90 mg/mL vial contains 153 mg of teclistamab in a 1.7 mL nominal fill volume per vial. The teclistamab finished product do not have an overage. Overall, the composition of both presentations of teclistamab finished product (10 mg/mL and 90 mg/mL) are adequately described.

The target product profile for teclistamab finished product required the development of a sterile liquid dosage form in a glass vial, for subcutaneous administration. The formulation composition for teclistamab finished product was developed as part of an extensive formulation development effort which evaluated parameters including pH, buffer type and stabilisers, based on prior knowledge with similar monoclonal antibody products administered by subcutaneous route of administration. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients and no excipients of human or animal origin used in the finished product formulation. Two finished product presentations at 10 mg/mL and 90 mg/mL were required to enable the strengths necessary to achieve the prescribed dose in a practical volume for clinical administration. The intended commercial formulation compositions are identical with the ones used during clinical studies.

The commercial finished product manufacturing process was the result of development efforts that occurred in parallel with the clinical development programme. The manufacturing process was characterised and validated to ensure consistent product quality for each manufacturing run. The cumulative process understanding that was gained from development studies, development production campaigns, early to late phase clinical production campaigns and pharmacovigilance was used to establish the appropriate control strategy for the commercial manufacturing process.

The container closure system for teclistamab finished product is composed of either a 2 mL (for 90 mg/mL presentation) or a 6 R (for 10 mg/mL presentation) vial manufactured from clear Type 1 borosilicate glass, grey chlorobutyl rubber stopper with fluoropolymer film and cross-linkable polydimethylsiloxane coating and silver coloured aluminum seal with an orange (for 2 mL vial) or royal blue (for 6 R vial) plastic flip off cap. Representative diagrams and information on the critical dimensions of the components are presented. The container closure system material complies with Ph. Eur. and EC requirements.

The 10 mg/mL and 90 mg/mL finished products contain no preservatives and they are manufactured using an aseptic process. Container closure integrity tests were performed to validate the integrity of the container closure system and its ability to prevent microbial contamination. The choice of the container has been validated by stability data and is adequate for the intended use of the product. Studies to determine the extractables and potential leachables from the stopper have been conducted, in line with relevant guidelines. The data obtained indicate that there are no leachables related to the stoppers observed above the threshold of concern to patient safety. Therefore, the results support the use of the selected vial and stopper container closure system in the manufacturing of teclistamab.

Physicochemical compatibility studies were executed to investigate the in-use stability and compatibility between teclistamab 10 mg/mL and 90 mg/mL finished products and the materials that are in direct contact with the finished product during dose preparation and administration by subcutaneous injection. Based on the results obtained, total in-use storage time (including dose preparation, transportation and administration for the undiluted finished product) is supported. For commercial use, the total in-use storage time will be limited to not exceed 20 hours. This conclusion is considered acceptable.

In conclusion, pharmaceutical development of 10 mg/mL and 90mg/mL teclistamab finished products is adequately described.

Manufacture of the product and process controls

The teclistamab finished product is manufactured, filled, packaged, inspected and tested in accordance with GMP. Janssen Biologics B.V., The Netherlands, is responsible for batch release of the finished product.

The 10 mg/mL and 90 mg/mL finished products are manufactured using frozen 90 mg/mL teclistamab active substance. The manufacturing process consists of the thawing and storage of thawed active substance, compounding and storage of bulk finished product solution, sterile filtration, aseptic filling and stoppering of finished product vials, capping and optical inspection.

The manufacturing process is, in general, described with sufficient details. Process parameters and IPCs are adequately set to control the process leading to consistent quality. There are no reprocessing steps and no intermediates in the finished product manufacturing process.

A compounding batch size (which represents the commercial manufacturing scale) was validated during process validation. Validation of the manufacturing process for teclistamab 10 mg/mL and 90 mg/mL finished product consisted of clinical manufacturing batches and consecutive process validation batches at the commercial manufacturing site. The analytical procedures have been either appropriately verified as suitable for use or validated according to ICHQ2(R1). Unit operations studied were active substance thaw, finished product compounding, sterile filtration, aseptic filling, stoppering/capping, post-fill process steps.

Sufficient information is provided on hold times, media fills, sterile filtration time, process validation batch consistency, the extractable and leachable risk assessment for polymeric product contact materials, filter validation, shipping validation and ongoing process verification. Risk based approaches will be used to evaluate excursions, trends and process shifts for any potential impact to product Critical Quality Attributes or process performance that are part of the short-term continued validation programme. The submitted data demonstrate that the process is generally well controlled, with little variation in the reported results, which were all within defined limits.

In conclusion, the teclistamab finished product manufacturing process is considered appropriately validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The proposed finished product release and shelf-life specifications for the teclistamab finished product are presented.

The release specification includes general tests (appearance of primary container, colour, pH, extractable volume, osmolality, turbidity), Polysorbate 20, visible foreign particles, visible translucent

particles, sub-visible particles, identity (dot blot), quantity (A280 protein concentration), potency, charge heterogeneity (IE-HPLC), purity (SE-HPLC, cSDS reduced, cSDS non-reduced), post-translational modifications (MAM peptide mapping) and contaminants (endotoxin, sterility, CCS integrity).

The strategy for setting acceptance criteria is described. The statistical methods used for setting specifications are described. Tightening of the release and stability acceptance criteria was requested during the assessment for some parameters.

Overall, the parameters included in the finished product specification are found adequate to control the quality of the finished product at release and shelf-life. The acceptance criteria currently proposed for both active substance and finished product are recommended to be re-evaluated once data from both 30 commercial active substance batches and of 30 commercial drug product batches are available.

Process-related impurities for 10 mg/mL and 90 mg/mL finished product include the same impurities characterised for the active substance and encompass those derived from the active substance manufacturing process. No additional process related impurities derived from the finished product manufacturing process were identified.

Product-related impurities in 10 mg/mL and 90 mg/mL finished product are monitored by appropriate release and stability tests to ensure product quality.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report - Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

Teclistamab finished product is tested using a combination of compendial and non-compendial analytical tests. Compendial analytical methods used for finished product release testing include Colour of Solution, pH, Extractable Volume, Osmolality, Turbidity, Particulate matter (sub-visible and visible foreign), Sterility and Endotoxin (Kinetic Chromogenic Assay). Colour of Solution and pH are also used for active substance release testing. The methods are conducted as described by relevant sections of Ph. Eur. and have been verified for use using teclistamab test articles. Results of the verification for the tests for sterility and endotoxin were also provided.

Non-compendial analytical methods used for teclistamab active substance and finished product batch release include Polysorbate 20 concentration, Identity by Dot Blot, Protein Concentration by A280, Potency assay, Charge Heterogeneity by IE-HPLC, SE-HPLC, Purity by Capillary Sodium Dodecyl Sulfate Gel Electrophoresis (cSDS, Reduced and Non-Reduced) and Post Transitional Modifications by MAM Peptide Mapping. In addition, the tests for Appearance of primary container, Particulate Matter (Visible Translucent By MDI) and Container and Closure Integrity Test used only for finished product release are presented.

Many of the analytical methods are performed and co-validated at several sites. In general, sufficiently detailed descriptions of all the non-compendial analytical methods, including a high-level listing of reagents, materials and equipment for the assays, system suitability and assay/test article acceptance criteria and formulae for calculating the results, were provided. Appropriate parameters were included in the validation of all non-compendial methods. In many cases the method validation was performed using only active substance test articles, which are considered representative of the finished product test articles, as the protein concentration and formulation are highly similar. As many of the methods were co-validated at several sites, the validation activities also covered evaluation of equivalence of the assays between the different sites. All pre-determined validation acceptance criteria were met and equivalent performance of the methods between different sites was confirmed.

Overall, the non-compendial analytical methods have been appropriately validated according to ICH Q2 (R1) guideline.

Batch analysis

The applicant has provided batch analysis results for toxicology, clinical and process validation batches of teclistamab finished product. The process validation batches are representative of the commercial manufacturing process. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

See active substance section on Reference materials.

Stability of the product

The applicant proposed a shelf-life of 18 months at 5°C ± 3°C for the finished product, based on stability data provided at the long-term storage condition (5°C ± 3°C), at the accelerated storage condition and at the stress storage condition The presented stability data has been generated using both 10mg/mL and 90 mg/mL presentations and both clinical and PV material. The stability samples have been stored in different size containers, representative of the commercial scale and material, which is acceptable. The stability-indicating properties of the analytical procedures for potency assay, SE-HPLC, cSDS reduced, cSDS non-reduced, MAM peptide mapping and charge heterogeneity IE-HPLC used in the stability studies were demonstrated during method validation.

An assessment of the stability data at the recommended (5°C ± 3°C) storage condition for the 90 mg/mL and 10 mg/mL finished product strengths showed that similar stability trends are observed for most quality attributes. The applicant's approach is considered justified and acceptable. The stability studies are planned to continue up to 36 months at the long-term conditions.

No significant trends can be observed in the provided stability data and the proposed commercial release and stability acceptance criteria were met over the proposed 18-month shelf-life when stored at the recommended storage condition of 5°C ± 3°C, in the proposed container.

Photostability studies were performed in accordance with ICH Q1B. The studies showed evidence of finished product degradation upon light exposure, which was not seen upon shielding of the finished product in its secondary packaging (opaque paperboard carton), the finished product was recommended to be stored in its outer carton to protect it from light. This is considered satisfactory.

A temperature cycling study was performed to provide stability data to support potential temperature excursions that may be encountered during transportation, storage and handling. A 10mg/mL and a 90mg/mL batch were subjected to temperature cycles and then placed on a long-term stability programme. Results of the study are currently available only for the initial time point (T=0). However,

all physical and biochemical product quality attributes tested conform to the proposed commercial stability acceptance criterion and the initial data is consistent with results without the prior freeze/thaw cycle.

Overall, the stability of teclistamab finished product has been adequately addressed in line with current ICH Q5C and ICH Q1A(R2) guidelines. The applicant commits to complete the stability studies as described. Confirmed out of specifications (OOS) results obtained at the recommended storage temperature will be reported to the health authorities.

Based on available stability data, the finished product shelf-life of 18 months and storage conditions as stated in the SmPC (*Store in a refrigerator (2°C - 8°C)*. *Do not freeze. Store in the original carton in order to protect from light*) are acceptable. For the prepared syringe for subcutaneous administration, this should be administered immediately. If immediate administration is not possible, in-use storage times of the prepared syringe should be no longer than 20 hours at 2°C - 8°C or ambient temperature (15°C – 30°C).

Adventitious agents

Mycoplasma and microbial bioburden are adequately controlled through use of a sanitary process design and appropriate in-process testing. It can also be concluded that there is minimal risk of contamination by TSE in the final product.

The results of viral testing performed as part of cell line qualification demonstrate that MCB and WCB used for preparing anti-CD3 and anti-BCMA antibodies are free of adventitious and endogenous viral agents. These results also indicate that no viral contamination occurred during cell line development and cell banking MCB and WCB testing is reviewed as part of the active substance control, as well as the control of raw materials. Any viral agents would be detected by the in vitro assay performed during anti-CD3 and anti-BCMA manufacturing as a routine basis for the ongoing assessment of adventitious viruses. MCB, WCB and End of Production Cells are adequately tested for adventitious agents.

Viral clearance studies were performed with a suitable panel of model viruses on qualified small-scale models. The total process clearance determined by summation of removal/inactivation methods. The safety margin over the estimated retroviral burden per Retrovirus-like particles is considered satisfactory.

In conclusion, the evaluation of adventitious agents has been adequately performed.

GMO

N/A

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The active substance and finished product manufacturing processes and process controls are appropriately described and the processes are appropriately validated. Characterisation of teclistamab active substance was performed using an extensive panel of appropriate methods. Comprehensive control strategy for teclistamab manufacture is in place. Overall, the test parameters proposed to be

included in the teclistamab active substance and finished product specifications are considered appropriate and in line with relevant guidance. Sufficient stability data to support the claimed shelf-life for both active substance and finished product have been provided.

At the time of the CHMP opinion, there is one minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to the acceptance criteria for active substance and finished product specification. These points are put forward and agreed as recommendation for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends a point for investigation.

3.2. Non-clinical aspects

3.2.1. Introduction

The nonclinical programme for teclistamab was conducted in accordance with the ICH guidelines S9 and S6(R1), as well as S7A, S2(R1), M3(R2), S3A, and S5(R3). Nonclinical studies were performed to investigate the primary pharmacology of teclistamab, identify a toxicology species for teclistamab, investigate the pharmacokinetics and potential immunogenicity of teclistamab in the test species, and to investigate the potential general toxicity associated with teclistamab.

3.2.2. Pharmacology

Pharmacology studies evaluated the tissue expression of BCMA, determined teclistamab in vitro mechanism of action including bi-specific target binding activity (CD3 and BCMA) and specificity, and efficacy in BCMA+ multiple myeloma cell lines and in patient-derived primary myeloma cells, and efficacy in vivo in xenograft tumour rodent models.

Primary pharmacodynamic studies

In vitro studies

Target binding affinity and specificity

Teclistamab's bispecific binding activity was demonstrated: teclistamab bound to human BCMA (hBCMA) with high affinity, with average Kd of 0.18 nM and to CD3 with Kd of 28.03 nM. Teclistamab bound with nanomolar affinity to cynomolgus monkey BCMA (cBCMA) with average Kd of 6.5 nM (36-fold weaker affinity than to hBCMA), and to CD3 with Kd of 38.48 nM. Teclistamab binds only weakly to rodent BCMA and does not cross-react with rodent or rabbit CD3. Hence, rodents and rabbits are not a

pharmacologically relevant animal species for toxicity evaluation of teclistamab. The cynomolgus monkey was selected as the most pharmacologically relevant species for the teclistamab safety evaluation.

Teclistamab bound specifically to the BCMA$^+$ multiple myeloma cell lines (H929, MM.1R and RPMI 8226) with half-maximal effective concentration (EC50) values ranging from 0.5 to 2.6 nM.

Functional activity (T-cell activation and cytotoxicity)

Teclistamab *in vitro* functionality was demonstrated in CHO cells expressing BCMA and multiple myeloma cell lines. In BCMA$^+$CHO cells and in the presence of T-cells (effector:target (E:T) ratio of 5:1) teclistamab induced T-cell activation with EC50 value of 0.22-0.32 nM, and cytotoxicity leading to death of BCMA-expressing cells with EC50 of 0.31-0.89 nM. In cBCMA expressing CHO cells and with cynomolgus monkey T-cells, EC50 value for T-cell activation 1.38-3.9 nM, and for cytotoxicity was 0.64-3.3 nM. The interspecies comparison of biological activity of teclistamab is shown in **Table 2**.

Table 2. Teclistamab binding affinity and functional activity to human and cynomolgus monkey BCMA and in BCMA$^+$ cells

Binding Affinity to BCMA (nM)		Cytotoxicity EC50 (nM)		T Cell Activation EC50 (nM)	
Human	**Cynomolgus**	**Human**	**Cynomolgus**	**Human**	**Cynomolgus**
0.15-0.20	5.36-7.27	0.31-0.86	0.64-3.3	0.2-0.32	1.38-3.9

In BCMA$^+$ myeloma cell lines, teclistamab led to T cell-mediated cytotoxicity *ex vivo* in the presence healthy donors of T cells (E:T ratio of 5:1) with EC50 of 0.07 - 0.7 nM (EC20 of 0.04 – 0.34 nM). Induction of activation marker CD25, on T cells was specific for BCMA$^+$ cells and was observed with EC50 values of 0.15 - 0.50 nM in these experiments. No lysis was observed in the BCMA$^-$ cell line MV4-11 or with control bispecific antibodies.

Teclistamab -related T-cell activation correlated with the release of the INF-gamma, TNF-alpha, IL-2, IL-6, IL-8 and IL-10 cytokines in BCMA$^+$ multiple myeloma cell lines.

Functional activity in whole blood (*ex vivo* physiological model)

Teclistamab dose-dependently resulted in BCMA$^+$ multiple myeloma cells cytotoxicity up to 88.5% when spiked into the blood of 6 healthy donors at an E:T ratio of 5:1. The mean cytotoxicity EC50 value was 1.26 nM (range from 0.305 to 3.422 nM).

Teclistamab dose-dependently activated T-cells up to 63.1% (as measured by % of CD3+/CD25+ T-cells). The mean EC50 value for activation was 1.406 nM (range from 0.486 to 2.2 nM).

Teclistamab induced release of the INF-gamma, TNF-alpha, IL-2, IL-4, IL-6, IL-8, IL-1beta, IL12p70 and IL-30 cytokines. The arithmetic mean EC50 values for the most sensitive cytokines IL-6 and IL-2 were 1.207 and 1.275 nM, respectively.

Functional activity in patient-derived CD138+ MM bone marrow cells *ex vivo*

Teclistamab bound to, activated T-cells and induced cytotoxicity in a dose-dependent manner when primary CD138+ cells were co-cultured with healthy donor T-cells (**Table 3**). The following average

efficacy values were obtained from 5 patient samples: T cell activation EC50 [EC20] = 1.33 [0.70] nM and cytotoxicity EC50 [EC20] = 2.53 [1.03] nM. A cytotoxicity EC90 value of 41.29 nM (6039 ng/mL) was estimated and used to model clinical efficacy dose predictions.

Control bispecific antibodies did not lead to significant cytotoxicity or T cell activation in 4 patient samples, 1 out of 5 patients had minimal cytotoxicity at concentrations >67 nM.

Table 3. Teclistamab cytotoxicity and T-cell activation ex vivo in multiple myeloma patients bone marrow mononuclear cells.

JNJ-64007957 T cell activation values using MM patient MNCs					
Patient ID:	MM240BM	MM259BM	MM270BM	MM276BM	MM277BM	*Average*
EC50	1.688	1.032	1.746	0.9296	1.239	*1.33*
EC20	1.03	0.6338	0.6901	0.3945	0.7753	*0.70*

JNJ-64007957 cytotoxicity values using MM patient MNCs					
Patient ID:	MM240BM	MM259BM	MM270BM	MM276BM	MM277BM	*Average*
EC50	1.977	1.47	1.591	4.208	3.398	*2.53*
EC20	1.23	1.316	0.5007	0.996	1.09	*1.03*

<u>Effect of teclistamab on BCMA downstream signaling and APRIL and BAFF ligand binding</u>

Teclistamab had no agonistic activity on BCMA receptor signalling as measured by phosphorylation of p38. In the presence of BCMA ligands APRIL and BAFF, teclistamab inhibited p38 phosphorylation by 50%.

<u>Effect of soluble BCMA, APRIL and BAFF on teclistamab BCMA binding and functionality</u>

High levels of soluble BCMA (sBCMA) have been measured in MM patient plasma samples (mean levels of 15.27±4.58 nM). The median serum levels of APRIL have been 3.3 nM and BAFF 0.61 nM in MM patients.

sBCMA or BAFF did not affect the binding of teclistamab to BCMA at physiologically relevant concentrations, and is not expected to have an impact on *in vivo* efficacy of teclistamab. BCMA ligand APRIL inhibited the binding of teclistamab to BCMA^{+} cells at physiologically relevant concentrations of ≥0.6 nM.

The T-cell mediated cytotoxic potential of teclistamab was reduced by 2-fold in the presence of 167 nM sBCMA and 16 nM APRIL. BAFF had no impact on teclistamab mediated cytotoxicity at concentrations up to 51 nM.

<u>BCMA expression on haematological and nonhaematological tissues</u>

Analyses conducted to evaluate BCMA expression in normal human tissues using flow cytometry, qPCR and immunohistochemistry collectively demonstrated that BCMA was expressed mostly by plasma cells and subsets of mature B cells.

Teclistamab bound only to T cells (CD4+ and CD8+) of whole blood from normal human donors and to mononuclear cells of multiple myeloma patients, and not in any other peripheral blood cell population (*i.e.* basophils, plasmacytoid dendritic cells, monocytes, neutrophils, or eosinophils).

Immunohistochemistry studies performed with a commercially available anti-BCMA antibody on normal human tissue microarray showed weak cytoplasmic staining in all 3 tissue microarrays in the adrenal gland and the brain. Weak cytoplasmic staining patterns were observed in 1 or 2 tissue microarrays for the following gastrointestinal tract tissues: stomach, basal crypts of the stomach, oesophagus, ileum, caecum, colon, rectum, and glandular mucosa.

In vivo studies

In vivo efficacy of teclistamab was assessed in three studies in humanised immunocompromised NSG mice tumour models. CD3×null or BCMA×null bispecific antibodies failed to suppress tumorigenesis in these models.

Teclistamab significantly reduced tumour (origin of H929 BCMA$^+$ multiple myeloma cells) growth at doses of 0.025 and 0.05 mg/kg in the NSG mice, when administered at the time of implantation of tumour cells.

Teclistamab inhibited tumour (origin of RPMI 8226 BCMA$^+$ multiple myeloma cells) growth by 53% on Day 28 as compared to PBS-treated controls (p<0.05) at dose of 0.005 mg/kg in xenograft mice model (RPMI 8226 xenograft, T-cell model). The higher 0.05 mg/kg dose showed limited efficacy. In the repeated study in the same model, 0.05 mg/kg teclistamab dose was not effective, but higher 0.5 and 2.5 mg/kg doses (administered IP every 3 or every 4 days for 8 total treatments post implantation of human pan T-cells) inhibited significantly the tumour growth (TGI). On Day 60 at 0.5 and 2.5 mg/kg doses, the TGI was 79% and 87%, respectively. At the end of study, 9 of 10 animals at 2.5 mg/kg dose group had durable and complete TGI responses.

Secondary pharmacodynamic studies

No specific secondary pharmacology studies were conducted with teclistamab. In the tissue reactivity analyses, teclistamab bound selectively only to CD4+ and CD8+ T -cells of whole blood from normal human donors and to mononuclear cells of multiple myeloma patients (data not shown).

Safety pharmacology programme

Cardiovascular, respiratory, and observational CNS safety pharmacology endpoints were incorporated into the pivotal 5-week repeat-dose toxicity GLP study (with an 8-week recovery period) in cynomolgus monkeys (see Section 2.5.4). The data suggested that teclistamab would not have adverse effects on the vital functions at the therapeutic dose levels. There were no significant increases in circulating cytokines in cynomolgus monkeys dosed with teclistamab.

Pharmacodynamic drug interactions

No dedicated pharmacodynamic drug interactions studies were submitted, as teclistamab is unlikely to have pharmacodynamic interactions with co-administered drugs due to its high binding specificity for its targets, BCMA and CD3.

3.2.3. Pharmacokinetics

Absorption

Exploratory single and 5-week repeat-dose IV tolerability study in cynomolgus monkeys (T-2015-030)

The PK/TK profile of teclistamab was evaluated in male cynomolgus monkeys (3/group) administered IV a single dose of 1 or 10 mg/kg or 5 weekly doses of 0.1, 1, or 10 mg/kg.

In the single-dose groups, serum teclistamab C_{max} and AUC_{last} values increased with dose in a dose-proportional manner from 1 to 10 mg/kg. Teclistamab concentrations for 2 animals in the 1 mg/kg group and all 3 animals in the 10 mg/kg group showed a fast decrease after Day 15, which was likely due to ADA development. Therefore, AUC_{inf}, CL, and $T_{1/2}$ were not reported for these animals.

In the repeat-dose groups, all teclistamab-treated animals had quantifiable serum teclistamab concentrations throughout the 5-week treatment period, with the exception of 1 animal at 1 mg/kg/week with concentrations below the lowest quantifiable concentration (0.15630 µg/mL) at the Day 29 predose time point. Teclistamab exposure increased with dose in an approximately dose-proportional manner. There was an approximately 2-fold increase in teclistamab exposure in the systemic circulation from the first to fifth dose, indicating moderate drug accumulation, except for 1 animal at 1 mg/kg/week with lower exposure following the fourth dose on Day 22 likely due to the presence of ADA. Mean pK parameters following dosing on Days 1 and 22 are presented in **Table 4**.

Table 4. Mean (SD) serum teclistamab pharmacokinetic/toxicokinetic parameter estimates following a single dose or 4 weekly doses of teclistamab IV in male cynomolgus monkeys in a non-GLP 5-week study

Single-dose groups					
Dose (mg/kg)	C_{max} (µg/mL)	AUC_{last} (µg·day/mL)	AUC_{inf} (µg·day/mL)	CL (mL/day/kg)	$T_{1/2}$ (day)
1	22.05 (4.32)	108.64 (49.58)	202.70[a,b]	4.93[a,b]	27.35[a,b]
10	216.19 (16.25)	901.23 (105.52)	NR[b]	NR[b]	NR[b]

Repeat-dose groups					
	Following Dose on Day 1		Following Dose on Day 22		
Dose (mg/kg)	C_{max}^{a} (µg/mL)	AUC_{Day1-8}^{a} (µg·day/mL)	C_{max}^{a} (µg/mL)	$AUC_{Day22-29}^{a}$ (µg·day/mL)	R^{c}
0.1	2.01 (0.14)	5.04 (0.23)	2.52 (0.11)	8.35 (0.81)	1.65 (0.11)
1	22.25 (2.40)	55.21 (2.22)	33.28 (6.73)	107.62 (72.40)	1.93 (1.24)
10	203.41 (9.68)	586.21 (51.74)	336.55 (29.02)	1348.35 (311.75)	2.28 (0.36)

a Value for 1 animal

b Serum teclistamab concentrations for 2 animals in the 1 mg/kg group and all 3 animals in the 10 mg/kg group showed a fast decrease after Day 15 (360 hours), which was likely due to ADA development (which was not tested); therefore, AUCinf, CL, and T1/2 were not reported for these animals.

c Mean of individual ratios.

Pivotal 5-week IV toxicity study with an 8-week recovery period in cynomolgus monkeys (T-2016-030)

A pivotal 5-week repeat-dose toxicity GLP study with a recovery period evaluated the toxicokinetic profile and immunogenicity of teclistamab in male and female cynomolgus monkeys. Main study animals (3/sex/group) and recovery animals (2/sex/group) received weekly IV doses of 1, 10, or 30 mg/kg teclistamab for 5 weeks followed by an 8-week treatment-free period.

Teclistamab-treated animals had quantifiable serum teclistamab concentrations throughout the 5-week treatment period, except for 2 monkeys (1 each in the 1 and 10 mg/kg/week groups) with concentrations below the lowest quantifiable concentration in a sample (0.15630 µg/mL) at the Day 29 predose time point. Teclistamab exposure (mean C_{max} and AUC) increased approximately dose proportionally from 1 to 30 mg/kg/week following dosing on Days 1 and 22.

Following 4 doses, the mean accumulation ranged from 1.65 to 2.04. Exposure was lower following the fourth dose on Day 22 than on Day 1 in 5 animals (1, 2, and 2 in the 1, 10, and 30 mg/kg/week groups, respectively) due to the presence of ADA in these animals. No apparent differences in toxicokinetic parameters were observed between male and female animals. At the end of the recovery period, serum teclistamab concentrations were below the lowest quantifiable concentration in 4 of 12 animals (3 animals at 1 mg/kg/week and 1 animal at 10 mg/kg/week). Mean toxicokinetic parameters following the doses on Day 1 and 22 are presented in **Table 5.**

Table 5. Mean (SD) serum teclistamab toxicokinetic parameter estimates in male and female cynomolgus monkeys administered 4 weekly IV doses in a GLP 5-week study

Dose (mg/kg)	Following Dose on Day 1		Following Dose on Day 22		
	$C_{max}{}^a$ (µg/mL)	$AUC_{Day1-8}{}^a$ (µg•day/mL)	$C_{max}{}^a$ (µg/mL)	$AUC_{Day22-29}{}^a$ (µg•day/mL)	R^b
1	26.77 (2.46)	63.36 (2.76)	38.58 (2.57)	128.93 (38.00)	2.04 (0.62)
10	300.30 (29.31)	719.86 (98.94)	417.75 (55.52)	1181.22 (521.40)	1.65 (0.70)
30	785.45 (80.12)	2032.35 (183.80)	1084.01 (121.41)	3549.19 (1361.69)	1.75 (0.62)

a 5/sex/group. Toxicokinetic evaluations included results for ADA-positive animals (8 each at 1 and 10 mg/kg and 5 at 30 mg/kg); exposure was lower in 5 ADA-positive animals during the Day 22 dosing period (1, 2, and 2 at 1, 10, and 30 mg/kg, respectively) and 2 ADA-positive animals on Day 29 (1 each at 1 and 10 mg/kg) compared with ADA-negative animals in the same dose group.

b Mean of individual ratios.

Distribution, metabolism and excretion

Traditional distribution studies were not conducted for teclistamab, which is an antibody with a molecular weight of 146.261 kDa. Due to its molecular size, teclistamab is expected to be primarily confined to the vascular space with only limited distribution to the extracellular space, which is typical for IgG-based mAbs.

As an IgG-based antibody, teclistamab is presumed to be catabolised and eliminated by processes involved in the turnover and degradation of endogenous IgGs.

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were conducted, which is acceptable.

3.2.4. Toxicology

The non-clinical toxicology programme for teclistamab characterised general toxicity and toxicokinetics (see Pharmacokinetics Section 4.2.3 of this report) in cynomolgus monkeys following IV administration. Repeated weekly doses of teclistamab IV were evaluated in a pivotal 5-week toxicity study in cynomolgus monkeys. To support transition from IV to SC dosing in humans, the local

tolerance of teclistamab SC was evaluated in rabbits. Tissue cross reactivity, cytokine release, serum compatibility, and haemolytic potential of teclistamab was assessed *in vitro*.

Single and repeat dose toxicity

The nonclinical toxicology programme for teclistamab characterised general toxicity and toxicokinetics in cynomolgus monkeys following IV administration. Repeated weekly doses of teclistamab IV were evaluated in a pivotal 5-week toxicity study in cynomolgus monkeys (see Pharmacokinetics Section 4.2.3 of this report).

Teclistamab IV was well tolerated in cynomolgus monkeys. No teclistamab-related effects were noted in major body systems or in pathology assessments, survival, or clinical observations at doses expected to be pharmacologically active. The NOEL in the pivotal 5-week study was 30 mg/kg/week (highest dose). No microscopic findings were noted on histopathological examination, and no teclistamab-mediated effects were noted from overall cellularity of T cells (CD4, CD8), B cells (CD20), and anti-plasma cells on formalin-fixed spleen, mandibular lymph node, mesenteric lymph node, and bone marrow (sternum). Teclistamab did not significantly increase in circulating cytokines in cynomolgus monkeys. No off-target toxicities were noted in monkeys.

Exposure in monkeys after 4 doses at 30 mg/kg/week teclistamab IV was 43 times C_{max} and 22 times AUC_{tau} human steady-state exposure at 1.5 mg/kg teclistamab SC weekly, the recommended weight-based dose regimen, for subjects with relapsed/refractory multiple myeloma in Phase 1/2 study MajesTEC-1 (**Table 6**).

Table 6. Exposure margins at the NOEL in pivotal teclistamab 5-week repeat-dose toxicity study

Species	Teclistamab Dose Regimen	Cmax (µg/mL)	AUC (µg·day/mL)	Exposure Margin	
				Cmax (µg/mL)	AUC (µg·day/mL)
Human exposure	1.5 mg/kg SC weekly	25.3	162.71		
Monkey exposure	30 mg/kg IV weekly (NOEL)	1084.01	3549.19	**42.85**	**21.81**

Genotoxicity and carcinogenicity

Genotoxicity and carcinogenicity studies have not been conducted with teclistamab, as these are not required for biotechnology-derived pharmaceuticals.

Reproductive and developmental toxicity

BCMA is not expressed in female or male reproductive organs. In cynomolgus monkeys, no test article-related microscopic findings were noted in the histopathology examination including male (epididymis, prostate, and testis) and female (cervix, uterus, and vagina) reproductive tissues in pivotal toxicology study. Based on the weight of evidence (EoW)risk assessment, teclistamab is not expected to pose a risk to reproduction or be teratogenic.

Local Tolerance

In the SC local tolerance GLP study (**T-2018-019**), male New Zealand White rabbits (6/group) received a single SC injection (2 mL dose volume) in the scapular region of 20 mg (10 mg/mL) teclistamab or sterile saline on the right side and formulation buffer on the left side. The formulation buffer (aqueous solution containing 10 mM sodium acetate, 8% (w/v) sucrose, 0.04% (w/v)

polysorbate 20, and 20 µg/mL ethylenediaminetetraacetic acid, at pH 5.2) contains the same components as the drug product. Injection sites were evaluated for up to 72 hours post-dose, and animals were necropsied on Day 4.

Two of the 6 teclistamab-treated rabbits had ≤Grade 2 erythema at the injection site. In 1 animal, the maximal erythema of Grade 2 on Day 2 resolved by the Day 4 necropsy. The other animal had Grade 1 erythema on Days 2 through 4. There were no gross or microscopic findings in the injection sites or draining lymph nodes of teclistamab treated or control animals. Because rabbits are not a pharmacologically relevant species, the study tested the local tolerance of the buffer formulation that contains the same components as the drug substance formulation at a teclistamab concentration of 10 mg/mL.

In the repeat-dose IV toxicity studies in cynomolgus monkeys where teclistamab was administered at up to 30 mg/kg/week for 5 weeks, there were no teclistamab related effects at IV injection sites based on clinical observations and histopathology evaluation.

Other toxicity studies

Antigenicity

The development of ADA to teclistamab was evaluated in the pivotal 5-week IV toxicity study in cynomolgus monkeys (T-2016-030). ADA was detected in 21 of 30 teclistamab-treated animals (**Table 7**).

Table 7. Summary of the detection of serum anti-teclistamab antibody status following weekly IV doses of teclistamab in cynomolgus monkeys in a GLP 5-week study

Dose (mg/kg/week)		0	1	10	30
Number of animals with appropriate samples for ADA status evaluation[a]		10	10	10	10
Animals POSITIVE for anti-teclistamab antibodies at any time during study	All animals	0/10	8/10	8/10	5/10
	Male	0/5	4/5	4/5	3/5
	Female	0/5	4/5	4/5	2/5
Animals NEGATIVE for anti-teclistamab antibodies		10/10	2/10	2/10	5/10

a 5/sex/group (3/sex/main study animals + 2/sex/recovery animals)

Serum samples for ADA analysis were obtained from blood collected from all animals at predose on Days 1, 22, and 29 and from recovery animals on Days 43, 62, 76, and 87.

Immunotoxicity

The flow cytometry for whole blood CD3 receptor occupancy, immunophenotyping of whole blood, immunophenotyping of spleen and bone marrow tissue, plasma cytokine analysis (eg. IL-2, IL-6, IL-10, IFN-γ, TNF-α), and serum IgG and IgM level were assessed in cynomolgus monkeys (T-2015-030 and T-2016-030). The repeat-dose toxicity studies revealed no apparent teclistamab-related adverse effects on the immune system.

The tissue cross-reactivity (Studies T-2016-031/App5 for T-2015-051, T-2016-031)

Studies confirmed the expected binding pattern which is limited to the cells of the B cell lineage. Binding was observed in tissues where BCMA expressing cells reside. The binding was essentially similar between cynomolgus monkey and human tissues.

*Haemolytic potenti*al (T-2016-047, T-2016-048)

Serum and blood samples used in the assays were collected from normal human volunteers (3 donors/study). No teclistamab-related serum precipitation or haemolysis was observed. Based on these results, teclistamab concentrations up to 10 mg/mL were considered compatible with human serum and blood.

Cytokine release (T-2016-046)

Teclistamab was shown to induce a statistically significant low-level secretion of IL-8, IFN-γ and TNF-α in normal human cells at concentrations of ≥82 ng/mL. The risk of cytokine release syndrome is a known risk clinically and it managed with tocilizumab treatment.

3.2.5. Ecotoxicity/environmental risk assessment

Teclistamab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no studies as part of the Environmental Risk Assessment for teclistamab are required.

3.2.6. Discussion on non-clinical aspects

Pharmacology

Teclistamab function requires the formation of a trimolecular complex by the binding to CD3 on T-cells and to BCMA on target cells to elicit pharmacologic activity. The pharmacology characterisation of teclistamab demonstrated the bi-specific binding with high nanomolar affinity to BCMA and CD3, and that teclistamab selectively promoted the T-cell dependent elimination of human cells expressing BCMA on their surface *in vitro* and *in vivo*. The T-cell mediated cytotoxic effect on BCMA+ MM cells of teclistamab at nM concentrations, and induction of cytokine secretion was also demonstrated in physiologically relevant conditions *ex vivo* in whole blood.

The dose necessary for near (or full) elimination of tumours (cytotoxic EC90 of 41.29 nM) was estimated (and used to model clinical efficacy dose predictions) based on the *ex vivo* studies on primary CD138+ cells (5 patient samples) co-cultured with healthy donor T-cells, in which teclistamab activated T-cells and induced cytotoxicity with EC50 values of 1.3 and 2.5 nM (EC20, i.e. 20 % of maximal efficient dose values were 0.70 – 1 nM). The cytotoxic effect was appeared selective, but in one patient sample, low cytotoxicity at control bispecific antibody at >67 nM concentration was triggered.

In xenograft mice tumour models, 10 and 50 mg/kg teclistamab doses (when delivered IP every 3 or 4 days for 8 total treatments post human pan T cells implantation) significantly inhibited the tumour growth by the study D60 of 79% - 87%, and by the end of study 9 of 10 animals (dosed with 50 mg/kg of teclistamab) had durable and complete responses. Significant reduction of tumour growth was also noted in another xenograft tumour model (H929 BCMA+) with lower teclistamab doses, *i.e.* 0.025 and 0.05 mg/kg. The elimination of BCMA+ tumour cells seemed occur in wide range of teclistamab doses (0.05 – 50 mg/kg). Nevertheless, these studies provided the proof of concept for *in vivo* functionality for this bi-specific Mab.

IHC data on normal tissues collectively provide evidence that, in nonmalignant cells, BCMA is expressed mostly by plasma cells and subsets of mature B cells, which also supports the data from previously published reports on BCMA expression pattern. The weak signal detected in brain and

adrenal gland appeared to be unspecific staining and does not represent true BCMA expression in these tissues. This is also supported by the information from the literature. Studies by Carpenter (2013) and Bu (2018) found no expression in these tissues outside of resident plasma cells.

BCMA RNA levels have been found to be negligible in normal brain tissues, but BCMA has been reported by Osorio et al. (2014) to have a role in neural development. Based on a recent publication reporting potential BCMA RNA expression in the basal ganglia (Mohyddin 2021), the applicant performed an assessment of BCMA expression in the brain (Marella 2022). According to these analyses, BCMA expression or mRNA was negligible in healthy donor of over 30 years of age brain and tibial nerve samples. Thus, the potential for neurotoxicity related on-target/off-tumour toxicity was concluded unlikely.

Cynomolgus monkey was selected as a pharmacologically relevant species. hBCMA shares >90% sequence homology with cBCMA, and relative target binding affinities and functional activity in cell-based assays of teclistamab supported the use of the cynomolgus monkey in toxicology studies. However, teclistamab binds with 36-fold lower affinity to cBCMA compared to hBCMA and the functional activities such as cytotoxicity and T cell activation were somewhat lower (2-20 fold) in cynomolgus monkeys than in humans. Although the cynomolgus monkey can be considered as a pharmacologically relevant animal species for evaluation of toxicity, results from studies in normal healthy monkeys (in which only very low amounts of BCMA+ cells are present) may have limited translatability to multiple myeloma patients, and the toxicity data should be interpreted with caution.

High levels of soluble BCMA (sBCMA) have been measured in MM patient plasma samples (mean levels of 15.27±4.58 nM), and BCMA ligands APRIL and BAFF, and these ligands could interfere the activity of teclistamab. It was demonstrated that soluble BCMA or BAFF ligand did not affect the binding of teclistamab to BCMA at physiologically relevant concentrations, and is not expected to have an impact on the efficacy of teclistamab. APRIL reduced teclistamab cytotoxicity by 2-fold up to 16.4 nM, and the highest concentration of APRIL tested (48.1 nM) caused around 6-fold reduction of potency (EC50) for both cytotoxicity and T-cell activation. The levels of APRIL in multiple myeloma patients range around 5 nM. Therefore, the activity and clinical efficacy of teclistamab are not anticipated to be affected by the presence of physiological levels of APRIL.

Pharmacokinetics

Teclistamab pharmacokinetics/toxicokineitcs is sufficient and no questions are raised. Serum teclistamab exposure, C_{max} and AUC_{last} values increased with a dose-proportional manner in cynomolgus monkeys. Serum concentrations of teclistamab were adequately maintained throughout the dosing periods in the studies conducted in cynomolgus monkeys, except for approximately 10% of the treated animals, likely due to presence of ADAs.

Formation of ADA was clearly triggered by teclistamab in cynomolgus monkeys. ADAs were detected in most of the teclistamab-treated cynomolgus monkeys (21 out of 30 animals) in pivotal repeated dose toxicology/toxicokinetic study, and ADAs impacted the PK in many of the animals. Residual teclistamab concentrations in some of the ADA samples from ADA-negative animals were above the drug concentration tolerance limit for the ADA assay (100 µg/mL). Therefore, potential interference of ADA detection by residual teclistamab cannot be excluded, and the numbers for ADA positive animals could have been underestimated. Similar to repeated-dose toxicology study, after a single teclistamab dose in cynomolgus monkeys, a fast decrease in teclistamab serum concentrations was noted after Day 15, which was also likely due to ADA development. In repeated dose pivotal toxicology study, of 21 ADA-positive animals, 14 had drug exposure comparable and 7 had lower to that of ADA-negative animals in the same dose groups. Despite the presence of ADAs in most of the animals, 28 out of 30 animals had continuous exposure to teclistamab during the entire study. Of a further note, the immunogenicity in animals towards human proteins is of a limited predictive value for the human immunogenicity.

Overall, mean serum concentrations throughout the studies in monkeys were higher than the EC50 (0.09 to 0.48 µg/mL) for cytotoxicity with cynomolgus monkey T cells against cBCMA-expressing target cells. It could be concluded that monkeys were sufficiently exposed to teclistamab in pivotal study, and the safety margins (at NOEL 30 mg/kg IV weekly dosing) were adequate, i.e. 48 times the C_{max} and 22 times the AUC_{tau} compared to subjects with relapsed/refractory multiple myeloma in Phase 1/2 study MajesTEC-1 (at steady-state exposure at 1.5 mg/kg SC weekly, the recommended weight-based dose regimen).

Toxicology

Teclistamab was well tolerated in cynomolgus monkeys up to highest dose tested, 30 mg/kg, and the teclistamab exposures were sufficient and with adequate exposure multiples (AUC 22-fold) compared to exposures at steady state in Phase 1 (of phase I/II) study in multiple myeloma patients. Nevertheless, there were some limitations in the toxicology studies, including lower (36-fold) affinity of teclistamab to cBCMA compared to hBCMA and 2-20-fold lower functional activity (cytotoxicity, T-cell activation) in cynomolgus monkeys and lack of pharmacologic and toxicologic effects in the cynomolgus monkey serum concentrations higher than the EC50 for T-cell cytotoxicity. These results from studies in normal healthy monkeys (in which only very low amounts of BCMA+ cells are present) may have limited translatability to multiple myeloma patients.

The applicant provided a comprehensive risk assessment for reproduction and developmental toxicity risk based on the weight of evidence to the clinical use of teclistamab. Teclistamab does not bind to rodent CD3 and binds only weakly to rodent BCMA, thus excluding normal rodents as a potential species for development and reproductive toxicology studies. In the 5-week repeat-dose toxicity study in cynomolgus monkeys, there were no notable effects in the male and female reproductive organs at doses up to 30 mg/kg/week (approximately 22 times the maximum recommended human dose, based on AUC exposure) intravenously for five weeks. It was concluded in WoE risk assessment that teclistamab is not expected to pose a risk to reproduction or be teratogenic. It is agreed that no animal studies are needed to address the risk to reproduction, and that the potential risks can be concluded based on the mechanism of action (including on-target/off-tumour toxicity, cytokine release syndrome, and secondary cytokine-mediated effects), which may have an impact on the developing fetus, and in the mother during pregnancy. These are appropriately reflected in the SmPC section 4.6 Fertility, pregnancy and lactation and section 5.3.

3.2.7. Conclusion on the non-clinical aspects

From a non-clinical point of view Tecvayli (teclistamab) has been adequately characterised and is recommended for marketing authorisation.

3.3. Clinical aspects

3.3.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Type					
Study ID EudraCT Number First Patient First Visit / Completion date (day Month year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated[a] (by Treatment Group)
64007957MMY1001 (MajesTEC-1) Synopsis 2016-002122-36 08 June 2017 Not applicable Ongoing	Belgium, Canada, France, Germany, Italy, Netherlands, Spain, Sweden, the United Kingdom, and the United States: 39	Phase 1/2 Open-label, single-arm, multicenter study Men or women ≥18 years of age with relapsed/refractory multiple myeloma 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	Enrolled: 340 Phase 1 (Dose Escalation/Dose Expansion): 177 subjects[b] Phase 2 Cohort A: 125 subjects Cohort C: 38 subjects	teclistamab SC or teclistamab IV Part 1 (Dose Escalation): *Up to proposed RP2Ds:* Q2W or weekly therapy with either teclistamab IV (treatment doses of 0.0003 to 0.0192 mg/kg Q2W and 0.0192 to 0.72 mg/kg weekly) or teclistamab SC (treatment doses of 0.08 to 1.5 mg/kg weekly). *Higher than RP2D:* 3 mg/kg weekly, other dosing schedules with treatment doses of 6 mg/kg, and flat dose Part 2 (Dose Expansion): treatment doses expanded to 0.72 mg/kg teclistamab IV weekly and 1.5 mg/kg teclistamab SC weekly Part 3 (Phase 2): 1.5 mg/kg teclistamab SC weekly Until disease progression, unacceptable toxicity, withdrawal of consent, death, or end of study (defined as 2 years after the last subject's first dose)	**All Treated Analysis Sets:** Pivotal RP2D: 165 subjects Phase 1 (Dose Escalation/Dose Expansion): 177 subjects Cohort C (Prior Anti-BCMA Therapy Exposure): 38 subjects **Efficacy Analysis Sets:** Pivotal RP2D: 150 subjects Phase 1: 156 subjects Cohort C: 25 subjects

3.3.2. Clinical pharmacology

Pharmacokinetics

The PK data in this submission consisted of interim results from, study 64007957MMY1001 (referred thereafter as stud MMY1001 in this report), which was a first-in-human (FIH), Phase 1/2, open-label, multi-center dose escalation study with dose expansion to identify the recommended phase 2 dose (RP2D) and to evaluate the safety, tolerability, pharmacokinetics, and preliminary antitumour activity of teclistamab administered to adult subjects with relapsed or refractory multiple myeloma.

The Phase 1 part of the study comprised of a dose escalation (Part 1) and a dose expansion (Part 2). The Phase 2 (Part 3 of the study) had sparse PK sampling and consisted of Cohorts A and C. Cohort A included approximately 100 subjects with multiple myeloma who were triple class exposed (PI, IMiD, and anti-CD38 mAb) and have previously received treatment with ≥3 prior lines of therapy. Cohort C included approximately 38 subjects who have previously received ≥3 prior lines of therapy that included a PI, an IMiD, an anti-CD38mAb and an anti-BCMA treatment (with CAR-T or an ADC).

Study MMY1001 non-compartmental PK results, RP2D

In Phase 1, a total of 40 subjects were treated at RP2D and had evaluable teclistamab PK data. PK parameters for these subjects were estimated using non-compartmental analysis. The PK parameters are summarised in **Table 8**.

Table 8. Pharmacokinetic Parameters of Teclistamab Following the First Treatment Dose of 1.5 mg/kg SC in Cycle 1 and Cycle 3 in Subjects with Multiple Myeloma; Pharmacokinetics Analysis Set (Study MMY1001, Pivotal RP2D [Phase 1 Only])

Pharmacokinetics of Teclistamab	60.0/300 then 1500 µg/kg SC, QW (Part 1 + Part 2) mean (SD); T_{max}: median (range)
Pharmacokinetic Analysis Set	40
Cycle 1 Day 1	
n	40[a]
C_{max}, µg/mL	8.74 (3.65)
T_{max}, h,	72.02 (45.83; 192.73)[b]
AUC_{tau}, h·µg/mL	1169 (481)
AUC_{last}, h·µg/mL	1133 (495)
Cycle 1 Day 8	
n	38
C_{trough}, µg/mL	7.67 (3.52)
Cycle 3 Day 1	
n	15[c]
C_{max}, µg/mL	25.3 (11.1)
T_{max}, h	48.88 (0.00; 165.52)
AUC_{tau}, h·µg/mL	3905 (1748)
AUC_{last}, h·µg/mL	3540 (1886)
CL/F, L/h	0.0345 (0.0181)
AR_{Cmax}	2.71 (1.02)
AR_{AUCtau}	3.05 (1.24)
Cycle 3 Day 8	
n	27
C_{trough}, µg/mL	22.1 (10.9)

AR_{Cmax}= accumulation ratio of C_{max} (ie, $C_{max, cycle 3}$/ $C_{max, cycle 1}$); AR_{AUCtau}= accumulation ratio of AUC_{tau} (ie, $AUC_{tau, cycle 3}$/ $AUC_{tau, cycle 1}$); AUC_{tau}=area under the concentration-time curve during a dosing interval; AUC_{last}=area under the concentration-time curve from time zero to last measurable concentration; C_{max}=maximum observed serum concentration; C_{trough}=observed predose serum concentration; CL/F=total apparent clearance; T_{max}=time to reach the C_{max}.
[a] n=38 for AUC_{tau}.

[b] One subject received Cycle 1 Day 8 dose on Cycle 1 Day 9 (ie, 192.73 hours).
[c] n=13 for AUC_{tau}, CL/F and AR_{AUCtau}.

The AR_{Cmax} was defined as $C_{max, cycle 3}$/ $C_{max, cycle 1}$, and $AR AUC_{tau}$ was defined as $AUC_{tau, cycle 3}$/ $AUC_{tau, cycle 1}$.

PK steady-state was attained in Cycle 3 following the RP2D. Following the treatment dose of teclistamab at RP2D (Phase 1 and Cohort A), mean Ctrough was maintained above the maximum EC90 value identified in the ex vivo cytotoxicity assay.

Population PK model

The population pharmacokinetic analysis used serum teclistamab concentration data from Phase 1/2 Study MMY1001 Part 1 (Phase 1 dose escalation), Part 2 (Phase 1 dose expansion), and Part 3 (Phase 2 dose expansion) with the pharmacokinetics data cutoff on 1st of December 2021.

A total of 4840 measurable serum teclistamab concentration records from 338 subjects with relapsed or refractory multiple myeloma who received at least 1 teclistamab dose were used for the nonlinear

mixed-effects modeling. This included 83 subjects who received teclistamab IV administration and 255 subjects who received SC administration.

The observed concentration-time data of teclistamab were described by a 2-compartment model with first-order absorption and parallel time-independent (representing the nonspecific clearance for IgG) and time-dependent (representing changes in capacity of the target-mediated clearance) elimination pathways. The model was parameterised in terms of time-independent clearance (CL_1), time-dependent clearance (CL_t), volume of distribution of the central compartment (V_1), inter-compartmental clearance (Q), volume of distribution of the peripheral compartment (V_2), first-order absorption rate constant (Ka), and SC bioavailability (F).

The covariates assessed in the population pharmacokinetic analysis included demographic characteristics (body weight, age, sex, race, region, ethnicity [Hispanic vs non-Hispanic; Asian vs non-Asian]), disease characteristics and biomarkers (baseline total T cells, baseline soluble BCMA and soluble BCMA over time, baseline bone marrow percent plasma cells, baseline plasmacytoma, baseline type of myeloma, baseline lesion number, baseline lytic lesion, baseline Eastern Cooperative Oncology Group [ECOG] status, baseline International Staging System [ISS] staging, baseline revised ISS staging, cytogenetic risk), clinical laboratory characteristics (baseline creatinine clearance, baseline albumin, baseline alanine aminotransferase, baseline alkaline phosphatase, renal function, hepatic function), prior treatment and refractory status (prior use of anti-CD38 antibodies, prior use of daratumumab, prior use of anti-programmed cell death protein 1 [PD1]/anti-programmed death-ligand 1 [PD-L1], prior use of anti-BCMA treatment, triple refractory status, penta refractory status, number of prior lines of therapies [≤3 vs >3]), antibodies to teclistamab status, and drug product.

After the covariate selection procedure, the covariate effects retained in the final model were the effect of body weight on CL_1, V_1, and V_2, the effects of ISS staging on CL_1, and the effect of type of myeloma (IgG vs non-IgG) on CL_1 and CL_2. Other covariates tested were not statistically significant.

The parameters of the final population pharmacokinetic model are summarised in **Table 9**.

Table 9. Parameter Estimates of Teclistamab for the Final Population Pharmacokinetic Model

Parameters, unit	Estimate	RSE (%)	IIV (%CV)	RSE (%)	Shrinkage (%)
CL$_1$ (L/day)[a]	0.449	8.87	53.6	14.3	14.4
BWT on CL$_1$	0.704	21.8			
IISS=II on CL$_1$	1.31	7.83			
IISS=III on CL$_1$	1.67	11.1			
TPMM2=Non-IgG on CL$_1$	0.689	7.76			
CL$_2$ (L/day)[b]	0.547	15.6	107	20.5	33.8
TPMM2=Non-IgG on CL$_2$	0.295	21.6			
V$_1$ (L)[c]	4.13	4.40	48.8	50.6	29.5
BWT on V$_1$	0.358	60.9			
K$_{DES}$ (day^{-1})	0.0292	13.0			
Q (L/day)	0.0390	55.5			
V$_2$ (L)[d]	1.34	26.1			
BWT on V$_2$	1.40	25.5			
Ka (day^{-1})	0.133	7.73	45.2	32.1	44.3
F	0.718	7.38			
ADD ERR (%CV)	41.7	4.35			

ADD ERR=additive error term on the log-scale; BWT=baseline body weight in kilograms; CL$_1$=time-independent clearance; CL$_2$=clearance associated with time-dependent clearance (CL$_t$), which decreases over time through a first-order rate (K$_{DES}$); CV=coefficient of variation; F=subcutaneous bioavailability; IgG=immunoglobulin G; IISS=International Staging System (1=I, 2=II, 3=III); IIV=inter-individual variability; calculated as (variance)$^{1/2}$×100%; Ka=first-order absorption rate constant; K$_{DES}$=first-order rate constant for CL$_2$ decrease over time; Q=inter-compartmental clearance; RSE=relative standard error; TPMM2=multiple myeloma type (0=Non-IgG,1=IgG); V$_1$=volume of distribution of the central compartment; V$_2$=volume of distribution of the peripheral compartment.

[a] $CL_1(L/day) = 0.449 \times \left(\frac{BWT}{74}\right)^{0.704} \times 1.31^{ISS=II} \times 1.67^{ISS=III} \times 0.689^{TPMM=Non-IgG}$

[b] $CL_2(L/day) = 0.547 \times 0.295^{TPMM=Non-IgG}$
$CL = CL_1 + CL_2 \times e^{-0.0292 \times Time(in\ days)}$

[c] $V_1(L) = 4.13 \times \left(\frac{BWT}{74}\right)^{0.358}$

[d] $V_2(L) = 1.34 \times \left(\frac{BWT}{74}\right)^{1.40}$

To compare the effects of covariates on exposure to teclistamab for the subjects in study MMY1001, subgroup analyses were conducted on predicted exposure metrics based on the individual pharmacokinetic parameters from the final population pharmacokinetic model following the teclistamab RP2D, ie, 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg.

The model-predicted individual pharmacokinetic exposure metrics, predicted average concentration of the first treatment dose (C$_{ave,1stdose}$) and predicted steady-state trough concentration (C$_{trough,ss}$) at the RP2D, were compared across different strata for covariates of interest. No clinically meaningful differences (i.e., <20-30%) in the exposure to teclistamab were observed in subjects with different body weight when teclistamab was administered on the weight proportional dosing regimen. Exposure of teclistamab largely overlapped across body weight subgroups.

The disease status variables including multiple myeloma type (IgG vs non-IgG) and ISS staging (II vs I and III vs I) affected teclistamab exposure. The simulated C$_{ave,1stdose}$ and C$_{trough,ss}$ were approximately 33% and 47% lower in subjects with IgG type of multiple myeloma, respectively, compared with those with non- IgG type of multiple myeloma. The simulated C$_{ave,1stdose}$ and C$_{trough,ss}$ were approximately 15% and 31% lower in subjects with ISS stage II, respectively, compared with those with ISS stage I. The simulated C$_{ave,1stdose}$ and C$_{trough,ss}$ were approximately 28% and 43% lower in subjects with ISS stage III, respectively, compared with those with ISS stage I. The applicant states that further clinical

efficacy subgroup analyses and E-R analyses demonstrated that these covariates had no clinically relevant effect on efficacy at the recommended dose regimen.

Absorption

Following teclistamab SC administration, the typical value of Ka was approximately 0.133 day^{-1} based on population pharmacokinetic evaluation. The observed individual Tmax occurred 2 to 7 days after the SC administration of teclistamab on Cycle 1 Day 1. Both noncompartmental and population PK analyses estimate an SC bioavailability of approximately 70%. The noncompartmental SC bioavailability value should be interpreted with caution, as it is not based on individual results and combines the results of multiple cohorts.

Distribution

Typical IgG-4 mAbs are primarily confined in the vascular system. The population PK model-estimated typical volume of distribution for the central compartment was 4.13 L (**Table 9**). Volume of distribution increased with body weight. The typical peripheral volume was estimated to be 1.34 L.

Elimination

As an IgG-4 mAb, teclistamab is presumably biotransformed in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and undergoes similar elimination.

In a population PK model, the elimination of teclistamab was described by parallel CL_1 and time-dependent clearance ($CL_t=CL_2*exp(-K_{DES}\cdot Time)$). The CL_1 component is thought to reflect the endogenous catabolic processes of IgG degradation. The CL_t component corresponds to the decrease in drug clearance as disease status improves over time post treatment, which may be related to tumour burden or target amount. The model estimated typical CL_1 and CL_2 were 0.449 L/day and 0.547 L/day, and K_{DES} was 0.0328 day^{-1}.

Dose proportionality and time dependencies

Following teclistamab IV dosing, exposure (C_{max} and AUC) increased approximately dose-proportionally across the dose range of 0.0192 to 0.72 mg/kg, both after the first dose and after repeated dosing. Following teclistamab SC dosing, exposure increased in an approximately dose-proportional manner across the dose range of 0.08 to 6 mg/kg after the first dose, and across the dose range of 0.08 to 3 mg/kg after repeated dosing.

Special populations

The effect of renal impairment as defined using the Modification of Diet in Renal Disease formula (normal [n=90, 29.2%], mild [n=141, 45.8%], moderate [n=76, 24.7%], and severe [n=1, 0.3%]) was evaluated in population pharmacokinetic analysis and was not identified as significant covariate on teclistamab pharmacokinetics. Also, mild hepatic impairment (n=34, 11%) was not identified as a significant covariate on teclistamab PK.

No effect of gender, race or age on teclistamab PK was identified in the population PK analysis.

The number of elderly subjects for whom PK data were available is shown in **Table 10.**

Table 10. Number of older subjects for whom PK data are available (Dec 2021 data cutoff)

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	117/338	41/338	0/338

Body weight effect on teclistamab pharmacokinetics was evaluated and the final population pharmacokinetic model included body weight as covariates on the clearance and volume of distribution parameters. The effect of bodyweight on teclistamab PK is taken into account via the use of mg/kg dosing.

in addition to the effects of bodyweight on PK, the population PK analysis found that the type of multiple myeloma (IgG vs non-IgG) and International Staging System score were predictors of teclistamab clearance. The simulated $C_{ave,1stdose}$ and $C_{trough,ss}$ were approximately 28% and 43% lower in subjects with ISS stage III, respectively, compared with those with ISS stage I. Moreover, the simulated $C_{ave,1stdose}$ and $C_{trough,ss}$ were approximately 33% and 47% lower in subjects with IgG type of multiple myeloma, respectively, compared with those with non- IgG type of multiple myeloma.

Pharmacokinetic interaction studies

No clinical studies examining the interaction between teclistamab and other products have been conducted. Teclistamab is not metabolised via CYP enzymes and is not expected to directly affect the CYP enzymes.

Pharmacodynamics

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 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 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 MHC Class 1 molecules on the surface of antigen presenting cells for activation, leading to cell death of the BCMA+ cells.

Primary and Secondary pharmacology

Phase 1

Soluble BCMA

Following teclistamab IV or SC administration in the Phase 1 study, majority of responders had a decrease in sBCMA on Cycle 4 Day 1 (54 of 69 subjects [78.3%]), and a majority of non-responders had an increase in sBCMA on Cycle 4 Day 1 (10 of 16 subjects [62.5%]) compared with baseline values. Additionally, a greater reduction in sBCMA was observed in subjects with deeper responses to teclistamab (**Figure 1**).

Figure 1. Percent sBCMA Change from Baseline on Cycle 4 Day 1 by Best Response as Assessed by Investigator; PK Evaluable Analysis Set in the Efficacy Analysis Set (Phase 1)
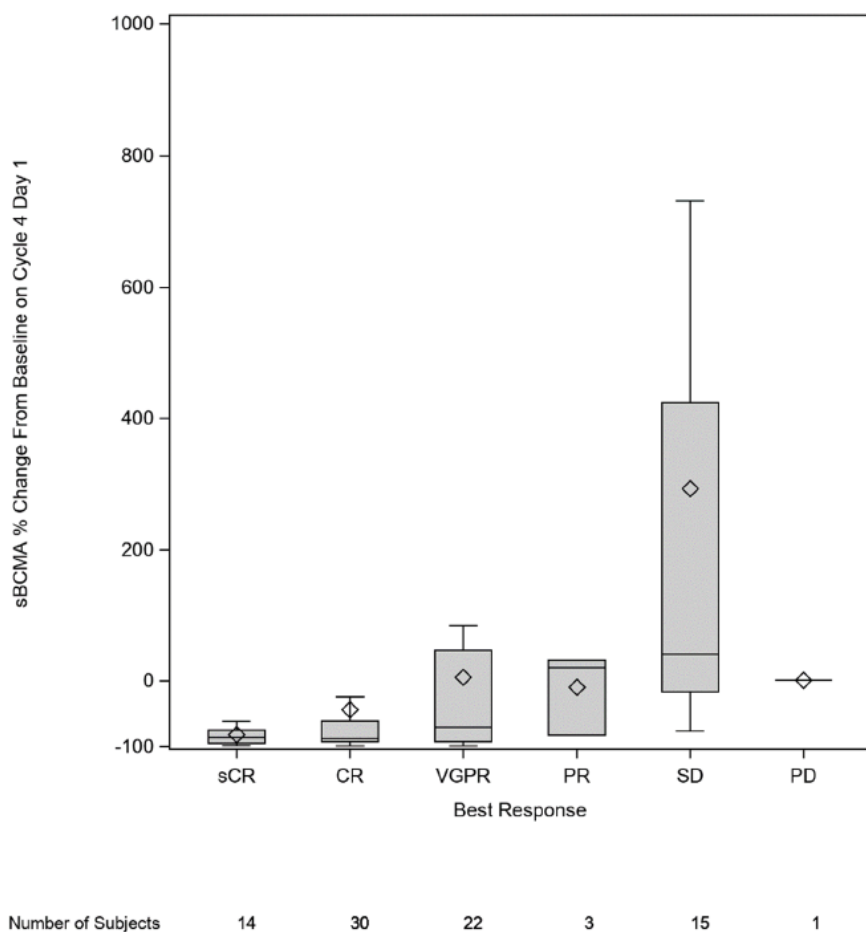
Key: sCR=stringent complete response; CR=complete response; VGPR=very good partial response; PR=partial response; SD=stable disease; PD=progressive disease; sBCMA=soluble B Cell Maturation Antigen

Adverse Events of Clinical Interest and Teclistamab Concentration

To investigate the potential correlation between CRS and teclistamab PK exposure or incidence of antibodies to teclistamab, serum samples were collected at a CRS event of Grade ≥2 (at onset, then 24 and 48 hours after [72 hours instead of 48 hours for the initial IV cohorts before Protocol Amendment 5]) in Phase 1, if feasible.

Teclistamab concentrations ranged from 0.0676 to 7.79 µg/mL on or within 48 hours from the onset of CRS events (including step-up and treatment doses). Based on the available data, it seems that there was no clear correlation between the presence or grade of CRS and teclistamab concentration. No serum sample collected during a CRS event was identified to be positive for antibodies to teclistamab, indicating a lack of correlation between CRS and immunogenicity.

Serum samples were also collected at a sARR event of Grade ≥2 (at onset, then 24 and 48 hours after [72 hours instead of 48 hours for the initial IV cohorts before Protocol Amendment 5]) in Phase 1, if feasible. PK data were available from 3 of 5 subjects who experienced sARR, with teclistamab concentrations ranging from 0.105 to 2.02 µg/mL. No serum sample collected during a sARR event was identified to be positive for antibodies to teclistamab in these subjects.

Pivotal RP2D

<u>Soluble BCMA</u>

Following teclistamab at RP2D, a rapid decrease in sBCMA was observed in the majority of the responders (PR or better) within the first month of treatment. A majority of responders had a decrease in sBCMA on Cycle 2 Day 1 (40 of 59 subjects [67.8%]), and a majority of non-responders had an increase in sBCMA on Cycle 2 Day 1 (27 of 28 subjects [96.4%]) compared with baseline values (Attachment TPKCONC03ARP2D). Responders to teclistamab also showed a trend of sBCMA reduction over time.

On Cycle 4 Day 1, a majority of responders had a decrease in sBCMA (63 of 72 subjects [87.5%]), and all non-responders had an increase in sBCMA (9 of9 subjects [100%]; fewer non-responders provided data on Cycle 4 Day 1 due to early treatment discontinuation). In addition, a greater reduction in sBCMA was observed in subjects with deeper responses to teclistamab (**Figure 2**).

Figure 2. Percent sBCMA Change from Baseline on Cycle 4 Day 1 by Best Response as Assessed by IRC; Pharmacokinetics Evaluable Analysis Set in the Efficacy Analysis Set (Pivotal RP2D)
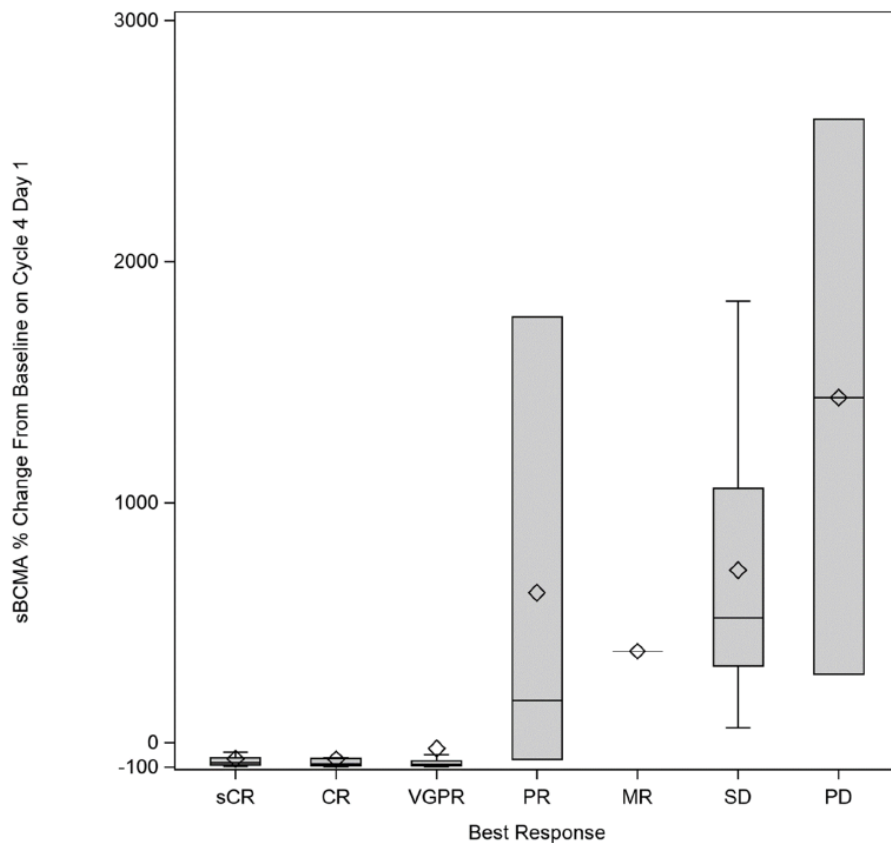
Key: RP2D=recommended Phase 2 dose; sCR=stringent complete response; CR=complete response; VGPR=very good partial response; PR=partial response; MR= minimal response; SD=stable disease; PD=progressive disease; sBCMA=Soluble B Cell Maturation Antigen

<u>Adverse Events of Clinical Interest and Teclistamab Concentration</u>

Based on the available data, it seems that there was no clear correlation between the presence or grade of CRS and teclistamab concentration. No serum sample collected during a CRS event was

identified to be positive for antibodies to teclistamab, indicating a lack of correlation between CRS and immunogenicity.

Teclistamab concentrations ranged from 0.0549 to 7.58 µg/mL on or within 48 hours from the onset of CRS events (including step-up and treatment doses). This information can be useful also to have information on the range of concentrations at which the CRS can occur, often below the serum concentrations leading to a response.

T Cell Redistribution

T cell redistribution was observed in patients treated at the pivotal RP2D, as demonstrated by reduction in peripheral CD4+ and CD8+ T cells after the initial doses of teclistamab.

Although the T-cell redistribution is observed at RP2D, a return to baseline value seems to be observed.

B Cell Reduction

Reduction of CD19+ B cells was observed in subjects treated at pivotal RP2D within the first cycle. Persistently decreased levels were noted at Cycle 3 (**Figure 3**).

Figure 3. B-cell reduction over time, Study MMY1001
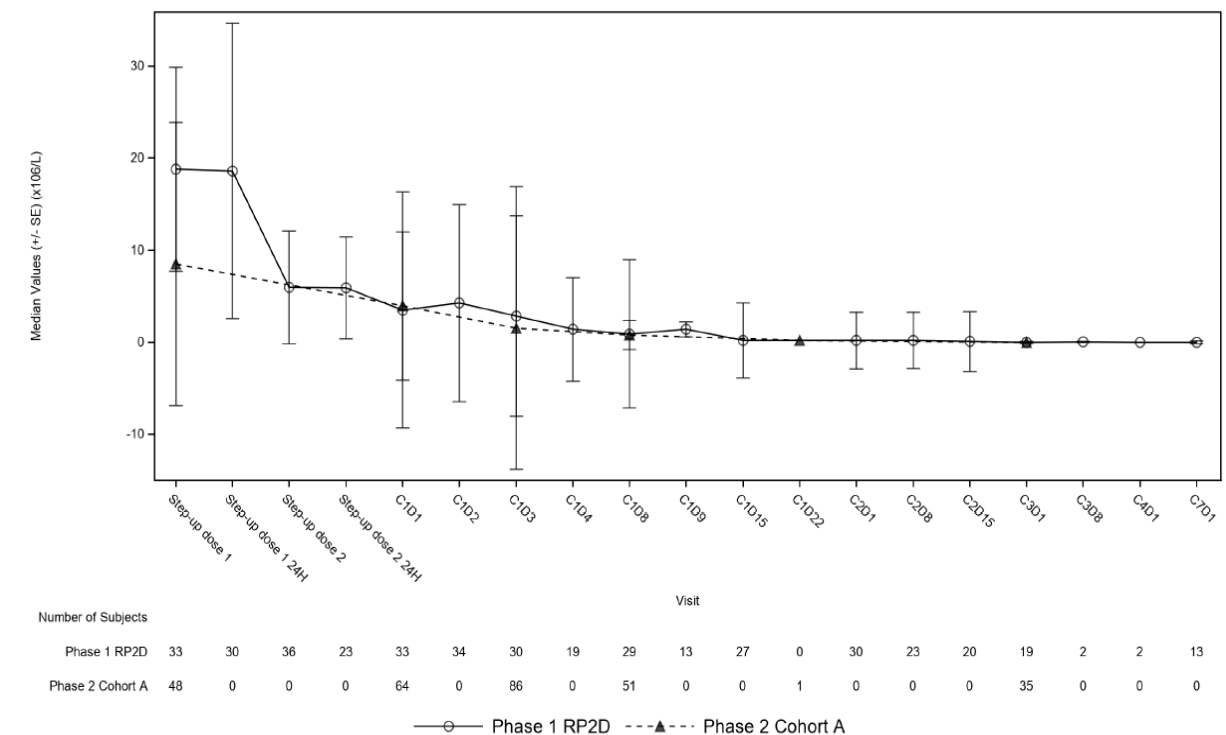
Clinical Pharmacodynamics

Subjects who received teclistamab SC starting at 0.24 mg/kg dose level demonstrated consistent pharmacodynamic changes indicative of the proposed mechanism of action, including T-cell activation, induction of cytokines, and T-cell redistribution. Optimal pharmacodynamic changes were observed in subjects who received 1.5 mg/kg SC. Greater induction of T-cell activation markers such as PD1, CD38, LAG-3, TIM-3, and HLA-DR was seen for subjects treated at 1.5 mg/kg doses level compared with the increases observed for subjects treated at 0.72 mg/kg SC dose level.

Markers for T-cell activation did not increase consistently with further increases in dose. Consistent increases in cytokines such as IL-10, IL-2Rα, and IL-6 were observed for subjects treated at the 1.5 mg/kg SC dose level. Optimal activation of cytokines was observed at 1.5 mg/kg as evidenced by consistently high median values for maximum fold change of cytokines when compared with other dose levels evaluated.

Exposure-response model

The objectives of the exposure-response (E-R) analyses of teclistamab were to explore the E-R relationship for selected efficacy endpoints, focusing on the primary endpoint of overall response rate (ORR) and other efficacy endpoints, including duration of response (DOR), progression-free survival (PFS), and overall survival (OS), in subjects who received teclistamab SC. A further objective was to explore the E-R relationship for selected adverse events (AEs), including Grade ≥3 anaemia, neutropenia, lymphopenia, thrombocytopenia, and infection, in subjects who received teclistamab SC.

Various model-derived exposure metrics based on actual dose schedule information were estimated and used to investigate the relationship between teclistamab exposure and the selected efficacy and safety endpoints. The exposure metrics for efficacy E-R analyses included the predicted average concentration of the first treatment dose ($C_{ave,1stdose}$) and the predicted trough concentration after the first 4 weekly treatment doses ($C_{trough,4doses}$). The exposure metrics for safety E-R analyses included the predicted maximum concentration following the first treatment dose ($C_{max,1stdose}$) and the first 4 weekly treatment doses ($C_{max,4doses}$). These metrics were selected to maximise the number of subjects included in the analyses, and to avoid potential bias caused by exclusion of non-responder subjects with early discontinuation and potential confounded E-R relationships due to time-varying clearance as a result of disease status improvement following treatment.

The populations included for different efficacy and E-R analyses are listed in **Table 11**.

Table 11. Datasets for E-R Efficacy and Safety Analyses

E-R Analyses	Population
RP2D ORR, DOR, PFS, OS	RP2D cohorts in Part 1 and Part 2, and Part 3 Cohort A, treated on or before 18 March 2021 (N=150: 40 from Part 1 and Part 2; 110 from Part 3)
Pooled OS	SC cohorts in Part 1 and Part 2, and Part 3 Cohort A, treated on or before 18 March 2021 (N=182: 72 from Part 1 and Part 2; 110 from Part 3)
Phase 1 ORR	SC cohorts in Part 1 and Part 2, treated on or before 18 March 2021 (N=72: 28 in <RP2D; 40 in RP2D; 4 in >RP2D cohorts)
Safety: Grade ≥3 hematologic TEAEs and infections	SC cohorts in Part 1 and Part 2, and Part 3 Cohort A, treated before the clinical cutoff (07 September 2021) (N=199: 79 from Part 1 and Part 2; 120 from Part 3)

DOR=duration of response; E-R=exposure-response; N=total number of subjects with data; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; RP2D=recommended Phase 2 dose, which is 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; SC=subcutaneous; TEAE=treatment-emergent adverse event.
Note: E-R analyses focuses on SC cohorts and subjects included in the population pharmacokinetic analysis with estimable exposure metrics.

Exposure-efficacy results

For pivotal RP2D efficacy data, the primary analysis population included 150 subjects at the RP2D in the Efficacy Analysis Set. The primary endpoint for the pivotal efficacy analysis of RP2D was ORR. The E-R relationships between the selected exposure metrics and other efficacy endpoints, ie, PFS, DOR, and OS were also explored in these subjects (ie, RP2D only).

Near flat E-R relationship was observed between the RP2D ORR and $C_{ave,1stdose}$ and $C_{trough,4doses}$. For RP2D ORR, responders and non-responders had comparable $C_{ave,1stdose}$ exposures. Teclistamab $C_{trough,4doses}$ for responders and non-responders overlapped in their interquartile ranges (bottom panel). Overall, these results suggest no apparent associations between teclistamab exposure and the ORR in RP2D subjects, given that the exposure are comparable between responders and non-responders.

The Kaplan-Meier plots for DOR, PFS, and OS in the pivotal RP2D subjects showed overlapping confidence intervals and no statistically significant relationship with either $C_{ave,1stdose}$ or $C_{trough,4doses}$. In addition, the Cox proportional hazard regression of DOR, PFS, and OS vs exposure also resulted in 95% confidence intervals containing 1, indicating no significant difference in these efficacy endpoints across the exposure tertile groups.

As supporting analysis, since the ORR was assessed by the investigator (International Myeloma Working Group 2011 criteria) in Phase 1, E-R relationship in Phase 1 subjects receiving teclistamab SC dosing (n=72; 28 in <RP2D, 40 in RP2D, and 4 in >RP2D cohorts) between ORR and $C_{ave,1stdose}$ and $C_{trough,4doses}$ were explored. Positive E-R relationship was observed, and the response at the concentration range associated with RP2D is approaching the ORR plateau (or maximum response).

Exposure-safety results

All subjects who received teclistamab SC treatment in Part 1, Part 2, and Part 3 Cohort A were included in the exposure-safety analyses.

Part 1 and Part 2 subjects who received SC doses and Part 3 Cohort A subjects were included for the exposure-safety analyses (N=199; 28 in <RP2D, 160 in RP2D, and 11 in >RP2D cohorts). The E-R relationships for the safety endpoints including Grade ≥3 TEAEs of neutropenia, lymphopenia, thrombocytopenia, and infections showed no apparent increase in the AE occurrence rates with increasing exposure ($C_{max,1stdose}$ and $C_{max,4doses}$) quartile groups. A slight decrease in rate of Grade ≥3 anemia with increasing exposure was observed, and this apparent relationship is likely confounded by the fact that subjects with more severe disease such as ISS staging II or III have a higher rate of Grade ≥3 anemia, while at the same time have lower teclistamab exposure compared with ISS staging I. Consistently, teclistamab exposures were overall comparable between subjects with or without these TEAEs, indicating no apparent E-R trend.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

The PK data contained in this MAA submission consisted of interim results from one phase 1/2 study, MMY1001.

The PK analyses consisted of noncompartmental analyses and population PK modelling.

The PK data showed that mean Ctrough were comparable between Cycle 3, Cycle 4, and subsequent cycles following the RP2D. The mean Ctrough was maintained above the maximum EC90 value following the treatment dose of teclistamab at RP2D in Phase 1 and Cohort A of Phase 2. The population PK analysis features a two-compartment model with both time-varying and time-independent clearance components, both of which are linear. The time-dependent change in clearance (decreased clearance over time) may be caused by a decrease in target concentrations over time as the treatment progresses, or by a general improvement in patients' physical condition as the treatment progresses. Even though the time-dependent change in clearance may be caused by a change in target concentrations, changes in soluble BCMA concentrations over time were not found to correlate with

changes in clearance over time. Grade or presence of cytokine release syndrome did not correlate with change in clearance, and therefore it is unlikely that time-dependent changes in clearance would be caused by inflammation mediated by cytokine release at the start of treatment.

The non-compartmental plots of dose-normalised exposure as a function dose suggest linear PK. The population PK model features linear PK. Teclistamab displays time-dependent PK.

The population PK model had a fairly strict criterion of p<0.001 for the inclusion of covariate effects. As such, it is expected that only the most obvious covariates were captured within the model. No effect of gender, race or age on teclistamab PK was identified in the population PK analysis. The SmPC information regarding these covariates is considered sufficient.

In accordance with Scientific Advice received from the CHMP the applicant did not conduct renal and hepatic impairment studies. Results of the population pharmacokinetic analyses indicate that mild renal impairment (60 mL/min/1.73 m2 ≤ estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m2) or moderate renal impairment (30 mL/min/1.73 m2 ≤ eGFR <60 mL/min/1.73 m2) did not significantly influence the pharmacokinetics of teclistamab. Limited data are available from patients with severe renal impairment.

Results of population pharmacokinetic analyses indicate that mild hepatic impairment (total bilirubin >1 to 1.5 times upper limit of normal (ULN) and any aspartate aminotransferase (AST), or total bilirubin ≤ULN and AST>ULN) did not significantly influence the pharmacokinetics of teclistamab. No data are available in patients with moderate and severe hepatic impairment.

No pharmacokinetic interaction studies have been conducted, which is in line with the received Scientific Advice. As had been advised, the applicant has included a warning in Section 4.5 of the SmPC that the initial release of cytokines associated with the start of TECVAYLI treatment could suppress CYP450 enzymes and that the highest risk of interaction is expected to be from initiation of teclistamab step-up schedule up to 7 days after the first treatment dose or during a CRS event. During this time period, medicinal product concentrations (e.g., cyclosporine) should be monitored in patients who are receiving concomitant CYP450 substrates with a narrow therapeutic index. The dose of the concomitant medicinal product should be adjusted as needed.

Because grade or presence of cytokine release syndrome did not correlate with change in teclistamab clearance, it is also unlikely that cytokine release at the start of treatment would affect the PK of other monoclonal antibodies to a significant extent.

Pharmacodynamics

Dose-proportional increases were observed in concentrations of various soluble factors and cytokines. Many soluble factors and cytokines reported in literature to correlate with CRS and neurotoxicity, were highly induced within 24 hours after teclistamab treatment and significantly associated with CRS. Early post-infusion, IL-10, IFN-γ, TNF-α, or IL-6 concentrations were increased and a trend was also observed for higher induction of CD38, TIM-3, or LAG-3 on CD4+T cells among subjects with a higher grade of CRS. However, and no marker that could be used to identify patients at high risk of these events was identified. Moreover, for the majority of subjects, the highest cytokine levels induced by teclistamab treatment did not correspond to the exact timing of occurrence of the CRS event.

Soluble BCMA is a peripherally accessible biomarker of myeloma disease burden that correlates with the total number of normal and malignant plasma cells. Thus, declining concentrations in responders, and stable / elevated concentrations in non-responders are expected. However, the data available is insufficient to inform whether baseline level of sBCMA could predict the efficacy of treatment with

teclistamab. To address this issue, the applicant should further investigate the impact of sBCMA on teclistamab PK, PD and efficacy in the ongoing/planned phase III studies.

The applicant justifies the selected dose for RP2D by stating that "optimal pharmacodynamic changes and optimal activation of cytokines were observed and in subjects who received 1.5 mg/kg SC". This assumption is partially supported by data showing increases in cytokines such as IL-2Rα, and IL-6 (no data provided for IL-10) at the 1.5 mg/kg SC dose level.

The pharmacodynamics markers seem to describe the anti-tumour activity of teclistamab, but do not provide tools to guide patient selection, identification of high-risk patients in terms of toxicities, or clinically relevant new tools for monitoring treatment.

Exposure-response model

The exposure-efficacy and exposure-safety analyses conclude a lack relationship between exposure and efficacy/safety at the RP2D. However, an exposure-efficacy relationship was observed in study MMY1001 Part 1 data. This is unsurprising, since the Part 1 of the study included very low doses, which consequently were associated with low response rates. The applicant concludes that the RP2D, the dose for which indication is being sought, lies in the flat part of the observed exposure-response-safety curve. While the model suggests that the exposure-response profile is flat, it is important to point out that the PK model predicts that ISS stage II and III patients will have lower exposures than ISS stage I patients. At the same time, a trend of higher ISS stage and lower efficacy can be observed. In other words, potential trends are present of lower exposures correlating with lower response probability, even though these trends did not reach statistical significance within the exposure-response model.

The chosen exposure metrics reflect the PK at the start of treatment, and do not necessarily reflect the PK as the treatment progresses. The applicant argued that time-dependent changes in clearance may be caused by the response, and therefore the traditional assumption that exposure affects response does not necessarily hold; response may affect exposure. Therefore, the applicant argued that in order to avoid confounding, the exposure metrics used in the exposure-response analysis should reflect exposures at the start of treatment. This reasoning is understood. However, it is also known that for immune checkpoint inhibitors, which often contain time-dependent clearance, the magnitude of change in time-dependent clearance is correlated with probability of response. Since teclistamab PK also contains time-dependent clearance, the applicant was requested for additional analyses, where the magnitude of clearance decrease is used as a predictor of response probability and as a predictor of AE probability. In response, the applicant provided graphical analyses of %change in clearance versus response type, and %change in clearance versus AE frequency. There appeared to be a correlation between %change in clearance and response, with responders having a higher decrease in clearance. In this case, it seems likely that the response causes a decrease in clearance, and it seems unlikely that the decrease in clearance (and consequent increase in exposure) would cause the response. No graphical trends were apparent in plots of %change in clearance versus AE frequency.

3.3.1. Conclusions on clinical pharmacology

The applicant has adequately characterised the pharmacokinetic and pharmacodynamic properties of teclistamab which therefore can be recommended for (conditional) marketing authorisation.

The CHMP considers the following measures necessary to address the missing pharmacology data:

- The applicant should further investigate the impact of sBCMA on teclistamab PK, PD and efficacy in the ongoing/planned phase III studies.

3.3.2. Clinical efficacy

Dose response study

Dose response was evaluated as a part of the pivotal phase 1/2, open-label, multi-centre, study 64007957MMY1001 (MajesTEC-1).

Selection of RP2D

The registrational treatment dose of teclistamab monotherapy (1.5 mg/kg SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg) was selected based on the PK, pharmacodynamic, safety, and efficacy data available from Phase 1 dose escalation. Phase 2 further established 1.5 mg/kg SC weekly as a safe and effective dose for the treatment of relapsed or refractory MM. The data presented in this section were collected through the clinical cut-off for this primary analysis.

Target Exposure Based on Modelling (please also refer to PK section).

During dose escalation, PK modelling and simulation were performed to predict a dose of teclistamab SC that would provide trough levels comparable to or higher than the maximum EC90 values identified in an *ex vivo* cytotoxicity assay. This assay assessed the ability of teclistamab to induce killing using mononuclear cells from bone marrow samples from patients with multiple myeloma in coculture with T cells from healthy donors. PK results showed that mean trough levels following the first 1.5 mg/kg SC dose were comparable with or higher than the maximum EC90 values. At lower dose levels, the exposure dropped below the maximum EC90. In addition, SC dosing had a more favourable PK profile, with a low peak-to-trough ratio compared to IV infusion.

Clinical Pharmacodynamics

Subjects who received teclistamab SC starting at the 0.24 mg/kg weekly dose level demonstrated consistent pharmacodynamic changes indicative of the proposed mechanism of action, including T cell activation, induction of cytokines, and T cell redistribution. Optimal pharmacodynamic changes were observed in subjects who received 1.5 mg/kg SC. Greater induction of T cell activation markers such as PD-1, CD38, LAG-3, TIM-3, and HLA-DR was seen for subjects treated at the 1.5 mg/kg SC weekly dose level compared with the increases observed for subjects treated at the 0.72 mg/kg SC dose weekly level Markers for T cell activation did not increase consistently with further increases in dose. Consistent increases in cytokines such as IL-10, IL-2Rα, and IL-6 were observed for subjects treated at the 1.5 mg/kg SC weekly dose level. Optimal activation of cytokines was observed at 1.5 mg/kg SC weekly, as evidenced by consistently high median values for maximum fold change of cytokines when compared to other dose levels evaluated. These data represent maximum fold changes through Cycle 1.

Clinical Safety

The safety profile observed at the 1.5 mg/kg SC weekly dose level was consistent with that observed at lower dose levels. Step-up doses were used to mitigate the risk of high-grade CRS. As of 07 September 2021, 165 subjects were evaluated for safety at 1.5 mg/kg SC weekly. No DLTs were observed at this dose level among subjects evaluated by the SET for this purpose. The most frequently reported (≥20%) TEAEs were CRS (71.5%), neutropenia (65.5%), anaemia (49.7%), thrombocytopenia (38.2%), lymphopenia (33.9%), injection site erythema (25.5%), fatigue (24.8%), nausea (24.2%), headache (21.8%), and diarrhea (20.6%). Overall, a low rate of treatment

discontinuation due to TEAE was observed, with only 1 subject ((<1%) discontinuing treatment due to TEAE, and no subject reducing the dose of teclistamab. No subject died due to aTEAE judged by the investigator as related to teclistamab.

CRS was manageable and reversible. Eighty-two subjects (49.7%) experienced maximum Grade 1 CRS and 35 (21.2%) experienced maximum Grade 2 CRS. One subject experienced Grade 3 CRS in the context of concurrent pneumonia. Sixty subjects (36.4%) were treated with tocilizumab, 13 (7.9%) received steroids, and 21 (12.7%) received low-flow oxygen to treat CRS. The subject who experienced Grade 3 CRS required a single vasopressor. No subject required treatment discontinuation for CRS; all events resolved.

Neurotoxicity was observed infrequently (21 subjects [12.7%]) and was low grade at 1.5 mg/kg SC weekly. The most frequently reported neurotoxicity event was headache. Five subjects (3.0%) had ICANS, all Grade 1 or Grade 2. Nearly all neurotoxicity (33/36 events) resolved, with events of Grade 2 hypoesthesia, Grade 2 dysgeusia, and Grade 1 headache ongoing as of the clinical cut-off.

None of the subjects who received RP2D developed ADAs against teclistamab.

At 3 mg/kg SC weekly (n=5), the CRS and neurotoxicity profile appeared consistent with those for 1.5 mg/kg SC weekly; however, 1 subject had a dose reduction to 1.5 mg/kg SC weekly for TEAEs of vomiting, nausea, and diarrhea. The safety profile at 6 mg/kg SC weekly appears consistent with that for lower dose levels, but analysis for this dose level is limited by short duration of follow-up.

Clinical Efficacy (detailed results from this part of the study are presented under Section 2.6.5.6 in this report).

As of 07 September 2021, 150 subjects were included in the Efficacy Analysis Set at 1.5 mg/kg SC weekly. This dose of teclistamab led to a compelling efficacy profile for heavily pre-treated patients with myeloma, with an ORR of 62.0% (95% CI: 53.7% to 69.8%) and rapid median onset of response of approximately 1 month. Responses to teclistamab deepened over time, where 58.0%of patients achieved VGPR or better and 28.7% achieved CR or better. Among patients who achieved CR or better, the MRD-negativity rate at 10^{-5} was 41.9%. Responses were durable, with a median DOR that was not reached. The probabilities of responders remaining in response at and 9 months were 92.5% (95% CI: 80.6% to 97.2%) and 85.9% (95% CI: 70.0% to 93.7%).

At SC dose levels below 0.72 mg/kg SC weekly, the ORR was lower (n=13, ORR was 46.2%). Subjects assigned to the 0.72 mg/kg SC weekly dosing cohort had an ORR of 60% (9 of 15 subjects); however, 1 of 9 responders had their first response observed after increasing the teclistamab dose to 1.5 mg/kg. Importantly, the 6-month event-free rate for DOR at the 0.72 mg/kg SC weekly dose level was only 77.8%, compared with 92.1% for responders treated at 1.5 mg/kg SC weekly in Phase 1 (n=26). Efficacy analysis for subjects treated at 3 mg/kg SC weekly is limited by small numbers or short duration of follow-up, but it appears consistent with the 1.5 mg/kg SC weekly dose level.

Main study

Study 64007957MMY1001 (MajesTEC-1): A phase 1/2, open-label, multicenter, study to evaluate the efficacy, safety, tolerability, PK, of teclistamab the efficacy and safety of teclistamab monotherapy in participants with relapsed and refractory multiple myeloma (RRMM).

Methods

The study was conducted in 3 parts: dose escalation (Part 1) to identify the <u>recommended phase 2 dose(s) [RP2D(s)]</u>, dose expansion at RP2Ds (Part 2), and phase 2 dose expansion in cohorts of subjects with relapsed or refractory multiple myeloma who previously received at least 3 prior lines of therapy and were triple-class exposed (Part 3).

Part 3 was added to the study protocol after an amendment in July 2020 to evaluate efficacy and safety at RP2D administered SC in cohorts of subjects with relapsed or refractory multiple myeloma with unmet medical need given their heavily pre-treated status.

The study was initiated with a biweekly (every 2 weeks; Q2W) IV dosing schedule. Based on review of the safety, efficacy, pharmacokinetics and pharmacodynamic data, an RP2D treatment dose of 1500 µg/kg of teclistamab SC was selected for Part 3.

The phase 2 was divided in two cohorts:

- in Cohort A, subjects received at least 3 prior lines of therapy, including a PI, an IMiD and an anti-CD38 monoclonal antibody.

- In Cohort C, subjects received an anti BCMA therapy (antibody drug conjugate [ADC] or chimeric antigen receptor T cell [CAR-T]) in addition to the therapeutic classes and lines of therapy required for Cohort A.

The study was divided into 3 periods: a screening phase, a treatment phase, and a posttreatment follow-up phase.

- **Study Participants**

<u>The key inclusion criteria were the following:</u>

1. ≥18 years of age.

2. Documented diagnosis of MM according to IMWG diagnostic criteria.

3. <u>Part 1 and Part 2</u>

   Measurable multiple myeloma that is relapsed or refractory to established therapies with known clinical benefit in relapsed/refractory MM or be intolerant of those established MM therapies, and a candidate for teclistamab treatment in the opinion of the treating physician. Prior lines of therapy must include a PI, an IMiD, and an anti-CD38 monoclonal antibody in any order during the course of treatment. Subjects who could not tolerate a PI, IMiD, or an anti-CD38 monoclonal antibody are allowed. In Part 2 (dose expansion), in addition to above criteria, MM must be measurable per current IMWG published guidelines by central laboratory assessment. If central laboratory assessment is not available, relevant local laboratory measurement must exceed the minimum required level by at least 25%.

   <u>Part 3</u>

   Measurable disease Cohort A, Cohort B, and Cohort C: MM must be measurable by central laboratory assessment: – Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or – Light chain MM 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%.

Prior treatment

– Cohort A: Subjects must have 1) received ≥3 prior lines of therapy and 2) previously received a PI, an IMiD, and an anti-CD38 monoclonal antibody.

– Cohort B: received ≥4 prior lines of therapy and whose disease is penta-drug refractory to an anti-CD38 monoclonal antibody, ≥2 PIs, ≥2 IMiDs (refractory multiple myeloma as defined by IMWG consensus criteria).

– Cohort C: received ≥3 prior lines of therapy that included a PI, an IMiD, an anti-CD38 monoclonal antibody, and an anti-BCMA treatment (with CAR-T cells or an ADC).

4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1.

5. Haemoglobin ≥8 g/dL (≥5 mmol/L) (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted)

Platelets ≥75×10^9 /L for subjects in whom 50% of bone marrow nucleated cells are plasma cells; otherwise platelet count ≥50×10^9 /L (without transfusion support in the 7 days prior to the laboratory test)

Absolute Neutrophil Count (ANC) ≥1.0×10^9 /L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)

AST and ALT ≤3.0×upper limit of normal (ULN)

Creatinine or Creatinine clearance/ glomerular filtration rate Serum creatinine: ≤1.5 mg/dL or Creatinine clearance: ≥40 mL/min/1.73 m^2 or estimated glomerular filtration rate ≥40 mL/min/1.73 m2 based upon calculation

Total bilirubin ≤2.0×ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5×ULN is required)

Corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L) or free ionised calcium <6.5 mg/dL (<1.6 mmol/L).

The key exclusion criteria were the following:

1. Prior treatment with any BCMA-targeted therapy, with the exception of Cohort C in Part 3.

2. Prior antitumour therapy as follows, before the first dose of study drug:

   • Targeted therapy, epigenetic therapy, or treatment with an investigational drug or used an invasive investigational medical device within 21 days or at least 5 half-lives, whichever is less.

   • Monoclonal antibody treatment for multiple myeloma within 21 days.

   • Cytotoxic therapy within 21 days.

   • Proteasome inhibitor therapy within 14 days.

   • Immunomodulatory agent therapy within 7 days.

   • Gene modified adoptive cell therapy (eg, chimeric antigen receptor modified T cells, natural killer [NK] cells) within 3 months

   • Radiotherapy within 14 days or focal radiation within 7 days.

3. Toxicities from previous anticancer therapies that have not resolved to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy.

4. Received a cumulative dose of corticosteroids equivalent to ≥140 mg of prednisone within the 14-day period before the first dose of study drug (does not include pretreatment medication).

5. Stem cell transplantation:

   An allogeneic stem cell transplant within 6 months. Subjects who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks without signs of graft versus-host disease.

   Received an autologous stem cell transplant ≤12 weeks before the first dose of study drug.

6. Known active CNS involvement or exhibits clinical signs of meningeal involvement of multiple myeloma.

7. Stroke or seizure within 6 months.

8. Plasma cell leukaemia ($>2.0 \times 10^9$ /L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary amyloid light-chain amyloidosis.

9. Known to be seropositive for human immunodeficiency virus or acquired immune deficiency syndrome.

10. Hepatitis B infection or at risk for hepatitis B virus (HBV) reactivation. Active Hepatitis C infection.

11. Pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation.

12. Known allergies, hypersensitivity, or intolerance to the study drug (teclistamab) or its excipients.

- **Treatments**

Teclistamab was administered by SC injection at 60 and 300 µg/kg (priming doses) followed by a 1500 µg/kg (1.5 mg/kg) weekly treatment dose.

Priming Dose Schedule: The priming schedule consists of 2 priming doses: a first priming dose of 60 µg/kg followed by a second priming dose of 300 µg/kg. Each priming dose is separated by 2 to 4 days and to be completed 2 to 4 days prior to the first treatment dose.

If there are no delays in treatment, the first treatment dose should be administered 4-8 days after the first priming dose and 2-4 days after the second priming dose.

Treatment Dose Schedule: full doses on each dosing day.

Weekly dosing: Days 1, 8, 15, and 22 of a 28-day cycle.

- **Objectives**

Part 3

Primary Objective

- To evaluate the efficacy of teclistamab at the RP2D

Secondary Objectives

- To further assess the efficacy of teclistamab at the RP2D

- To evaluate MRD at the RP2D

- To further assess the safety and tolerability of teclistamab at the RP2D

- To characterise the pharmacokinetics of teclistamab at the RP2D

- To assess the immunogenicity of teclistamab

- To assess PROs after treatment with teclistamab

- To evaluate the efficacy of teclistamab in high risk molecular subgroups

Disease evaluations were performed at screening and within 3 days before Day 1 of each cycle, before study drug was administered. Disease evaluations continued until disease progression, using the IMWG-based response criteria (2016).

A central laboratory was used for disease evaluations (M-protein and serum free light chain measurements, and immunofixation determinations in serum and 24-hour urine). Bone marrow samples to assess for plasma cell percentage and clonality were analysed locally; bone marrow samples to assess for MRD negativity were analysed centrally.

- **Outcomes/endpoints**

Primary Efficacy Endpoint

Overall Response Rate

The primary efficacy endpoint of the study was ORR, defined as sCR+CR+VGPR+PR, according to 2016 International Myeloma Working Group (IMWG) Response Criteria and as assessed by IRC.

Secondary Efficacy Endpoints

Duration of Response

DoR is defined as the time from first documented evidence of PR or better until the earliest date of disease progression (PD) per IMWG, or death due to PD among participants or death due to PD, whichever occurs first. Relapse from CR is not considered as disease progression. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

VGPR or better/CR or better/sCR is defined as the proportion of subjects who achieve a VGPR or better response according to the IMWG (2016) criteria.

Time to Response

TTR is defined as the time between date of first dose of study drug and the first efficacy evaluation that the subject has met all criteria for PR or better.

Progression-Free Survival

PFS is defined as the 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 have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

Overall Survival

OS is defined as the time from the 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.

Time to Next Treatment (TTNT)

TTNT is defined as the time from the date of first dose of study drug to the start of the next line treatment.

Minimal Residual Disease

Exploratory Minimal Residual Disease (MRD) negative rate is the proportion of subjects who achieved MRD-negative status to a threshold of 10^{-5} at any timepoint after initial dose of teclistamab and before disease progression or starting subsequent therapy.

Patient-reported Outcome Analyses

Change from baseline in overall HRQoL, symptoms, and functioning were capture using the following PRO measures:

- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC QLQ-C30).

- EuroQol Five Dimension Five Level Questionnaire (EQ-5D-5L).

- Patient Global Impression of Severity (PGIS).

- **Sample size**

Part 3 (Phase 2)

The sample size requirements for the cohorts enrolled in Phase 2 were as follows:

- Cohort A: With approximately 100 subjects treated with teclistamab, there would be >85% power to declare the ORR is higher than 30% at the 1-sided significance level of 0.025 with the assumption that ORR among those treated with teclistamab would be at least 45%. Subjects treated with teclistamab who have a non-evaluable response would be counted as non-responders in the ORR assessment. An interim analysis for futility was to occur after 30 subjects in Cohort A became evaluable for futility (received at least 8 weeks of study treatment and completed at least 2 postbaseline disease assessments, progressed, died, or discontinued treatment for reasons other than disease progression).

  To achieve >90% power to declare the ORR was higher than 30%, at least 112 subjects would need to receive RP2D.

  o Cohort C: Simon's 2-stage design was used to test the null hypothesis that the ORR was at most 15%, against the alternative that the ORR was at least 35%. With a 1-sided significance level of 0.025 and a power of 80%, Cohort C needed 34 response-evaluable subjects. Assuming a non-evaluable rate of 10%, the total sample size required for Cohort C was approximately 38 subjects. An interim analysis to assess futility occurred when 21 subjects were enrolled and had been followed for at least 2 cycles to be evaluable for response or discontinued early. At that time, 25 subjects were evaluable for safety.

- **Randomisation and Blinding (masking)**

This was an open-label study.

- **Statistical methods**

For the pivotal RP2D, ORR (per IRC assessment) and 2-sided 95% exact CI were calculated for each cohort, based on the IMWG 2016 response criteria.

Homogeneity of ORR treatment effect was assessed across prespecified subgroups. Sensitivity analyses of ORR were performed for pivotal RP2D data using disease response based on:

- Computerised algorithm according to IMWG 2016 response criteria (Phase 1 at RP2D and Phase 2)

- Investigator assessment according to IMWG 2016 response criteria for Phase 2) and IMWG 2011 response criteria for Phase 1.

- Kappa statistics and 95% CI were calculated for assessing agreement between IRC assessment and computerised algorithm assessment for response (response [PR or better] vs no response).

A sensitivity analysis was performed for ORR in which subjects who died due to COVID-19 and were not evaluable for response were excluded.

Supplementary analyses of ORR were performed for the Response Evaluable Analysis Set.

VGPR or better rate, CR or better rate, sCR rate, and ORR in subjects with high-risk cytogenetics at baseline, and their 2-sided 95% exact CI were calculated, as assessed by the IRC, based on the IMWG 2016 response criteria.

Time-to-event endpoints, including DOR, PFS, and OS, and TTNT were evaluated using Kaplan-Meier method, and the median value and corresponding 95% CI were provided for each.

MRD-negativity rate and its 2-sided 95% exact CI were calculated and TTR, PROs, and biomarker data were summarised descriptively.

An interim analysis for futility was performed for Cohort A in Phase 2 after 30 subjects in this cohort became evaluable for futility. The stopping boundary for Cohort A was exceeded (more than 6 of 30 subjects had responded).

Results

- **Participant flow**

In total, 165 subjects (40 in Phase 1 and 125 in Cohort A in Phase 2) received at least 1 dose of teclistamab at RP2D on or before the clinical cut-off of 07 September 2021 and were included in the All Treated Analysis Set for pivotal RP2D data. Subjects in the All Treated Analysis Set for pivotal RP2D were included in the Efficacy Analysis Set for this population if they received their first dose of teclistamab by 18 March 2021.

For subjects in the pivotal RP2D in the Efficacy Analysis Set, 104 (69.3%) remained in the study as of the clinical cut-off. As of the clinical cut-off date, the median follow-up in this set was 9.8 months (range: 0.5 [subject died] to 20.3 months. Seventy-five subjects (50.0%) remained on treatment; the primary reason for treatment discontinuation was progressive disease (51 of 75 subjects).

Updated efficacy results with clinical cut-off of 16 March 2022 were provided. Among the 104 responders in the All Treated Analysis set (N=165), the median follow-up time was 14.1 months (range: 2.4 [subject died] to 24.4 months).

- **Recruitment**

Study initiation date: first subject was screened on 8 June 2017.

- **Conduct of the study**

Summary of main protocol amendments:

There were 11 global amendments to the original protocol. The main changes are summarised below:

Amendment 1 (20 March 2017)

- To add a definition of measurable disease and also note that prior lines of therapy for subjects in Part 1 and Part 2 must include a PI and an IMiD

Amendment 4 (26 March 2018)

- To increase the dosing frequency from Q2W to weekly in new subjects enrolled in the study to allow to sufficient teclistamab exposure over the dosing interval

Amendment 6 (12 March 2019)

- To investigate an SC administration method of teclistamab, which would reduce study drug administration duration and was hypothesised to reduce the risk of CRS, compared with IV dosing

Amendment 9 02 July 2020

- To add Part 3 (Phase 2)

  Amendment 10 (26 October 2020)

- To provide updated data for RP2D

- To clarify that subjects enrolled in Part 1 and Part 2 should have received or been intolerant of an anti-CD38 monoclonal antibody

- To clarify that subjects enrolled in Part 3 must have received ≥3 prior lines of therapy (ie, double refractory to PI and an IMiD is not sufficient for inclusion in this this cohort)

- Protocol Deviations

All protocol deviations of eligibility criteria and those deviations that could impact subject safety or primary endpoint were considered major protocol deviations. Major protocol deviations were reported for 13 subjects (7.9%). The most frequent major protocol deviation was not meeting eligibility criteria (7 subjects [4.3%]).

- **Baseline data**

Table 12 summarises the demographics characteristics for all treated patients in the efficacy population (RP2D dose). The baseline disease characteristics are presented in **Table 13**.

Table 12. Demographic Characteristics (MajesTEC-1study, RP2D, phase 1 and Cohort A, phase 2)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Age, years			
N	40	125	165
Category, n (%)			
< 65 years	23 (57.5%)	63 (50.4%)	86 (52.1%)
65 - <75 years	12 (30.0%)	43 (34.4%)	55 (33.3%)
≥75 years	5 (12.5%)	19 (15.2%)	24 (14.5%)
Mean (SD)	62.4 (9.99)	64.4 (9.49)	63.9 (9.62)
Median	62.5	64.0	64.0
Range	(39; 84)	(33; 83)	(33; 84)
Sex			
N	40	125	165
Female	14 (35.0%)	55 (44.0%)	69 (41.8%)
Male	26 (65.0%)	70 (56.0%)	96 (58.2%)
Race			
N	40	125	165
Asian	0	3 (2.4%)	3 (1.8%)
Black or African American	1 (2.5%)	20 (16.0%)	21 (12.7%)
White	34 (85.0%)	100 (80.0%)	134 (81.2%)
Multiple	0	1 (0.8%)	1 (0.6%)
Other	1 (2.5%)	1 (0.8%)	2 (1.2%)
Not reported	4 (10.0%)	0	4 (2.4%)
Ethnicity			
N	40	125	165
Hispanic or Latino	2 (5.0%)	13 (10.4%)	15 (9.1%)
Not Hispanic or Latino	33 (82.5%)	111 (88.8%)	144 (87.3%)
Not reported	4 (10.0%)	1 (0.8%)	5 (3.0%)
Unknown	1 (2.5%)	0	1 (0.6%)
Weight, kg			
N	40	125	165
Mean (SD)	77.80 (14.716)	74.13 (17.291)	75.02 (16.734)
Median	76.10	72.00	73.00
Range	(50.0; 103.5)	(41.0; 138.9)	(41.0; 138.9)
Height, cm			
N	40	125	165
Mean (SD)	171.18 (11.698)	166.25 (11.703)	167.44 (11.857)
Median	172.50	167.00	168.00
Range	(147.3; 192.0)	(123.0; 193.0)	(123.0; 193.0)
Baseline ECOG score			
N	40	125	165
0	17 (42.5%)	38 (30.4%)	55 (33.3%)
1	23 (57.5%)	86 (68.8%)	109 (66.1%)
3	0	1 (0.8%)	1 (0.6%)

Key: ECOG=eastern cooperative oncology group; RP2D=recommended Phase 2 dose

Table 13. Baseline disease characteristics (MajesTEC-1study, RP2D, phase 1 and Cohort A, phase 2)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Type of myeloma by immunofixation or serum FLC assay			
N	40	125	165
IgG	17 (42.5%)	74 (59.2%)	91 (55.2%)
IgA	8 (20.0%)	21 (16.8%)	29 (17.6%)
IgM	0	2 (1.6%)	2 (1.2%)
IgD	2 (5.0%)	1 (0.8%)	3 (1.8%)
IgE	0	0	0
Light chain	11 (27.5%)	25 (20.0%)	36 (21.8%)
Kappa	7 (17.5%)	8 (6.4%)	15 (9.1%)
Lambda	4 (10.0%)	16 (12.8%)	20 (12.1%)
FLC-Kappa[a]	0	1 (0.8%)	1 (0.6%)
FLC-Lambda[b]	0	0	0
Biclonal	2 (5.0%)	2 (1.6%)	4 (2.4%)
Negative immunofixation	0	0	0
Type of measurable disease per IMWG			
N	40	125	165
Serum only	15 (37.5%)	53 (42.4%)	68 (41.2%)
Serum and urine	4 (10.0%)	24 (19.2%)	28 (17.0%)
Urine only	4 (10.0%)	16 (12.8%)	20 (12.1%)
Serum FLC	16 (40.0%)	31 (24.8%)	47 (28.5%)
Not evaluable	1 (2.5%)	1 (0.8%)	2 (1.2%)
ISS staging[c]			
N	39	123	162
I	24 (61.5%)	61 (49.6%)	85 (52.5%)
II	11 (28.2%)	46 (37.4%)	57 (35.2%)
III	4 (10.3%)	16 (13.0%)	20 (12.3%)
R-ISS staging[d]			
N	37	119	156
I	15 (40.5%)	28 (23.5%)	43 (27.6%)
II	19 (51.4%)	81 (68.1%)	100 (64.1%)
III	3 (8.1%)	10 (8.4%)	13 (8.3%)
Time from multiple myeloma diagnosis to first dose (years)			
N	40	125	165
Mean (SD)	5.895 (3.6520)	6.860 (3.8075)	6.626 (3.7822)
Median	5.578	6.190	6.023
Range	(0.76; 17.37)	(0.88; 22.68)	(0.76; 22.68)
Number of lytic bone lesions			
N	40	125	165
None	5 (12.5%)	15 (12.0%)	20 (12.1%)
1-3	5 (12.5%)	15 (12.0%)	20 (12.1%)
4-10	11 (27.5%)	32 (25.6%)	43 (26.1%)
More than 10	19 (47.5%)	63 (50.4%)	82 (49.7%)
Number of extramedullary plasmacytomas			
N	40	125	165
0	32 (80.0%)	105 (84.0%)	137 (83.0%)
≥1	8 (20.0%)	20 (16.0%)	28 (17.0%)
% Plasma cells, bone marrow biopsy/aspirate[e]			
N	38	122	160

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
<5	16 (42.1%)	36 (29.5%)	52 (32.5%)
≥5 - ≤30	14 (36.8%)	45 (36.9%)	59 (36.9%)
>30 - <60	5 (13.2%)	26 (21.3%)	31 (19.4%)
≥60	3 (7.9%)	15 (12.3%)	18 (11.3%)
% Plasma cells, bone marrow biopsy			
N	23	49	72
<5	9 (39.1%)	12 (24.5%)	21 (29.2%)
≥5 - ≤30	7 (30.4%)	14 (28.6%)	21 (29.2%)
>30 - <60	5 (21.7%)	13 (26.5%)	18 (25.0%)
≥60	2 (8.7%)	10 (20.4%)	12 (16.7%)
% Plasma cells, bone marrow aspirate			
N	36	120	156
<5	18 (50.0%)	39 (32.5%)	57 (36.5%)
≥5 - ≤30	13 (36.1%)	49 (40.8%)	62 (39.7%)
>30 - <60	3 (8.3%)	19 (15.8%)	22 (14.1%)
≥60	2 (5.6%)	13 (10.8%)	15 (9.6%)
Cytogenetic risk			
N	37	110	147
Standard risk	25 (67.6%)	84 (76.4%)	109 (74.1%)
High risk	12 (32.4%)	26 (23.6%)	38 (25.9%)
del(17p)	9 (24.3%)	14 (12.7%)	23 (15.6%)
t(4;14)	4 (10.8%)	12 (10.9%)	16 (10.9%)
t(14;16)	1 (2.7%)	3 (2.7%)	4 (2.7%)
Bone marrow cellularity by biopsy			
N	23	45	68
Hypercellular	4 (17.4%)	16 (35.6%)	20 (29.4%)
Normocellular	12 (52.2%)	20 (44.4%)	32 (47.1%)
Hypocellular	3 (13.0%)	6 (13.3%)	9 (13.2%)
Indeterminate	4 (17.4%)	3 (6.7%)	7 (10.3%)

Key: FLC=free light chain; ISS=international staging system; NE=not evaluable; RP2D=recommended Phase 2 dose; IMWG=international myeloma working group

[a] Includes subjects without a positive immunofixation but with evidence of free light chain kappa by FLC testing.

[b] Includes subjects without a positive immunofixation but with evidence of free light chain lambda by FLC testing.

[c] ISS staging is derived based on serum β2-microglobulin and albumin.

[d] R-ISS is derived based on the combination of serum β2-microglobulin and albumin, genetic risk, and level of lactate dehydrogenase level (LDH).

[e] Maximum value from bone marrow biopsy or bone marrow aspirate is selected if both the results are available.

Note: Percentages calculated with the number of subjects in the all treated analysis set with available data as denominator.

Prior anti-cancer medications for MM are presented in **Table 14**.

Table 14. Prior Anti-Cancer Medications for MM (MajesTEC-1study, RP2D, phase 1 and Cohort A, phase 2)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Total number of subjects with any prior therapies for multiple myeloma	40 (100.0%)	125 (100.0%)	165 (100.0%)
Number of prior lines of therapy[a]			
N	40	125	165
Category			
2	3 (7.5%)	2 (1.6%)	5 (3.0%)
3	9 (22.5%)	29 (23.2%)	38 (23.0%)
4	4 (10.0%)	31 (24.8%)	35 (21.2%)
5	9 (22.5%)	25 (20.0%)	34 (20.6%)
> 5	15 (37.5%)	38 (30.4%)	53 (32.1%)
Mean (SD)	5.1 (2.19)	5.1 (2.17)	5.1 (2.17)
Median	5.0	5.0	5.0
Range	(2; 11)	(2; 14)	(2; 14)
Prior PI	40 (100.0%)	125 (100.0%)	165 (100.0%)
Bortezomib	39 (97.5%)	123 (98.4%)	162 (98.2%)
Carfilzomib	32 (80.0%)	87 (69.6%)	119 (72.1%)
Ixazomib	9 (22.5%)	31 (24.8%)	40 (24.2%)
Prior IMiD	40 (100.0%)	125 (100.0%)	165 (100.0%)
Lenalidomide	39 (97.5%)	122 (97.6%)	161 (97.6%)
Pomalidomide	31 (77.5%)	108 (86.4%)	139 (84.2%)
Thalidomide	12 (30.0%)	48 (38.4%)	60 (36.4%)
Prior anti-CD38	40 (100.0%)	125 (100.0%)	165 (100.0%)
Daratumumab	40 (100.0%)	112 (89.6%)	152 (92.1%)
Isatuximab	0	21 (16.8%)	21 (12.7%)
Prior Selinexor	1 (2.5%)	5 (4.0%)	6 (3.6%)
Prior Melphalan Flufenamide	1 (2.5%)	0	1 (0.6%)
Prior PI+IMiD	40 (100.0%)	125 (100.0%)	165 (100.0%)
Prior PI+IMiD+anti-CD38	40 (100.0%)	125 (100.0%)	165 (100.0%)
Prior penta-exposed	26 (65.0%)	90 (72.0%)	116 (70.3%)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Prior transplantation	34 (85.0%)	101 (80.8%)	135 (81.8%)
Autologous	34 (85.0%)	101 (80.8%)	135 (81.8%)
1	28 (70.0%)	84 (67.2%)	112 (67.9%)
≥ 2	6 (15.0%)	17 (13.6%)	23 (13.9%)
Allogenic	4 (10.0%)	4 (3.2%)	8 (4.8%)
Prior radiotherapy	18 (45.0%)	49 (39.2%)	67 (40.6%)
Prior cancer-related surgery/procedure	5 (12.5%)	19 (15.2%)	24 (14.5%)

Key: PI=proteasome inhibitor; IMiD=Immunomodulatory agent; RP2D=recommended Phase 2 dose
[a] Based on data recorded on prior systemic therapy eCRF page.
Note: PI includes bortezomib, carfilzomib, ixazomib; IMiD includes thalidomide, lenalidomide, and pomalidomide; anti-CD38 includes daratumumab and isatuximab. Penta includes at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.
Note: Percentages calculated with the number of all treated subjects as denominator.

The refractoriness status of the patients to prior anti-cancer therapies are presented in **Table 15**.

Table 15. Participants Refractory to Prior Anti-MM Therapy ((MajesTEC-1study, RP2D, phase 1 and Cohort A, phase 2)

| | RP2D | | |
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Refractory at any point to prior therapy	40 (100.0%)	124 (99.2%)	164 (99.4%)
Refractory status			
Any PI	34 (85.0%)	108 (86.4%)	142 (86.1%)
Any IMiD	38 (95.0%)	114 (91.2%)	152 (92.1%)
Any anti-CD38 antibody	39 (97.5%)	109 (87.2%)	148 (89.7%)
Double (PI+IMiD)	33 (82.5%)	100 (80.0%)	133 (80.6%)
Triple (PI+IMiD+anti-CD38 antibody)	32 (80.0%)	96 (76.8%)	128 (77.6%)
Penta (2 PI, 2 IMiD, anti-CD38 antibody)	16 (40.0%)	34 (27.2%)	50 (30.3%)
Refractory to last line of prior therapy	33 (82.5%)	115 (92.0%)	148 (89.7%)
Refractory to			
Bortezomib	21 (52.5%)	62 (49.6%)	83 (50.3%)
Carfilzomib	27 (67.5%)	68 (54.4%)	95 (57.6%)
Ixazomib	8 (20.0%)	24 (19.2%)	32 (19.4%)
Lenalidomide	34 (85.0%)	99 (79.2%)	133 (80.6%)
Pomalidomide	29 (72.5%)	98 (78.4%)	127 (77.0%)
Thalidomide	5 (12.5%)	11 (8.8%)	16 (9.7%)
Daratumumab	39 (97.5%)	95 (76.0%)	134 (81.2%)
Isatuximab	0	21 (16.8%)	21 (12.7%)
Selinexor	0	4 (3.2%)	4 (2.4%)
Melphalan Flufenamide	1 (2.5%)	0	1 (0.6%)

Key: PI=proteasome inhibitor; IMiD=Immunomodulatory agent; RP2D=recommended Phase 2 dose
Note: Refractory to each medication refers to refractory to any medication-containing line. Percentages calculated with the number of subjects in all treated analysis set as denominator.

- **Numbers analysed**

Numbers analysed in each analysis set are presented in **Table 16**.

Table 16. Numbers analysed in each analysis set (MajesTEC-1study, RP2D, phase 1 and Cohort A, phase 2)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
All Treated Analysis Set	40	125	165
Efficacy Analysis Set[a]	40 (100.0%)	110 (88.0%)	150 (90.9%)
Per protocol Analysis Set	39 (97.5%)	104 (94.5%)	143 (95.3%)
Response Evaluable Analysis Set	40 (100.0%)	104 (94.5%)	144 (96.0%)
Pharmacokinetics Analysis Set	40 (100.0%)	123 (98.4%)	163 (98.8%)
Immunogenicity Analysis Set	39 (97.5%)	107 (85.6%)	146 (88.5%)
Cytogenetic Evaluable Analysis Set	37 (92.5%)	110 (88.0%)	147 (89.1%)

Key: RP2D=recommended Phase 2 dose
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator except for per-protocol and response evaluable analysis sets which use efficacy analysis set as denominator.
[a] Includes subjects who received first dose on or before 18MAR2021.

- **Outcomes and estimation**

Primary efficacy endpoint

The primary efficacy endpoint for the study was ORR per IMWG as determined by IRC. The ORR as assessed by IRC was 62.0% (95% CI: 53.7% to 69.8%). Most responses occurred rapidly, by the start of Cycle 2. Many responses deepened over time, from an initial response of PR or VGPR, to a best response of VGPR or better.

Similar results were obtained by sensitivity analysis via computerised algorithm. In addition, there was a high degree of concordance between the assessments by IRC and by computerised algorithm: Prevalence Adjusted and Bias Adjusted Kappa (PABAK) of 0.97 (95% CI: 0.94 to 1.00) and observed agreement of 98.7%.

Updated data cut-off, 16 March 2022.

As of the updated clinical cutoff, ORR (PR or better) as assessed by the IRC based on IMWG 2016 criteria was 63.0% (95% CI: 55.2% to 70.4%) for subjects treated at pivotal RP2D (All Treated Analysis Set; N=165,**(Table 17**).

Table 17. Best Confirmed Response based on IRC (MajesTEC-1study, RP2D, phase 1 and Cohort A, phase 2, data cut-off:16 March 2022)

	Phase 1		Phase 2 Cohort A		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: All Treated	40		125		165	
Response category						
Stringent complete response (sCR)	15 (37.5%)	(22.7%, 54.2%)	39 (31.2%)	(23.2%, 40.1%)	54 (32.7%)	(25.6%, 40.5%)
Complete response (CR)	4 (10.0%)	(2.8%, 23.7%)	7 (5.6%)	(2.3%, 11.2%)	11 (6.7%)	(3.4%, 11.6%)
Very good partial response (VGPR)	6 (15.0%)	(5.7%, 29.8%)	26 (20.8%)	(14.1%, 29.0%)	32 (19.4%)	(13.7%, 26.3%)
Partial response (PR)	1 (2.5%)	(0.1%, 13.2%)	6 (4.8%)	(1.8%, 10.2%)	7 (4.2%)	(1.7%, 8.5%)
Minimal response (MR)	0	(NE, NE)	2 (1.6%)	(0.2%, 5.7%)	2 (1.2%)	(0.1%, 4.3%)
Stable disease (SD)	7 (17.5%)	(7.3%, 32.8%)	20 (16.0%)	(10.1%, 23.6%)	27 (16.4%)	(11.1%, 22.9%)
Progressive disease (PD)	7 (17.5%)	(7.3%, 32.8%)	17 (13.6%)	(8.1%, 20.9%)	24 (14.5%)	(9.5%, 20.9%)
Not evaluable	0	(NE, NE)	8 (6.4%)	(2.8%, 12.2%)	8 (4.8%)	(2.1%, 9.3%)
Overall response (sCR + CR + VGPR + PR)	26 (65.0%)	(48.3%, 79.4%)	78 (62.4%)	(53.3%, 70.9%)	104 (63.0%)	(55.2%, 70.4%)
VGPR or better (sCR + CR + VGPR)	25 (62.5%)	(45.8%, 77.3%)	72 (57.6%)	(48.4%, 66.4%)	97 (58.8%)	(50.9%, 66.4%)
CR or better (sCR + CR)	19 (47.5%)	(31.5%, 63.9%)	46 (36.8%)	(28.4%, 45.9%)	65 (39.4%)	(31.9%, 47.3%)

Key: CI = confidence interval; NE = not estimable; RP2D = recommended Phase 2 dose; IRC = independent review committee; IMWG = international myeloma working group
Note: Response was assessed by IRC, based on IMWG consensus criteria (2016).
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.
Note: Exact 95% confidence intervals are provided.

ORR was examined based on the IRC data in prespecified subgroups, including number of lines of prior therapy, refractoriness to prior therapy and cytogenetic risk at baseline. Subgroup analyses demonstrated that teclistamab delivered generally consistent ORR in subjects treated at RP2D across pre-specified clinically relevant subgroups (**Figure 4**).

Figure 4. Forest Plot of Subgroup Analyses on ORR Based on IRC Assessment; Efficacy Analysis Set (MajesTEC-1study, pivotal RP2D, data cut-off:16 March 2022)

Total RP2D

	Overall response rate (95% CI)	N	ORR – n(%)	95% CI(%)
All subjects		165	104 (63.0%)	(55.2%, 70.4%)
Age				
< 65 years		86	56 (65.1%)	(54.1%, 75.1%)
65 -< 75 years		55	35 (63.6%)	(49.6%, 76.2%)
>= 75 years		24	13 (54.2%)	(32.8%, 74.4%)
Sex				
Male		96	60 (62.5%)	(52.0%, 72.2%)
Female		69	44 (63.8%)	(51.3%, 75.0%)
Race				
White		134	84 (62.7%)	(53.9%, 70.9%)
African American/Black		21	16 (76.2%)	(52.8%, 91.8%)
Other		10	4 (40.0%)	(12.2%, 73.8%)
Region				
North America		67	40 (59.7%)	(47.0%, 71.5%)
Europe		98	64 (65.3%)	(55.0%, 74.6%)
Baseline renal function				
<=60 mL/min/1.73m^2		44	27 (61.4%)	(45.5%, 75.6%)
>60 mL/min/1.73m^2		121	77 (63.6%)	(54.4%, 72.2%)

Percent

Total RP2D

	Overall response rate (95% CI)	N	ORR - n(%)	95% CI(%)
Baseline ECOG performance score				
0		55	38 (69.1%)	(55.2%, 80.9%)
>= 1		110	66 (60.0%)	(50.2%, 69.2%)
Number of lines of prior therapy				
<= 3		43	32 (74.4%)	(58.8%, 86.5%)
> 3		122	72 (59.0%)	(49.7%, 67.8%)
Refractory to				
PI+IMiD		133	82 (61.7%)	(52.8%, 69.9%)
Triple		128	80 (62.5%)	(53.5%, 70.9%)
Penta		50	30 (60.0%)	(45.2%, 73.6%)
Last line of prior therapy		148	90 (60.8%)	(52.5%, 68.7%)
Prior autologous stem cell transplant				
Yes		135	84 (62.2%)	(53.5%, 70.4%)
No		30	20 (66.7%)	(47.2%, 82.7%)
Prior allogenic stem cell transplant				
Yes		8	7 (87.5%)	(47.3%, 99.7%)
No		157	97 (61.8%)	(53.7%, 69.4%)

Percent: 0 25 50 75 100

Total RP2D

	Overall response rate (95% CI)	N	ORR - n(%)	95% CI(%)
Type of myeloma				
IgG		91	61 (67.0%)	(56.4%, 76.5%)
Non-IgG		74	43 (58.1%)	(46.1%, 69.5%)
Baseline ISS				
I		85	64 (75.3%)	(64.7%, 84.0%)
II		57	32 (56.1%)	(42.4%, 69.3%)
III		20	7 (35.0%)	(15.4%, 59.2%)
Baseline Revised ISS (R-ISS)				
I		43	33 (76.7%)	(61.4%, 88.2%)
II		100	61 (61.0%)	(50.7%, 70.6%)
III		13	5 (38.5%)	(13.9%, 68.4%)
Cytogenetic risk				
High-risk		38	23 (60.5%)	(43.4%, 76.0%)
Standard-risk		110	71 (64.5%)	(54.9%, 73.4%)
Bone marrow % plasma cells				
<= 30		111	75 (67.6%)	(58.0%, 76.1%)
> 30 to < 60		31	18 (58.1%)	(39.1%, 75.5%)
>= 60		18	8 (44.4%)	(21.5%, 69.2%)
Baseline tumor BCMA expression (%)				
>= median value		65	38 (58.5%)	(45.6%, 70.6%)
< median value		65	42 (64.6%)	(51.8%, 76.1%)
Baseline extramedullary plasmacytomas				
0		137	94 (68.6%)	(60.1%, 76.3%)
>= 1		28	10 (35.7%)	(18.6%, 55.9%)

Percent (x-axis: 0, 25, 50, 75, 100)

Duration of Response

The median DOR was not reached as of the initial data cut-off. Among responders, median follow-up was 8.0 months (range: 2.4 [subject died] to 18.0) and 91.4% had at least 6 months of follow-up.

With a median follow-up of 14.1 months (data cut-off: 16 March 2022), median DOR for subjects treated at pivotal RP2D (All Treated Analysis Set) was 18.4 months (95% CI: 14.9 to NE) with 68.3% of responders censored **Table 18**).

Results for DOR were generally similar across subgroups (data not shown).

Table 18. DOR Based on IRC assessment (MajesTEC-1 study, data cut-off: 16 March 2022)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: Responders in All Treated Analysis Set	26	78	104
Duration of response (months)[a]			
Number of events (%)	9 (34.6%)	24 (30.8%)	33 (31.7%)
Number of censored (%)	17 (65.4%)	54 (69.2%)	71 (68.3%)
Kaplan-Meier estimate (months)			
25% percentile (95% CI)	13.5 (5.8, NE)	9.2 (6.9, 14.9)	9.5 (7.6, 14.9)
Median (95% CI)	NE (13.5, NE)	14.9 (14.9, NE)	18.4 (14.9, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (14.9, NE)	NE (NE, NE)
Range	(3, 24+)	(1, 16+)	(1, 24+)
6-month event-free rate % (95% CI)	92.1 (72.1, 98.0)	89.5 (80.1, 94.6)	90.1 (82.4, 94.6)
9-month event-free rate % (95% CI)	88.1 (67.6, 96.0)	78.2 (66.9, 86.1)	80.8 (71.5, 87.3)
12-month event-free rate % (95% CI)	76.1 (54.4, 88.5)	66.7 (54.0, 76.6)	68.5 (57.7, 77.1)

Key: CI = confidence interval; NE = not estimable; + = censored observation; RP2D = recommended Phase 2 dose; IRC = independent review committee; IMWG = international myeloma working group; PR = partial response

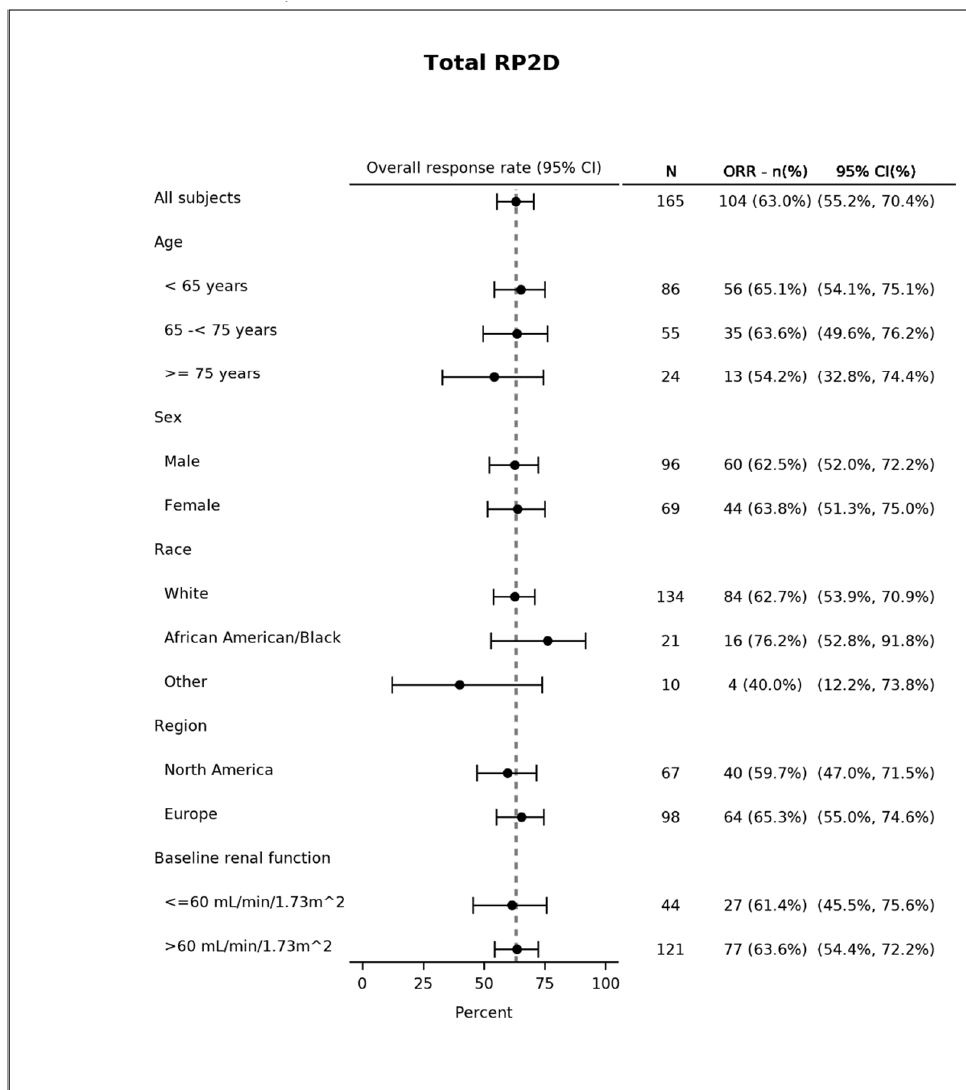[a] Duration of response is calculated as the number of months from first documented response to progression, death due to any cause, or date of censoring.

Note: Number of events refers to number of responders (PR or better) who developed disease progression or died due to any cause.

Note: Response and progression were assessed by IRC, based on IMWG consensus criteria (2016).

Many responses deepened over time (**Figure 5**), with an improved CR or better rate as of the updated clinical cutoff of 39.4%.

Figure 5. Response and follow-up based on Independent Review Committee (IRC) assessment; Responders in the All Treated Analysis Set (MajesTEC-1 study, pivotal RP2D, data cut-off: 16 March 2022)
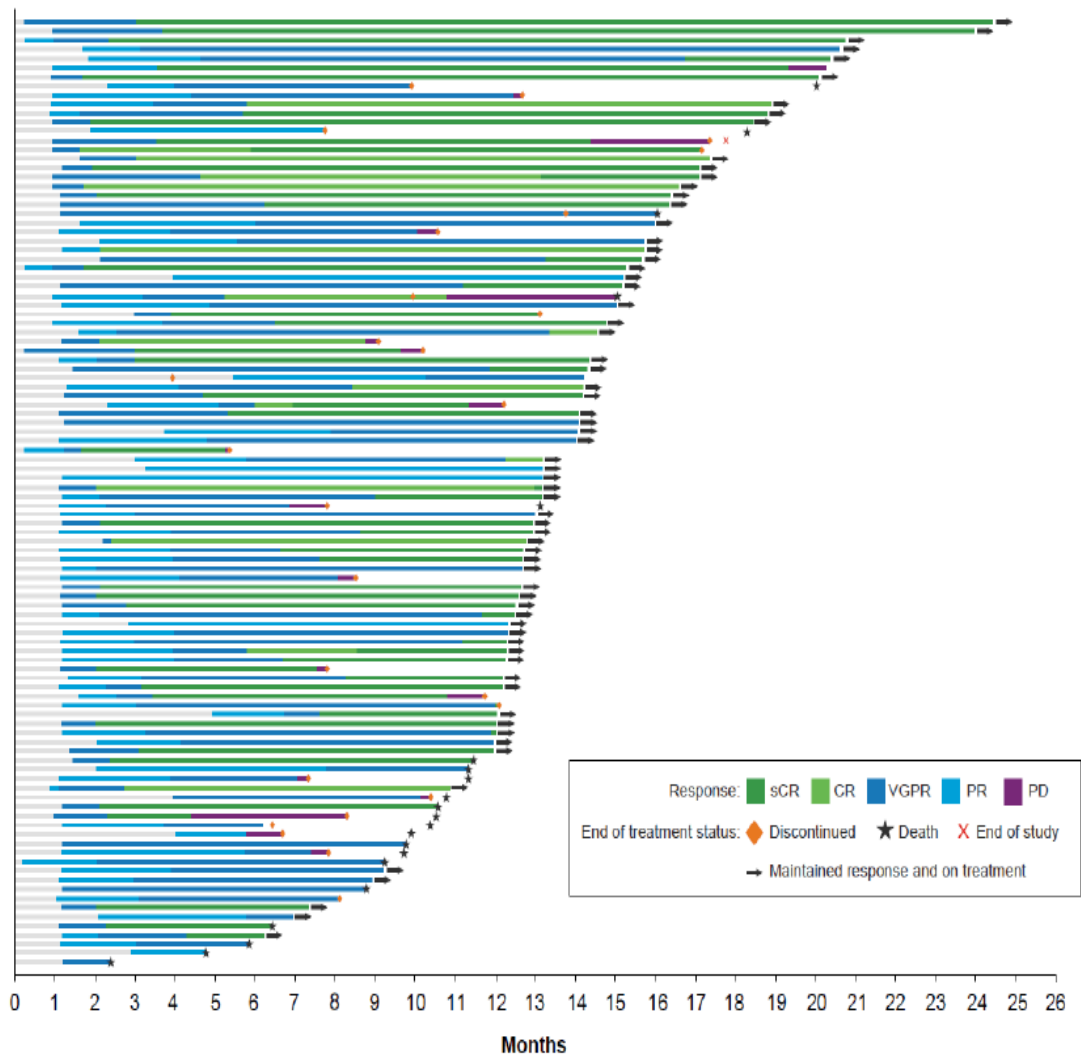
VGPR or better

A best response of VGPR or better as assessed by the IRC was reported for 58.0% (95% CI: 49.7% to 66.0%) of subjects and sCR was reported for 21.3% (95% CI; 15.1% to 28.8%) of subjects at the initial data cut-off of 9 November 2021.

At the updated data cut-off of 16 March 2022 the VGPR or better rate, as assessed by IRC, was 58.8% (95% CI: 50.9% to 66.4%; **Table 19**)

Table 19. Overall Best Confirmed Response based on IRC (MajesTEC-1study, RP2D, phase 1 and Cohort A, phase 2, data cut-off:16 March 2022)

| | RP2D | | | | | |
| | Phase 1 | | Phase 2 Cohort A | | Total | |
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: All Treated	40		125		165	
Response category						
Stringent complete response (sCR)	15 (37.5%)	(22.7%, 54.2%)	39 (31.2%)	(23.2%, 40.1%)	54 (32.7%)	(25.6%, 40.5%)
Complete response (CR)	4 (10.0%)	(2.8%, 23.7%)	7 (5.6%)	(2.3%, 11.2%)	11 (6.7%)	(3.4%, 11.6%)
Very good partial response (VGPR)	6 (15.0%)	(5.7%, 29.8%)	26 (20.8%)	(14.1%, 29.0%)	32 (19.4%)	(13.7%, 26.3%)
Partial response (PR)	1 (2.5%)	(0.1%, 13.2%)	6 (4.8%)	(1.8%, 10.2%)	7 (4.2%)	(1.7%, 8.5%)
Minimal response (MR)	0	(NE, NE)	2 (1.6%)	(0.2%, 5.7%)	2 (1.2%)	(0.1%, 4.3%)
Stable disease (SD)	7 (17.5%)	(7.3%, 32.8%)	20 (16.0%)	(10.1%, 23.6%)	27 (16.4%)	(11.1%, 22.9%)
Progressive disease (PD)	7 (17.5%)	(7.3%, 32.8%)	17 (13.6%)	(8.1%, 20.9%)	24 (14.5%)	(9.5%, 20.9%)
Not evaluable	0	(NE, NE)	8 (6.4%)	(2.8%, 12.2%)	8 (4.8%)	(2.1%, 9.3%)
Overall response (sCR + CR + VGPR + PR)	26 (65.0%)	(48.3%, 79.4%)	78 (62.4%)	(53.3%, 70.9%)	104 (63.0%)	(55.2%, 70.4%)
VGPR or better (sCR + CR + VGPR)	25 (62.5%)	(45.8%, 77.3%)	72 (57.6%)	(48.4%, 66.4%)	97 (58.8%)	(50.9%, 66.4%)
CR or better (sCR + CR)	19 (47.5%)	(31.5%, 63.9%)	46 (36.8%)	(28.4%, 45.9%)	65 (39.4%)	(31.9%, 47.3%)

Key: CI = confidence interval; NE = not estimable; RP2D = recommended Phase 2 dose; IRC = independent review committee; IMWG = international myeloma working group
Note: Response was assessed by IRC, based on IMWG consensus criteria (2016).
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.
Note: Exact 95% confidence intervals are provided.

Time to Response

The median time to first response (PR or better), best response, VGPR or better, and CR or better was 1.2, 3.8, 2.1, and 3.5 months, respectively at the time of the 16 March 2022 data cut-off, consistent with the initial 9 November cut-off date. (1.2, 3.1, 2.1, and 3 months, respectively).

Progression-Free Survival

At the time of the initial 9 November cut-off date, median PFS was 10.1 months (95% CI: 8.0 to NE) in the Efficacy Analysis Set (N=150). With a median follow-up of 14.1 months, median PFS based on assessment was 11.3 months (95% CI: 8.8 to 17.1 months) in the All Treated Analysis Set. The estimated PFS rate at 12 months was 48.3% (95% CI: 40.0% to 56.0%). months) in the All Treated Analysis Set. The estimated PFS rate at 12 months was 48.3% (95% CI: 40.0% to 56.0%).

Overall Survival

With a median follow-up of 14.1 months (16 March 2022 data cut-off), median OS based on IRC assessment was 18.3 months (95% CI: 15.1 months to NE) in the All Treated Analysis Set and not yet mature. Estimated OS at 6 months was 80.3% (95% CI: 72.9% to85.9%) and at 9 months it was 77.2% (95% CI: 69.2% to 83.4%).

Minimal Residual Disease

With a median follow-up of 14.1 months, 44 subjects (26.7%; 95% CI: 20.1% to 34.1%) achieved MRD negativity at 10^{-5}. Among subjects with CR or better by IRC, 30 of 65 subjects (46.2%; 95% CI: 33.7% to 59.0%) achieved MRD negativity at 10^{-5}.

Exploratory endpoints

Time to Next Treatment

Subsequent anti-myeloma therapy and/or death due to progressive disease was reported for 51 subjects (34.0%), with a median time to next treatment of 12.7 months (95% CI: 10.7 to NE).

Patient-reported Outcomes

EORTC QLQ-C30

Meaningful improvement from baseline to Cycles 2, 4, and 6 was reported by up to 35.8% of subjects for global health status, up to 23.9% of subjects for physical functioning, up to 68.7% of subjects for fatigue, and up to 78.8% of subjects for pain score.

EQ-5D-5L

Meaningful (7-point) improvement from baseline in VAS scores using the literature-based at Cycles 2, 4, and 6 was reported by 23.8%, 28.6%, and 30.2% of subjects, respectively

Patient Global Impression

At baseline, 13.7% of subjects reported disease severity was none or mild; at Cycles 2, 4, and 6, 25.9%, 47.7%, and 55.4% of subjects, respectively, reported disease severity was none or mild.

- **Ancillary analyses**

Efficacy data from phase 2 part of the study 64007957MMY1001 (Cohort C)

A total of 40 subjects received at least 1 dose of teclistamab in Cohort C (i.e., subjects with prior anti-BCMA therapy) in Phase 2 on or before the clinical cutoff of 16 March 2022 and were included in the All-Treated Analysis Set for Cohort C (**Table 20**).

Table 20.Treatment disposition; All Treated Analysis Set (MajesTEC-1 study; Cohort C, data cut-off date: 16 March 2022)

	Phase 2 Cohort C
Analysis set: All Treated	40
Subjects who are still on treatment	17 (42.5%)
Subjects who discontinued study drug	23 (57.5%)
Reason for discontinuation	
Progressive disease	14 (35.0%)
Death	7 (17.5%)
Death - COVID-19	2 (5.0%)
Physician decision	2 (5.0%)

Of the total deaths (n=17), 6 (15% of all subjects treated in Cohort C) occurred within 60 days of the first dose of teclistamab. During this time period, 3 subjects (7.5%) died due to progressive disease, 1 subject died due to COVID-19 (reported as an AE), 1 subject died due to cardiac failure (reported as an AE), and 1 subject died due to coronary artery dissection (reported as an AE).

Median follow-up of 12.5 months (range 0.66 [subject died] to 14.42).

Demographics and baseline characteristics

In the All-Treated Analysis Set, the median age of subjects treated in Cohort C was 63.5 years (range: 32 to 82). Twenty-five subjects (57.5%) were male and 15 (36.8%) were female. Most subjects (30 [75%]) had an ECOG score of 1.

The median time from diagnosis of multiple myeloma to enrollment in the study was 6.5 years (range: 1.1 to 24.1). Eleven subjects (28.9%) had 1 or more extramedullary plasmacytomas at baseline. Of the 34 subjects with baseline cytogenetic data reported, 11 subjects (32.4%) had at least 1 high-risk abnormality, most commonly del(17p). Among all subjects treated in Cohort C, 20 (52.6%) were ISS Stage I and 9 (23.7%) were ISS Stage III.

Prior Exposure

All subjects treated in Cohort C received at least 3 prior lines of multiple myeloma therapy, 11 subjects (28.9%) received 5 prior lines of therapy, and 20 (52.6%) received more than 5 prior lines of therapy. The median number of lines of prior therapy was 6 (range: 3 to 14). All 38 subjects (100.0%) were triple-class exposed (PI, IMiD, and anti-CD38 monoclonal antibody) and a majority were penta-exposed (at least 2 PIs, at least 2 IMiDs, and at least 1 anti-CD38 monoclonal antibody; 30 subjects [78.9%]). Per inclusion criteria for Cohort C, all subjects (100.0%) received prior anti-BCMA therapy. Among those treated in Cohort C, 89.5% had prior transplant.

Overall Response Rate by IRC

ORR (PR or better) as assessed by the IRC was 52.5% (95% CI: 36.1% to 68.5%; **Table 21**).

Table 21. Summary of Overall Best Confirmed Response based on IRC Assessment; Efficacy Analysis Set (MajesTEC-1 study; Cohort C, data cut-off: 16 March 2022)

	Phase 2 Cohort C	
	n (%)	95% CI for %
Analysis set: All Treated	40	
Response category		
Stringent complete response (sCR)	11 (27.5%)	(14.6%, 43.9%)
Complete response (CR)	0	(NE, NE)
Very good partial response (VGPR)	8 (20.0%)	(9.1%, 35.6%)
Partial response (PR)	2 (5.0%)	(0.6%, 16.9%)
Minimal response (MR)	0	(NE, NE)
Stable disease (SD)	6 (15.0%)	(5.7%, 29.8%)
Progressive disease (PD)	10 (25.0%)	(12.7%, 41.2%)
Not evaluable	3 (7.5%)	(1.6%, 20.4%)
Overall response (sCR + CR + VGPR + PR)	21 (52.5%)	(36.1%, 68.5%)
VGPR or better (sCR + CR + VGPR)	19 (47.5%)	(31.5%, 63.9%)
CR or better (sCR + CR)	11 (27.5%)	(14.6%, 43.9%)

Key: CI = confidence interval; NE = not estimable; IRC = independent review committee; IMWG = international myeloma working group
Note: Response was assessed by IRC, based on IMWG consensus criteria (2016).
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.
Note: Exact 95% confidence intervals are provided.
[tefresp01cohc.rtf] [jnj-64007957/mmy1001_p3/dbr_asco_ash_ema/re_asco_ash_ema/tefresp01cohc.sas] 29APR2022, 00:40

Seven responses deepened over time, from an initial response of PR or VGPR, to a best response of VGPR or better. Responses were ongoing for 8 of 10 subjects at the clinical cut-off.

Subgroup Analysis of ORR

ORR by prior anti-BCMA therapy was 55.2% (95% CI: 35.7% to 73.6%) among subjects who had progressed after receiving a BCMA-directed ADC and 53.3% (95% CI: 26.6% to 78.7%)) among subjects who had progressed after receiving a BCMA-directed CAR-T (16 March 2022 data cut-off).

A similar percentage of subjects in Cohort C responded to teclistamab after prior anti-BCMA therapy, regardless of refractoriness to prior therapies. ORR was generally similar across other prespecified subgroups, but small sample sizes limits interpretation.

Duration of Response

With a median follow-up of 11.8 months (representing >6 months of additional follow-up) among responders in the All Treated Analysis set of Cohort C, median DOR (time from first response to disease progression or death due to any cause) was not reached. At 12 months, it was estimated that 63.5% (95% CI: 26.0% to 85.8%) of subjects were still in response, with 4 of 21 responders (19%) at risk at this time point at the clinical cutoff.

Minimal Residual Disease Negativity

7 subjects (17.5%; 95% CI: 7.3% to 32.8%) achieved MRD negativity at 10^{-5}. Among subjects with CR or better by IRC, 7 of 11 subjects (63.6%; 95% CI: 30.8% to 89.1%) achieved MRD negativity at 10^{-5}.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22. Summary of Efficacy for trial Summary of efficacy for trial 64007957MMY1001 (MajesTEC-1)

Title: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanised BCMA×CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma		
Study identifier	**64007957MMY1001 (MajesTEC-1), 2016-002122-36, NCT03145181 (Phase 1), NCT04557098 (Phase 2), CR108859**	
Design	Single-arm, first-in-human, open-label, multi-centre, Phase 1/2 Study.	
	The study includes 3 parts: Part 1 (dose escalation), Part 2 (dose expansion), and Part 3 (Phase 2)	
	Duration of main phase:	First subject dosed on 28 June 2017 and the study is currently ongoing; Clinical cut-off 16 March 2022.
		Study drug to be administered to subjects until disease progression, unacceptable toxicity, withdrawal of consent, death, or end of study (defined as 2 years after the last subject's first dose).
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable

Hypothesis	Part 1 & 2 (Phase 1): Exploratory:
	• Part 1: To identify the proposed RP2D(s) and schedule assessed to be safe for teclistamab
	• Part 2: To characterise the safety and tolerability of teclistamab at the proposed RP2D(s)
	Part 3 (Phase 2): To evaluate the efficacy of teclistamab at the RP2D:
	Cohort A: Patients who were triple-class exposed (PI, IMiD, and anti CD38 monoclonal antibody) and received ≥3 prior lines of therapy
	• Treatment with teclistamab will have significant anti-myeloma activity (lower limit of the two-sided 95% confidence interval for ORR is greater than 30%)
	Cohort C: Patients who have previously received ≥3 prior lines of therapy that included a PI, an IMiD, an anti-CD38 monoclonal antibody, and an anti-BCMA treatment (with CAR T cells or ADC).
	• Treatment with teclistamab will result in an ORR >15%

Treatments groups	**Part 1 -Dose Escalation** **Intravenous (IV)**	Intravenous (IV) dosing ranging from 0.0003 to 0.0192 mg/kg once every two weeks (Q2W) at start and switched to weekly dosing range of 0.0192 to 0.72 mg/kg. Half of all IV treatment doses were preceded by step-up dosing. Cycles were 21 days in length.
		• Eight cohorts no step-up dose. Treatment dose of 0.0003-0.0192 mg/kg. Seven cohorts with Q2W dosing, 1 with weekly dosing.
		• 0.0384 mg/kg weekly dosing. One cohort without step-up dosing and one cohort with one step-up dose.
		• 0.0576 mg/kg weekly dosing. One-step up dose.
		• 0.08 mg/kg weekly dosing. One cohort with one step-up dose. One cohort with two step-up doses
		• 0.12 mg/kg weekly dosing with two step-up doses
		• 0.18 mg/kg weekly dosing with two step-up doses
		• 0.27 mg/kg weekly dosing with two step-up doses
		• 0.72 mg/kg weekly dosing with three step-up doses
	Part 1 -Dose Escalation **Subcutaneous (SC)**	Subcutaneous (SC) dosing ranging from 0.08 to 1.5mg/kg weekly dosing. All SC treatment doses were preceded by step-up dosing.
		• 0.08 mg/kg weekly dosing with one step-up dose
		• 0.24 mg/kg weekly dosing with two step-up doses
		• 0.72 mg/kg weekly with two step-up doses
		• 1.5 mg/kg weekly with two step-up doses
		• 3 mg/kg weekly with three step-up doses
		• 6 mg/kg weekly with three step-up doses
		Additional cohorts exploring weekly weight-based treatment higher than RP2D and other dosing schedules for SC administration (up to 6 mg/kg and with flat dosing) also evaluated to inform future schedules.
	Part 2 – Dose Expansion	Weekly treatment at proposed RP2D for either IV (0.72mg/kg) or SC (1.5mg/kg)

	Part 3 – Phase 2		Weekly SC dose of 1.5mg/kg preceded by 2 step up doses; cycles were 28 days in length • Cohort A – 110 subjects who prior to enrolment in trial received at least 3 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody and excluding a BCMA-targeting treatment • Cohort C –25 subjects in efficacy set whose prior therapy must have included an anti-BCMA treatment (ADC or CAR-T) in addition to requirement to have received at least 3 prior lines of therapy that included the 3 therapeutic classes above.
Endpoints and definitions	Phase 1 (Parts 1 and 2) - Primary endpoint	MTD and RP2D	Determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D).
	Phase 2 (Part 3) – Primary endpoint	ORR	ORR defined as the proportion of subjects who achieve a partial response (PR) or better during or after study treatment but before the start of subsequent anti-myeloma therapy. ORR was accessed by the Independent Review Committee (IRC) and based on International Myeloma Working Group (IMWG) criteria.
	Phase 2 (Part 3)- Key secondary endpoints	VGPR or better rate	Very good partial response (VGPR) or better rate was defined as the proportion of participants achieving VGPR, complete response (CR), or stringent complete response (sCR) according to the IMWG criteria, during or after the study intervention but before the start of subsequent anti-myeloma therapy.
		CR or better rate	Complete response (CR) or better rate was defined as the proportion of participants achieving CR or sCR according to the IMWG response criteria, during or after the study intervention but before the start of subsequent anti-myeloma therapy.
		sCR rate	Stringent complete response (sCR) rate was defined as the proportion of participants achieving sCR according to the IMWG response criteria, during or after the study intervention but before the start of subsequent antimyeloma therapy.
		DOR	Duration of response (DOR) was to be calculated among responders (with a PR or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease (PD) as defined in the IMWG Criteria, or death due to any cause, whichever occurs first
		MRD-negativity	Minimal residual disease (MRD) negativity rate is defined as the proportion of subjects who have negative MRD at 10^{-5} threshold of sensitivity by bone marrow aspirate at any time point after initial dosage and before disease progression or starting subsequent therapy or retreatment
		Time to Response (TTR)	Time to first response (PR or better), best response, and CR or better; based on IRC assessment

		PFS	Progression-free survival (PFS) is defined as the time from the date of initial treatment to the date of first documented disease progression based on IMWG criteria, or death due to any cause, whichever occurs first.
		OS	Overall survival (OS) is measured from the date of initial treatment to the date of the subject's death.
Database lock (DBL)	The protocol-specified clinical cut-off date for the primary analysis: 07 September 2021 The updated clinical cut-off which provided updated efficacy results for the primary efficacy endpoint and key secondary efficacy endpoints with an additional 2 months of follow up: 09 November 2021		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Primary efficacy data are presented for subjects from the pivotal RP2D, which includes 40 subjects treated in Phase 1 and 125 subjects treated in Cohort A in Phase 2 (n=165). Efficacy analyses for the primary and key secondary efficacy analyses in these subjects were based on a 16 March 2022 clinical cut-off. The median duration of follow-up for all 104 responders in the Efficacy Analysis Set was 14.1 months (range: 2.4 [subject died] to 24.4 months)	
Descriptive statistics and estimate variability	**Treatment Group**	**Efficacy Analysis Set**
	n	165
	ORR (%)	63.0
	95% CI (%)	55.2% to 70.4%
	VGPR or better rate (%)	58.8
	95% CI (%)	50.9 to 66.4
	CR or better rate (%)	39.4
	95% CI (%)	31.9% to 47.3%
	sCR rate (%)	32.7
	95% CI (%)	25.6% to 40.5%
	Median DOR (months)[1]	18.4
	95% CI (months)	14.9 to not evaluable
	Probability of Patients with DOR (%)	At 6 months: 91.0 At 9 months: 80.8 At 12 months: 68.5
	95% CI (%)	At 6 months: 82.4 to 94.6 At 9 months: 71.5 to 87.3 At 12 months:57.7 to 77.9
	MRD-negativity (at 10^{-5} threshold of sensitivity) (%)	26.7

95% CI (%)	20.1% to 34.1%	
Time to Response (months)	Time to first response (PR or better): 1.2 Time to best response: 3.8 Time to VGPR or better: 2.1 Time to CR or better: 3.5	
PFS[2] (median months)	11.3	
95% CI	8.8 to 17.1	
OS[3] (median months)	18.3	
95% CI (months)	18.3 to not evaluable	

Notes	1. At the clinical cut-off, median duration of follow-up for 104 responders was 14.1 months and all of these subjects had at least ~10 months of follow-up from initial treatment or had progressed or died 2. PFS calculated with a median follow-up of 14.1 months. 3. OS data are not mature with 58.8% of subjects censored.
Effect estimate per comparison	Not applicable, single-arm study

Clinical studies in special populations

Elderly patients included in the pivotal RP2D population (N=165), all subjects treated in the study who were naïve to prior anti-BCMA therapy (N=302), and the All Treated Analysis Set for Cohort C (ie, subjects with prior anti- BCMA therapy) in Phase 2 are summarised in **Table 23**.

Table 23. Summary of elderly subjects in pivotal studies with teclistamab

	Age 65-74 (Older subjects number/total number)	Age 75-84 (Older subjects number/total number)	Age 85+ (Older subjects number/total number)
Pivotal RP2D Population (N=165)	55/165 subjects (33.3%)	24/165 subjects (14.5%)	0
All anti-BMCA-naïve Subjects Treated in MajesTEC-1	103/302 subjects (34.1%)	39/302 subjects (12.9%)	0
Cohort C	14/40 subjects (35.0%)	3/40 subjects (7.5%)	0

In vitro biomarker test for patient selection for efficacy

No biomarker test is proposed to be used for patient selection.

Teclistamab targets BCMA, a receptor expressed on differentiated plasma cells, a subset of mature B cells in lymphoid tissue, and on myeloma cells. BCMA expression increases with disease progression and soluble BCMA in serum acts as a prognostic factor for survival and indicator for response for therapy. Myeloma cells express BCMA almost uniformly, level ranging from 400 to 4000 receptors/cell.

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Supportive study

Efficacy data from phase 1 part of the study 64007957MMY1001 (MajesTEC-1) (dose escalation/ dose expansion)

A total of 177 subjects received at least 1 dose of teclistamab in Phase 1 on or before the clinical cut-off of 07 September 2021 and were included in the All Treated Analysis Set for Phase 1.

From the All Treated Analysis Set, 74 subjects (41.8%) treated in Phase 1 have discontinued study participation. Sixty-five subjects (36.7%) completed the study at time of death, 6 (3.4%) withdrew consent, and 3 (1.7%) were lost to follow-up

The proportion of subjects enrolled in cohorts for teclistamab IV who discontinued the study (57.1%) is larger than that for teclistamab SC (28.0%), commensurate with lower treatment doses evaluated for teclistamab IV and the fact that the first response was not observed until the tenth dose escalation cohort for teclistamab IV (treatment dose of 0.0384 mg/kg, with a step-up dose of 0.0192 mg/kg; see Section 5.4.2.1). Additionally, enrollment for teclistamab IV occurred earlier in the conduct of the study. A higher incidence of subjects discontinued from the study due to death in cohorts examining teclistamab IV (48.8%) compared with teclistamab SC (25.8%)

As of the clinical cut-off, median duration of follow-up for all subjects treated in Phase 1 (All Treated Analysis Set, was 17.3 months (range: 0.4 to 45.9). Similar to the above, median duration of follow-up was longer for subjects enrolled in cohorts for teclistamab IV (21.4 months [range: 0.6 to 45.9]) compared with that for teclistamab SC (12.6 months [range: 0.4 to 24.9]).

At least 1 subject in the following 10 cohorts had follow-up exceeding 24 months: 0.0024 mg/kg and 0.0096 mg/kg IV Q2W; 0.0384 mg/kg, 0.0576, 0.08, 0.12, 0.18, 0.27 mg/kg IV weekly; and 0.08 mg/kg SC weekly. Median duration of follow-up for subjects treated at RP2D in Phase 1 (All Treated Analysis Set,) was 12.2 months (range: 1.18 [subject died] to 18.0).

Median follow-up in Efficacy Analysis Set was 18.2 months (range: 0.62 to 45.9) and median follow-up responders (per investigator) was 17.5 months (range: 5.42 [subject died] to 34.9).

Treatment Disposition

Overall, 112 subjects (63.3%) treated in Phase 1 (All Treated Analysis Set) have discontinued teclistamab as of the clinical cut-off (**Table 24**).

Table 24. Treatment Disposition; All Treated Analysis Set (MajesTEC-1 Study, Phase 1, data cut-off: 07 September 2021)

| | Phase 1 IV | | Phase 1 SC | | | | | | | |
| | μg/kg | | μg/kg | | | | | | | |
	10/60/240 then 720	IV Total	20 then 80 & 40/80 then 240	60/240 then 720	60/300 then 1500	60/300/1500 then 3000	60/300/1500 then 6000[a]	30/90/300/1500 then 6000 monthly[b]	SC Total	Overall Total
Analysis set: All Treated	15	84	13	15	40	5	10	7	93	177
Subjects who are still on treatment	5 (33.3%)	14 (16.7%)	5 (38.5%)	4 (26.7%)	20 (50.0%)	3 (60.0%)	10 (100.0%)	6 (85.7%)	51 (54.8%)	65 (36.7%)
Subjects who discontinued study drug	10 (66.7%)	70 (83.3%)	8 (61.5%)	11 (73.3%)	20 (50.0%)	2 (40.0%)	0	1 (14.3%)	42 (45.2%)	112 (63.3%)
Reason for discontinuation										
Progressive disease	7 (46.7%)	54 (64.3%)	6 (46.2%)	8 (53.3%)	16 (40.0%)	1 (20.0%)	0	0	31 (33.3%)	85 (48.0%)
Adverse event	3 (20.0%)	8 (9.5%)	1 (7.7%)	2 (13.3%)	0	0	0	0	3 (3.2%)	11 (6.2%)
Adverse event - COVID-19	0	0	0	0	0	0	0	0	0	0
Physician decision	0	4 (4.8%)	1 (7.7%)	1 (6.7%)	3 (7.5%)	0	0	1 (14.3%)	6 (6.5%)	10 (5.6%)
Death	0	3 (3.6%)	0	0	0	1 (20.0%)	0	0	1 (1.1%)	4 (2.3%)
Death – COVID-19	0	2 (2.4%)	0	0	0	0	0	0	0	2 (1.1%)
Withdrawal by subject	0	1 (1.2%)	0	0	1 (2.5%)	0	0	0	1 (1.1%)	2 (1.1%)

Key: IV = intravenous; SC = subcutaneous
[a] 6000μg/kg (weekly for 2 cycles, then biweekly, and then monthly after 6 cycles).
[b] 6000μg/kg monthly after step-up doses.
Note: IV total includes all IV treatment groups. SC dosing was weekly except 6000μg/kg (weekly for 2 cycles, then biweekly, and then monthly after 6 cycles), 6000μg/kg monthly, and 300mg flat dosing (150mg weekly for 2 cycles, then 300mg biweekly which is only included in the SC and overall total).
Note: Percentages are based on the number of all treated subjects.

Demographics

In the All Treated Analysis Set, the median age of subjects treated in phase 1 was 64.0 years (range: 24 to 84), with 11.3% being at least 75 years of age. Three subjects were 80 years or older. Ninety-five subjects (53.7%) were male and 82 (46.3%) were female.

Most subjects (104 [58.8%]) had an ECOG score of 1 and 88 subjects (49.7%) were enrolled at sites in the EU (including the UK). Of the 147 subjects with baseline cytogenetic data reported, 45 (30.6%) had at least 1 high-risk abnormality, most commonly del(17p). Of the 174 subjects with baseline ISS data reported, 84 (48.3%) were ISS Stage I and 35 (20.1%) were ISS Stage III.

Prior Systemic Therapies

Overall, 170 of the 177 subjects treated in Phase 1 received at least 3 prior lines of multiple myeloma therapy. Among all subjects treated in Phase 1, the median number of lines of prior therapy was 5.0 (range: 2 to 14). One hundred and seventy-one subjects (96.6%) were triple-class exposed (PI, IMiD, and anti-CD38 monoclonal antibody) and a majority were penta-exposed (at least 2 PIs, at least 2 IMiDs, and at least 1 anti-CD38 monoclonal antibody; 117 subjects [66.1%]). Among all subjects treated in Phase 1, 83.6% has prior transplant.

Refractory Status

Among all subjects treated in Phase 1, 160 (90.4%) were refractory to their last line of therapy. One hundred-and-forty subjects (79.1%) were triple-class refractory (PI, IMiD, and anti-CD38 monoclonal antibody), and 67 (37.9%) were penta-refractory (at least 2 PIs, at least 2 IMiDs, and at least 1 anti-CD38 monoclonal antibody). Among the 40 subjects treated at RP2Din phase 1, 32 (80.0% of the cohort) were triple-class refractory and 16 (40.0% of the cohort) were penta-refractory. Refractory status in the Efficacy Analysis Set for subjects treated in phase 1 and key cohorts and was not notably different from that in the All Treated Analysis Set.

Efficacy

For dose escalation/dose expansion efficacy data, the Efficacy Analysis Set for Phase 1 included 156 subjects who received their first dose of teclistamab on or before 18 March 2021.

Selected efficacy endpoints were analysed in the subset of these subjects who responded to teclistamab (PR or better).

Efficacy results in this section are exploratory and are intended to be supportive of the primary efficacy analyses at pivotal RP2D.

This section focuses on the robust efficacy results observed in Phase 1 for RP2D of 1.5 mg/kg SC weekly (N=40) and for 0.72 mg/kg SC weekly (N=15), which supported dose selection for RP2D. Efficacy results are also discussed for the dose-expansion cohort of 0.72 mg/kg IV weekly (N=15).

In the Efficacy Analysis Set for phase 1, responses (PR or better) were seen at treatment doses of 0.0384 mg/kg (with 0.0192 mg/kg step-up dose) IV weekly or higher, and in every SC weekly dosing cohort (**Table 25**).

Table 25. Summary of Overall Best Confirmed Response Based on Investigator Assessment; Efficacy Analysis Set ((MajesTEC-1 Study, Phase 1, data cut-off: 07 September 2021)

	Phase 1 IV	Phase 1 SC				
	µg/kg	µg/kg				
	10/60/240 then 720	20 then 80 & 40/80 then 240	60/240 then 720	60/300 then 1500	60/300/1500 then 3000	SC Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Analysis set: Efficacy	15	13	15	40	4	72
Response category						
Stringent complete response (sCR)	1 (6.7%)	0	2 (13.3%)	9 (22.5%)	1 (25.0%)	12 (16.7%)
Complete response (CR)	5 (33.3%)	6 (46.2%)	3 (20.0%)	9 (22.5%)	1 (25.0%)	19 (26.4%)
Very good partial response (VGPR)	4 (26.7%)	0	4 (26.7%)	7 (17.5%)	2 (50.0%)	13 (18.1%)
Partial response (PR)	0	0	0	1 (2.5%)	0	1 (1.4%)
Minimal response (MR)	0	0	0	0	0	0
Stable disease (SD)	2 (13.3%)	4 (30.8%)	2 (13.3%)	7 (17.5%)	0	13 (18.1%)
Progressive disease (PD)	3 (20.0%)	3 (23.1%)	4 (26.7%)	7 (17.5%)	0	14 (19.4%)
Not evaluable (NE)	0	0	0	0	0	0
Overall response						
(sCR + CR + VGPR + PR)	10 (66.7%)	6 (46.2%)	9 (60.0%)	26 (65.0%)	4 (100.0%)	45 (62.5%)
VGPR or better (sCR + CR + VGPR)	10 (66.7%)	6 (46.2%)	9 (60.0%)	25 (62.5%)	4 (100.0%)	44 (61.1%)
CR or better (sCR + CR)	6 (40.0%)	6 (46.2%)	5 (33.3%)	18 (45.0%)	2 (50.0%)	31 (43.1%)

Key: CI=confidence interval; NE=not estimable; IV=intravenous; SC=subcutaneous; IMWG=international myeloma working group
Note: Response and progression were assessed by investigator based on IMWG consensus criteria (2011).
Note: Percentages calculated with the number of subjects in the efficacy analysis set as denominator.
Note: Exact 95% confidence intervals are provided.

Responses were also observed at treatment doses of 0.0384 mg/kg IV weekly (with step-up dosing) or higher and 0.080 mg/kg SC weekly or higher. Responders in the lower dosing cohorts were enrolled earlier and thus had longer follow-up. Many responders to lower doses had durable responses with prolonged follow-up. However, those other dosing cohorts were smaller, limiting interpretation of efficacy-

In Part 2 (dose expansion), a majority of subjects responded to treatment doses of 0.72 mg/kg IV weekly (ORR, 66.7%) or RP2D (ORR, 65.0%). A majority of subjects also responded to the SC dosing regimen of 0.72 mg/kg SC weekly (ORR, 60.0%). ORR was similar across these 3 cohorts.

All responses in the 0.72 mg/kg IV weekly cohort and most responses in the SC weekly cohorts (44 of 45 responses) were VGPR or better. Similar results for ORR were seen among response-evaluable subjects in Phase 1.

Among 10 responders in the 0.72 mg/kg IV weekly cohort, responses were maintained until the clinical cutoff for 7 subjects (all were ongoing responses >6 months from the first treatment dose): 2 subjects were alive after disease progression and 1 subject died (after disease progression).

Among 45 responders to any SC weekly treatment dose for teclistamab, responses were maintained until the clinical cutoff for 32 subjects (all were ongoing responses >6 months after the first treatment dose): 7 subjects were alive after disease progression and 6 subjects died (3 after disease progression, 1 died after discontinuing treatment due to an AE, and 2 after discontinuing treatment for other reasons).

Duration of Response

At treatment doses of 0.72 mg/kg IV weekly, 0.72 mg/kg SC weekly, and RP2D, respectively, 70.0%, 66.7%, and 80.8% of responders were censored with ongoing response, resulting in median DOR that was not reached in these cohorts. The probability of responders remaining in response at 9 months at these doses was 90.0% (95% CI: 47.3% to 98.5%) for 0.72 mg/kg IV weekly, 77.8% (95% CI: 36.5% to 93.9%) for 0.72 mg/kg SC weekly, and 87.5% (95% CI: 66.0% to 95.8%) for RP2D.

Progression-Free Survival

With a median follow-up of 18.2 months overall in the Efficacy Analysis Set, median PFS for 0.72 mg/kg IV weekly was 13.9 months (95% CI: 1.0 to not evaluable) and 7 subjects (among 10 subjects who responded) were censored before a PFS event occurred.

In the 0.72 mg/kg SC weekly cohort, median PFS by investigator assessment was 14.2 months (95% CI: 0.9 to not evaluable) and 6 subjects (among 9 subjects who responded) were censored before a PFS event occurred.

At RP2D, median PFS by investigator assessment was 12.5 months (95% CI: 4.4 to not evaluable) and 23 subjects (among 26 subjects who responded) were censored before a PFS event occurred.

Overall Survival

With a median follow-up of 18.2 months overall in the Efficacy Analysis Set, median OS was 18.9 months (95% CI: 2.8 to not evaluable) for 0.72 mg/kg SC weekly; median OS was not reached for any other SC weekly dose or for 0.72 mg/kg IV weekly.

3.3.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This Conditional Marketing Authorisation (CMA) application is supported by efficacy data from a single, uncontrolled, Phase I/II pivotal study (MMY1001; MajesTEC-1) in triple-exposed subjects with multiple myeloma (i.e. patients with prior exposure to at least an IMiD, a PI and an anti-CD38 mAb). The indication initially claimed for teclistamab was for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior therapies including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

The target population on the pivotal phase 1/2 study represents a MM patient population with multi-refractory disease and most patients were previously treated with several (median of 5 previous) lines

of therapies. The CHMP however requested that the indication proposed by the applicant should be revised to better reflect the patient population of the pivotal study. The enrolled patient population was largely triple refractory, had demonstrated disease progression on the last therapy and was treated with teclistamab monotherapy. The Applicant modified the teclistamab indication to 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.

Dose response was evaluated as a part of the pivotal phase 1/2, study. The dose of 1.5 mg/kg SC weekly (termed as pivotal RP2D) achieved exposure consistently above the EC_{90}.

One limitation of the study is the single-arm design, since the phase 1/2 study was conducted without an active control arm. Because there is no standard treatment for these patients, the missing control arm may therefore be considered acceptable. Single arm study setting always brings uncertainties to efficacy assessment and contextualisation of the results. Concerns regarding single arm study setting in relation to patient population were discussed in Scientific advice procedures during clinical development. On a general level, the CHMP agreed that patients with relapsed and/or refractory multiple myeloma who are triple-class exposed to PI, IMiD and anti-CD38 monoclonal antibody represent a population with poor prognosis and limited therapeutic options.

ORR has been selected as primary endpoint for the Phase II part of study MMY1001: this is acceptable considering the exploratory nature of the trial and the significant rate of refractoriness expected in the study population. Additional measures of depth of response (VGPR or better/CR or better/sCR/MRD negative rates) have also been included to further characterise the extent of cytoreduction with teclistamab. The use of the 2016 IMWG response criteria is in line with current guidelines (see e.g. Dimopoulos MA et al, Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Ann Oncol 2021, and the NCCN guidelines for multiple myeloma, v 5.2022) and endorsed.

The relevance of ORR to inform clinical benefit evaluations is, however, per se, limited, and robust demonstrations of durable responses are needed to conclude for clinical benefit. In this regard, however, reliable interpretations of PFS and OS data, which are the most relevant clinical endpoints to support B/R evaluations in RRMM, are not possible in the absence of proper controls. The importance of sufficient follow-up time and characterisation of duration of response (DOR) is, therefore, emphasised and exposure times should be sufficient to cover the projected exposure periods in clinical practice.

The applicant also included PROs analyses using the EORTC QLQ-C30, EQ-5D-5L and PGIS instruments to investigate changes from baseline in HR-QoL, symptoms and functional parameters. HR-QoL is of pivotal importance for patients with relapsed and refractory MM, since the burden of both disease symptoms and treatment-related toxicity can be considerable. PROs evaluation in an uncontrolled, open-label study is, however, of limited value, since it is not possible to exclude with reasonable certainty that relevant bias (e.g. the positive impact of concomitant treatments aimed at improving symptoms) are present.

The patient population included is a combination of high-risk disease features, high number of prior lines of therapy, high proportion of patients refractory to other treatment options, but with good performance status and of relatively young age. Although exclusion of patients with significant comorbidities is understood from the safety perspective, the criteria applied selected mostly healthy patients, and thus information on tolerability of the treatment in a less fit, older patient population is currently limited. Only patients with a baseline ECOG PS score of 0 or 1 could be enrolled in study MMY1001. It is noted that the inclusion of subjects with an ECOG PS of 2 was advised by the CHMP

(see e.g. EMA/SA/0000050045) to increase results generalisability to frailer patients. To adequately describe the enrolled patient population, this information is now included in section 5.1 of the SmPC.

Sample size calculations for Cohorts A and C in study MMY1001 are formally correct and acceptable. The clinical relevance of the assumed ORR thresholds to claim efficacy, especially for Cohort A (i.e. ORR 30%), is however uncertain when the currently available alternatives in advanced MM are taken into account (e.g. the ORR is 67% with idecabtagene vicleucel in the ITT population, and 32% and 25.3% with belantamab mafodotin and selinexor, respectively, in a more pre-treated population).

In line with the early, exploratory nature of study MMY1001, the applicant has made several, important amendments to the original study, the most important one being introducing Part 3 (Phase 2) to the initially planned phase 1 study and replacing the originally proposed iv administration with SC dosing instead. While this continuum is most likely due to a rationale to speed up the development programme of teclistamab, a phase 2 study with a more carefully considered, prespecified and treated (SC) patient population would have been a more preferred solution.

The applicant has also included an explorative cohort to study the efficacy of teclistamab in patients with a previous anti-BCMA treatment (antibody-drug or CAR-T cell) in addition of being at least triple-exposed. Considering the higher unmet medical need of these patients, results from Cohort C are considered of value to further support the possible benefit of the immediate availability of teclistamab through a CMA.

Efficacy data and additional analyses

Dose-response studies in a relapsing/remitting condition such as MM should take into consideration both depth and duration of response as the main efficacy variables to inform dose selection. In this regard, it is agreed that, compared to what observed at the RP2D, the limited available data with lower dose regimens (e.g. 0.72 mg/kg/weekly s.c.) showed a similar ORR (60%) yet with a trend towards reduced response duration. On the other hand, efficacy data with doses higher than 1.5 mg/kg/weekly are limited, especially with respect to the 6 mg/kg sc regimens.

Published data (see e.g. Chen H et al, Leuk Res 2019) highlighted how the binding of anti-BCMA antibodies to target cells might be negatively impacted by high serum BCMA (sBCMA) levels. Lower response rates were observed in the pivotal study in patients with the highest baseline sBCMA levels (e.g. ≥ third quartile) when compared to patients with lower baseline sBCMA levels: ORR by IRC was 26.8% (95%CI 14.2, 42.9) vs. 75.2% (95%CI 66.5, 82.6), sCR+CR rate 17.1% (95%CI 7.2, 32.1) vs. 46.3% (95%CI 37.2, 55.6). However, PK data did not show a similar effect in terms of teclistamab clearance. The applicant pointed out how subjects in the high baseline sBCMA subgroup were more likely to have features associated with high tumour burden, such as presence of plasmocytoma (36.6% vs. 9.9% in the "higher" and "lower" sBCMA subgroups, respectively), massive bone marrow plasma cell infiltrate (≥60% 20.5% vs. 7.6%, respectively) and advanced ISS stage (stage III 30% vs. 6.7%, respectively). Whether high sBCMA levels should be regarded as generally prognostic or predictive of teclistamab efficacy cannot be answered in the absence of controlled data. The applicant is thus recommended to further investigate the impact of sBCMA on teclistamab PK, PD and efficacy in the ongoing/planned phase III studies

The most updated results (16 March 2022 data cut-off) from patients who received teclistamab at the RP2D in the pivotal trial showed an ORR of 63.0% (95% CI: 55.2% to 70.4%), which can be considered of clinical relevance when contextualised in the current treatment landscape. With the limits of such indirect comparisons in a heterogeneous condition such as MM, the ORR in study MMY1001 compared favourably with the results observed with selinexor and dexamethasone (ORR 25.3%), belantamab mafodotin (ORR 32%) and is in line with idecabtagene vicleucel (ORR 67.1% in the ITT

population) and ciltacabtagene autoleucel (ORR 84%) in advanced settings of relapsed and refractory MM. Several subgroups analyses were performed for the ORR with no clear differences in responses, except in patients with extramedullary disease.

The most updated VGPR or better rate (58.8%, 95% CI: 50.9% to 66.4%), CR or better rate (39.4%, 95% CI: 31.9% to 47.3%) and MRD negativity rate with teclistamab (26.7%; 95% CI: 20.1% to 34.1%)are also considered of interest in such advanced disease setting. It is unclear, however, to what extent teclistamab, being a bispecific antibody, can interfere with immunofixation assays that are required to confirm CR in MM. Since teclistamab is a modified IgG lambda antibody, interference with immunofixation assays could not be excluded. However, CR was adjudicated in a similar fraction of subjects with IgG kappa and IgG lambda M protein, although time to CR was slightly longer for subjects with IgG lambda MM. This finding would suggest that the interference of teclistamab in the assessment of CR by immunofixation might be limited, yet the small sample size does not allow for definitive conclusions. The Applicant is recommended to further evaluate the possible interference of teclistamab in immunofixation techniques.

Subgroup analyses showed that the activity of teclistamab in study MMY1001 was overall consistent irrespectively of age, sex, renal function, ECOG PS score, extent of refractoriness, serological type of MM and cytogenetic risk class. Limited numbers in subgroups do not allow, however, for definitive conclusions. It is noticed, however, how a possible trend towards a reduced activity of teclistamab (in terms of both rate/depth of response and response duration) was observed in subgroups defined by measures of increased disease burden (e.g. in subjects with higher ISS stage or with increased bone marrow plasma cells). Limited information is available to address this issue: no data on the effect of higher doses of teclistamab in subjects with high MM burden was available, and the relative weight of tumour burden and sBCMA levels on the observed reduction of teclistamab activity could not be disentangled due to the limited sample size and the absence of controlled data. Additional data from the ongoing phase III studies are needed to further understand the role of measures of tumour burden on teclistamab efficacy and the adequacy of the proposed dosing regimen for all subjects in the claimed indication.

This MAA for teclistamab is supported by a single, uncontrolled pivotal trial. Considering the limited sample size and the lack of control, it is important to note that response rates were consistent across all regions/sites.

Duration of response is essential for demonstration of clinical benefit. At the time of the initial submission, median DOR was not estimable with 80.9% of responders censored in the Efficacy Analysis Set (N=150). With a median follow-up of 14.1 months (representing >4 months of additional follow-up) as of the updated clinical cutoff, median DOR for subjects treated at pivotal RP2D (All Treated Analysis Set) was 18.4 months (95% CI: 14.9 to NE) with 68.3% of responders censored. The 12-month DOR rate was estimated to be 68.5%

At the time of the initial submission, median PFS was 10.1 months (95% CI: 8.0 to NE) in the Efficacy Analysis Set (N=150). With a median follow-up of 14.1 months, median PFS based on IRC assessment was 11.3 months (95% CI: 8.8 to 17.1 months). The estimated PFS rate at 12 months was 48.3% (95% CI: 40.0% to 56.0%).

Progression-free survival was defined as the time from the date of first dose of study intervention to the date of first documented disease progression or death due to any cause, whichever occurs first. For participants who have not progressed and are alive, data were censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. However, according to the EMA guideline (Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man. Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials, EMA/CHMP/27994/2008/Rev.1), "informative" censoring should be taken into account. A

sensitivity analysis was performed to address this issue. This analysis considers 13 additional subjects to have had a PFS event compared with the initial analysis, 11 of whom had discontinued treatment. By this more conservative definition, median PFS was 9.8 months (95% CI: 6.9 to 12.5 months). The estimated PFS rate at 12 months was 43.8 % (95% CI: 36.0% to 51.4%).

With a median follow-up of 14.1 months, median OS based on IRC assessment was 18.3 months (95% CI: 15.1 months to NE) and not yet mature.

The provided MRD data suggest that most of the CR/sCR responses are deep which is important. From the pooled MRD data from the literature, even in the last line treatment, it seems that with deeper responses at least the DOR could be improved. With a median follow-up of 14.1 months (representing >4 months of additional follow-up), 44 subjects (26.7%; 95% CI: 20.1% to 34.1%) achieved MRD negativity at 10-5.). Among subjects with CR or better by IRC, 30 of 65 subjects (46.2%; 95% CI: 33.7% to 59.0%) achieved MRD negativity at 10-5.

The study included an additional independent cohort of (Cohort C) 38 participants who had also received prior anti-BCMA targeted therapy. The updated ORR for 40 evaluable patients was 52.5% (95% CI: 36.1% to 68.5%) and prior ADC was 55.2% (95% CI: 35.7% to 73.6%) and 53.3% (95% CI: 26.6% to 78.7%) among receiving a prior BCMA-directed CAR-T. The median DOR was 11.8 months.

Additional efficacy data needed in the context of a conditional MA

The demonstration of efficacy relies on one pivotal single arm study. This poses well known limitations with regards to interpretation of data, in particular with regards to assessment of time to event endpoints. These uncertainties will be addressed by results from the ongoing Phase III study (MMY3001; MajesTEC-3) investigating the efficacy of teclistamab in combination with sc. daratumumab vs. investigator's choice (DPd or DVd) in adults with relapsed/refractory multiple myeloma in an earlier treatment stage (i.e. 1 to 3 prior lines of therapy including lenalidomide and a PI). Although the study enrols a less heavily pre-treated patient population, and teclistamab is administered in combination with daratumumab, the study is considered adequate to address this issue and provide relevant data on PFS (primary endpoint) and OS. Completion of this study is expected in Q1 2028.

The pivotal study MajesTEC-1 is currently on-going. Although additional follow-up data as requested by the CHMP (most recent data cut-off 16 March 2022) have been provided during the procedure, long-term efficacy and safety cannot yet be comprehensively characterised, and the final CSR of the study MajesTEC-1 will be provided.

3.3.4. Conclusions on the clinical efficacy

The clinical efficacy data submitted in this MAA support the benefit of teclistamab in the final agreed indication.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- Final study report of the pivotal study 64007957MMY1001 (MajesTEC-1) should be provided.

- Final study report additional efficacy (particularly time-dependent endpoints PFS and OS) and safety data from study MMY3001; MajesTEC-3 investigating the efficacy of teclistamab in

combination with sc. daratumumab vs. investigator's choice (DPd or DVd) in adults with relapsed/refractory multiple myeloma should be provided.

In addition, it is recommended that the Applicant further evaluates the possible interference of teclistamab in immunofixation techniques.

3.3.5. Clinical safety

Patient exposure

In total, safety data are provided for 342 subjects who received at least 1 dose of teclistamab monotherapy by 16 March 2022. Primary safety data are summarised for 165 subjects on the pivotal recommended Phase 2 dose (RP2D; 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg) in MajesTEC-1, who received their first dose of teclistamab by 16 March 2022. Supportive safety data are presented for 137 subjects treated with other subcutaneous (SC) teclistamab doses (i.e., non-RP2D [n=53]) or with intravenous (IV) teclistamab (n=84) in Phase 1 of MajesTEC-1, as well as for 40 subjects in Cohort C of MajesTEC-1 Phase 2 (i.e., subjects having received a prior anti-BCMA therapy), who received their first dose of teclistamab before the clinical cut-off. The maximum dose explored with SC dosing has been 6 mg/kg teclistamab weekly for 2 cycles, then biweekly, and then monthly after 6 cycles.

The "Total All Treated Analysis Set", includes 302 subjects on pivotal RP2D, SC non-RP2D, or IV treatment but excludes Cohort C subjects.

In addition to the 342 subjects in MajesTEC-1, 54 subjects have been treated with teclistamab in combination with daratumumab SC with and without pomalidomide in Study 64407564MMY1002 (TriMM-2), 39 subjects have been treated with teclistamab in combination with talquetamab and daratumumab in Study 64007957MMY1003 (RedirecTT-1), and 42 subjects have been treated in the platform study 64007957MMY1004 (MajesTEC-2). Apart from an integrated assessment of all hepatobiliary events, no safety data from these other studies exploring combination therapies has been provided for assessment.

In the All Treated Analysis Set, median age was 64.0 years (range: 24 to 84), with 39 subjects (12.9%)
≥75 years old; 165 subjects (54.6%) were male and 137 (45.4%) were female. The median time from diagnosis to enrolment in the study was 6.4 years (range: 0.5 to 26.2). Apart from 6 subjects not previously exposed to an anti-CD38 antibody, all 302 subjects were triple-class exposed (prior PI, prior IMiD, and prior anti-CD38 monoclonal antibody), and 207 subjects (68.5%) were penta-exposed (at least 2 prior PIs, at least 2 prior IMiDs, and at least 1 prior anti-CD38 monoclonal antibody). The median number of lines of prior therapy was 5 (range: 2 to 14). Two hundred forty-nine subjects (82.5%) had prior autologous or allogeneic stem cell transplantation.

In the RP2D group, median age was 64.0 years (range: 33 to 84), with 24 subjects (14.5%) ≥75 years old; 96 subjects (58.2%) were male and 69 (41.8%) were female. The median time from diagnosis to enrolment in the study was 6.0 years (range: 0.8 to 22.7). All 165 subjects (100.0%) were triple-class exposed (prior PI, prior IMiD, and prior anti-CD38 monoclonal antibody), and 116 subjects (70.3%) were penta-exposed (at least 2 prior PIs, at least 2 prior IMiDs, and at least 1 prior anti-CD38 monoclonal antibody). The median number of lines of prior therapy was 5 (range: 2 to 14). One hundred thirty-five subjects (81.8%) had prior autologous or allogeneic stem cell transplantation.

Subject disposition and a summary of the duration of follow-up in the All-Treated analysis set are presented in **Table 26** and **Table 27** respectively.

Table 26. Subject Disposition in MajesTEC-1; All Treated Analysis Set, data cut-off: 16 March 2022

	SC		IV	Total
	RP2D	Non-RP2D		
Analysis set: All Treated	165	53	84	302
Discontinued the study	74 (44.8%)	17 (32.1%)	54 (64.3%)	145 (48.0%)
Reason for discontinuation				
Death	67 (40.6%)	17 (32.1%)	47 (56.0%)	131 (43.4%)
Death – COVID-19	13 (7.9%)	1 (1.9%)	5 (6.0%)	19 (6.3%)
Withdrawal by subject	7 (4.2%)	0	4 (4.8%)	11 (3.6%)
Lost to follow-up	0	0	3 (3.6%)	3 (1.0%)

Key: RP2D=recommended phase 2 dose, SC= Subcutaneous, IV= Intravenous.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Percentages are based on the number of all treated subjects.

Table 27. Summary of Study Duration of Follow-up in MajesTEC-1; All Treated Analysis Set, data cut-off: 16 March 2022

	SC		IV	Total
	RP2D	Non-RP2D		
Analysis set: All Treated	165	53	84	302
Duration of follow-up (months)				
N	165	53	84	302
Mean (SD)	10.824 (5.7088)	14.209 (9.5857)	17.371 (11.9348)	13.239 (9.0019)
Median[a]	14.062	20.731	27.368	16.329
Range	(0.26+; 24.41)	(1.05+; 31.05)	(0.62; 49.35)	(0.26+; 49.35)

Key: RP2D = recommended Phase 2 dose, SC= Subcutaneous, IV= Intravenous.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Duration of follow-up is relative to the date of the first dose (first step-up dose if applicable).
+ Denotes subjects who died.
[a] Based-on Kaplan-Meier product limit estimate.

Treatment disposition is summarised in **Table 28**.

Table 28. Treatment Disposition in MajesTEC-1; All Treated Analysis Set, data cut-off: 16 March 2022

	SC		IV	Total
	RP2D	Non-RP2D		
Analysis set: All Treated	165	53	84	302
Subjects who are still on treatment	70 (42.4%)	28 (52.8%)	11 (13.1%)	109 (36.1%)
Subjects who discontinued study drug	95 (57.6%)	25 (47.2%)	73 (86.9%)	193 (63.9%)
Reason for discontinuation				
Progressive disease	61 (37.0%)	17 (32.1%)	55 (65.5%)	133 (44.0%)
Death	15 (9.1%)	2 (3.8%)	5 (6.0%)	22 (7.3%)
Death – COVID-19	8 (4.8%)	1 (1.9%)	3 (3.6%)	12 (4.0%)
Physician decision	11 (6.7%)	3 (5.7%)	4 (4.8%)	18 (6.0%)
Adverse event	2 (1.2%)	3 (5.7%)	8 (9.5%)	13 (4.3%)
Adverse event - COVID-19	0	0	0	0
Subject refused further treatment[a]	5 (3.0%)	0	1 (1.2%)	6 (2.0%)
Other	1 (0.6%)	0	0	1 (0.3%)

Key: RP2D=recommended phase 2 dose, SC= Subcutaneous, IV= Intravenous.
[a] Subject refused further treatment includes "Withdrawal by subject" from Phase 1.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Percentages are based on the number of all treated subjects.

The median duration of study treatment for the total All Treated Analysis Set was 7.1 months (range: 0.03 to 40.87). One hundred sixty-five subjects (54.6%) received teclistamab monotherapy for at least 6 months, 124 subjects (41.1%) for at least 9 months, 93 subjects (30.8%) for at least 12 months,35 subjects (11.6%) for at least 18 months, and 17 subjects (5.6%) for at least 24 months. The median relative dose intensity for all study treatment, including step-up doses, was 95.9% for the total All Treated Analysis Set.

In the RP2D group, the median duration of treatment was 8.5 months (range: 0.2 to 24.4). Ninety-eight subjects (59.4%) received teclistamab monotherapy for at least 6 months, 79 subjects (47.9%) for at least 9 months, 58 subjects (35.2%) for at least 12 months, 10 subjects (6.1%) for at least 18 months, and 1 subject (0.6%) for at least 24 months. Subjects received a median of 10 treatment cycles (range: 1 to 29; cycle duration for RP2D was 21 days in Phase 1 and 28 days in Phase 2). The median relative dose intensity for all study treatment, including step-up doses, was 93.7%.

The study protocol for MajesTEC-1 allowed investigators to adjust study treatment in response to treatment toxicity using cycle delay, dose reduction, and dose interruption (i.e., delay within a cycle and dose skips). In the total All Treated Analysis Set, cycle delays were reported in 169 subjects (56.0%), dose delays in 52 subjects (17.2%), and dose skips in 185 subjects (61.3%). Dose reductions were reported for 4 subjects (1.3%) for any reason, 1 of whom was receiving pivotal RP2D, 2 of whom were receiving SC non-RP2D, and 1 of whom received IV treatment. In the RP2D group, cycle delays were reported in 96 subjects (58.2%), dose delays in 24 subjects (14.5%) and dose skips in 117 subjects (70.9%). AEs were the most frequently cited reason for cycle delays and both types of dose interruption. The nature of AEs leading to treatment modifications are discussed in Section 2.6.8.8.

Adverse events

As seen in **Table 29**, all subjects in both the total All Treated Analysis Set and the RP2D group experienced at least 1 TEAE, and most experienced at least 1 Grade 3 or Grade 4 TEAE.

Table 29. Overall Summary of Treatment-emergent Adverse Events; All Treated Analysis Set (Study MajesTEC-1)

	SC		IV	Total
	RP2D	Non-RP2D		
Analysis set: All Treated	165	53	84	302
Any TEAE	165 (100.0%)	53 (100.0%)	84 (100.0%)	302 (100.0%)
Study drug-related[a]	153 (92.7%)	45 (84.9%)	71 (84.5%)	269 (89.1%)
Maximum toxicity grade				
Grade 1	1 (0.6%)	0	1 (1.2%)	2 (0.7%)
Grade 2	8 (4.8%)	8 (15.1%)	7 (8.3%)	23 (7.6%)
Grade 3	32 (19.4%)	16 (30.2%)	29 (34.5%)	77 (25.5%)
Grade 4	97 (58.8%)	25 (47.2%)	41 (48.8%)	163 (54.0%)
Grade 5	27 (16.4%)	4 (7.5%)	6 (7.1%)	37 (12.3%)
Any serious TEAE	107 (64.8%)	32 (60.4%)	51 (60.7%)	190 (62.9%)
Study drug-related[a]	48 (29.1%)	16 (30.2%)	18 (21.4%)	82 (27.2%)
TEAE leading to discontinuation of study drug[b]	2 (1.2%)	3 (5.7%)	8 (9.5%)	13 (4.3%)
TEAE with outcome death[c]	27 (16.4%)	4 (7.5%)	6 (7.1%)	37 (12.3%)
Death due to COVID-19	12 (7.3%)	1 (1.9%)	3 (3.6%)	16 (5.3%)
COVID-19 TEAEs	30 (18.2%)	7 (13.2%)	7 (8.3%)	44 (14.6%)
COVID-19 serious TEAEs	24 (14.5%)	5 (9.4%)	7 (8.3%)	36 (11.9%)

Key: TEAE = treatment-emergent adverse event; IV = intravenous, SC = subcutaneous, RP2D=recommended Phase 2 dose; CRS=cytokine release syndrome; ICANS= immune effector cell-associated neurotoxicity syndrome.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 μg/kg, 3000 μg/kg, 6000 μg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.
Note: Adverse events are graded according to the NCI-CTCAE Version 4.03, with the exception of ICANS and CRS. CRS was originally graded by Lee criteria (Lee et al 2014) in Phase 1 and by ASTCT consensus grading system (Lee et al 2019) in Phase 2, with conversion of grade in Phase 1 RP2D to ASTCT based on data in eCRF. Toxicity grade for CRS by ASTCT is presented in this table, for both Phase 1 RP2D and Phase 2. For IV and SC Non-RP2D CRS toxicity grading is presented based on Lee criteria. Toxicity grade for ICANS by ASTCT is also presented in this table.
[a] TEAEs related to study drug
[b] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
[c] TEAE with outcome death on the AE eCRF page.

Common adverse events

Overview of common adverse events

A summary of the most common TEAEs (occurring in ≥20% of subjects in the total All Treated Analysis Set) is displayed in

Table 30.

Table 30. Most Common (At Least 20% in Total All Treated Analysis Set) Treatment-emergent Adverse Events by System Organ Class and Preferred Term in MajesTEC-1; All Treated Analysis Set

	SC		IV	Total
	RP2D	Non-RP2D		
Analysis set: All Treated	165	53	84	302
Subjects with 1 or more TEAEs	165 (100.0%)	53 (100.0%)	84 (100.0%)	302 (100.0%)
MedDRA system organ class / preferred term				
Blood and lymphatic system disorders	151 (91.5%)	47 (88.7%)	74 (88.1%)	272 (90.1%)
Neutropenia	117 (70.9%)	36 (67.9%)	48 (57.1%)	201 (66.6%)
Anaemia	86 (52.1%)	33 (62.3%)	55 (65.5%)	174 (57.6%)
Thrombocytopenia	66 (40.0%)	21 (39.6%)	37 (44.0%)	124 (41.1%)
Lymphopenia	57 (34.5%)	9 (17.0%)	16 (19.0%)	82 (27.2%)
Leukopenia	29 (17.6%)	12 (22.6%)	26 (31.0%)	67 (22.2%)
General disorders and administration site conditions	132 (80.0%)	42 (79.2%)	55 (65.5%)	229 (75.8%)
Pyrexia	45 (27.3%)	17 (32.1%)	28 (33.3%)	90 (29.8%)
Fatigue	46 (27.9%)	13 (24.5%)	23 (27.4%)	82 (27.2%)
Immune system disorders	122 (73.9%)	37 (69.8%)	44 (52.4%)	203 (67.2%)
Cytokine release syndrome	119 (72.1%)	32 (60.4%)	44 (52.4%)	195 (64.6%)
Musculoskeletal and connective tissue disorders	99 (60.0%)	42 (79.2%)	53 (63.1%)	194 (64.2%)
Arthralgia	36 (21.8%)	17 (32.1%)	16 (19.0%)	69 (22.8%)
Back pain	27 (16.4%)	15 (28.3%)	22 (26.2%)	64 (21.2%)
Gastrointestinal disorders	107 (64.8%)	35 (66.0%)	47 (56.0%)	189 (62.6%)
Diarrhoea	47 (28.5%)	19 (35.8%)	29 (34.5%)	95 (31.5%)
Nausea	45 (27.3%)	17 (32.1%)	21 (25.0%)	83 (27.5%)
Respiratory, thoracic and mediastinal disorders	81 (49.1%)	22 (41.5%)	47 (56.0%)	150 (49.7%)
Cough	33 (20.0%)	15 (28.3%)	24 (28.6%)	72 (23.8%)
Nervous system disorders	77 (46.7%)	32 (60.4%)	38 (45.2%)	147 (48.7%)
Headache	39 (23.6%)	22 (41.5%)	22 (26.2%)	83 (27.5%)

Key: RP2D=recommended Phase 2 dose, SC= Subcutaneous, IV= Intravenous; TEAE = treatment-emergent adverse event; CRS = cytokine release syndrome.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: The output includes the diagnosis of CRS; the symptoms of CRS are excluded.

- ***Adverse drug reactions considered for inclusion in SmPC***

The applicant's proposed list of ADRs resulting from an analysis based on the combined assessment of AE incidence, overall trends, biological plausibility, medical judgment, and individual case review, displayed in order of decreasing frequency, is displayed in **Table 31** , and is proposed to be used in Section 4.8 of the SmPC.

Table 31. Proposed List of Adverse Drug Reactions based on MajesTEC-1

System Organ Class	Adverse Reaction	Frequency (all grades)	RP2D (N=165) n (%) Any Grade	Grade 3 or 4
Infections and infestations	Upper respiratory tract infection[1]	Very common	61 (37%)	4 (2.4%)
	Pneumonia[2]	Very common	46 (28%)	32 (19%)
	COVID-19[3]	Very common	30 (18%)	20 (12%)
	Sepsis[4]	Common	13 (7.9%)	11 (6.7%)
	Cellulitis	Common	7 (4.2%)	5 (3.0%)
Blood and lymphatic system disorders	Neutropenia	Very common	117 (71%)	106 (64%)
	Anemia[5]	Very common	90 (55%)	61 (37%)
	Thrombocytopenia	Very common	66 (40%)	35 (21%)
	Lymphopenia	Very common	57 (35%)	54 (33%)
	Leukopenia	Very common	29 (18%)	12 (7.3%)
	Febrile neutropenia	Common	6 (3.6%)	5 (3.0%)
Immune system disorders	Hypogammaglobulinaemia[6]	Very common	123 (75%)	3 (1.8%)
	Cytokine release syndrome	Very common	119 (72%)	1 (0.6%)
Metabolism and nutrition disorders	Hypokalaemia	Very common	23 (14%)	8 (4.8%)
	Hypomagnesaemia	Very common	22 (13%)	0
	Decreased appetite	Very common	20 (12%)	1 (0.6%)
	Hypophosphataemia	Very common	20 (12%)	10 (6.1%)
	Hypercalcaemia	Very common	19 (12%)	5 (3.0%)
	Hyponatraemia	Common	13 (7.9%)	8 (4.8%)
	Hypocalcaemia	Common	12 (7.3%)	0
	Hyperkalaemia	Common	8 (4.8%)	2 (1.2%)
	Hyperamylasaemia	Common	6 (3.6%)	4 (2.4%)
	Hypoalbuminaemia	Common	4 (2.4%)	1 (0.6%)
Nervous system disorders	Headache	Very common	39 (24%)	1 (0.6%)
	Neuropathy peripheral[7]	Very common	26 (16%)	1 (0.6%)
	Encephalopathy[8]	Common	16 (9.7%)	0
	Immune effector cell-associated neurotoxicity syndrome	Common	5 (3.0%)	0
Vascular disorders	Hypertension[9]	Very common	21 (13%)	9 (5.5%)
	Hemorrhage[10]	Very common	20 (12%)	5 (3.0%)
Respiratory, thoracic and mediastinal disorders	Cough[11]	Very common	39 (24%)	0
	Dyspnea[12]	Very common	22 (13%)	3 (1.8%)
	Hypoxia	Common	16 (9.7%)	6 (3.6%)
Gastrointestinal disorders	Diarrhoea	Very common	47 (28%)	6 (3.6%)
	Nausea	Very common	45 (27%)	1 (0.6%)
	Constipation	Very common	34 (21%)	0
	Vomiting	Very common	21 (13%)	1 (0.6%)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[13]	Very common	85 (52%)	14 (8.5%)
General disorders and administration site conditions	Fatigue[14]	Very common	67 (41%)	5 (3.0%)
	Injection site reaction[15]	Very common	62 (38%)	1 (0.6%)
	Pyrexia	Very common	45 (27%)	1 (0.6%)
	Pain[16]	Very common	34 (21%)	3 (1.8%)
	Edema[17]	Very common	23 (14%)	0

System Organ Class	Adverse Reaction	Frequency (all grades)	RP2D (N=165) n (%)	
			Any Grade	Grade 3 or 4
Investigations	Blood alkaline phosphatase increased	Very common	18 (11%)	3 (1.8%)
	Gamma-glutamyltransferase increased	Common	16 (9.7%)	5 (3.0%)
	Transaminase elevation[18]	Common	16 (9.7%)	4 (2.4%)
	Lipase increased	Common	10 (6.1%)	2 (1.2%)
	Blood creatinine increased	Common	9 (5.5%)	0

Key: RP2D = recommended phase 2 dose, CRS = cytokine release syndrome, ICANS = immune effector cell-associated neurotoxicity.

Note: RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.

Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.

Note: Adverse events are graded according to the NCI-CTCAE Version 4.03, with the exception of ICANS and CRS. CRS was originally graded by Lee criteria (Lee et al 2014) in Phase 1 and by ASTCT consensus grading system (Lee et al 2019) in Phase 2, with conversion of grade in Phase 1 to ASTCT based on data in eCRF. Toxicity grade for CRS by ASTCT is presented in this table, for both Phase 1 and Phase 2. Toxicity grade for ICANS by ASTCT is also presented in this table.

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.

Note: The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.

[1]Upper respiratory tract infection includes Bronchitis, Nasopharyngitis, Pharyngitis, Respiratory tract infection, Respiratory tract infection bacterial, Rhinitis, Rhinovirus infection, Sinusitis, Tracheitis, Upper respiratory tract infection and Viral upper respiratory tract infection.

[2]Pneumonia includes Enterobacter pneumonia, Lower respiratory tract infection, Lower respiratory tract infection viral, Metapneumovirus pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia adenoviral, Pneumonia bacterial, Pneumonia klebsiella, Pneumonia moraxella, Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia staphylococcal and Pneumonia viral.

[3]COVID-19 includes Asymptomatic COVID-19 and COVID-19.

[4]Sepsis includes Bacteraemia, Meningococcal sepsis, Neutropenic sepsis, Pseudomonal bacteraemia, Pseudomonal sepsis, Sepsis and Staphylococcal bacteraemia.

[5]Anemia includes Anaemia, Iron deficiency and Iron deficiency Anaemia.

[6]Hypogammaglobulinaemia includes patients with adverse events of hypogammaglobulinaemia, hypoglobulinaemia, immunoglobulins decreased; and/or patients with laboratory IgG levels below 500 mg/dL following treatment with Teclistamab.

[7]Neuropathy peripheral includes Dysaesthesia, Hypoaesthesia, Hypoaesthesia oral, Neuralgia, Paraesthesia, Paraesthesia oral, Peripheral sensory neuropathy and Sciatica.

[8]Encephalopathy includes Confusional state, Depressed level of consciousness, Lethargy, Memory impairment and Somnolence.

[9]Hypertension includes Essential hypertension and Hypertension.

[10]Hemorrhage includes Conjunctival haemorrhage, Epistaxis, Haematoma, Haematuria, Haemoperitoneum, Haemorrhoidal haemorrhage, Lower gastrointestinal haemorrhage, Melaena, Mouth haemorrhage and Subdural haematoma.

[11]Cough includes Allergic cough, Cough, Productive cough and Upper-airway cough syndrome.

[12]Dyspnea includes Acute respiratory failure, Dyspnoea and Dyspnoea exertional.

[13]Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain and Pain in extremity.

[14]Fatigue includes Asthenia, Fatigue and Malaise.

[15]Injection site reaction includes Injection site bruising, Injection site cellulitis, Injection site discomfort, Injection site erythema, Injection site haematoma, Injection site induration, Injection site inflammation, Injection site oedema, Injection site pruritus, Injection site rash, Injection site reaction and Injection site swelling.

[16]Pain includes Ear pain, Flank pain, Groin pain, Non-cardiac chest pain, Oropharyngeal pain, Pain, Pain in jaw, Toothache and Tumour pain.

[17]Edema includes Face oedema, Fluid overload, Oedema peripheral and Peripheral swelling.

[18]Transaminase elevation includes Alanine aminotransferase increased and Aspartate aminotransferase increased.

Note: Frequency Grouping: Frequencies are defined as Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing frequency.

Serious adverse event/deaths/other significant events

Serious adverse events

At least 1 serious TEAE was reported for 190 subjects (62.9%) in the total All Treated Analysis Set, and for 107 subjects (64.8%) in the RP2D group. In the RP2D group, the most frequently involved SOC was Infections and Infestations (40.6%). A summary of the most frequently reported serious TEAEs is provided in **Table 32**.

Table 32. Most common (At Least 2% in Total All Treated Analysis Set) Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term in MajesTEC-1; All Treated Analysis Set

	SC		IV	Total
	RP2D	Non-RP2D		
Analysis set: All Treated	165	53	84	302
Subjects with 1 or more serious TEAEs	107 (64.8%)	32 (60.4%)	51 (60.7%)	190 (62.9%)
MedDRA system organ class / preferred term				
Infections and infestations	67 (40.6%)	19 (35.8%)	28 (33.3%)	114 (37.7%)
COVID-19	24 (14.5%)	5 (9.4%)	7 (8.3%)	36 (11.9%)
Pneumonia	17 (10.3%)	3 (5.7%)	9 (10.7%)	29 (9.6%)
Sepsis	3 (1.8%)	3 (5.7%)	6 (7.1%)	12 (4.0%)
Pneumocystis jirovecii pneumonia	6 (3.6%)	2 (3.8%)	1 (1.2%)	9 (3.0%)
Bacteraemia	2 (1.2%)	2 (3.8%)	2 (2.4%)	6 (2.0%)
Cellulitis	4 (2.4%)	1 (1.9%)	1 (1.2%)	6 (2.0%)
General disorders and administration site conditions	22 (13.3%)	4 (7.5%)	8 (9.5%)	34 (11.3%)
Pyrexia	9 (5.5%)	1 (1.9%)	4 (4.8%)	14 (4.6%)
General physical health deterioration	9 (5.5%)	1 (1.9%)	0	10 (3.3%)
Immune system disorders	14 (8.5%)	7 (13.2%)	7 (8.3%)	28 (9.3%)
Cytokine release syndrome	14 (8.5%)	7 (13.2%)	7 (8.3%)	28 (9.3%)
Musculoskeletal and connective tissue disorders	13 (7.9%)	4 (7.5%)	5 (6.0%)	22 (7.3%)
Bone pain	4 (2.4%)	1 (1.9%)	1 (1.2%)	6 (2.0%)
Pain in extremity	1 (0.6%)	2 (3.8%)	3 (3.6%)	6 (2.0%)
Gastrointestinal disorders	10 (6.1%)	3 (5.7%)	5 (6.0%)	18 (6.0%)
Diarrhoea	5 (3.0%)	0	2 (2.4%)	7 (2.3%)
Blood and lymphatic system disorders	8 (4.8%)	2 (3.8%)	5 (6.0%)	15 (5.0%)
Febrile neutropenia	4 (2.4%)	2 (3.8%)	3 (3.6%)	9 (3.0%)
Renal and urinary disorders	9 (5.5%)	0	4 (4.8%)	13 (4.3%)
Acute kidney injury	8 (4.8%)	0	4 (4.8%)	12 (4.0%)
Metabolism and nutrition disorders	5 (3.0%)	0	5 (6.0%)	10 (3.3%)
Hypercalcaemia	3 (1.8%)	0	3 (3.6%)	6 (2.0%)

Key: TEAE = treatment-emergent adverse event; IV = intravenous, SC = subcutaneous, RP2D=recommended Phase 2 dose; CRS=cytokine release syndrome.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.
Note: The output includes the diagnosis of CRS; the symptoms of CRS are excluded.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.
Note: CRS was originally graded by Lee criteria (Lee et al 2014) in Phase 1 and by ASTCT consensus grading system (Lee et al 2019) in Phase 2, with conversion of grade in Phase 1 RP2D to ASTCT based on data in eCRF. Toxicity grade for CRS by ASTCT is presented in this table, for both Phase 1 RP2D and Phase 2. For IV and SC Non-RP2D CRS toxicity grading is presented based on Lee criteria.

- *Grade 3 or 4 events*

A summary of Grade 3 or 4 TEAEs occurring in ≥5% of subjects in the total All Treated Analysis Set is provided in **Table 33**.

Table 33. Most Common (At Least 5% in Total All Treated Analysis Set) Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set

	SC		IV	Total
	RP2D	Non-RP2D		
Analysis set: All Treated	165	53	84	302
Subjects with 1 or more grade 3 or 4 TEAEs	156 (94.5%)	44 (83.0%)	76 (90.5%)	276 (91.4%)
MedDRA system organ class / preferred term				
Blood and lymphatic system disorders	143 (86.7%)	40 (75.5%)	68 (81.0%)	251 (83.1%)
Neutropenia	106 (64.2%)	30 (56.6%)	43 (51.2%)	179 (59.3%)
Anaemia	61 (37.0%)	12 (22.6%)	34 (40.5%)	107 (35.4%)
Lymphopenia	54 (32.7%)	9 (17.0%)	14 (16.7%)	77 (25.5%)
Thrombocytopenia	35 (21.2%)	10 (18.9%)	21 (25.0%)	66 (21.9%)
Leukopenia	12 (7.3%)	5 (9.4%)	14 (16.7%)	31 (10.3%)
Infections and infestations	74 (44.8%)	17 (32.1%)	24 (28.6%)	115 (38.1%)
Pneumonia	21 (12.7%)	3 (5.7%)	8 (9.5%)	32 (10.6%)
COVID-19	20 (12.1%)	5 (9.4%)	5 (6.0%)	30 (9.9%)
Metabolism and nutrition disorders	43 (26.1%)	9 (17.0%)	16 (19.0%)	68 (22.5%)
Hypophosphataemia	10 (6.1%)	6 (11.3%)	6 (7.1%)	22 (7.3%)
Vascular disorders	14 (8.5%)	4 (7.5%)	8 (9.5%)	26 (8.6%)
Hypertension	9 (5.5%)	4 (7.5%)	4 (4.8%)	17 (5.6%)

Key: TEAE = treatment-emergent adverse event; IV = intravenous, SC = subcutaneous, RP2D=recommended Phase 2 dose.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.

Deaths

For the total All Treated Analysis Set, 132 subjects (43.7%) had died as of the clinical cut-off, with disease progression cited as the primary cause of death for most subjects (84 subjects [27.8%]) (**Table 34**).

Table 34. Summary of Deaths and Cause of Death in MajesTEC-1; All Treated Analysis Set

	SC		IV	Total
	RP2D	Non-RP2D		
Analysis set: All Treated	165	53	84	302
Total number of subjects who died during study	68 (41.2%)	17 (32.1%)	47 (56.0%)	132 (43.7%)
Primary cause of death				
Adverse event	19 (11.5%)	4 (7.5%)	7 (8.3%)	30 (9.9%)
Study drug related[a]	5 (3.0%)	2 (3.8%)	1 (1.2%)	8 (2.6%)
Adverse event - COVID-19	2 (1.2%)	1 (1.9%)	0	3 (1.0%)
AE(s) unrelated	14 (8.5%)	2 (3.8%)	6 (7.1%)	22 (7.3%)
Adverse event - COVID-19	10 (6.1%)	0	3 (3.6%)	13 (4.3%)
Disease progression	41 (24.8%)	9 (17.0%)	34 (40.5%)	84 (27.8%)
Other	8 (4.8%)	4 (7.5%)	6 (7.1%)	18 (6.0%)
Other - COVID-19 related	1 (0.6%)	0	2 (2.4%)	3 (1.0%)
Total number of subjects who died within 30 days of last study treatment dose	25 (15.2%)	4 (7.5%)	7 (8.3%)	36 (11.9%)
Primary cause of death				
Adverse event	11 (6.7%)	2 (3.8%)	2 (2.4%)	15 (5.0%)
Study drug related[a]	2 (1.2%)	0	1 (1.2%)	3 (1.0%)
Adverse event - COVID-19	0	0	0	0
AE(s) unrelated	9 (5.5%)	2 (3.8%)	1 (1.2%)	12 (4.0%)
Adverse event - COVID-19	5 (3.0%)	0	1 (1.2%)	6 (2.0%)
Disease progression	13 (7.9%)	2 (3.8%)	4 (4.8%)	19 (6.3%)
Other	1 (0.6%)	0	1 (1.2%)	2 (0.7%)
Other - COVID-19 related	0	0	0	0
Total number of subjects who died within 60 days of first study treatment dose	18 (10.9%)	3 (5.7%)	6 (7.1%)	27 (8.9%)
Primary cause of death				
Adverse event	6 (3.6%)	0	0	6 (2.0%)
Study drug related[a]	0	0	0	0
Adverse event - COVID-19	0	0	0	0
AE(s) unrelated	6 (3.6%)	0	0	6 (2.0%)
Adverse event - COVID-19	4 (2.4%)	0	0	4 (1.3%)
Disease progression	11 (6.7%)	3 (5.7%)	5 (6.0%)	19 (6.3%)
Other	1 (0.6%)	0	1 (1.2%)	2 (0.7%)
Other - COVID-19 related	0	0	0	0

Key: AE = adverse event; RP2D = recommended Phase 2 dose, SC= Subcutaneous, IV= Intravenous.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
[a] Related if assessed by the investigator as possibly, probably, or very likely related to study agent. There is a subject with lack of investigator's assessment of AE relationship and is categorized as related in the table.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.

In the RP2D group, 68 subjects (41.2%) had died as of the clinical cut-off. According to investigator assessment of primary cause of death, 41 subjects (24.8%) died due to disease progression, 19 (11.5%) died due to AE, and 8 (4.8%) died due to other causes. Of the 19 deaths due to an AE, 12 were a result of COVID-19. In total, 18 Grade 5 TEAEs were reported in subjects treated at pivotal RP2D who died due to AE: COVID-19 (12 subjects) and pneumonia, haemoperitoneum, pneumonia

streptococcal, progressive multifocal leukoencephalopathy, hepatic failure, and hypovolaemic shock in one subject each. The events of hepatic failure, pneumonia streptococcal, progressive multifocal leukoencephalopathy, and one event of COVID-19 were judged by the investigator as possibly or probably related to teclistamab. The investigator-assessed relationship to teclistamab is missing for one subject who experienced a Grade 5 TEAE of COVID-19.

Disease progression was also the most common cause of death in the SC non-RP2D and IV groups. Four Grade 5 TEAEs were reported in subjects treated at SC non-RP2D doses who died due to AE: COVID-19, pneumonia, sepsis, general physical health deterioration, and myelodysplastic syndrome. The events of COVID-19 and myelodysplastic syndrome were judged by the investigator as possibly related to teclistamab. Six Grade 5 TEAEs were reported in subjects treated at IV doses who died due to AE: COVID-19 (3 subjects) and pneumonia, pneumonia aspiration, and respiratory failure in one subject each. The event of pneumonia was judged by the investigator as possibly related to teclistamab.

Adverse events of special interest

Cytokine release syndrome (CRS) and neurotoxicity events were anticipated events in the MajesTEC-1 study based on the mechanism of action of teclistamab, specifically the activation of T cells. Multiple myeloma as a disease state is associated with cytopenias, hypogammaglobulinemia, and an increased risk of infection. Other adverse events of clinical interest relate to administration of teclistamab and include systemic administration-related reactions (sARRs) and injection-site reactions.

- *Cytokine release syndrome*

The MajesTEC-1 protocol required administration of specific premedication, comprising steroids, antipyretics (paracetamol) and antihistamines (H1 receptor antagonists), before one or more doses of study treatment in all subjects (ie, required prior to each step-up dose, the first treatment dose, and for subsequent doses following prespecified AEs). The observed frequencies and severities thus largely reflect occurrence of CRS despite the use of premedication.

The main characteristics of CRS in the R2PD group are summarised in **Table 35**.

Table 35. Summary of Treatment-emergent Cytokine Release Syndrome (CRS) Events; RP2D group within All Treated Analysis Set (Study 64007957MMY1001)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Number of subjects with CRS	28 (70.0%)	91 (72.8%)	119 (72.1%)
Maximum toxicity grade			
Grade 1	19 (47.5%)	64 (51.2%)	83 (50.3%)
Grade 2	9 (22.5%)	26 (20.8%)	35 (21.2%)
Grade 3	0	1 (0.8%)	1 (0.6%)
Grade 4	0	0	0
Grade 5	0	0	0
Number of subjects with CRS leading to discontinuation of study drug	0	0	0
Number of subjects with multiple CRS events	12 (30.0%)	43 (34.4%)	55 (33.3%)
Grade of CRS worsened at any subsequent event	0	4 (3.2%)	4 (2.4%)
Number of subjects with supportive measures to treat CRS[a]	28 (70.0%)	82 (65.6%)	110 (66.7%)
Anti-IL6 receptor tocilizumab	16 (40.0%)	44 (35.2%)	60 (36.4%)
Multiple doses at any time during study	1 (2.5%)	4 (3.2%)	5 (3.0%)
>1 dose for a single CRS event	1 (2.5%)	3 (2.4%)	4 (2.4%)
Corticosteroids	5 (12.5%)	9 (7.2%)	14 (8.5%)
IV Fluids	9 (22.5%)	14 (11.2%)	23 (13.9%)
Vasopressor used	0	1 (0.8%)	1 (0.6%)
Single	0	1 (0.8%)	1 (0.6%)
Multiple	0	0	0
Oxygen used	5 (12.5%)	16 (12.8%)	21 (12.7%)
Blow-by	0	0	0
Nasal cannula low flow (≤6L/min)	5 (12.5%)	16 (12.8%)	21 (12.7%)
Nasal cannula high flow (>6L/min)	0	0	0
Face mask	0	0	0
Non-Rebreather mask	0	0	0
Venturi mask	0	0	0
Other	0	0	0
Positive pressure	0	0	0
Continuous Positive Airway Pressure	0	0	0
Bilevel Positive Airway Pressure	0	0	0
Intubation/ Mechanical Ventilation	0	0	0
Other	26 (65.0%)	75 (60.0%)	101 (61.2%)
Occurrence of CRS[b]			
Step-up Dose 1	18 (45.0%)	54 (43.2%)	72 (43.6%)
Step-up Dose 2	13 (32.5%)	45 (36.0%)	58 (35.2%)
Repeat Step-up[c]	0	1 (0.8%)	1 (0.6%)
Cycle 1 Day 1	7 (17.5%)	33 (26.4%)	40 (24.2%)
Cycle 1 Day 8	2 (5.0%)	6 (4.8%)	8 (4.8%)
Cycle 1 Day 15	2 (5.0%)	2 (1.6%)	4 (2.4%)
Cycle 1 Day 22	-	2 (1.6%)	2 (1.2%)
Cycle 2+*	2 (5.0%)	4 (3.2%)	6 (3.6%)
Time from last injection of Teclistamab to new onset of CRS, hours[d]			
Number of CRS events		136	
Mean (SD)		34.683 (16.7771)	
Median		31.125	
Range		(3.83; 120.50)	

| | RP2D | | |
	Phase 1	Phase 2 Cohort A	Total
Time from last injection of Teclistamab to new onset of CRS, days			
Number of CRS events	45	150	195
Mean (SD)	2.2 (0.93)	2.5 (0.78)	2.4 (0.82)
Median	2.0	2.0	2.0
Range	(1; 6)	(1; 6)	(1; 6)
Duration of CRS, hours[d]			
Number of CRS events		128	
Mean (SD)		19.486 (22.0302)	
Median		11.792	
Range		(0.33; 151.05)	
Duration of CRS, days			
Number of CRS events	45	150	195
Mean (SD)	2.3 (1.55)	1.9 (1.21)	2.0 (1.30)
Median	2.0	2.0	2.0
Range	(1; 8)	(1; 9)	(1; 9)
Outcome of CRS			
N	45	150	195
Recovered or resolved	45 (100.0%)	150 (100.0%)	195 (100.0%)
Not recovered or not resolved	0	0	0
Recovered or resolved with sequelae	0	0	0
Recovering or resolving	0	0	0
Fatal	0	0	0
Unknown	0	0	0
Missing	0	0	0

Key: CRS = cytokine release syndrome; RP2D = recommended Phase 2 dose
[a] Supportive measures to treat CRS and CRS symptoms are included.
[b] Subjects may appear in more than one category. Occurrence is based on the last treatment visit on or prior to the day in which the TEAE occurred.
[c] Prior to Cycle 1.
[d] Hours only displayed for Phase 2, start and end times of CRS events were not collected uniformly in Phase 1.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of CRS for which percentages are calculated with the number of CRS events in the all-treated analysis set as denominator.
Note: CRS was originally graded by Lee criteria (Lee et al 2014) in Phase 1 and by ASTCT consensus grading system (Lee et al 2019) in Phase 2, with conversion of grade in Phase 1 to ASTCT based on data in eCRF. Toxicity grade by ASTCT is presented in this table, for both Phase 1 and Phase 2.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: Day 8 is not applicable for subjects on a biweekly or monthly dosing schedule, Day 15 is not applicable for subjects on a monthly dosing schedule, and Day 22 is not applicable for subjects on a monthly dosing schedule or Phase 1 subjects on a weekly dosing schedule (21-day cycle).
Note: Time from last injection to new onset is defined as start date of CRS – date of last dose +1. Duration is defined as end date of CRS – start date of CRS +1. For calculating in days, the date is used without time. For hours the date and time is used and those with time portion missing will be excluded.
* Two subjects had CRS following a repeat step-up dose in C2+

The protocol for MajesTEC-1 provided guidance for management of CRS with specific recommendations for the use of tocilizumab and corticosteroids based on the severity of presenting symptoms. However, the guidance was not prescriptive, and management was ultimately based on physician discretion and standard of care at the investigational site. The use of supportive measures to treat CRS is replicated in **Table 36**.

Table 36. Number of Subjects Receiving Supportive Measures to Treat CRS; All Treated Analysis Set (Study 64007957MMY1001)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Number of subjects with supportive measures to treat CRS[a]	28 (70.0%)	82 (65.6%)	110 (66.7%)
Anti-IL6 receptor tocilizumab	16 (40.0%)	44 (35.2%)	60 (36.4%)
Multiple doses at any time during study	1 (2.5%)	4 (3.2%)	5 (3.0%)
>1 dose for a single CRS event	1 (2.5%)	3 (2.4%)	4 (2.4%)
Corticosteroids	5 (12.5%)	9 (7.2%)	14 (8.5%)
IV Fluids	9 (22.5%)	14 (11.2%)	23 (13.9%)
Vasopressor used	0	1 (0.8%)	1 (0.6%)
Single	0	1 (0.8%)	1 (0.6%)
Multiple	0	0	0
Oxygen used	5 (12.5%)	16 (12.8%)	21 (12.7%)
Blow-by	0	0	0
Nasal cannula low flow (≤6L/min)	5 (12.5%)	16 (12.8%)	21 (12.7%)
Nasal cannula high flow (>6L/min)	0	0	0
Face mask	0	0	0
Non-Rebreather mask	0	0	0
Venturi mask	0	0	0
Other	0	0	0
Positive pressure	0	0	0
Continuous Positive Airway Pressure	0	0	0
Bilevel Positive Airway Pressure	0	0	0
Intubation/ Mechanical Ventilation	0	0	0
Other	26 (65.0%)	75 (60.0%)	101 (61.2%)

The characteristics of CRS events in the SC non-RP2D and IV groups were generally similar to the RP2D group.

- ***Neurologic adverse events and neurotoxicity***

A *"neurologic adverse event"* was defined as any TEAE reported in either the Nervous System Disorders or Psychiatric Disorders SOC, regardless of the investigator's causality assessment. *"Neurotoxicity"* was a neurologic AE judged by the investigator to be causally related to teclistamab.

Neurologic adverse events

The most common neurologic AEs in the RP2D group are displayed in **Table 37**.

Table 37. Neurologic TEAEs of any grade reported in ≥2% of subjects in the RP2D group in MajesTEC-

Preferred term	n (%)
Headache	39 (23.6)
Encephalopathy[a]	15 (9.1)
Insomnia	11 (6.7)
Dizziness	9 (5.5)
Hypoesthesia	9 (5.5)
Peripheral sensory neuropathy	8 (4.8)
Anxiety	8 (4.8)
Paraesthesia	6 (3.6)
Dysgeusia	6 (3.6)
Tremor[b]	5 (3.0)
Delirium[c]	5 (3.0)
Presyncope	4 (2.4)
Immune effector cell-associated neurotoxicity syndrome	4 (2.4)
Lethargy	4 (2.4)

[a] Grouped term including the preferred terms confusional state (11 subjects [6.7%]), somnolence (3 subjects [1.8%]), depressed level of consciousness (1 subject [0.6%]), and memory impairment (1 subject [0.6%]).

[b] Grouped term including the preferred term tremor (5 subjects [3.0%]).

[c] Grouped term including the preferred terms agitation (2 subjects [1.2%]), delirium (2 subjects [1.2%]), and hallucination (1 subject [0.6%]).

Neurotoxicity events

The characteristics of reported neurotoxicity events are summarised in **Table 38**.

Table 38. Summary of Treatment-emergent Neurotoxicity Events in MajesTEC-1; All Treated Analysis Set

	SC		IV	Total
	RP2D	Non-RP2D		
Analysis set: All Treated	165	53	84	302
Number of subjects with Neurotoxicity events	24 (14.5%)	10 (18.9%)	16 (19.0%)	50 (16.6%)
Maximum toxicity grade				
Grade 1	14 (8.5%)	8 (15.1%)	9 (10.7%)	31 (10.3%)
Grade 2	9 (5.5%)	2 (3.8%)	5 (6.0%)	16 (5.3%)
Grade 3	0	0	1 (1.2%)	1 (0.3%)
Grade 4	1 (0.6%)	0	1 (1.2%)	2 (0.7%)
Grade 5	0	0	0	0
Number of subjects with Neurotoxicity leading to discontinuation of study drug	0	0	1 (1.2%)	1 (0.3%)
Number of subjects with supportive measures to treat Neurotoxicity[a]	14 (8.5%)	6 (11.3%)	8 (9.5%)	28 (9.3%)
IL-1 receptor antagonist anakinra	0	0	1 (1.2%)	1 (0.3%)
Anti-IL6 receptor tocilizumab	3 (1.8%)	0	0	3 (1.0%)
Levetiracetam	2 (1.2%)	0	1 (1.2%)	3 (1.0%)
Dexamethasone	3 (1.8%)	0	2 (2.4%)	5 (1.7%)
Gabapentin	1 (0.6%)	2 (3.8%)	0	3 (1.0%)
Pregabalin	0	0	1 (1.2%)	1 (0.3%)
Other	12 (7.3%)	4 (7.5%)	5 (6.0%)	21 (7.0%)
Occurrence of Neurotoxicity[b]				
Step-up Dose 1	3 (1.8%)	2 (3.8%)	8 (9.5%)	13 (4.3%)
Step-up Dose 2	4 (2.4%)	3 (5.7%)	2 (2.4%)	9 (3.0%)
Step-up Dose 3	-	0	0	0
Step-up Dose 4	-	0	-	0
Repeat Step-up[c]	0	0	0	0
Cycle 1 Day 1	6 (3.6%)	0	2 (2.4%)	8 (2.6%)
Cycle 1 Day 8	5 (3.0%)	1 (1.9%)	1 (1.2%)	7 (2.3%)
Cycle 1 Day 15	0	0	1 (1.2%)	1 (0.3%)
Cycle 1 Day 22	3 (1.8%)	-	-	3 (1.0%)
Cycle 2+*	12 (7.3%)	6 (11.3%)	6 (7.1%)	24 (7.9%)
Time from last injection of Teclistamab to new onset of Neurotoxicity, days				
Number of Neurotoxicity events	43	15	26	84
Mean (SD)	3.2 (2.36)	3.0 (1.65)	1.9 (1.34)	2.8 (2.04)
Median	3.0	3.0	1.0	2.0
Range	(1; 13)	(1; 7)	(1; 7)	(1; 13)
Duration of Neurotoxicity, days				
Number of Neurotoxicity events	40	10	25	75
Mean (SD)	23.4 (62.05)	15.6 (23.30)	13.0 (30.80)	18.9 (49.26)
Median	7.0	1.5	2.0	3.0
Range	(1; 291)	(1; 55)	(1; 148)	(1; 291)

	SC		IV	Total
	RP2D	Non-RP2D		
Outcome of Neurotoxicity				
Number of events	43	15	26	84
Recovered or resolved	40 (93.0%)	10 (66.7%)	25 (96.2%)	75 (89.3%)
Not recovered or not resolved	3 (7.0%)	5 (33.3%)	1 (3.8%)	9 (10.7%)
Recovered or resolved with sequelae	0	0	0	0
Recovering or resolving	0	0	0	0
Fatal	0	0	0	0
Unknown	0	0	0	0
Missing	0	0	0	0

Key: TEAE=treatment-emergent adverse event; IV = intravenous, SC = subcutaneous, RP2D=recommended Phase 2 dose ; CRS=cytokine release syndrome; ICANS= immune effector cell-associated neurotoxicity syndrome; ASTCT=American society for transplantation and cellular therapy.

Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.

Note: Duration of Neurotoxicity includes those that recovered/resolved.

Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.

Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator, except for outcome of neurotoxicity for which percentages are calculated with the number of neurotoxicity events in the all treated analysis set as denominator.

Note: Neurotoxicity events are graded according to the NCI-CTCAE Version 4.03, with the exception of ICANS, which were evaluated according to the ASTCT consensus grading system.

Note: Neurotoxicity includes adverse events in the Nervous System Disorders SOC or Psychiatric Disorders SOC that are considered related by investigator. Symptoms of CRS and ICANS are excluded.

Note: Day 8 is not applicable for subjects on a biweekly or monthly dosing schedule, Day 15 is not applicable for subjects on a monthly dosing schedule, and Day 22 is not applicable for subjects on a monthly dosing schedule or Phase 1 subjects on a weekly dosing schedule (21-day cycle).

Note: 1 of the events of confusional state reported in a subject treated at RP2D in Phase 1 is considered by the sponsor to be consistent with ICANS and presented as such in summaries of ICANS events.

[a] Supportive measures to treat Neurotoxicity and symptoms of ICANS are included.

[b] Subjects may appear in more than one category. Occurrence is based on the last treatment visit on or prior to the day in which the TEAE occurred.

[c] Prior to Cycle 1.

*One RP2D subject and one IV subject had a neurotoxicity event following a repeat step-up dose in C2+

Immune effector cell – associated neurotoxicity syndrome (ICANS)

Per the ASTCT definition, ICANS is "a disorder characterised by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema." ICE score data required for formal identification of ICANS was only collected in Phase 2 of MajesTEC-1, but data for subjects treated at pivotal RP2D in Phase 1 were retrospectively evaluated for neurotoxicity events and neurologic AEs for events that would be clinically consistent with ICANS. The characteristics of ICANS events are summarised in Table 39. The reported individual symptoms of ICANS included dysgraphia and confusional state, aphasia, dyscalculia, disorientation, and mental status changes. Most ICANS events were concurrent with CRS (i.e., during or within 7 days of CRS resolution).

Table 39. Summary of Treatment-emergent ICANS Events in MajesTEC-1; RP2D Group within All Treated Analysis Set

	RP2D
Analysis set: All Treated	165
Number of subjects with ICANS	5 (3.0%)
Maximum toxicity grade	
Grade 1	3 (1.8%)
Grade 2	2 (1.2%)
Grade 3	0
Grade 4	0
Grade 5	0
Number of subjects with ICANS leading to discontinuation of study drug	0
Number of subjects with multiple ICANS events	2 (1.2%)
Number of subjects with supportive measures to treat ICANS[a]	4 (2.4%)
IL-1 receptor antagonist anakinra	0
Anti-IL6 receptor tocilizumab	3 (1.8%)
Corticosteroids	3 (1.8%)
Dexamethasone	3 (1.8%)
Methylprednisolone sodium succinate	0
Levetiracetam	1 (0.6%)
Pethidine	0
Other	2 (1.2%)
Occurrence of ICANS[b]	
Step-up Dose 1	1 (0.6%)
Step-up Dose 2	0
Repeat Step-up[c]	0
Cycle 1 Day 1	2 (1.2%)
Cycle 1 Day 8	1 (0.6%)
Cycle 1 Day 15	0
Cycle 1 Day 22	-
Cycle 2+	2 (1.2%)
Time from last injection of Teclistamab to new onset of ICANS, days	
Number of ICANS events	9
Mean (SD)	3.7 (1.00)
Median	4.0
Range	(2; 5)
Duration of ICANS, days	
Number of ICANS events	9
Mean (SD)	5.8 (6.12)
Median	3.0
Range	(1; 20)

	RP2D
Outcome of ICANS	
Number of ICANS events	9
Recovered or resolved	9 (100.0%)
Not recovered or not resolved	0
Recovered or resolved with sequelae	0
Recovering or resolving	0
Fatal	0
Unknown	0
Missing	0
Concurrent CRS[d]	
Yes	7 (77.8%)
No	2 (22.2%)

Key: RP2D=recommended Phase 2 dose; TEAE = treatment-emergent adverse event; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome

[a] Supportive measures to treat ICANS and ICANS symptoms are included.
[b] Subjects may appear in more than one category. Occurrence is based on the last treatment visit on or prior to the day in which the TEAE occurred.
[c] Prior to Cycle 1.
[d] Concurrent CRS considers ICANS events that occur during or within 7 days of the end date of CRS.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator, except for the onset and outcome of ICANS and concurrent CRS for which percentages are calculated with the number of ICANS events in the all treated analysis set as denominator.
Note: Time from last injection to new onset is defined as start date of ICANS - date of last dose +1. Duration is defined as end date of ICANS – start date of ICANS +1. For calculating in days, the date is used without time. For hours the date and time is used and those with time portion missing will be excluded.
Note: The subject treated at RP2D in Phase 1 is reported in the database as experiencing a TEAE of confusional state. This event is considered by the sponsor to be consistent with ICANS and presented as such in this summary. The Ph1 TEAE considered as ICANS was originally graded by NCI-CTCAE version 4.03. and by ASTCT consensus grading system (Lee et al 2019) in Phase 2, with conversion of grade in Phase 1 to ASTCT based on data in eCRF. Toxicity grade by ASTCT is presented in this table, for both Phase 1 and Phase 2.
Note: Day 8 is not applicable for subjects on a biweekly or monthly dosing schedule, Day 15 is not applicable for subjects on a monthly dosing schedule, and Day 22 is not applicable for subjects on a monthly dosing schedule or Phase 1 subjects on a weekly dosing schedule (21-day cycle).

Peripheral neuropathies

As of the updated clinical cutoff, there were 26 subjects who experienced at least 1 peripheral neuropathy. Of these, 17 subjects experienced maximum Grade 1 events, 8 experienced maximum Grade 2 events, and 1 subject experienced a maximum Grade 3 event. None of these TEAEs led to interruption of teclistamab treatment and only 1 (the maximum Grade 3 event) worsened over time.

- **Cytopenias**

Cytopenias were among the most frequently reported TEAEs for subjects treated in MajesTEC-1. The characteristics of cytopenias reported as TEAEs for the total All Treated Analysis Set and for the RP2D group are summarised in. Cytopenias were frequently managed with myeloid growth factors, platelet transfusions and transfusions with packed red blood cells.

Table 40. Number of Subjects with Treatment-emergent Cytopenic Adverse Events by MedDRA Preferred Term, and Maximum Toxicity Grade of 3 or Higher in MajesTEC-1; All Treated Analysis Set

	SC							
	RP2D				Non-RP2D			
				Leading to Disc. n				Leading to Disc. n
	Total	Grade 3 or 4	Grade 5	(%)	Total	Grade 3 or 4	Grade 5	(%)
Analysis set: All Treated	165				53			
Subjects with 1 or more TE cytopenic event	151 (91.5%)	142 (86.1%)	0	0	47 (88.7%)	40 (75.5%)	0	0
MedDRA preferred term								
Neutropenia[a]	117 (70.9%)	106 (64.2%)	0	0	36 (67.9%)	30 (56.6%)	0	0
Neutropenia	117 (70.9%)	106 (64.2%)	0	0	36 (67.9%)	30 (56.6%)	0	0
Febrile neutropenia	6 (3.6%)	5 (3.0%)	0	0	5 (9.4%)	5 (9.4%)	0	0
Neutropenic sepsis	1 (0.6%)	1 (0.6%)	0	0	0	0	0	0
Anemia[a]	86 (52.1%)	61 (37.0%)	0	0	33 (62.3%)	12 (22.6%)	0	0
Anaemia	86 (52.1%)	61 (37.0%)	0	0	33 (62.3%)	12 (22.6%)	0	0
Thrombocytopenia[a]	66 (40.0%)	35 (21.2%)	0	0	21 (39.6%)	10 (18.9%)	0	0
Thrombocytopenia	66 (40.0%)	35 (21.2%)	0	0	21 (39.6%)	10 (18.9%)	0	0
Lymphopenia[a]	57 (34.5%)	54 (32.7%)	0	0	9 (17.0%)	9 (17.0%)	0	0
Lymphopenia	57 (34.5%)	54 (32.7%)	0	0	9 (17.0%)	9 (17.0%)	0	0

Key: TE = treatment-emergent event; IV = intravenous, SC = subcutaneous, RP2D=recommended Phase 2 dose.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Adverse events are coded using MedDRA Version 24.0.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: Percentages in the total column and toxicity grade columns are calculated with the number of all treated subjects as denominator.
[a] Preferred term grouping.

	IV				Total			
				Leading to Disc. n				Leading to Disc. n
	Total	Grade 3 or 4	Grade 5	(%)	Total	Grade 3 or 4	Grade 5	(%)
Analysis set: All Treated	84				302			
Subjects with 1 or more TE cytopenic event	73 (86.9%)	68 (81.0%)	0	0	271 (89.7%)	250 (82.8%)	0	0
MedDRA preferred term								
Neutropenia[a]	48 (57.1%)	43 (51.2%)	0	0	201 (66.6%)	179 (59.3%)	0	0
Neutropenia	48 (57.1%)	43 (51.2%)	0	0	201 (66.6%)	179 (59.3%)	0	0
Febrile neutropenia	4 (4.8%)	4 (4.8%)	0	0	15 (5.0%)	14 (4.6%)	0	0
Neutropenic sepsis	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0
Anemia[a]	55 (65.5%)	34 (40.5%)	0	0	174 (57.6%)	107 (35.4%)	0	0
Anaemia	55 (65.5%)	34 (40.5%)	0	0	174 (57.6%)	107 (35.4%)	0	0
Thrombocytopenia[a]	37 (44.0%)	21 (25.0%)	0	0	124 (41.1%)	66 (21.9%)	0	0
Thrombocytopenia	37 (44.0%)	21 (25.0%)	0	0	124 (41.1%)	66 (21.9%)	0	0
Lymphopenia[a]	16 (19.0%)	14 (16.7%)	0	0	82 (27.2%)	77 (25.5%)	0	0
Lymphopenia	16 (19.0%)	14 (16.7%)	0	0	82 (27.2%)	77 (25.5%)	0	0

Key: TE = treatment-emergent event; IV = intravenous, SC = subcutaneous, RP2D=recommended Phase 2 dose.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Adverse events are coded using MedDRA Version 24.0.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: Percentages in the total column and toxicity grade columns are calculated with the number of all treated subjects as denominator.
[a] Preferred term grouping.

In total, there were 154 subjects (93.3%) treated at pivotal RP2D who had at least 1 laboratory finding of Grade 3 or 4 thrombocytopenia, neutropenia, or lymphopenia. The events were considered prolonged in 109 subjects (66.1%). This incidence was driven primarily by lymphopenia (86 subjects [52.1%]), while prolonged neutropenia and prolonged thrombocytopenia were reported in 17.6% and 7.9% of subjects, respectively. Median duration of thrombocytopenia and neutropenia were similar (25.5 and 22.0 days, respectively), while that for lymphopenia was longer (39.0 days).

Haemorrhagic TEAEs were reported for 29 subjects (17.6%) with most having a maximum severity of Grade 1 or Grade 2. Higher grade haemorrhagic TEAEs occurred in 6 subjects.

- ***Hypogammaglobulinemia***

The incidence of hypogammaglobulinemia was assessed based on both AE reporting by investigators (i.e., the grouped term hypogammaglobulinemia, which included the preferred terms hypogammaglobulinemia, blood immunoglobulin G decreased, and hypoglobulinemia), as well as by clinical laboratory data (where hypogammaglobulinemia was defined as a postbaseline IgG value <500 mg/dL). As seen in **Table 41** hypogammaglobulinemia, was identified for the majority of subjects based on clinical laboratory criteria.

Table 41. Summary of Treatment-emergent Hypogammaglobulinemia Adverse Events and Immunoglobulin G (mg/dL) Laboratory Values in MajesTEC-1; All Treated Analysis Set

	SC		IV	Total
	RP2D	Non-RP2D		
Analysis set: All Treated	165	53	84	302
Subjects with 1 or more Hypogammaglobulinemia [a] TEAEs	26 (15.8%)	14 (26.4%)	6 (7.1%)	46 (15.2%)
Blood immunoglobulin G decreased	0	0	0	0
Hypogammaglobulinaemia	24 (14.5%)	14 (26.4%)	6 (7.1%)	44 (14.6%)
Hypoglobulinaemia	1 (0.6%)	0	0	1 (0.3%)
Immunoglobulins decreased	1 (0.6%)	0	0	1 (0.3%)
Subjects with 1 or more post-baseline IgG value <500mg/dL	122 (73.9%)	45 (84.9%)	49 (58.3%)	216 (71.5%)
Subjects with 1 or more Hypogammaglobulinaemia [a] TEAEs or post-baseline IgG value <500mg/dL	123 (74.5%)	45 (84.9%)	49 (58.3%)	217 (71.9%)
Subjects who received IVIg [b]	65 (39.4%)	25 (47.2%)	21 (25.0%)	111 (36.8%)

Key: TEAE = treatment-emergent adverse event; IV = intravenous, SC = subcutaneous, RP2D=recommended Phase 2 dose; IVIg=intravenous immunoglobulin.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.
[a] Preferred term grouping.
[b] Includes subjects who started IVIg prior to teclistamab.

- ***Infections***

For the total All Treated Analysis Set, TEAEs in the Infections and Infestations SOC were reported for 226 subjects (74.8%), with Grade 3 or 4 infections reported for 96 subjects (31.8%). Grade 5 infections were reported for 21 of 28 subjects who had AE identified as their primary cause of death by investigators, including 15 subjects with Grade 5 COVID-19.

In the RP2D group, treatment-emergent infections were reported for 126 subjects (76.4%). The following infections of any grade were reported for ≥5% of subjects:

Preferred term	n (%)
Pneumonia	30 (18.2)
COVID-19	29 (17.6)
Bronchitis	22 (13.3)
Upper respiratory tract infection	18 (10.9)
Nasopharyngitis	16 (9.7)
Sinusitis	14 (8.5)
Urinary tract infection	11 (6.7)

Maximum Grade 3 or 4 infections were reported for 60 subjects (36.4%) in the RP2D group, with the following treatment-emergent Grade 3 or 4 infections reported in ≥2% of subjects:

Preferred term	n (%)
Pneumonia	20 (12.1)
COVID-19	9 (5.5)
Pneumocystis jirovecii pneumonia	7 (4.2)
Cellulitis	5 (3.0)
Urinary tract infection	4 (2.4)

For subjects treated at pivotal RP2D, 21 (12.7%) experienced Grade ≥3 neutropenia or febrile neutropenia concurrently or within 2 weeks prior to a Grade ≥3 infection. A similar proportion (23 subjects [13.9%]) experienced a Grade ≥3 infection within 4 weeks of Grade ≥3 neutropenia or febrile neutropenia.

Serious infections were reported for 67 subjects (40.6%) in the RP2D group, and Grade 5 infections were reported for 15 of 18 subjects with AE cited by investigators as the primary cause of death. These fatal infections included COVID-19 (12 subjects) and pneumonia, pneumonia streptococcal, and progressive multifocal leukoencephalopathy (1 subject each).

Overall, COVID-19 (as a grouped term including COVID-19, asymptomatic COVID, suspected COVID, COVID-19 pneumonia, and SARS-COV-2 positive) was reported for 44 subjects (14.6%) in the total All Treated Analysis Set. The maximum severity of COVID-19 was Grade 3 or higher for most subjects, and Grade 5 COVID-19 was reported for 16 subjects.

Opportunistic infections were reported for 19 subjects (6.3%) in the total All Treated Analysis Set. A summary of opportunistic infections by pathogen origin is displayed in **Table 42**.

Table 42. Number of Subjects with Treatment-emergent Opportunistic Infections by System Organ Class and Preferred Term in MajesTEC-1; All Treated Analysis Set

	SC		IV	Total
	RP2D	Non-RP2D		
Analysis set: All Treated	165	53	84	302
Subjects with TE opportunistic infections	13 (7.9%)	3 (5.7%)	3 (3.6%)	19 (6.3%)
MedDRA system organ class / preferred term				
Infections and infestations	13 (7.9%)	3 (5.7%)	3 (3.6%)	19 (6.3%)
Pneumocystis jirovecii pneumonia	7 (4.2%)	2 (3.8%)	1 (1.2%)	10 (3.3%)
Adenovirus infection	2 (1.2%)	0	0	2 (0.7%)
Cytomegalovirus infection reactivation	1 (0.6%)	0	1 (1.2%)	2 (0.7%)
Hepatitis B reactivation	1 (0.6%)	0	1 (1.2%)	2 (0.7%)
Adenovirus reactivation	1 (0.6%)	0	0	1 (0.3%)
Aspergillus infection	1 (0.6%)	0	0	1 (0.3%)
BK virus infection	1 (0.6%)	0	0	1 (0.3%)
Cytomegalovirus viraemia	1 (0.6%)	0	0	1 (0.3%)
Gastrointestinal fungal infection	0	1 (1.9%)	0	1 (0.3%)
Pneumonia adenoviral	1 (0.6%)	0	0	1 (0.3%)
Progressive multifocal leukoencephalopathy	1 (0.6%)	0	0	1 (0.3%)

Key: TEAE = treatment-emergent adverse event; TE = treatment-emergent; JMQ=Janssen MedDRA query; RP2D = recommended Phase 2 dose, SC= Subcutaneous, IV= Intravenous.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.
Note: Opportunistic infection TEAEs were defined using JMQ including standard MedDRA query of narrow scope and sponsor identified terms of Adenovirus reactivation, Hepatitis B reactivation, Adenovirus infection, Pneumonia adenoviral and Human herpesvirus 6 infection.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.

Source: D90 responses, Table 55

In the total All Treated Analysis Set, oral herpes was reported in 9 subjects (3.0%), and herpes zoster in 4 subjects (1.3%); in the RP2D group, oral herpes was reported in 4 subjects (2.4%), and herpes zoster in 2 subjects (1.2%). Prophylactic antiviral medication for herpes was prescribed for 88.4% of subjects in the total All Treated Analysis Set, and for 92.7% of subjects in the RP2D group.

A case of progressive multifocal leukoencephalopathy (PML) was also reported in a patient more than a year after initiation of treatment with teclistamab.

- ***Immune-mediated adverse events***

Any grade immune-mediated TEAEs were reported for 6 subjects (2.0%) in the total All Treated Analysis Set; all were considered by the investigator to be related to study treatment. In the RP2D group, Grade 2 immune-mediated lung disease was reported in two subjects, with Grade 2 immune-mediated arthritis and Grade 1 immune-mediated enterocolitis reported in one subject each. In the SC non-RP2D group, Grade 2 immune-mediated enterocolitis was reported in one subject, and in the IV

group, one subject was reported with Grade 3 immune-mediated arthritis and Grade 2 immune-mediated lung disease.

According to the applicant, PK exposure in these subjects was comparable with other subjects who received the same teclistamab dose.

- ***Tumour lysis syndrome***

One case of Grade 3 tumour lysis syndrome (TLS), considered a serious event and judged by the investigator to be very likely related to teclistamab, was reported in the RP2D group. The subject had no clinical symptoms and TLS was diagnosed by the site based on elevated uric acid results only (potassium and phosphate levels were normal). TLS was not reported for subjects who received SC non-RP2D or IV treatment.

- ***Second primary malignancies***

For the total All Treated Analysis Set, 13 subjects (4.3%) experienced second primary malignancies after median follow-up of 16.3 months (range: 0.26 [subject died] to 49.4).

- ***Adverse events associated with administration of teclistamab***

In the total All Treated Analysis Set, 6 subjects (2.0%) experienced Grade 1 (4 subjects [1.3%]) or Grade 2 (2 subjects [0.7%]) treatment-emergent systemic administration-related reactions (sARRs). Four of these subjects received IV treatment, while 2 subjects (1.2%) treated at pivotal RP2D experienced sARRs. In the RP2D group, the first subject experienced Grade 1 tongue swelling associated with Step-up Dose 1, and the second subject experienced recurrent Grade 1 pyrexia associated with doses at Cycle 3 Day 8, Cycle 7 Day 1, and Cycle 7 Day 8. Median sARR duration was 1 day (range: 1 to 2), and all sARR events resolved.

In the RP2D group, a total of 148 injection-site reactions were reported for 60 subjects (36.4%). These comprised injection site erythema in 43 subjects (26.1%), injection site pruritus in 13 subjects (7.9%), and injection site rash in 10 subjects (6.1%). The maximum severity was Grade 1 for 52 subjects (31.5%) and Grade 2 for 8 subjects (4.8%). Median time from last dose of study treatment to injection-site reaction onset was 2 days (range: 1 to 11). Median duration was 4 days (range: 1 to 328); out of the 148 injection-site reactions, 136 reactions were reported as resolved as of clinical cut-off, 2 reactions were resolving, and 10 reactions were not resolved. Eighteen subjects (10.9%) received supportive treatment for injection-site reactions: topical steroids were administered for 15 subjects (9.1%) and antihistamines for 6 subjects (3.6%). Eight of 60 subjects treated at pivotal RP2D who experienced an injection-site reaction had at least 1 atopy/allergy condition in their medical history.

- ***Dose-limiting toxicities***

Two subjects experienced dose-limiting toxicities during the dose escalation portion (Phase 1) of MajesTEC-1; the events were Grade 4 delirium and Grade 4 thrombocytopenia, reported for 1 subject each. Both subjects received treatment with IV teclistamab, with the day of onset and onset dose being reported as day 3 / 20 ug/kg for delirium, and day 9 / 180 ug/kg for thrombocytopenia. The events resolved upon study drug discontinuation and interruption, respectively.

Laboratory findings

Summaries of worst toxicity grade for haematology, chemistry, and coagulation laboratory values collected during treatment is provided for the total All Treated Analysis Set and the RP2D group in **Table 43** and **Table 44**, respectively.

Table 43. Summary of Worst Toxicity Grade in Chemistry, Haematology, Coagulation During Treatment in MajesTEC-1; total All Treated Analysis Set

	Total	Total				
		Worst Toxicity Grade				
	Total	0	1	2	3	4
Analysis set: All Treated	302					
Hematology						
Anemia	302 (100.0%)	4 (1.3%)	69 (22.8%)	122 (40.4%)	107 (35.4%)	0
Platelet count decreased	302 (100.0%)	53 (17.5%)	131 (43.4%)	47 (15.6%)	42 (13.9%)	29 (9.6%)
Neutrophil count decreased	302 (100.0%)	35 (11.6%)	33 (10.9%)	50 (16.6%)	69 (22.8%)	115 (38.1%)
Lymphocyte count decreased	301 (99.7%)	6 (2.0%)	0	29 (9.6%)	87 (28.9%)	179 (59.5%)
White blood cell decreased	302 (100.0%)	12 (4.0%)	52 (17.2%)	108 (35.8%)	106 (35.1%)	24 (7.9%)
Chemistry						
Aspartate aminotransferase increased	302 (100.0%)	146 (48.3%)	128 (42.4%)	19 (6.3%)	7 (2.3%)	2 (0.7%)
Alkaline phosphatase increased	302 (100.0%)	172 (57.0%)	101 (33.4%)	24 (7.9%)	5 (1.7%)	0
Creatinine increased	302 (100.0%)	149 (49.3%)	92 (30.5%)	53 (17.5%)	8 (2.6%)	0
Blood bilirubin increased	302 (100.0%)	268 (88.7%)	21 (7.0%)	8 (2.6%)	3 (1.0%)	2 (0.7%)
GGT increased	301 (99.7%)	159 (52.8%)	82 (27.2%)	36 (12.0%)	24 (8.0%)	0
Hyperglycemia	301 (99.7%)	277 (92.0%)	0	0	23 (7.6%)	1 (0.3%)
Hypernatremia	302 (100.0%)	262 (86.8%)	39 (12.9%)	1 (0.3%)	0	0
Hyponatremia	302 (100.0%)	160 (53.0%)	112 (37.1%)	0	28 (9.3%)	2 (0.7%)
Hyperkalemia	302 (100.0%)	237 (78.5%)	49 (16.2%)	11 (3.6%)	5 (1.7%)	0
Hypokalemia	302 (100.0%)	176 (58.3%)	0	114 (37.7%)	12 (4.0%)	0
Hyperuricemia	302 (100.0%)	208 (68.9%)	78 (25.8%)	0	0	16 (5.3%)
Hypercalcemia	302 (100.0%)	172 (57.0%)	97 (32.1%)	20 (6.6%)	4 (1.3%)	9 (3.0%)
Hypocalcemia	302 (100.0%)	182 (60.3%)	89 (29.5%)	24 (7.9%)	5 (1.7%)	2 (0.7%)
Coagulation						
INR increased	199 (65.9%)	163 (81.9%)	29 (14.6%)	3 (1.5%)	4 (2.0%)	0
Activated partial thromboplastin time prolonged	218 (72.2%)	179 (82.1%)	30 (13.8%)	7 (3.2%)	2 (0.9%)	0
Fibrinogen decreased	213 (70.5%)	164 (77.0%)	30 (14.1%)	15 (7.0%)	4 (1.9%)	0

Key: RP2D=recommended phase 2 dose, SC= Subcutaneous, IV= Intravenous; GGT = gamma glutamyl transferase; INR = International Normalised Ratio.

Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.

Note: Grade 0 means normal. Subjects reported as Grade 0 are subjects with normal values or a value in the opposite direction (for laboratory tests with bidirectional toxicities defined).

Note: For each parameter, the total column includes all subjects with available data at baseline; percentages in the total column are calculated with the number of subjects in the all treated analysis set as denominator. Percentages for toxicity grade sub-group are calculated with the number of subjects in the total column as denominator per laboratory parameter.

Table 44. Summary of Worst Toxicity Grade in Chemistry, Haematology, Coagulation During Treatment in MajesTEC-1; RP2D group within total All Treated Analysis Set

		SC				
		RP2D				
		Worst Toxicity Grade				
	Total	0	1	2	3	4
Analysis set: All Treated	165					
Hematology						
Anemia	165 (100.0%)	3 (1.8%)	43 (26.1%)	58 (35.2%)	61 (37.0%)	0
Platelet count decreased	165 (100.0%)	30 (18.2%)	73 (44.2%)	24 (14.5%)	21 (12.7%)	17 (10.3%)
Neutrophil count decreased	165 (100.0%)	13 (7.9%)	19 (11.5%)	28 (17.0%)	35 (21.2%)	70 (42.4%)
Lymphocyte count decreased	164 (99.4%)	4 (2.4%)	0	15 (9.1%)	52 (31.7%)	93 (56.7%)
White blood cell decreased	165 (100.0%)	8 (4.8%)	20 (12.1%)	63 (38.2%)	62 (37.6%)	12 (7.3%)
Chemistry						
Aspartate aminotransferase increased	165 (100.0%)	83 (50.3%)	68 (41.2%)	9 (5.5%)	3 (1.8%)	2 (1.2%)
Alkaline phosphatase increased	165 (100.0%)	84 (50.9%)	60 (36.4%)	16 (9.7%)	5 (3.0%)	0
Creatinine increased	165 (100.0%)	82 (49.7%)	51 (30.9%)	27 (16.4%)	5 (3.0%)	0
Blood bilirubin increased	165 (100.0%)	149 (90.3%)	7 (4.2%)	6 (3.6%)	3 (1.8%)	0
GGT increased	164 (99.4%)	90 (54.9%)	44 (26.8%)	14 (8.5%)	16 (9.8%)	0
Hyperglycemia	164 (99.4%)	149 (90.9%)	0	0	14 (8.5%)	1 (0.6%)
Hypernatremia	165 (100.0%)	151 (91.5%)	14 (8.5%)	0	0	0
Hyponatremia	165 (100.0%)	93 (56.4%)	51 (30.9%)	0	19 (11.5%)	2 (1.2%)
Hyperkalemia	165 (100.0%)	128 (77.6%)	29 (17.6%)	5 (3.0%)	3 (1.8%)	0
Hypokalemia	165 (100.0%)	109 (66.1%)	0	47 (28.5%)	9 (5.5%)	0
Hyperuricemia	165 (100.0%)	112 (67.9%)	43 (26.1%)	0	0	10 (6.1%)
Hypercalcemia	165 (100.0%)	98 (59.4%)	50 (30.3%)	10 (6.1%)	3 (1.8%)	4 (2.4%)
Hypocalcemia	165 (100.0%)	105 (63.6%)	45 (27.3%)	12 (7.3%)	2 (1.2%)	1 (0.6%)
Coagulation						
INR increased	69 (41.8%)	53 (76.8%)	12 (17.4%)	2 (2.9%)	2 (2.9%)	0
Activated partial thromboplastin time prolonged	86 (52.1%)	70 (81.4%)	12 (14.0%)	2 (2.3%)	2 (2.3%)	0
Fibrinogen decreased	82 (49.7%)	66 (80.5%)	8 (9.8%)	6 (7.3%)	2 (2.4%)	0

Key: RP2D=recommended phase 2 dose, SC= Subcutaneous, IV= Intravenous; GGT = gamma glutamyl transferase; INR = International Normalised Ratio.
Note: IV includes all IV treatment groups; SC Non-RP2D includes ≤720 µg/kg, 3000 µg/kg, 6000 µg/kg and flat SC treatment groups; RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Grade 0 means normal. Subjects reported as Grade 0 are subjects with normal values or a value in the opposite direction (for laboratory tests with bidirectional toxicities defined).
Note: For each parameter, the total column includes all subjects with available data at baseline; percentages in the total column are calculated with the number of subjects in the all treated analysis set as denominator. Percentages for toxicity grade sub-group are calculated with the number of subjects in the total column as denominator per laboratory parameter.

Haematology

Worsening postbaseline shifts of 1 to 2 toxicity grades were commonly observed, but on the level of mean values, trends were limited to transient decreases in lymphocytes, platelets and haemoglobin at early stages of treatment.

Blood chemistry

A seen in Table 43 and Table 44 Grade 1 to 2 toxicity was commonly observed for many chemistry analytes, but Grade 3 to 4 toxicity was relatively infrequent. There were no clinically relevant changes in mean chemistry values over time.

Coagulation

In Phase 1 of MajesTEC-1, coagulation was assessed at screening, at each step-up dose, at the first 2 treatment doses, and as clinically indicated thereafter (including if a subject developed CRS). In Phase 2, coagulation was assessed at screening and as clinically indicated thereafter (including if a subject developed CRS). As seen in Table 43 and Table 44, Grade 3 abnormalities were infrequent, and Grade 4 worsening was not observed.

An analysis of the 302 subjects treated in MajesTEC-1 who were naïve to prior anti-BCMA identified two subjects who experienced laboratory Grade 3 elevation in aPTT and 4 who experienced Grade 3 laboratory hypofibrinogenemia. No DIC and bleeding events were reported in these subjects. Four of the 6 subjects had either aPTT prolongation or hypofibrinogenemia concurrently with CRS or within 15 days after CRS events. One subject had Grade 3 decreased fibrinogen with concurrent Grade 3 adenovirus infection. One subject experienced Grade 3 increased aPTT on Study Day 8 without concurrent CRS or infection. The majority of the laboratory events occurred in the context of CRS. Overall, 5 of the 6 subjects with Grade 3 hypofibrogenemia or aPTT prolongation were associated with CRS or infection. No clinical events of bleeding or thrombosis were associated with these events, though Grade 2 DIC was reported as a symptom of CRS for a subject enrolled in the 0.18 mg/kg teclistamab IV cohort in Phase 1.

Safety in special populations

Pregnancy and lactation

Pregnant and breastfeeding women were excluded from participation in MajesTEC-1. According to the applicant, there were no reports of pregnancy or breastfeeding during the study.

Safety in elderly patients

No notable trends were seen in an analysis of age-relevant adverse events (**Table 45**).

Table 45. Number and Percentage of Subjects with Treatment-emergent Adverse Events by Age in MajesTEC-1; RP2D group within total All Treated Analysis Set

	Age			
	< 65 years	65 - 74 years	75 - 84 years	≥ 85 years
Analysis set: All Treated	86	55	24	-
Total TEAEs	86 (100.0%)	55 (100.0%)	24 (100.0%)	-
Serious TEAEs	56 (65.1%)	35 (63.6%)	16 (66.7%)	-
Fatal	17 (19.8%)	6 (10.9%)	4 (16.7%)	-
Hospitalization/prolong existing hospitalization	55 (64.0%)	34 (61.8%)	16 (66.7%)	-
Life threatening	15 (17.4%)	7 (12.7%)	3 (12.5%)	-
Significant disability	1 (1.2%)	1 (1.8%)	1 (4.2%)	-
Other medically important event	4 (4.7%)	3 (5.5%)	2 (8.3%)	-
TEAEs leading to discontinuation of study drug[a]	1 (1.2%)	1 (1.8%)	0	-
MedDRA system organ class				
Psychiatric disorders	23 (26.7%)	9 (16.4%)	5 (20.8%)	-
Nervous system disorders	39 (45.3%)	27 (49.1%)	11 (45.8%)	-
Cardiac disorders	18 (20.9%)	7 (12.7%)	3 (12.5%)	-
Vascular disorders	25 (29.1%)	18 (32.7%)	8 (33.3%)	-
Infections and infestations	65 (75.6%)	43 (78.2%)	18 (75.0%)	-
Accidents and injuries[b]	10 (11.6%)	8 (14.5%)	4 (16.7%)	-
Cerebrovascular disorders[c]	1 (1.2%)	3 (5.5%)	1 (4.2%)	-
Anticholinergic syndrome[d]	5 (5.8%)	6 (10.9%)	4 (16.7%)	-
Postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[e]	11 (12.8%)	10 (18.2%)	5 (20.8%)	-

Key: RP2D = recommended Phase 2 dose, TEAE=treatment-emergent adverse event
[a] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
[b] Accidents and injuries are the adverse events defined by Standardized MedDRA Queries (SMQ) with the first subcategory of accidents and injuries of narrow scope
[c] Cerebrovascular disorders are the adverse events defined by Standardized MedDRA Queries (SMQ) with the first subcategory of central nervous system vascular disorders
[d] Anticholinergic syndrome are the adverse events defined by Standardized MedDRA Queries (SMQ) with the first subcategory of anticholinergic syndrome of narrow scope and broad scope category
[e] Includes preferred terms of orthostatic hypotension, fall, faint, syncope, dizziness, ataxia, acetabulum fracture, clavicle fracture, femur fracture, fracture pain, hand fracture, hip fracture, humerus fracture, lower limb fracture, lumbar vertebral fracture, metaphyseal corner fracture, pathological fracture, pelvic fracture, rib fracture, scapula fracture, spinal compression fracture, tooth fracture, upper limb fracture.
Note: The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.

Immunological events

Among subjects who received the Pivotal Recommended Phase 2 Dose 1.5 mg/kg subcutaneous weekly (RP2D), 150 subjects were ADA evaluable with at least 1 post-dose ADA sample at data cut-off. Of these subjects 79 and 9 subjects had evaluable ADA data at ≥6 months and ≥1 year after the first dose of study treatment. None of them (0%) were identified as positive for antibodies to teclistamab.

Among subjects who received SC non-RP2D in Phase 1, 53 subjects were ADA evaluable with at least 1 post dose ADA sample, and 19 and 13 subjects had evaluable ADA data at ≥6 months and ≥1 year

after the first dose of study treatment. One of these subjects was identified as positive for ADA at the end of treatment. No PK data were collected for the subject at or after the end of treatment to allow assessment of the effect of ADA on teclistamab PK.

Among subjects who received RP2D in Cohort C in Phase 2, 35 subjects were ADA evaluable with at least 1 post dose ADA sample, and 10 subjects had evaluable ADA data at ≥6 months after the first dose of study treatment. None of these 35 subjects were identified as positive for ADAs

Among the 82 subjects treated with teclistamab IV who were ADA evaluable (31 and 21 subjects had evaluable ADA data at ≥6 months and ≥1 year after the first dose, respectively), one subject was identified as positive for antibodies to teclistamab. The PK parameters for this subject were comparable to those for ADA negative subjects.

Overall, 238 subjects receiving teclistamab SC were ADA evaluable. One of these subjects (0.4%) developed antibodies to teclistamab. The detected ADAs were neutralizing and of low-titer.

No serum sample collected during a CRS event was identified to be positive for antibodies to teclistamab, indicating a lack of correlation between CRS and immunogenicity.

No serum sample collected during a sARR event was identified to be positive for antibodies to teclistamab in the 5 subjects who experienced sARR.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been performed with teclistamab.

Discontinuation due to adverse events

Within the total All Treated Analysis Set, 13 subjects (4.3%) experienced TEAEs leading to discontinuation of study treatment.

- In the RP2D group, 2 subjects (1.2%) discontinued treatment, one due to Grade 3 adenoviral pneumonia that was considered by the investigator as very likely related to teclistamab, and one due to Grade 4 progressive multifocal leukoencephalopathy that was considered by the investigator as probably related to teclistamab.

- In the SC non-RP2D group, 3 subjects (5.7%) discontinued treatment due to TEAEs. The first subject discontinued treatment due to congestive cardiac failure, pleural effusion, and viral pneumonia, all considered unrelated to teclistamab by the investigator. The second subject discontinued treatment due to myelodysplastic syndrome, considered possibly related to study drug. The third subject discontinued study drug due to rectal haemorrhage, considered unrelated to study drug by the investigator.

- In the IV group, 8 subjects (9.5%) discontinued treatment due to TEAEs. Three subjects discontinued treatment due to multiple TEAEs; the first subject discontinued treatment due to cellulitis, sepsis, urinary tract infection, bone pain, and depressed level of consciousness. The second subject discontinued treatment due to nephropathy and proteinuria. The third subject discontinued treatment due to immune-mediated lung disease and immune-mediated arthritis. Two subjects (2.4%) discontinued treatment due to plasma cell leukaemia, and the following TEAEs each led to treatment discontinuation for 1 subject (1.2%): pneumonia, respiratory failure, and delirium. Immune-mediated lung disease, immune-mediated arthritis, and delirium were considered related to study drug by the investigator.

Within the total All Treated Analysis Set, 4 subjects (1.3%) experienced TEAEs leading to dose reduction. The reported TEAEs leading to dose reduction in those subjects were: neutropenia (Grade 4), nausea, vomiting, and diarrhoea (in one subject), muscular weakness and diarrhoea.

The occurrence of AEs frequently led to treatment modifications (cycle delays, dose delays and dose skips). Overall, cycle delays were reported in 169 subjects (56.0%), dose delays in 52 subjects (17.2%), and dose skips in 185 subjects (61.3%) in the total All Treated Analysis Set, with AEs being the most frequently cited reason for all categories. In the RP2D group, at least 1 TEAE leading to cycle delay or dose interruption (dose delay or dose skip) was reported in 123 subjects (74.5%). These events were most frequently reported in the SOCs of Infections and Infestations (84 subjects [50.9%]) and Blood and Lymphatic System Disorders (63 subjects [38.2%]). The following TEAEs led to cycle delay or dose interruption in ≥2% of subjects in any SOC:

Preferred term	n (%)
Neutropenia	57 (34.5)
COVID-19	23 (13.9)
Pneumonia	21 (12.7)
CRS	20 (12.1)
Pyrexia	17 (10.3)
Upper respiratory tract infection	12 (7.3)
Sinusitis	7 (4.2)
Bronchitis	6 (3.6)
Nasopharyngitis	5 (3.0)
Pneumocystis jirovecii pneumonia	5 (3.0)
Urinary tract infection	5 (3.0)
Cough	5 (3.0)
Febrile neutropenia	4 (2.4)
Cellulitis	4 (2.4)
Fatigue	4 (2.4)
Influenza like illness	4 (2.4)
Acute kidney injury	4 (2.4)
Thrombocytopenia	4 (2.4)

Supportive safety information

Supportive Safety Data for Subjects in Cohort C in Phase 2

The applicant provided interim safety data for 40 subjects enrolled in Cohort C in Phase 2 of MajesTEC-1; subjects in Cohort C are required to have received prior anti-BCMA therapy.

At the time of the latest data cut-off of 16 March 2022, seventeen subjects (42.5%) are still on treatment. Rason for discontinuation was reported as progressive disease in 14 subjects (35.0%) and death in 7 subjects.

Subjects in Cohort C received teclistamab for a median of 5.2 months (range: 0.2 to 13.6). Nineteen subjects (47.5%) received teclistamab for at least 6 months and 11 subjects (27.5%) received teclistamab for at least 9 months. Nineteen subjects (47.5%) were treated for at least 6 cycles and 16 (40.0%) were treated for at least 9 cycles. Median relative dose intensity was 99.7% in Cycle 1 and 94.2% in Cycle 2+. Median relative dose intensity for all treatment, including step-up doses, was 95.9% for all subjects treated in Cohort C.

Cycle delays occurred in 13 subjects (32.5%) treated in Cohort C. Dose interruption (dose delay[s] and dose skip[s]) occurred in 6 subjects (15.0%) and 25 subjects (62.5%), respectively. AE was the most frequently reported reason for cycle delays and both types of dose interruption.

TEAEs were reported for 40 subjects (100%) treated in Cohort C. Serious TEAEs were reported for 24 subjects (60.0%). Maximum Grade 3 TEAEs were reported for 9 subjects (22.5%) and maximum Grade 4 TEAEs were reported for 20 subjects (50.0%). No subjects experienced dose reduction or a TEAE leading to treatment discontinuation. TEAEs leading to cycle delay or dose interruption (dose delay and dose skip) were reported in 29 subjects (72.5%).

Eight subjects (20.0%) experienced Grade 5 TEAEs. Six of the 8 subjects with Grade 5 TEAEs had AE identified by the investigator as the primary cause of death. Grade 5 TEAEs for these 6 subjects included COVID-19 (2 subjects) and cardiac arrest, coronary artery dissection, sudden death, and cardiac failure (1 subject each). The event of cardiac arrest was judged by the investigator as possibly related to teclistamab. The other 2 Grade 5 TEAEs were acute kidney injury and multiple organ dysfunction syndrome in subjects for whom progressive disease was reported as the primary cause of death.

The most frequently reported individual TEAEs of any severity grade (≥20%) were:

Preferred term	n (%)
Neutropenia	27 (67.5)
CRS	26 (65.0)
Anemia	20 (50.0)
Thrombocytopenia	18 (45.0)
Lymphopenia	18 (45.0)
Constipation	14 (35.0)
Diarrhoea	14 (35.0)
Pyrexia	13 (32.5)
Injection site erythema	13 (32.5)
Arthralgia	10 (25.0)
Headache	9 (22.5)
Dyspnoea	9 (22.5)
Asthenia	8 (20.0)
Bone pain	8 (20.0)

At least 1 Grade 3 or 4 TEAE was reported for 37 subjects (92.5%) in Cohort C. Grade 3 or 4 events were most frequently reported in the SOC of Blood and Lymphatic System Disorders (34 subjects [85.0%]) and Infections and Infestations (12 subjects [30.0%]), with the following events occurring in ≥10% of subjects in any SOC:

Preferred term	n (%)
Neutropenia	25 (62.5)
Lymphopenia	17 (42.5)
Anemia	14 (35.0)
Thrombocytopenia	12 (30.0)

No individual infection other than COVID-19 (3 subjects [7.5%]) was reported as Grade 3 or 4 in more than 1 subject.

A total of 44 events of any-grade CRS were reported in 26 subjects (65.0%). The maximum severity grade by ASTCT criteria was Grade 1 in 21 subjects (52.5%) and Grade 2 in 5 subjects (12.5%). Most events occurred during step-up or Day 1 of Cycle 1; median time to onset from last injection of

teclistamab was 2 days (range: 2 to 6), and median duration was 2 days (range: 1 to 4). All CRS events were reported as resolved. Supportive measures to treat CRS were used in 23 subjects (57.5%), including tocilizumab in 12 subjects (30.0%).

Neurologic TEAEs were reported in 21 subjects (52.5%), with the following reported in more than 1 subject: headache (9 subjects [22.5%]); ICANS and insomnia (4 subjects [10.0%] each); peripheral sensory neuropathy (3 subjects [7.5%]); encephalopathy (2 subjects [5.0%], a grouped term including preferred terms of depressed level of consciousness and memory impairment in 1 subject each); and dizziness and motor dysfunction (2 subjects [5.0%] each). Grade 3 or 4 neurologic AEs included Grade 3 ICANS reported in 1 subject (2.5%) and Grade 3 spinal cord compression (reported term: spinal cord compression due to myeloma bone disease) reported in 1 subject (2.5%). Serious neurologic AEs included the Grade 3 ICANS and spinal cord compression events noted above, and Grade 2 psychomotor retardation that was considered unrelated to teclistamab.

Neurotoxicity events (i.e., neurologic AEs judged by the investigator as related to study treatment) were reported for 10 subjects (25.0%), with headache (5 subjects [12.5%]), and ICANS (4 subjects [10.0%]) reported for more than 1 subject. All neurotoxicity was Grade 1 or Grade 2 severity, except for the subject with serious Grade 3 ICANS.

Among the 4 subjects with ICANS, maximum ICANS severity was Grade 1 in 3 subjects and Grade 3 in 1 subject. All ICANS events were concurrent with CRS, and no subjects discontinued treatment due to ICANS. Median time to onset from last injection of teclistamab was 2.5 days (range: 2 to 4), and median duration was 1.5 days (range: 1 to 2). All ICANS events were reported as resolved. Supportive measures to treat ICANS were used in 2 subjects, with both of these subjects receiving tocilizumab.

Cytopenias were reported for 35 subjects (87.5%). Maximum Grade 3 or 4 neutropenia, anaemia, thrombocytopenia, and lymphopenia were reported in 67.5% (n=27), 50.0% (n=20), 45.0% (n=18), and 45.0% (n=18) of subjects, respectively. When considered as individual preferred terms, 5 subjects (12.5%) experienced serious TEAEs in SOC of Blood and Lymphatic System Disorders, including 3 subjects (7.5%) with febrile neutropenia and 2 (5.0%) with anaemia. Haemorrhagic events were reported for 5 subjects (12.5%), one of which was Grade 2 haematuria.

At least 1 any grade treatment-emergent infection was reported for 26 subjects (65.0%). The infections reported in more than 1 subject were COVID-19 (5 subjects [12.5%]); bronchitis (4 subjects [10.0%]); pneumonia (3 subjects [7.5%]); and cytomegalovirus infection reactivation, implant site infection, laryngitis, oesophageal candidiasis, pharyngitis, viral pneumonia, rhinitis, tooth infection, and urinary tract infection (2 subjects [5.0%] each). Ten subjects experienced maximum Grade 3 or 4 infections, with no individual preferred term reported in more than 1 subject; 2 subjects died of COVID-19. Infections were reported as serious in 10 subjects (25.0%). No subjects discontinued treatment due to infection.

Opportunistic infections were reported for 7 subjects (17.5%), with the following events reported in >1 subject: cytomegalovirus infection reactivation and esophageal candidiasis (2 subjects each). The following event terms were each reported in 1 subject: Adenovirus infection, Adenovirus reactivation, Aspergillus infection, BK virus infection, Human herpesvirus 6 infection, and Human herpesvirus 6 infection reactivation. No fatal infections were classified as opportunistic.

Immune-mediated TEAEs or TLS were not reported. A second primary malignancy was reported for 1 subject (2.5%); this was a breast lesion, considered a ductal carcinoma in situ, that was diagnosed on Day 145. The investigator considered this event to be doubtfully related to teclistamab. As of Day 226, the subject was continuing on teclistamab; the breast lesion was reported as not resolved.

As of the clinical cut-off, 17 subjects (42.5%) treated in Cohort C had died (Table 46). Of the total deaths (n=17), 6 (15.0% of all subjects treated in Cohort C) occurred within 60 days of the first dose

of teclistamab. During this time period, 3 subjects (7.5%) died due to progressive disease, 1 subject died due to COVID-19 (reported as an AE), 1 subject died due to cardiac failure (reported as an AE), and 1 subject died due to coronary artery dissection (reported as an AE).

At least 1 serious TEAE was reported for 24 subjects (60.0%) treated in Cohort C. Serious events were most frequently reported in the SOC of Infections and Infestations (10 subjects [25.0%]). The following serious TEAEs were reported in more than 1 subject in any SOC: COVID-19 (4 subjects [10.0%]); CRS and febrile neutropenia (3 subjects [7.5%] each); and anaemia (2 subjects [5.0%]). Serious TEAEs considered by the investigator as related to teclistamab included the following: CRS, COVID-19, adenovirus infection; cytomegalovirus infection reactivation; bacterial pneumonia; viral pneumonia; Moraxella infection, febrile neutropenia, cardiac arrest, pyrexia, pain in jaw, and ICANS. Within the events considered as related to teclistamab, CRS was reported for 3 subjects (7.5%), and all others reported for 1 subject each (2.5%).

Table 46. Summary of Deaths and Cause of Death in MajesTEC-1 Cohort C; All Treated Analysis Set

	Phase 2 Cohort C
Analysis set: All Treated	40
Total number of subjects who died during study	17 (42.5%)
Primary cause of death	
Adverse event	6 (15.0%)
Study drug related[a]	1 (2.5%)
Adverse event - COVID-19	0
AE(s) unrelated	5 (12.5%)
Adverse event - COVID-19	2 (5.0%)
Disease progression	10 (25.0%)
Other	1 (2.5%)
Other - COVID-19 related	0
Total number of subjects who died within 30 days of last study treatment dose	8 (20.0%)
Primary cause of death	
Adverse event	5 (12.5%)
Study drug related[a]	1 (2.5%)
Adverse event - COVID-19	0
AE(s) unrelated	4 (10.0%)
Adverse event - COVID-19	1 (2.5%)
Disease progression	3 (7.5%)
Other	0
Other - COVID-19 related	0
Total number of subjects who died within 60 days of first study treatment dose	6 (15.0%)
Primary cause of death	
Adverse event	3 (7.5%)
Study drug related[a]	0
Adverse event - COVID-19	0
AE(s) unrelated	3 (7.5%)
Adverse event - COVID-19	1 (2.5%)
Disease progression	3 (7.5%)
Other	0
Other - COVID-19 related	0

Key: AE = adverse event.
[a] Related if assessed by the investigator as possibly, probably, or very likely related to study agent.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator

Integrated analysis of hepatobiliary events

Based on new hepatobiliary events reported as of the updated clinical cut-off, an investigation was performed into hepatobiliary events observed in subjects treated in MajesTEC-1 as well as other subjects treated with teclistamab in combination with other therapies in other ongoing studies being conducted by the Applicant.

Data from MajesTEC-1

In the pivotal RP2D group, TEAEs of ALT increased, AST increased, ALP increased, and hyperbilirubinemia were reported for 20 subjects (12.1%), 15 subjects (9.1%), 18 subjects (10.9%), and 7 subjects (4.2%), respectively, treated at pivotal RP2D. The majority of these events were Grade 1 and Grade 2. Grade 3 or 4 ALT increased, AST increased, and ALP increased, were each reported for 3 subjects (1.8%), and Grade 3 or 4 hyperbilirubinemia was reported for 2 subjects (1.2%). Other Grade 3 or 4 TEAEs were GGT increased in 5 subjects (3.0%), cholestasis in 2 subjects (1.2%); and hepatic cytolysis and hepatitis acute in 1 subject (0.6%) each. One Grade 5 event of hepatic failure

was reported. The event of Grade 5 hepatic failure occurred on in a subject who had previously developed Grade 4 acute hepatitis and which had resulted in study drug interruption. Both the events of hepatic failure and acute hepatitis were considered possibly related to teclistamab by the investigator. This case also met Hy's law criteria.

Anther subject met laboratory criteria for drug-induced liver injury and developed Grade 3 hyperbilirubinemia, with Grade 3 AST elevation and Grade 1 ALT elevation. The subject also experienced TEAEs of Grade 1 fever, Grade 2 anorexia, Grade 3 pain in the left lower extremity, Grade 3 bacteremia, Grade 3 cellulitis, and Grade 2 Clostridium difficile colitis. The criteria were not met for Hy's law given the ongoing sepsis and other infectious complications and concurrent medications capable of causing the observed injury.

The incidence of worsening of laboratory abnormalities for ALT, AST, ALP, GGT, and bilirubin from baseline (any grade) in subjects receiving pivotal RP2D was 34.5%, 40.6%, 43.0%, 38.2%, and 8.5%, respectively. Most of these were Grade 1 and Grade 2, and <5% of these events were Grade 3 and Grade 4 for all events except GGT (9.1%).

According to the Applicant, analysis of the time course of ALT elevation and association with CRS revealed that a majority of ALT elevations occurred in the first cycle or early Cycle 2. This pattern is consistent with the occurrence of CRS. Most of ALT/AST elevations were under the context of CRS.

In the SC Non RP2D group, no subjects potentially met the laboratory criteria for Hy's law. In the IV group, one subject potentially met the laboratory criteria for Hy's law from Study Days 141 to 161. This subject also experienced TEAEs of Grade 4 hyperbilirubinemia and Grade 3 hyperbilirubinemia over the same study period.

Global Safety Database

As of 16 March 2022, 668 subjects have been treated with teclistamab from multiple ongoing studies. A search of the Global Safety Database for teclistamab (cumulative to 16 March 2022), which included all ongoing clinical studies, identified 20 cases (including 1 case of HLH [preferred term: Haemophagocytic lymphohistiocytosis]) of hepatic function abnormalities.

Nine cases involved biliary disorders (cholecystitis [4 subjects]; cholecystitis acute [3 subjects]; and cholangitis and obstructive pancreatitis [1 subject each]). All cases had underlying conditions (eg, cholelithiasis, polyps in the gallbladder) and/or an alternative etiology which provided a more plausible explanation for the TEAEs. In the remaining 11 cases (6 non-fatal and 5 fatal), the 6 non-fatal cases included 2 cases (hyperammonemia [history of encephalopathy] and hyperbilirubinemia) in the context of disease progression, including 1 with liver involvement; 3 cases (1 hepatitis B reactivation, 1 hepatitis E infection, and 1 liver abscess) where the etiology of the events may be different from drug-induced liver injury and likely due to an infectious process, and 1 case of hepatic cytolysis consistent with a pattern of liver injury associated with CRS (2 days after Step-up Dose 2 of teclistamab).

The 5 fatal cases included 3 fatal hepatic failure cases: 2 fatal cases were due to hepatic failure (1 of which had an additional preferred term of hepatitis acute) and 1 fatal case was due to disease progression. In the remaining 2 fatal cases, the fatality was due to hepatitis B reactivation and HLH.

Post marketing experience

Not applicable.

3.3.6. Discussion on clinical safety

The safety data available for teclistamab stem from the ongoing MajesTEC-1 study, in which a total of 342 subjects have been exposed to teclistamab monotherapy. Of these, 165 subjects have been exposed to the proposed registrational dosage (termed "recommended Phase 2 dose" [RP2D]), and the maximum dose explored with SC dosing has been 6 mg/kg (administered weekly for 2 cycles, then biweekly, and then monthly after 6 cycles).

Notably, MajesTEC-1 is a single-arm trial, and there is thus no concurrent control group against which the safety profile could be compared, which limits a comprehensive assessment.

Median duration of follow-up in the RP2D group was 14.1 months, and median duration of treatment was 8.5 months, with 42% of subjects remaining on treatment. Some dosage modifications, most commonly due to an AE, were required in a substantial proportion of subjects in the RP2D group. On the other hand, treatment discontinuation due to an AE was rare, being required in only two subjects in the RP2D group, which would support the view that dosage modifications are an efficient means to manage emerging tolerability issues. The nature of AE's requiring treatment modifications was consistent with the general safety profile of teclistamab, the most common reasons being neutropenia, CRS and infections. The modification guidelines provided for the RP2D group in the MajesTEC-1 study are reflected in the SmPC, and this is endorsed.

The most common TEAEs were in the System Organ Classes Blood and lymphatic system disorders, General disorders and administration site conditions, Immune system disorders, Gastrointestinal disorders and Nervous system disorders. CRS was the most commonly observed individual TEAE and was reported in over 70% of subjects in the RP2D group; in the Applicant's data displays, the individual symptoms of CRS have been excluded for subjects in whom CRS was diagnosed and this is considered acceptable. Haematological TEAEs, including neutropenia, anaemia, thrombocytopenia and lymphopenia were also commonly reported. Other common events included fatigue, pyrexia, headache and GI symptoms. Injection site erythema occurred on SC administration in over 20% of subjects.

Within the initially provided documentation, the applicant described the process of determining adverse drug reactions (ADRs) for labelling purposes based on the pivotal RP2D group. The methodology applied was endorsed by the CHMP, which however requested, an additional analysis from the applicant in the All Treated Analysis Set (302 patients). No additional ADRs were identified based on the analysis in the All Treated Analysis Set; a statement to this effect has been added in Section 4.8 of the SmPC. Grade 3 prolongation of activated partial thromboplastin time and Grade 3 fibrinogen decrease were observed in 2.9% and 2.4% of subjects, respectively, in the RP2D cohort. Moreover, lower grade INR increased, aPTT prolongation or hypofibrinogenemia occurred very frequently in the MajesTEC-1 study, even in contexts other than CRS and infections (one subject with Grade 3 increased aPTT on Study Day 8 without concurrent CRS or infection). Therefore, INR increased, aPTT prolongation and fibrinogen decreased should be included in the SmPC as ADRs.

As could be expected based on the mechanism of action, cytokine release syndrome was observed in a high proportion of subjects receiving teclistamab. These events were mostly Grade 1 or 2, mostly occurred during the early stages of treatment, were generally of a transient nature (median duration was 2 days), and there were very few cases of recurrent events that were worsening over time or cases with first occurrence beyond first Treatment Dose. Overall, the observed characteristics support a view that CRS occurring in the context of teclistamab use is manageable with diligent care.

In MajesTEC-1, the use of premedication was mandated according to a specific scheme provided in the protocol. The same scheme has been brought forward into the SmPC, and in light of the high frequency of CRS, the routine use of premedication is endorsed. Supportive measures, including the use of tocilizumab, were used for management of CRS in a substantial proportion of subjects. While

the guidelines provided in the MajesTEC-1 protocol for management of CRS were not prescriptive, it is particularly noted that tocilizumab was used as part of the treatment measures in 36% of all subjects (and over 50% of subjects requiring any supportive measures for treatment of CRS). Treatment guidelines for CRS consistent with those provided in the MajesTEC-1 protocol are included in the Product Information for teclistamab (see SmPC section 4.2).

Overall, the nature and characteristics of CRS reported with teclistamab portray a profile that seems less severe than that reported e.g. with CAR-T therapies. However, it is also noted that the profile is contingent on routine use of premedication, and that in MajesTEC-1, the use of supportive measures appears to have been relatively liberal (particularly with many subjects with Grade 2 CRS having been treated with tocilizumab). As the occurrence of CRS events is quite heavily concentrated into the early stages of therapy, the precautions regarding intensified monitoring, as currently proposed in the SmPC, are endorsed and that a monitoring recommendation of 48h after each dose in the Step-up dosing schedule is sufficient. To further minimise this risk, applicant will ensure that all patients treated with teclistamab will received a Patient Card in order to inform them about the risks of CRS and when to when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS occur. Additional safety information on this risk will be collected through the planned randomised study comparing teclistamab to other treatments used in relapsed and refractory multiple myeloma. The ongoing pivotal trial will also further characterise the long-term safety associated with teclistamab use.

The potential for neurotoxicity is a recognised safety concern for immune effector cell – activating therapies, and neurological AEs were observed in a high proportion of subjects. Most of the events were Grade 1 or 2 in severity, the most common individually reported AE being headache. Neurotoxicity events (i.e. neurologic AEs attributable to teclistamab) were reported in some 13% of subjects treated at RP2D, the most common event also in this category being headache. Grade 1 to 2 ICANS was observed in 3% of subjects treated at RP2D.

Similar to CRS, the events were mostly of limited duration, but supportive treatment including tocilizumab was used in most subjects developing ICANS; this should be noted in the context of most of the ICANS events occurring concurrently with CRS. As such, the inclusion of treatment guidelines for neurotoxicity, including potential ICANS, in the Product Information for teclistamab, is supported. The guidelines proposed by the applicant are consistent with those provided in the MajesTEC-1 protocol, and the inclusion of this evidence-based treatment scheme also in the PI for teclistamab is endorsed.

Within the Nervous system disorders SOC, any Grade peripheral neuropathies were reported with very common frequency in 26/165 subjects (16%), and Grade ≥3 in one subject (0.6%). Despite the prevailing understanding that its expression is limited to haematopoietic cells, BCMA appears to have a role in neural development, as reported by Osorio et al (Osorio et al. Mol Cell Neurosci 2014). In addition, BCMA seems to be expressed in the CNS as well as in the peripheral neural tissue (Mohyddin et al. Clin Rev Oncol 2021). Whether bispecific antibodies can cross the blood-brain remains unclear, but BCMA expression on basal ganglia may be a plausible explanation for the peripheral neuropathies observed with "very common" frequency after teclistamab, as a possible BCMA off-target toxicity. Therefore, newly diagnosed and/or worsening peripheral neuropathies and extrapyramidal symptoms with teclistamab should continue to be monitored in the ongoing clinical trials and in the post-marketing setting.

Cytopenias were among the most frequently reported adverse drug reactions (neutropenia 66%, anaemia 51%, thrombocytopenia 38% and lymphopenia 34%) and were clinically managed through standard of care. Although cytopenias can be considered known risks related to the underlying clinical condition, a potential role of teclistamab cannot be ruled out. Nevertheless, considering that the SmPC already considers neutropenia within the Warnings/Precautions section of the SmPC and neutropenia,

thrombocytopenia, and lymphopenia are also included as ADRs in the SmPC, additional precautions or other measures were not considered necessary.

Hypogammaglobulinemia is not an uncommon observation in MM patients. Thus, due to confounding caused by the underlying disease, assessment of a potential contributory role of teclistamab is complicated by the absence of a concurrent control group. Nevertheless, teclistamab is expected to reduce B cells which may lead to new onset or worsening hypogammaglobulinemia, eventually resulting in an increased risk of serious infections. However, as hypogammaglobulinemia is included in section 4.4 of the SmPC and is reported as an ADR in section 4.8, it is agreed that specific additional precautions ae not required. It is furthermore noted that in the SmPC, patients are recommended to be treated according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement.

Patients with MM have increased infectious liability due to their underlying condition, and a high rate of infectious complications is therefore not unexpected. A substantial proportion of the most severe infections resulted from the ongoing COVID-19 pandemic, which probably has resulted in a very dynamic and constantly evolving situation as regards serious infectious complications. Due to the absence of a control group, no robust conclusions can be made.

Opportunistic infections were reported in 7.9% of subjects (n=13) in the RP2D cohort). Pathogens included Pneumocystis jirovecii, adenovirus, aspergillus, BK virus, cytomegalovirus and hepatitis B. A Grade 3 event of adenoviral pneumonia led to treatment discontinuation. The low frequency of herpes viral infections likely results from the vast majority of subjects using prophylactic antiviral medication. The SmPC section 4.4 includes a recommendation to consider antiviral prophylaxis prior to starting teclistamab.

The reported case of PML, with a probable relationship to teclistamab, is potentially concerning. Whereas PML is known to sometimes occur in patients with haematological malignancies, it is also an adverse reaction known to be associated with many immunomodulatory drugs. Considering the severe nature of PML, treating physicians should be vigilant in monitoring for early signs of potential PML, and a specific mention of PML in the Infections subsection of SmPC Section 4.4 has been included. In the All Treated Analysis Set, 2.0% of subjects (n=6; n=4 in the pivotal RP2D group) experienced TEAEs classified as immune-mediated. In the RP2D group, Grade 2 immune-mediated lung disease was reported in two subjects, with Grade 2 immune-mediated arthritis and Grade 1 immune-mediated enterocolitis reported in one subject each. In the SC non-RP2D group, Grade 2 immune-mediated enterocolitis was reported in one subject, and in the IV group, one subject was reported with Grade 3 immune-mediated arthritis and Grade 2 immune-mediated lung disease. All events were considered by the investigators to be related to teclistamab and most of them were associated with treatment discontinuation and/or with clinical sequelae. In these subjects, PK exposure seems to be comparable with other subjects who received the same teclistamab dose. From in vitro specificity study, teclistamab demonstrated the specificity of T cell activation (except at concentrations >100 nM) and did not cause activation of T cells in the absence of target BCMA cells+. However, at the moment and in the absence of controlled data, a potential role of teclistamab on immunological activation related to lymphocytes' activation mediated by the non-specific binding with CD3+ molecules cannot be ruled out. The Applicant should continue to monitor immune-mediated toxicity in the ongoing clinical trials and in the post-marketing setting.

One patient who received teclistamab at pivotal RP2D experienced Grade 3 TLS, diagnosed on the basis of elevated uric acid. Signs and symptoms of TLS should be monitored, and events managed according to standard guidelines. The Applicant will continue to monitor TLS in the ongoing clinical studies and in the post-marketing setting, inclusion of TLS as an ADR in the SmPC is currently not warranted.

The incidence of second primary malignancies in MM patients has been reported to be between 0.5% and 5% with a latency period of >12 months (Areethamsirikul et al, Leukemia and Lymphoma. 2015). The times from initiation of teclistamab to diagnosis are relatively short in many of the reported cases, rendering any causal association less likely. For the myelodysplastic syndrome, a time to onset of approximately one year could be considered more plausible, but the risk of secondary myelodysplastic syndrome is also known to be generally elevated in MM patients. Overall, based on current evidence, it can be agreed that the reporting rate of second primary malignancies in MajesTEC-1 is consistent with medical literature.

Systemic administration-related reactions were overall uncommon, and their risk is likely mitigated by the premedication mandated by the MajesTEC-1 protocol. Local injection site reactions were relatively common, but mostly comprised transient mild erythema.

As of the updated clinical cut-off, 41.2% of RP2D subjects participating in MajesTEC-1 had died. Progressive disease was the most commonly reported cause of death, accounting for 60% of reported deaths in the RP2D group. Among AEs reported as the primary cause of death, COVID-19 was the most common event.

For the total All treated Analysis Set, 132 subjects (43.7%) had died, with "disease progression" reported as the primary cause of death for most subjects (n=84, 27.8%). Differences in the percentages of subjects who died due to disease progression could be related to differences in the duration of follow up between the different groups, particularly in subjects who received IV treatment early in dose escalation in Phase 1. The higher frequency of death related to disease progression within 30 days of last dose of teclistamab in the RP2D set of the pivotal study could be related to corresponding differences in baseline characteristics.

For the reported non-fatal serious TEAEs, the most common individual events were COVID-19, pneumonia and CRS, reported in 14.5%, 10.3% and 8.5% of RP2D subjects, respectively. Overall, no unexpected characteristics or clustering of events are seen among the reported deaths or non-fatal serious TEAEs.

Changes in haematological parameters are commonly observed in MM patients, and in the absence of a control group, the relative effect of teclistamab vs. disease-associated changes cannot be robustly assessed. While decreases in neutrophil, lymphocyte and platelet counts and haemoglobin concentration were observed in a high proportion of subjects, changes on the level of mean values were limited to transient effects on lymphocyte and platelet counts and haemoglobin concentration. Although Grade 1 to 2 abnormalities in clinical chemistry parameters were common, there were no clinically meaningful changes on the level of mean values. One case of fatal hepatic failure, meeting the formal criteria of Hy's law, was reported.

A separate investigation into hepatobiliary events that had occurred in MajesTEC-1 as well as other studies being conducted with teclistamab was undertaken. In total, 20 cases of hepatic function abnormalities, of which five were fatal, were identified in the Applicant's global safety database. The five fatal cases included three fatal hepatic failure cases: two fatal cases were due to hepatic failure (1 of which had an additional preferred term of hepatitis acute) and one fatal case was due to disease progression. In the remaining two fatal cases, the fatality was due to hepatitis B reactivation and haemophagocytic lymphohistiocytosis. While no obvious alternative aetiology was present for the acute hepatitis leading to fatal hepatic failure (which also formally met the criteria of Hy's law), confounding factors and alternative aetiologies are present for the majority of cases. Furthermore, most of the transaminase elevations associated with teclistamab occur in the context of CRS. As such, whereas the reported case of Hy's law warrants careful continued attention to hepatobiliary events, it can be agreed that in the absence of any identifiable mechanistic basis for direct hepatotoxicity, this monitoring currently can be performed within the context of the multiple manifestations of CRS.

Although the sample size for subjects with previous exposure to anti-BCMA therapy (Cohort C) is still limited, the currently available safety data is consistent with that observed in the wider RP2D group, although it is noted that the only currently reported case of Grade 3 ICANS occurred in a subject within this cohort. At the present time, no specific precautions in this patient group beyond the general principles outlined in the SmPC are considered necessary.

Over the course of Study MajesTEC-1, the overall incidence of antibodies to teclistamab was low, with all ADA-positive subjects (a total of 2) having low titers. No effect of immunogenicity on safety, including sARR and CRS was seen and there was no observable effect of ADA formation on pharmacokinetics or clinical efficacy.

Additional safety data needed in the context of a conditional MA

As duration of exposure to teclistamab and corresponding follow-up of patients in MajesTEC-1 is relatively short further data from subsequent data lock-points are expected in order to further characterise the long-term safety of teclistamab and the important identified risks associated with its use. This includes the final CSR for MajesTEC-1 which is expected to be available by the end of 2028.

Additional safety data for the known important identified risks with teclistamab, will be required from the ongoing comparative MajesTEC-3 study which will support eventual conversion to a full MA for Tecvayli.

3.3.7. Conclusions on the clinical safety

The safety profile of teclistamab monotherapy, when used in the management of MM patients, has been studied in a single-arm trial. The total number of subjects studied to date enables a reasonable characterisation of the overall safety profile and common adverse events, but the lack of a concurrent control group limits a comprehensive assessment.

Consistent with the mechanism of action of teclistamab, CRS was observed in over 70% of all subjects receiving RP2D teclistamab and can indeed be considered its key risk. It is however noted that CRS appeared to be transient in nature, mostly low-grade severity, and was manageable with diligent patient care. The inclusion of specific treatment guidelines for CRS, similar to those applied in the pivotal trial, in the Product Information together with the provision of a patient card to directly inform patients when to seek medical is expected to adequately minimise this risk. Provided information will also the management of ICANS (which often occurs concurrently with CRS). For other identified risks (such as cytopenias and infections), it is considered that treatment modification guidelines in the Product Information for teclistamab are sufficient.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional Marketing Authorisation:

- The final CSR for MajesTEC-1

- Data from the ongoing comparative MajesTEC-3 study will be required

3.4. Risk Management Plan

3.4.1. Safety concerns

Summary of safety concerns	
Important identified risks	Cytokine release syndrome
	Neurologic toxicity
	Serious infections
Important potential risks	Not applicable
Missing information	Long-term safety

3.4.2. Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanised BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma	The primary objective in Part 1 (dose escalation) is to identify the proposed RP2D(s) and schedule assessed to be safe for teclistamab. The primary objective in Part 2 (dose expansion) is to characterise the safety and tolerability of teclistamab at the proposed RP2D.	CRS Neurologic toxicity Serious infections Long-term safety	Updated Safety Report Final Report	Q4 2023 Q4 2028

3.4.3. Risk minimisation measures

Summary Table of Risk Minimisation Activities

Safety Concern	Risk Minimisation Measures
Cytokine release syndrome	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Usage of a step-up dosing schedule (ie Step-up dose 1, Step-up dose 2, and initial treatment dose) to reduce the incidence and severity of CRS is described in SmPC Sections 4.2 and 4.4.

Safety Concern	Risk Minimisation Measures
	• Instructions that pretreatment medications (corticosteroid, antihistamine, antipyretics) must be administered prior to each dose in the step-up dosing schedule to reduce the risk of CRS are provided in SmPC Sections 4.2 and 4.4.
	• Instruction for patients to remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of all doses in the step-up dosing schedule is provided in SmPC Sections 4.2 and 4.4.
	• Recommendation to withhold teclistamab until any Grade 1, Grade 2, or Grade 3 (<48 hours' duration) CRS event resolves is provided in SmPC Section 4.2 and Section 4.4.
	• Recommendation to permanently discontinue teclistamab for any Grade 3 (recurrent or >48 hours' duration) or Grade 4 CRS event is provided in SmPC Section 4.2.
	• Recommendation to administer pretreatment medication prior to the next dose for any patient with a CRS event of Grade 1, Grade 2, or Grade 3 (<48 hours' duration) is provided in SmPC Section 4.2 and in SmPC Section 4.4.
	• For patients who have a CRS event of Grade 2 or Grade 3 (<48 hours' duration), instruction that they should remain within the proximity of a healthcare facility and be monitored daily for 48 hours after the next dose is provided in SmPC Sections 4.2 and 4.4.
	• Recommendations that patients should be counselled to seek medical attention if signs and symptoms of CRS occur, that patients should be immediately evaluated for hospitalisation at the first sign of CRS, and that treatment should be instituted are provided in SmPC Section 4.4.
	• Recommendation to avoid the use of myeloid growth factors, particularly GM-CSF, during CRS is provided in SmPC Section 4.4.
	• Recommendations that CRS should be identified based on clinical presentation, and that other causes of fever, hypoxia, and hypotension should be evaluated and treated, are provided in SmPC Section 4.4.
	• Recommendation to administer supportive care as appropriate is provided in SmPC Section 4.4.
	• Recommendation that laboratory testing should be considered to monitor for disseminated intravascular coagulation, haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function is provided in SmPC Section 4.4.
	• Specific guidelines for the management of CRS with tocilizumab and/or corticosteroids, depending on toxicity grade and symptoms, is provided in tabular format in SmPC Section 4.4.
	• Patients should get medical help right away if signs of CRS occur, as described in PL Section 2 and Section 4.
	• The design of the packaging has been chosen to appropriately differentiate between the product strengths to ensure the medicine is used correctly during step-up dosing (where the 10 mg/mL vial should be used. Step-up dosing is designed to mitigate the severity of CRS.
	Additional risk minimisation measures:
	• Patient Card
Neurologic toxicity	**Routine risk minimisation measures:**
	• SmPC Section 4.2
	• SmPC Section 4.4
	• SmPC Section 4.7
	• PL Section 2
	• PL Section 4

Safety Concern	Risk Minimisation Measures
	• Recommendation to withhold teclistamab until any Grade 1, Grade 2, or first occurrence of a Grade 3 ICANS event resolves is provided in SmPC Section 4.2. • Recommendation to permanently discontinue teclistamab in the case of any recurrent Grade 3 or any Grade 4 ICANS event is provided in SmPC Section 4.2. • Instruction for patients to remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of the next dose of teclistamab following any Grade 2 or first occurrence of a Grade 3 ICANS event is provided in SmPC Sections 4.2 and 4.4. • Recommendation to monitor patients for signs and symptoms of neurologic toxicity and to treat promptly is provided in SmPC Section 4.4. • Recommendation to counsel patients to seek medical attention if signs or symptoms of neurologic toxicity occur is described in SmPC Section 4.4. • At the first sign of neurologic toxicity (including ICANS), recommendation to immediately evaluate and treat patients, consider neurologic evaluation, and rule out other causes of neurologic symptoms is provided in SmPC Section 4.4. • Recommendation to provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities is provided in SmPC Section 4.4. • Detailed guidelines on the management of ICANS, by severity, symptoms, and whether patients have concurrent CRS, including the use of tocilizumab, corticosteroids, and anti-seizure medications, are provided in tabular format in SmPC Section 4.4. • Recommendation to avoid driving and operating heavy or potentially dangerous machinery during and for 48 hours after completion of the teclistamab step-up dosing schedule, and in the event of new onset of any neurological symptoms, is provided in SmPC Sections 4.4 and 4.7. • Patients should get medical help right away if symptoms of ICANS or other neurologic toxicities occur, as described in PL Section 2 and Section 4. **Additional risk minimisation measures:** • None
Serious infections	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Recommendation to consider antiviral prophylaxis for the prevention of herpes zoster virus reactivation per local institutional guidelines is provided in SmPC Section 4.2. • Recommendation to not administer teclistamab step-up dosing schedule in patients with active infection (any grade) until the infection has resolved is provided in SmPC Section 4.2. • Recommendation that for subsequent dosing (ie, after step-up dosing), if patients develop an infection of Grade 3 or 4, then teclistamab should be withheld until the infection improves to Grade 2 or better is provided in SmPC Section 4.2. • Recommendations that patients should be monitored for signs and symptoms of infection prior to and during teclistamab treatment and treated appropriately, and that prophylactic antimicrobials should be administered according to local institutional guidelines, are described in SmPC Section 4.4. • Recommendation that teclistamab should not be administered in patients with active infection and should be withheld for subsequent dosing based on severity of infection is provided in SmPC Section 4.4.

Safety Concern	Risk Minimisation Measures
	• Recommendation that patients with positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during and for at least 6 months after teclistamab treatment is provided in SmPC Section 4.4. • Recommendation that for patients who develop reactivation of HBV, teclistamab should be withheld and this should be managed per local institutional guidelines is provided in SmPC Section 4.4. • Recommendation to monitor immunoglobulin levels during teclistamab treatment and treat hypogammaglobulinemia according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement, is included in SmPC Section 4.4. • Recommendations that patients with neutropenia should be monitored for signs of infection, treatment should be withheld based on severity, and blood cell counts should be monitored at baseline and periodically during treatment with supportive care provided per local institutional guidelines, are included in SmPC Section 4.4. • Patients should tell their doctor or nurse if they have any signs of infection, as described in PL Sections 2 and 4. **Additional risk minimisation measures:** • None
Long-term safety	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** • None

3.4.4. Conclusion

The CHMP considers that the risk management plan version 1.4 is acceptable.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

3.6. Product information

3.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3.6.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tecvayli (teclistamab) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

4. Benefit-Risk Balance

4.1. Therapeutic Context

4.1.1. Disease or condition

The applicant is submitting a Marketing Authorisation Application for consideration of conditional approval of teclistamab as monotherapy for adult patients with relapsed or refractory multiple myeloma who have received at least three prior therapies including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody

Treatment guidelines for MM do not give specific recommendations after multiple relapses, and treatments are chosen individually based on patient and disease characteristics and prior treatments. Although response rates and durations generally decline after several lines of treatment, patient populations are better defined by refractoriness to available treatments rather than number of therapies received. Generally, patients can be considered to have limited treatment options when they are refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and exhausted effective treatment options when they are penta-refractory, defined as being refractory to two immunomodulatory agents, two PIs and an anti-CD38 antibody. In addition, patients with a previous BCMA-targeting therapy represent the last line setting in the current therapeutic landscape.

4.1.2. Available therapies and unmet medical need.

Much progress has been made over the past decade in the understanding of myeloma disease biology and individualised treatment approaches. Several new classes of drugs have joined the traditional armamentarium (corticosteroids, alkylating agents and anthracyclines) and, along with high-dose

therapy and autologous haemopoietic stem cell transplantation, have led to deeper and durable clinical responses.

Due these achievement survival outcomes for patients with multiple myeloma (MM) have also significantly improved over the past 15 years. The introduction of novel classes of drugs [proteasome inhibitors (PIs) (bortezomib, carfilzomib, and ixazomib), immunomodulatory imide agents (IMiDs) (thalidomide, lenalidomide, and pomalidomide) and lately targeted therapies, such as monoclonal antibodies targeting CD38 (daratumumab) and SLAMF7 (elotuzumab) have enabled numerous combinations in the treatment armamentarium of MM. However, almost all patients with multiple myeloma eventually relapse and the remission duration in relapsed multiple myeloma decreases with each regimen.

With the approval of daratumumab and its wide use in combinations in earlier lines of MM treatment, a new population of patients is created who have become refractory to all available agents (including daratumumab). This population can be referred to as triple-class refractory MM and it encompasses those patients with disease refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb (such as daratumumab).

Therefore, an unmet medical need persists particularly in patients pre-treated with daratumumab, and new mechanisms of action are needed to overcome drug resistance. However, both Blenrep (belantamab mafodotin, a BCMA-targeting antibody-drug), Abecma (idecabtagene vicleucel) and Carvykti (ciltacabtagene autoleucel) (CAR t-cell products targeting BCMA) were recently authorised in patients who have previously received at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody. Thus, a new last line RRMM patient population now also includes treatment with a BCMA-targeting treatment.

4.1.3. Main clinical studies

The main evidence of efficacy submitted is derived from a single phase 1/2 study 64007957MMY1001 (MajesTEC-1). This was open-label, multicentre study to evaluate the efficacy and safety of teclistamab monotherapy (1.5 mg/kg SC administered weekly with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg) in RRMM patients. The pivotal population with regard to efficacy are the subjects treated at RP2D in phase 1 and subjects treated in Cohort A in phase 2 (n=165) with previous exposure to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb.

Supportive efficacy data, especially supporting the efficacy in patients also with previous BCMA-targeting treatment, is provided from Cohort C.

4.2. Favourable effects

The ORR according to the 2016 International Myeloma Working Group (IMWG) Response Criteria as assessed by the IRC was 63.0% (95% CI: 55.2% to 70.4%). The median DOR for subjects treated at pivotal RP2D (All Treated Analysis Set) was 18.4 months (95% CI: 14.9 to NE).

A best response of VGPR or better as assessed by the IRC was reported for 58.8% (95% CI: 50.9% to 66.4%) of subjects and sCR was reported for 32.7% (95% CI: 25.6% to 40.5%) of subjects.

The median time to response was 1.18 months (range: 0.2, 5.5), and the median time to best response (PR or better) was 3.79 months (range 1.1; 16.8).

The median PFS and OS based on IRC assessment were 11.3 months (95% CI: 8.8 to 17.1 months) and 18.3 months (95% CI: 15.1 months to NE) respectively

4.3. Uncertainties and limitations about favourable effects

Efficacy assessment relies on a single arm study, conducted without an active control arm. This poses well know limitations with regards to interpretation of data, in particular with regards to selection bias and assessment of time to event endpoints. Patient population defined by the proposed indication, adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, are currently eligible for other treatments. The presented results are considered compelling in this setting, and will be further confirmed in a randomised confirmatory study MMY3001 (MajesTEC-3).

Subjects in the pivotal study were generally fit and elderly patients were underrepresented. Subjects with active CNS involvement or with clinical signs of meningeal involvement by MM were excluded from trial participation, as well as patients with plasma cell leukaemia. The activity of teclistamab in these rare subsets of MM is unknown. The low percentage of subjects with severe MM signs/symptoms (e.g. anaemia, renal failure, hypercalcaemia) is in line with the study inclusion/exclusion criteria, yet raises uncertainties of the generalisability of results in study MMY1001 to the target population.

4.4. Unfavourable effects

Treatment-emergent adverse events were reported in all subjects, with at least one Grade 3 to Grade 4 event reported in over 90% of subjects in the RP2D group. These were most frequently reported in the Blood and lymphatic system disorders and Infections and infestations SOCs.

In the RP2D group, the most frequently reported TEAEs included CRS (72%), neutropenia (71%), anaemia (52%), thrombocytopenia (40%), lymphopenia (34%), injection site erythema (26%), diarrhoea (28%), fatigue (28%), nausea (27%), pyrexia (27%), and headache (24%). Cytopenias and infections were the most frequently reported Grade 3 or 4 TEAEs.

At least 1 event of any grade CRS was reported in 73% of subjects treated at pivotal RP2D. Most events occurred during the step-up stage of dosing. Median time to onset was 2 days, and median event duration was 2 days. CRS was frequently managed with supportive measures, including tocilizumab in over 50% of subjects requiring any supportive measures for treatment of CRS. No Grade 4 or 5 CRS was observed.

In the RP2D group, 14.5% of subjects experienced treatment-emergent neurotoxicity. One Grade 4 seizure was reported; other events had a maximum toxicity of Grade 1 or 2. The most common event was headache, reported in 8.5% of subjects. Grade 1 to 2 ICANS was reported in 3% of RP2D subjects. In addition, one subject in Cohort C experienced Grade 3 ICANS.

Cytopenic events were reported in the majority of subjects. In the RP2D group, Grade 3 to 4 neutropenia, anaemia and thrombocytopenia were reported in 64%, 37% and 21% of subjects, respectively. There was one case of Grade 5 haemoperitoneum in a subject with Grade 2 thrombocytopenia at baseline.

In the RP2D group, treatment-emergent infections were reported in 76% of subjects, and Grade 3 to 4 infections in 36% of subjects. The most common Grade 5 infection was COVID-19.

4.5. Uncertainties and limitations about unfavourable effects

The key uncertainty is related to the nature of the MajesTEC-1 study; it is a single-arm study, and the absence of a concurrent control group in a heavily pre-treated patient population with multiple disease-associated complications severely limits the ability to robustly assess the safety profile of teclistamab.

Despite the updated analyses submitted during the assessment, the limited duration of treatment and follow-up still complicate assessment of longer-term effects for a treatment that is foreseen to continue

until disease progression. The uncertainty is particularly pertinent related to effects that have a high underlying prevalence in the relevant patient population, i.e. cytopenias and infections. The long-term safety profile of teclistamab will be further characterised through the ongoing MajesTEC-1 study and additional information will be collected through the randomised phase 3 study MMY3001 (MajesTEC-3).

The overall size of the safety population, and particularly that of Cohort C, remains limited.

4.6. Effects Table

Table 47. Effects Table for Teclistamab, as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received three prior lines of therapy including an anti-CD38 antibody, a proteasome inhibitor, and an immunomodulatory agent (data cut-off 16 March 2022)

Effect	Short Description	Treatment	Result	Uncertainties/ Strength of evidence	Reference
Favourable Effects					
ORR (%)	Percentage of participants with a confirmed partial response (PR) or better (*i.e.*, PR, VGPR, CR and sCR, according to the 2016 IMWG Response Criteria by IRC.	1.5 mg/kg SC weekly	63.0% (95% CI: 55.2% to 70.4%)	No control arm other, interpretation of the observed ORR is. VGPR or better rate (%):58.8% (95% CI: 50.9% to 66.4%) sCR (%):32.7% (95% CI: 25.6% to 40.5%)	
DOR, (median, months)	Time from first documented evidence of PR or better until the earliest date of documented PD per IMWG, or death due to PD	1.5 mg/kg SC weekly	18.4 (95% CI: 14.9 to NE)	Median FUP time among responders 14.1 months, 68.3% of responders censored .	
Unfavourable Effects					
CRS	Any grade cytokine release syndrome	1.5 mg/kg SC weekly	72%		
Neurotoxicity	Treatment-related neurological TEAEs, any grade	1.5 mg/kg SC weekly	14%		
Infections		1.5 mg/kg SC weekly	All: 76% G3/4: 36%		
Cytopenias		1.5 mg/kg SC weekly	All: 92% G3/4: 86%		

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

The use of the teclistamab as a single-agent therapy demonstrated a clinically meaningful antitumour activity. With the limits of naïve indirect comparisons in a heterogeneous condition such as MM, the ORR of 63.0% is higher than what has been observed with other agents in similar patient populations: 32% ORR with recently approved belantamab mafodotin, and 26.2% with selinexor in combination with dexamethasone, and comparable to CAR T products idecabtagene vicleucel and ciltacabtagene autoleucel. Despite recent approvals of these products, limited treatment alternatives are available in these heavily pre-treated RRMM patients.

Observed high ORR in this last line of treatment is considered potentially relevant, providing a new alternative with a new MoA in the current therapeutic landscape of MM. The revised indication wording is considered to adequately reflect the last line patient population included in the pivotal study.

sCR rate of 32.7% and CR or better rate of 39.4% is considered high in a heavily pre-treated RRMM population. The updated data demonstrate that responses can continue to deepen with prolonged treatment.

Based on currently available data, the key risk associated with teclistamab is CRS. In general, it seems that CRS events can be managed firstly, with appropriate premedication being used for overall CRS risk mitigation, and secondly, with due vigilance particularly at the early stages of therapy and active use of supportive measures. The SmPC includes management guidelines for CRS that are consistent with those used in MajesTEC-1, which together with the additional risk minimisation measures included in the RMP are considered sufficient to minimise this risk.

The high underlying prevalence of infections and cytopenias in MM patients complicates the assessment of any contributory role of teclistamab for these complications; moreover, the infection profile is confounded by the highly dynamic COVID-19 landscape during the conduct of MajesTEC-1. While no outstanding safety concerns can currently be identified, a more comprehensive assessment in this respect will have to await results from controlled studies.

The limited follow-up and the overall limited size of the database also pose uncertainties particularly for assessment of very rare events such as PML and also hepatobiliary events; as such, the safety profile of teclistamab may still be evolving but will be further characterised through the ongoing MajesTEC-1 study and the randomised phase 3 study MajesTEC-3.

4.7.2. Balance of benefits and risks

The study population were heavily pre-treated and had received at least three prior therapies (median 5). All patients had been exposed to, and majority were refractory to at least one proteasome inhibitor (85.0%), at least one immunomodulatory agent (95%), and an anti-CD38 monoclonal antibody (97.5%). The observed efficacy is considered clinically relevant in this population. The CHMP requested that the indication for teclistamab is revised to 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 to better reflect the patient population of the pivotal study.

The limited follow-up and overall size of the safety database from MajesTEC-1 also limit a comprehensive assessment of the risks associated with the use of teclistamab. While the acute safety profile, including common adverse reactions, can be considered reasonably established, longer-term safety data, also from appropriately controlled studies, will be required; together with a more comprehensive understanding of efficacy, this will enable an improved overall contextualisation of the safety profile.

In the context of a CMA, the B/R balance is positive.

4.7.3. Additional considerations on the benefit-risk balance

It is acknowledged that conducting an RCT is challenging in a late line RRMM setting. However, it should be noted that "last line setting" in multiple myeloma is a moving target in this rapidly evolving field, and strictly only the Cohort C (patients exposed to a PI, an IMID, an anti-CD38 antibody and a BCMA-targeting therapy) serving as supportive data represent true last line setting in the current therapeutic landscape. This application is based on a single arm trial, and similar evidence base has supported several recent conditional marketing authorisations. Nevertheless, the evidence for efficacy generated in a single arm trial is less robust and subject to different types of bias, most notably selection bias. Time-to-event endpoints are considered important for demonstration of clinical benefit, but cannot be reliable assessed in a SAT setting. Thus, the pivotal SAT can be considered sufficient to demonstrate clinical benefit in this patient population, but not to provide comprehensive data.

No external comparison has been provided to contextualise the data. However, the natural history of the disease is well characterised, and multiple clinical trials with other medicinal products have been performed in comparable patient populations. An overview of the relevant clinical trials has been provided. The pharmacological rationale is strong and there are no doubts on causality of effects.

Even though ORR is accepted as an endpoint for regulatory purposes, the ultimate patient benefit as reflected in OS cannot be reliably determined in a single arm trial. The observed ORR is likely an over-estimation due to a selected patient population, but the magnitude is sufficient to assume clinically relevant efficacy also in a broader patient population. Moreover, the depth of the observed responses (CR/sCR), MRD) provides important supportive data. The median DOR is 18.4 months which is considered clinically relevant. Importantly, PFS and OS demonstrating (long-term) treatment benefit cannot be reliably determined in a single arm trial. Thus, the available efficacy data is not considered to be comprehensive but is sufficient to demonstrate clinical benefit.

In terms of safety, the number of patients exposed to teclistamab is limited but can be considered sufficient to characterise the expected overall safety profile. Teclistamab is administered until disease progression or unacceptable toxicity, and at the time of the updated data cut-off, over 40% of patients in the RP2D group were still on treatment. The patient population in the pivotal study is relatively young and fit considering the late line disease setting, and limited data on safety and tolerability of the treatment in less fit patients is available. Thus, the safety data cannot be considered to be comprehensive.

In summary the data provided for MA are not regarded as comprehensive due to lack of interpretable time-to-event endpoints to determine treatment benefit and the extent of exposure and length of follow-up for safety.

Based on the above, the clinical data are not considered comprehensive.

Conditional marketing authorisation

As comprehensive data on the product are not available as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

The product could fulfil the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive.

- It is likely that the applicant will be able to provide comprehensive data.

  The Applicant is conducting a randomised Phase 3 registration study, MajesTEC-3, in subjects with multiple myeloma who have been previously treated with 1 to 3 prior lines of therapy, including a PI and lenalidomide. In this study, subjects will be randomised to receive a combination of teclistamab and daratumumab (Tec-Dara) or an investigator's choice of DPd or DVd which are currently authorised therapies in this setting. Primary endpoint is progression free survival, and key secondary endpoints include overall response (PR or better), MRD negativity rate, patient reported outcomes and OS. Approximately 560 subjects will be randomised 1:1. This study will provide further confirmatory data on the safety and efficacy profile of teclistamab, and will address several aspects for lack of comprehensiveness of the available data, including limited number of patients, limited duration of follow-up, and especially lack of time-to-events endpoint data (PFS, OS) data to confirm clinical benefit of the treatment.

  The MajesTEC-3 study is currently ongoing, Aa with clinical cut-offs for interim and primary analyses expected in Q3 2023 and Q3 2024, respectively.

- Unmet medical needs will be addressed:

  Teclistamab will provide a novel, targeted option for the treatment of subjects with multiple myeloma, with a mechanism of action that is unique to all other approved therapies. It is thus expected that teclistamab will offer an additional option to patients that are no longer responsive to existing treatments for this condition.

  There are authorised treatments of MM in the EU, and multiple products reviewed by the Applicant have overlapping indications with the proposed indication with teclistamab. However, according to the current ESMO recommendations, once patients are refractory to an IMiD, PI, and anti-CD38 monoclonal antibody, the current recommendation is either belantamab mafodotin or selinexor. Both products are conditionally approved, and Teclistamab is expected to address the unmet medical need in the targeted patient population at least to a similar extent. Although comparison of response rates across single arm studies should be interpreted with caution, available data suggests superior response rates when compared with other available off-the-shelf therapies. However, it should be noted that the patient populations in the registration trials for these products were more heavily pre-treated as compared to MajesTEC-1 population. Belantamab mafodotin application was based on data from the DREAMM-2 study, in which all subjects were triple-class refractory. ORR in the 2.5 mg/kg cohort of DREAMM-2 was 32%. Selinexor in combination with dexamethasone was approved for the treatment of multiple myeloma in adult patients who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, 2 IMiDs, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. In the STORM study, a PR or better was observed in 25.3% of subjects and the median duration of response was 3.8 months.

  The CAR T therapies idecabtagene vicleucel and ciltacabtagene autoleucel which have also received conditional approvals, have shown comparable rates of response in this setting (ORR 67% and 84%, respectively). However, this treatment may not be suitable for all patients due to their potential to cause severe safety events and complexity of the treatment (limited availability in specialised treatment centres, delay in treatment related to the manufacturing process, need for bridging therapy). Teclistamab therefore offers an alternative therapeutic option that will be readily available to a broader patient population.

  Furthermore, preliminary data from Cohort C of the MajesTEC-1 study also suggest that teclistamab provides benefit for patients who have already been treated with a BCMA-targeting ADC or CAR-T therapy, where there are very limited treatment options and is an area of further unmet medical need.

- The benefits to public health of the immediate availability are considered to outweigh the risks inherent in the fact that additional data are still required, as an additional therapy option for RRMM patients with three or more previous systemic therapies is considered beneficial.

4.8. Conclusions

The overall benefit/risk balance of Tecvayli is positive, subject to the conditions stated in section 'Recommendations'.

5. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Tecvayli is not similar to Darzalex, Imnovid, Farydak, Kyprolis, Ninlaro, Blenrep, Abecma and Carkykti within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tecvayli is favourable in the following indication:

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.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

    The MAH shall ensure that in each Member State where TECVAYLI is marketed, all patients/carers who are expected to use teclistamab have access to/are provided with the Patient Card which will inform and explain to patients the risks of CRS. The Patient Card also includes a warning message for healthcare professionals treating the patient that the patient is receiving teclistamab.

    The Patient Card will contain the following key messages:

- A description of the key signs and symptoms of CRS

- A description of when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS present themselves

- The prescribing physician's contact details

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of Teclistamab 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, the MAH shall submit the results of study 64007957MMY3001, a Phase 3 Randomised Study Comparing Teclistamab in Combination with Daratumumab SC versus Daratumumab SC, Pomalidomide, and Dexamethasone (DPd) or Daratumumab SC, Bortezomib, and Dexamethasone (DVd) in Participants with Relapsed or Refractory Multiple Myeloma	March 2028
In order to further characterise the duration of response and long-term safety in subjects with multiple myeloma who have been previously treated with ≥3 prior lines of therapy, including an immunomodulatory agent, a PI and anti-CD38 antibody, the MAH shall submit the final study report of 64007957MMY1001, a Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanised BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma	December 2028

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that teclistamab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).