20 July 2023
EMA/365426/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Talvey

International non-proprietary name: talquetamab

Procedure No. EMEA/H/C/005864/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADR	Adverse drug reaction
AE	Adverse event
ASTCT	American Society for Transplantation and Cellular Therapy
ATT	Average treatment effect in the treated
AUC	Area under the concentration-time curve
AUCtau	Area under the concentration-time curve during a dosing interval
BCMA	B cell maturation antigen
CAR-T	Chimeric antigen receptor T cell
CD	Cluster of differentiation
CI	Confidence interval
CL0	Total clearance at time t=0
CLt	Time dependent clearance
Cmax	Maximum observed serum concentration
COVID-19	Coronavirus disease 2019
CR	Complete response
CRS	Cytokine release syndrome
CSR	Clinical study report
Ctrough,4doses	Predicted trough concentration after the first 4 weekly treatment doses
DOR	Duration of response
DP	Drug product
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECLIA	Electrochemiluminescence-based immunoassay
ECOG	Eastern Cooperative Oncology Group
EC90	90% maximal effective concentration
eCRF	Electronic case report form
EMA	European Medicines Agency
EOI	End of infusion after IV flush
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item

EQ-5D-5L	EuroQol Five Dimension Five Level Questionnaire
E-R	Exposure-response
EU-27	27 European (countries)
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridisation
FLC	Free light chain
GCP	Good Clinical Practice
GPRC5D	G protein-coupled receptor family C group 5 member D
HLA-DR	Human leukocyte antigen – DR isotype
HLH/MAS	Haemophagocytic lymphohistiocytosis/ macrophage activation syndrome
HRQoL	Health-related quality of life
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell-associated encephalopathy
IFN-γ	Interferon gamma
Ig	Immunoglobin
IL	interleukin
IL-2Rα	Interleukin-2 receptor alpha
IMiD	immunomodulatory imide drug
INR	International normalised ratio
IMWG	International Myeloma Working Group
IPW	Inverse probability weighting
IRC	Independent Review Committee
ISS	International staging system
IV	Intravenous(ly)
Ka	Firstorder absorption rate constant
LAG-3	lymphocyte activation gene-3
MCT	Meaningful change threshold
MRD	Minimal residual disease
mRNA	Messenger ribonucleic acid
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
PAA	Proline, alanine, alanine
PBRER	Periodic Benefit Risk Evaluation Report
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death-1 ligand 1
PFS	Progression-free survival
PGIS	Patient Global Impression of Severity
PI	Proteasome inhibitor
PO	Oral(ly)
PR	partial response
PRO	Patient-reported outcome
PV	Pharmacovigilance
Q2W	Once every 2 weeks
RP2D	Recommended Phase 2 dose
RWPC	Real-world physician's choice
SAP	Statistical Analysis Plan
sBCMA	Soluble BCMA
SC	Subcutaneous(ly)
SCE	Summary of Clinical Efficacy
sCR	Stringent complete response
SmPC	Summary of Product Characteristics
SOC	System organ class
t1/2	Half-life
T cell	T lymphocyte
TEAE	Treatment-emergent adverse event
TIM-3	T cell immunoglobulin and mucin domain-containing protein 3
TLS	Tumour lysis syndrome
Tmax	Time to reach the maximum observed serum concentration
TNF-α	Tumour necrosis factor alpha
TTNT	Time to next treatment
TTR	Time to response
V1	Central volume of distribution

VAS	Visual analogue scale
VGPR	Very good partial response

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 3 January 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Talvey through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Talvey was designated as an orphan medicinal product EU/3/21/2486 on 20 August 2021 in the following condition: treatment of multiple myeloma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Talvey as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/human/EPAR/Talvey

The applicant applied for the following indication: as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression or did not respond to the last therapy.

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 study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0395/2019 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 talquetamab 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

Talvey 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 but is somewhat limited by the short duration of exposure which does not allow estimation of duration of response.

- Uncertainty of reported effects is offset by novel mechanism of action, which would provide a genuine new option in a population with limited treatment options.

Upon granting of eligibility to PRIME, Alexandre Moreau was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 01 July 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
- further characterisation of GPRC5D expression
- the criteria for establishing similarity between the 800µg/kg q2w and 400µg/kg qw dosing regimens

1.7. Scientific Advice

The applicant received the following Scientific Advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 February 2021	EMA/SA/0000047518	Elena Wolff Holz and Adriana Andric
27 January 2022	EMA/SA/0000070065	Johanna Lähteenvuo and Livia Puljak
19 May 2022	EMA/SA/0000079497	Karri Penttila and Pierre Demolis
15 September 2022	EMA/SA/0000095359	Johanna Lähteenvuo and Livia Puljak

The Scientific Advice pertained to the following non-clinical, and clinical aspects:

- Proposed nonclinical toxicology package for MAA, including the strategy to evaluate cardiac toxicity, reproductive toxicity, drug-drug interactions and the GPRC5D normal human tissue expression profile.
- Proposed clinical pharmacology plan.
- Design of Phase 1/2 study 64407564MMY1001 (MonumenTAL-1) to support a conditional marketing authorisation (CMA), in particular with regards to the definition of the patient population, the use of overall response rate as the primary endpoint and the size of the safety database.
- Design of Phase 3 study 64407564MMY3002 (MonumenTAL-3) to provide confirmatory evidence of safety and efficacy for full marketing authorisation (MA) and extension of indication, in particular with regards to the definition of the patient population, the use of PFS as the primary endpoint, the choice of comparator, the statistical analysis plan and other methodological aspects.
- Proposal to use real-world data to contextualise the efficacy data from the single-arm Phase 1/2 MonumenTAL-1 study.
- Adequacy of the design of the Phase 3 study MonumenTAL-3 study to support conversion of a CMA into full MA.

1.8. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Armando Genazzani

The application was received by the EMA on	3 January 2023
Accelerated Assessment procedure was agreed-upon by CHMP on	10 November 2022
The procedure started on	25 January 2023

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	28 March 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 April 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 April 2023
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 April 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 April 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	9 June 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	20 June 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	6 July 2023
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 Talvey on	20 July 2023
The CHMP adopted a report on similarity of Talvey with Darzalex, Imnovid, Farydak, Kyprolis, Ninlaro, Blenrep, Abecma and Carvykti on	20 July 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	20 July 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Talvey is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression or did not respond to the last therapy.

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).

MM 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 characterised 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, multiple myeloma remains incurable. All patients eventually relapse and become refractory to existing treatments. Median OS in patients who have received at least three prior multiple myeloma 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 multiple myeloma, 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 multicentre retrospective, observational study investigated the natural history and outcomes of patients with multiple myeloma 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, multiple myeloma 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 tumor 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 multiple myeloma.

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 multiple myeloma 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 106 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.

Finally, on 24 August, teclistamab, a bispecific antibody against BCMA and cluster of differentiation 3 (CD3) receptors, 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.

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

Talquetamab is a novel, humanised IgG4 bispecific antibody designed to target the CD3 receptor complex on T cells and on GPRC5D-expressing multiple myeloma cells, resulting in T cell activation and subsequent lysis of GPRC5D-expressing multiple myeloma cells. As a stable bispecific IgG molecule generated through controlled Fab (fragment antigen binding) arm exchange following the method reported by Labrijn 2013, talquetamab is able to draw T cells in close proximity to myeloma cells, without regard to T cell receptor specificity.

The applicant targets the following indication: as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression or did not respond to the last therapy.

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 talquetamab 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 multicentre, randomised, open-label Phase 3 study ((64407564MMY3002) to determine whether talquetamab in combination with daratumumab and pomalidomide (Tal- DP; Arm A) and talquetamab in combination with daratumumab (Tal-D; Arm C) have better efficacy respectively than the combination of daratumumab, pomalidomide and dexamethasone (DPd; Arm B) in participants with relapsed or refractory multiple myeloma who have previously received at least 1 prior line of therapy. The applicant believes that the results from Study 64407564MMY3002 would provide sufficient evidence to confirm the findings of the single arm Phase ½ Study 64407564MMY1001, addressing any remaining uncertainties and would allow conversion of the conditional MA based on Study 64407564MMY1001 to a standard MA. It is anticipated that the interim analysis of Study 64407564MMY3002 will be completed by April 2027.
- Unmet medical needs will be addressed, as talquetamab 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. Patients who progress after having received therapies from the 3 main therapeutic classes (IMIDs, PIs, and anti CD38 monoclonal antibodies) have limited options that may be unsuitable in a heavily treated population. It is therefore of importance to identify alternative targets for T cell redirection for the treatment of relapsed or refractory multiple myeloma. Targeting the GPRC5D receptor, highly specific to malignant plasma cells, represents a novel mechanism of action and a new option for heavily pretreated patients. Because of the high

expression of GPRC5D in malignant plasma cells and low expression in normal human tissue, GPRC5D is a promising new target for immunotherapy in patients with multiple myeloma.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Talquetamab offers a promising new therapeutic option for triple-class exposed patients that will be readily available to all patients and has a favourable safety profile and superior efficacy compared with other off-the-shelf alternatives. Talquetamab also provides an option for patients who are unable to wait for manufacturing of CAR-T cells, are unfit for this modality of therapy, and/or in addition, have progressed after a BCMA therapy and are in need of alternative treatments. As such, the applicant considers that talquetamab fulfils an unmet medical need and will provide a major contribution to public health, specifically for multiple myeloma patients.

2.4. Quality aspects

2.4.1. Introduction

Talquetamab, the active substance in Talvey, is a humanised immunoglobulin G4 (IgG4)-proline, alanine, alanine (IgG4-PAA) bispecific monoclonal antibody (MAb) directed against G protein-coupled receptor family C group 5 member D (GPRC5D) and the CD3 receptors. It is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The finished product is presented as a solution for subcutaneous injection in 1.5 mL and 1 mL vials containing respectively 3 mg (2 mg/mL) and 40 mg (40 mg/mL) of talquetamab. The syringes and transfer needles used for administration are provided separately.

Talquetamab is formulated with EDTA disodium salt dehydrate, glacial acetic acid, polysorbate 20, sodium acetate trihydrate, sucrose, and water for injections.

2.4.2. Active substance

2.4.2.1. General information

Talquetamab is a humanised IgG4 bispecific antibody against GPRC5D and CD3 receptors. Talquetamab consists of 2 heavy chains (HC) and 2 light chains (LC), joined by disulfide bonds.

Talquetamab is prepared by controlled reduction and oxidation of JNJ-64386972 Protein A (anti-GPRC5D MAb) and JNJ-63483043 Protein A (anti-CD3 MAb) resulting in an exchange of the Fab arms. The Fab arm exchange was facilitated by amino acid substitution in the CH3 domain of the parental JNJ-63483043 HC, enhancing the stability of the heterodimer. Talquetamab has a molecular mass of 147,201 Da for the predominant glycoform.

1The bispecific design of the antibody allows for simultaneous engagement of T cells (CD3 binding) and malignant B cells (GPRC5D binding). The process of bringing the malignant B cells into close proximity of the T cells leads to killing of the cancer cells. The mechanism of action is thus based on functionality of both the CD3-binding and GPRC5D-binding domains.

2.4.2.2. Manufacture, characterisation and process controls

Manufacturing process

The active substance is manufactured at Janssen Sciences Ireland UC (JSI), Barnahely, Ringaskiddy, Co. Cork, Ireland. After thawing and pooling of the 2 parental antibodies, the individual parental antibody pools are combined and undergo reduction of the interchain disulfide bonds in the parental antibodies by a reducing agent to allow for bispecific antibody formation. Talquetamab is then purified by a series of chromatography steps, viral inactivation, viral filtration and ultrafiltration/diafiltration steps.

The description of manufacturing process and controls is appropriately detailed. Each production bioreactor of parental antibody derives from a single working cell bank (WCB) vial.

Reprocessing is not routinely performed as part of the active substance manufacturing process but some reprocessing steps have been prospectively identified and validated at small-scale. If reprocessing occurs, a verification protocol will be applied and a variation submitted as appropriate.

All sites involved in manufacture, control and storage of the active substance operate in accordance with EU GMP.

Control of materials

A list of raw materials used in the manufacturing process, including contact filters and chromatography resins, is provided. Raw materials are tested according to European pharmacopoeia where available. Non-compendial materials are tested and released according to active substance manufacturer's in-house specifications. Composition of the powder media used for the cell culture process are chemically defined and animal-component free.

Information on the source of the host cell line, the preparation and description of the expression vectors, and the establishment of the cell banks is provided. The cell lines for anti-GPRC5D MAb and anti-CD3 MAb parental antibodies were transfected independently. These cell lines were used to produce the finished product for all clinical trials and will be used to produce commercial product. Both master cell bank (MCB) and WCB were tested and characterised in accordance with ICH guidelines and were both confirmed to be of CHO origin. Expression of the expected cDNA sequences was confirmed. Genetic stability of the production cell line has been demonstrated for anti-GPRC5D MAb and for anti-CD3 MAb. Preparation and testing of future WCBs is described.

Control of critical steps and intermediates

Relevant process parameters and in-process controls (IPCs) were laid down in the process description with target and proven acceptable ranges (PARs). The proposed IPCs are overall acceptable.

Process validation

Process validation was executed on commercial-scale batches for the anti-GPRC5D MAb intermediate, commercial-scale batches for the anti-CD3 MAb intermediate, and commercial-scale batches for the active substance. For each process stage, a brief summary, results, and conclusions were provided.

Evaluation of quality attributes through release and characterisation testing, IPCs, and process performance attributes demonstrated that the manufacturing process is robust and reproducible where process parameters operate within their operating range.

Levels of residual impurities have been demonstrated to be reduced to acceptably low levels in the active substance.

Evaluation of process intermediates hold times was appropriately addressed using material taken from commercial-scale batches. Demonstration of stability included both biochemical and microbial aspects.

Chromatography resin lifetimes and shipping validation were adequately addressed. Overall, the active substance manufacturing process is considered validated.

Manufacturing process development

The strategy taken to develop the talquetamab active substance manufacturing process comprises the definition of critical quality attributes (CQAs), process development, risk assessment (Failure Mode Effects Analysis - FMEA), scale down model establishment, and process characterisation studies. This approach follows the principles described in ICH guidance (ICH Q8, Q9, Q10, and Q11). Overall the proposed control strategy has been thoroughly justified and is suitable to control the process and deliver a product with consistent quality, as confirmed by process validation. In responses to questions, few inconsistencies were satisfactorily addressed and some points were clarified.

Comparability studies were performed to evaluate the manufacturing changes made to the active substance and finished product during clinical development. The major process changes associated with each study were appropriately summarised and included notably changes in active substance and finished product concentrations, as well as an increase in active substance purification scale. The batches used in the last comparability studies were all used in Phase 1/2 pivotal study '64407564MMY1001'. The batches derived from commercial process can thus be considered as representative of clinical material.

Impact of the process changes on the quality attributes was assessed using combination of in-process, release, characterisation, ICH stability, and degradation rate data. Overall, the analytical assessments demonstrated that the pre-change and post-change materials were comparable and provided confidence that all of the manufacturing changes introduced during clinical development would not adversely impact the safety and efficacy of bispecific antibody.

Characterisation

Elucidation of structure

Characterisation of talquetamab includes primary structure, carbohydrate structure, disulfide structure and free thiols, intact mass and mass heterogeneity, charge heterogeneity, size heterogeneity, higher order structure, biological characterisation (Fab and Fc functions) and structure/function relationships.

Overall, the characterisation exercise is well established, both with regard to the type and number of orthogonal techniques employed and with regard to the experimental designs to evaluate the main degradative pathways. The ability of the various methods to identify the most important post-translational modifications (PTMs) classified as CQAs was also evaluated.

The studies concerning biological characterisation and structure/function relationships are considered largely satisfactory. The mechanism of action of talquetamab has been studied and characterised in detail using a comprehensive set of bioassays, necessary for such a complex antibody with multiple functions. Further characterisation data were provided to support the binding specificity to GPRC5D and the suitability of T cell activation assay. This data was considered adequate.

Impurities

Data provided by the applicant to support characterisation of impurities in the active substance is considered appropriate.

2.4.2.3. Specification

Specifications

The active substance specifications include control of identity, purity and impurities, potency and other general tests.

During the assessment, the acceptance criteria for some purity attributes were tightened and the new limits proposed for the specifications are overall considered acceptable.

The control of a complete list of the different impurities is included in the specification, together with the methods employed (at release or as IPC) for adequate monitoring.

The applicant agreed to strengthen the identity testing strategy to the active substance release specification. The additional identity testing will allow to confirm the identity of both anti-GPRC5D and anti-CD3 arms of talquetamab.

Analytical procedures

The proposed procedures were satisfactorily validated and they were considered suitable to control the active substance on a routine basis. Minor concerns were raised which were satisfactorily addressed.

Batch analysis

Batch analysis results are provided for batches representative of the final commercial process and batches derived from previous active substance concentration. Results confirm consistency and uniformity of the batches, indicating that the process is under control.

Reference standard

The applicant established appropriately characterised in-house primary and working reference materials, prepared from lots representative of production. Working reference material used in the testing of production lots was calibrated against the primary reference material. Documentation of the qualification, storage conditions and stability programme of primary and working reference materials was provided. Protocol for qualification of future primary and working reference materials was also described.

The same reference materials are used for active substance and finished product.

Container closure

The intermediates and talquetamab active substance are stored and shipped into polycarbonate bottles. The choice of the container closure system was chosen to pose low risk for extractables and leachables and to provide adequate protection from microbial contamination. Compatibility of the container with the active substance is demonstrated through stability studies.

2.4.2.4. Stability

Parental antibody intermediates

Batches of anti-GPRC5D MAb and anti-CD3 MAb were manufactured and placed in the stability monitoring programs. The long-term, real time, real conditions stability data show no significant trend over the claimed shelf-lives. The accumulated data for clinical, process validation and post process validation batches support the proposed shelf life for the anti-GPRC5D MAb and the anti-CD3 MAb when stored at the recommended conditions.

Active substance

The shelf-life for the active substance is based on stability studies that were carried out in accordance with current ICH/CPMP guidelines.

Primary stability studies were performed on clinical batches derived from the pre-change process and batches (clinical and process validation) derived from the commercial process. As comparability has been demonstrated between the pre-change active substance process and the commercial active substance process, this approach is agreed.

All batches were stored in representative containers (polycarbonate vials). The long-term, real time, real-condition stability studies showed no significant change over the proposed shelf life.

Accelerated and stressed stability studies were also conducted to assess the effect of these conditions on product quality. As for long-term studies, the results did not show any significant trend under accelerated and stressed storage conditions.

In addition, freeze-thaw cycling studies were performed, and the results support that the active substance met all acceptance criteria. The data collected to date demonstrate that the active substance remains in conformance with the proposed commercial stability acceptance criteria for all the attributes that were tested.

Based on stability data provided, the proposed shelf-life, when stored at the recommended temperature, can be granted for the active substance.

Post-approval stability protocol and stability commitment are also considered overall adequate. The choice to not include pH in active substance stability specification is considered acceptable, taking into account that the pH test is maintained at finished product level.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product (strengths of 2 mg/mL and 40 mg/mL) is supplied as a sterile liquid in a vial for subcutaneous administration. The finished product contains no preservative and is for single use only.

Each 2 mg/mL finished product vial contains 3 mg of talquetamab in a 1.5 mL nominal fill volume. The primary packaging consists of a 6R Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off cap.

Each 40 mg/mL finished product vial contains 40 mg of talquetamab in a 1.0 mL nominal fill volume. The primary packaging consists of 2 mL Type I glass vial with an elastomeric closure and an aluminium seal with a flip-off cap.

The final commercial finished product contains 2 mg/mL or 40 mg/mL talquetamab, EDTA disodium salt dehydrate, glacial acetic acid, polysorbate 20, sodium acetate trihydrate, sucrose, and water for injections. The pH is 5.2, stored at 2-8ºC.

Pharmaceutical development

The finished product formulation evolved from a frozen formulation to a liquid formulation. To facilitate late phase clinical studies, two new presentations, 2 mg/mL and 40 mg/mL liquid finished product, were developed to achieve the prescribed dose in a practical volume for subcutaneous administration.

There is no overage in the finished product. To ensure the nominal volume can be withdrawn and administered, an overfill is included in the vial.

An enhanced approach was used to develop the commercial manufacturing process and establish an appropriate control strategy for talquetamab finished product. This approach includes definition of the quality target product profile (QTPP), identification of the CQAs and CPPs through prior knowledge, risk assessments and characterisation studies. Data provided to justify the finished product control strategy are comprehensive.

A combination of lab-scale and at-scale process studies evaluating thawing and storage of thawed active substance, mixing, pumping, filtration, and filling were performed. Furthermore, hold time studies were performed to evaluate in-process hold steps and cumulative exposure to ambient light. Regarding sterile filtration, studies were performed with polyvinylidene fluoride (PVDF) membrane and quantity of flush was determined which is supported by process validation runs and deemed acceptable.

Compatibility of the container closure system with the dosage form was assessed with respect to physicochemical testing (i.e. extractables and leachables), stability testing, and container closure integrity testing.

Talquetamab finished product contains no preservative. The microbiological quality complies with EU requirements for sterile products and is ensured by a combination of various measures - sterile product-contact components, sterile in-line filtration, environmental and media monitoring - and is confirmed by microbiological IPC testing as well as sterility release testing.

The finished product is intended to be administered subcutaneously with a separately-obtained syringe. Physicochemical stability of the finished product was demonstrated for the durations and conditions as listed in the product information. From a microbiological point of view, although microbial challenge tests demonstrated that microbial proliferation was not observed in the vial of talquetamab finished product, the product should be used immediately.

2.4.3.2. Manufacture of the product and process controls

Manufacturing process

Janssen Biologics B.V. (Netherlands) is responsible for EU batch certification. All sites involved in manufacture, control and storage of the finished product operate in accordance with EU GMP.

A minimum and a maximum batch size is defined for both finished product strengths. The finished product manufacturing process is standard and starts with thawing of the active substance. The finished product solution is then compounded into a dilution buffer pre-filtrated and sterilised by filtration immediately prior to filling. The vials are stoppered, crimped and a 100% visual inspection is performed before shipping. The level of detail in the description of the manufacturing process has been updated in order to provide a more clear and comprehensive overview of the finished product manufacturing process and relative controls. In process controls are found overall adequate.

Process parameter ranges are supported by manufacturing process development. The established hold times are specified and validated. No reprocessing is claimed.

Process validation

Validation of the finished product manufacturing process is based on analysis of a number of consecutive process performance qualification (PPQ) batches. The adopted validation strategy has been further justified in terms of bracketing approach, number of runs needed to validate different strengths

and different batch sizes. The validation studies included control of all process parameters (CPPs and non-CPPs) and IPCs, as well as CQAs. The results met acceptance criteria, demonstrating the finished product manufacturing process is consistent throughout the different steps (thawing, filtration and filling).

The finished product manufacturing process, media-fill, filters, depyrogenation of the materials and the handling of the product during shipping are validated (or qualified). The acceptance criteria are met.

2.4.3.3. Product specification

Specifications and analytical procedures

The finished product specifications include control of identity, purity and impurities, potency and other general tests.

A combination of methods were confirmed to be sufficient for confirming the identity of talquetamab. Some tests that were included in the active substance are not included in the finished products specifications due to no significant changes in the levels of these attributes during finished product manufacturing and storage.

Acceptance criteria setting is based on a combination of several factors: clinical experience, stability and process effects, product-specific knowledge, prior knowledge, current compendia or regulatory guidelines, and formulation development studies. Overall, the proposed specifications are considered justified and sufficient to deliver product with consistent quality. Some limits initially proposed were tightened.

The methods for finished product were validated as per ICH Q2 R1 requirements.

Overall, the finished product specifications are considered acceptable.

Characterisation of impurities

The potential presence of nitrosamine impurities has been evaluated by taking into account the manufacturing process. As Talvey is a biological medicinal product with no chemically synthesised components, no meaningful exposure to the nitrosating agents is expected.

Based on a risk assessment of the manufacturing process, the risk is considered low since the structure, materials used in manufacture, manufacturing conditions, process, purification, and storage conditions are not conducive to nitrosation reactions.

A component-based risk assessment for the potential presence of elemental impurities in the finished product was conducted in accordance with the ICH Q3D(R1) Guideline for Elemental Impurities, taking into account potential contributions from the active substance, excipients, manufacturing equipment, container closure system (primary packaging), and processing water.

Batch analysis

Analytical results of finished product batches derived from process validation and clinical trials are provided. All batches from process validation were manufactured at the commercial site using the intended commercial process. All results comply with the defined acceptance criteria. Batch analysis has been updated to include also analytical results relative to clinical batches derived from previous process versions.

Container closure

The primary packaging consists of a Type 1 glass vial with an elastomeric closure and an aluminum seal with a flip-off cap. The choice of the container closure system is in line with pharmaceutical standards and the components comply with pharmacopeia requirements.

2.4.3.1. Stability of the product

The claimed shelf life of the finished product is 15 months when stored at 5 ± 3°C protected from light.

Clinical batches and process validation batches of finished product were manufactured and placed in the stability monitoring programs. The claimed shelf life is based on 15 months real-time stability data for finished product batches (40 mg/mL batches and 2 mg/mL batches). The stability data available to date for all clinical and process validation batches of finished product conformed to the proposed commercial stability acceptance criteria.

Supporting stability data obtained from accelerated and stressed storage conditions were also presented. A photostability study was conducted and the results from the study demonstrate that the surrogate package representative of the commercial secondary package will provide the finished product with adequate protection from the effects of the light conditions specified in ICH Q1B.

In addition, temperature cycling studies were performed and the results support the stability of finished product during potential temperature excursions that may be encountered during transportation, storage, and handling. The data collected to date demonstrate that the finished product will remain in conformance with the proposed commercial stability acceptance criteria that have been established for the 5 ± 3°C storage condition for all the analytical procedures used.

Following CHMP request, the applicant agreed to include pH and turbidity in the finished product stability specifications. The stability monitoring programme was updated accordingly.

Overall, the acceptable shelf life for the finished product is 15 months when stored protected from light in a refrigerator at 2°C to 8°C.

Chemical and physical in-use stability (prepared syringe) has been demonstrated for 24 hours at 2°C to 8°C followed by up to 24 hours at temperature of 15°C to 30°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless preparation has taken place in controlled and validated aseptic conditions.

The prepared syringe should be stored protected from light.

2.4.3.2. Adventitious agents

The use of animal- or human-derived material was restricted to cell line generation and is appropriately described, with certificates provided. No materials of direct or indirect animal or human origin are used in the talquetamab active substance and finished product manufacturing. The TSE risk can be considered as negligible.

The panel of microbiological, adventitious and endogenous virus tests performed on the MCB, WCB and EEPCB (extended end of production cell banks) for each parental monoclonal antibody is defined appropriately considering the species of the raw materials of biological origin, and the results are

compliant. The in-process tests performed in routine on the unprocessed bulk prior to harvest are appropriate given the CHO origin of the cell lines.

Viral safety was assessed throughout the process. Reduced-scale models of the chromatography steps and the dedicated viral inactivation and removal steps were used to evaluate viral clearance.

Viral clearance is achieved through orthogonal chromatographic steps, viral inactivation, and physical removal of virus. The virus clearance steps were evaluated in the active substance process.

The studies are mostly well designed, and the results are satisfactory. In summary, the adventitious agents safety evaluation is considered acceptable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Module 3 dossier of Talvey is of very good quality. Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. No major concern has been identified. A variety of concerns (Other Concerns) covering the different sections of the dossier were originally raised and have been resolved.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Talvey is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the marketing authorisation application for Talvey is considered approvable from the quality point of view.

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 recommended some points for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical testing strategy was developed to be consistent with the clinical indication (multiple myeloma), administration routes (SC and IV), and dosing regimen of talquetamab (also referred in this section as JNJ-64407564). Studies were designed and conducted in accordance with the ICH guidelines S6(R1), and S9, as well as S7A, M3(R2), S3A, and S5(R3).

2.5.2. Pharmacology

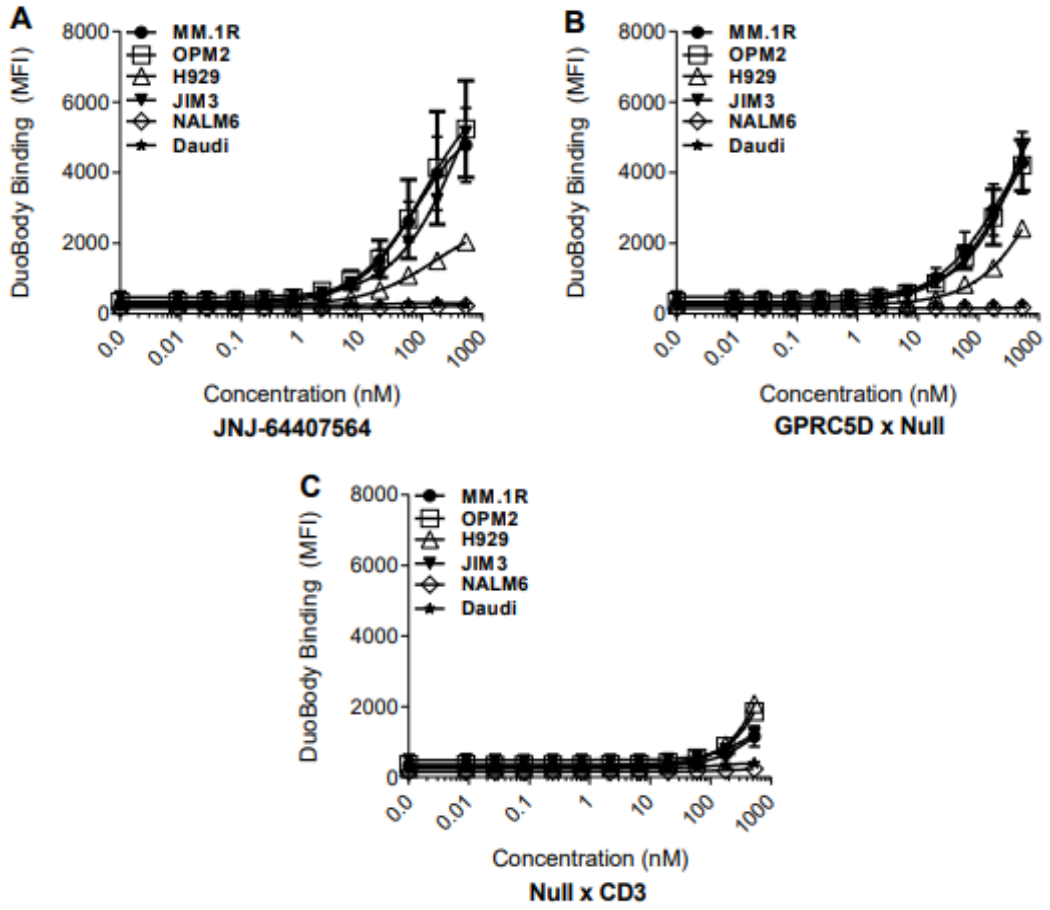
2.5.2.1. Primary pharmacodynamic studies

In vitro pharmacodynamics

Talquetamab Binding to Multiple Myeloma Cell Lines

Talquetamab binding to GPRC5D-positive human multiple myeloma cell lines (MM.1R, OPM-2, H929, and JIM-3) and GPRC5D-negative human cell lines (Daudi and NALM-6) was determined using flow cytometry methods (**Figure 2**). GPRC5D×null control antibody (containing 1 anti-GPRC5D arm) and null×CD3 were used as positive and negative controls respectively in these experiments.

Figure 2. Talquetamab Binding in GPRC5D-expressing multiple myeloma cell lines (Study report DD17025)



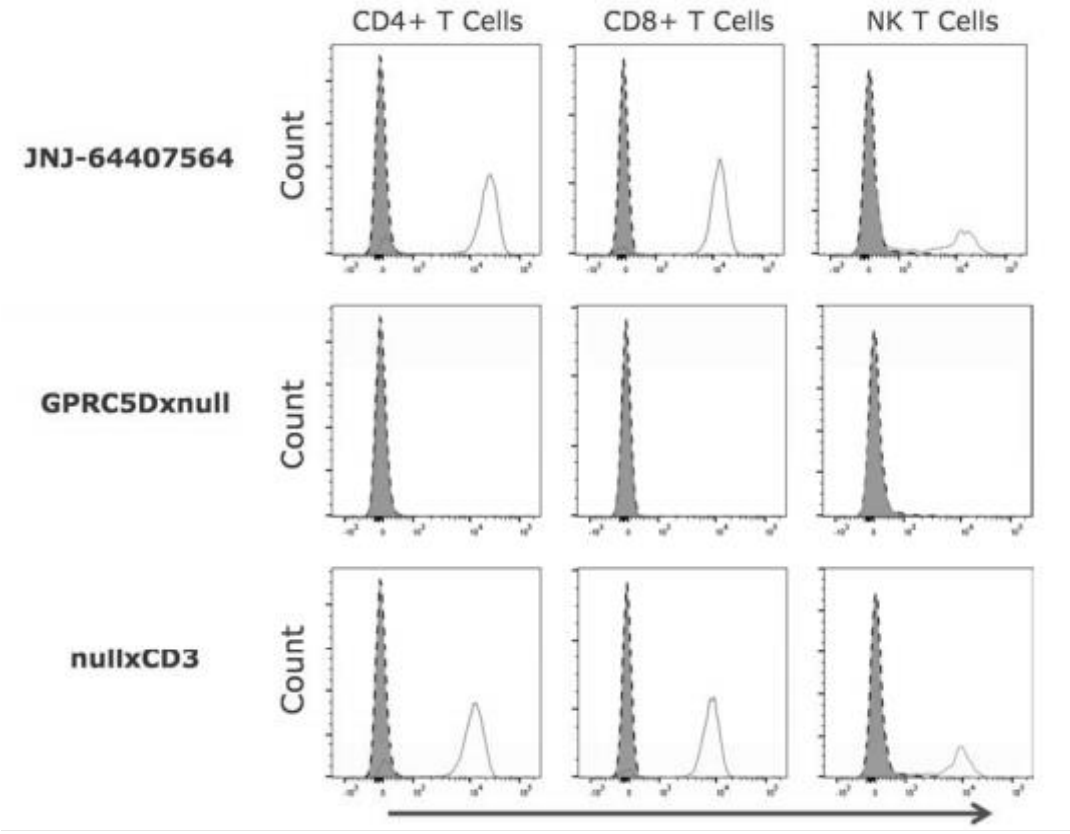
CD3 = cluster of differentiation 3; GPRC5D = G Protein-coupled receptor family C group 5 member D; MFI = mean fluorescence intensity.
Note: GPRC5D-positive and GPRC5D-negative cells with various concentrations of talquetamab (Panel A), GPRC5D × null (Panel B), and null × CD3 (Panel C) antibodies to measure the surface binding profiles (n=3). Binding is expressed as the geometrical mean (MFI).

Talquetamab binding profile in whole blood

To evaluate the binding of talquetamab on leukocytes, whole blood from healthy human donors and frozen bone marrow mononuclear cells from multiple myeloma subjects were stained with talquetamab and evaluated by FACS using the respective cell markers. Results indicated binding of talquetamab for CD4+, CD8+ and NK T cells (

Figure 3) but not for any other peripheral blood cell population evaluated (data not shown).

Figure 3. Binding profile of JNJ-64407564 and control antibodies to T cells and NKT cells in human whole blood



NK, natural killer; CD, cluster of differentiation.
Staining for one representative donor is shown, where the solid line trace is the test antibody (JNJ-64407564, GPRC5Dxnull, or nullxCD3) and dotted line with filled gray is the corresponding isotype control CNTO 9412.

GPRC5D expression on normal human tissues

Analysis of GPRC5D human normal tissue expression included a review of published literature and public domain data.

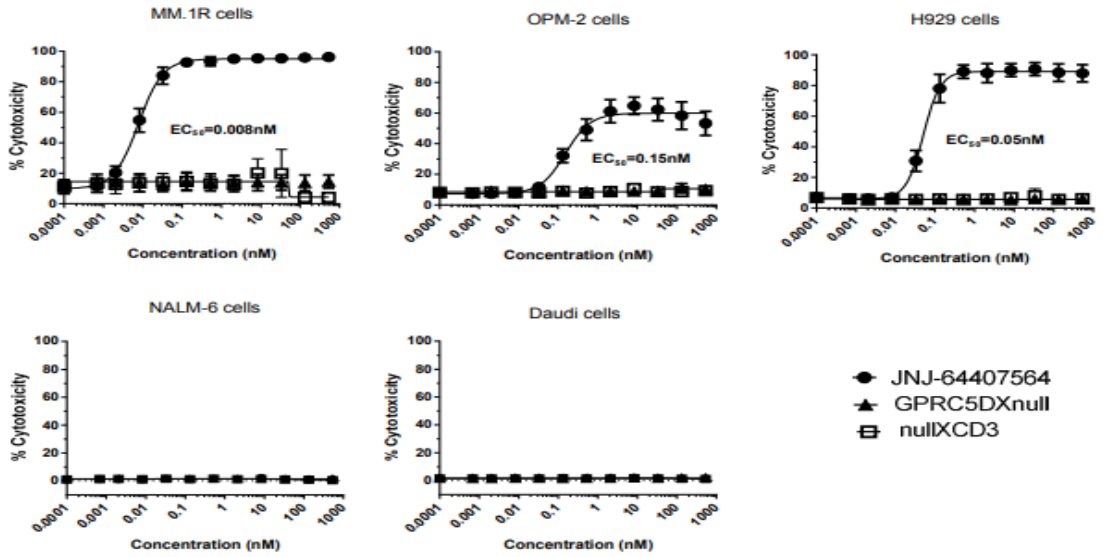
Published literature (Inoue 2004; Venkateshaiah 2013; Kodama 2019; Smith 2019; Verkleij 2021) and internally generated data (study reports 02212020, 04092020, 07242020, 10162020 and 06292022) show that GPRC5D expression is limited to normal plasma cells and specific epithelial cell types in keratinised tissues such as skin and tongue. GPRC5D is detected in plasma cells (Venkateshaiah 2013; Kodama 2019; Verkleij 2021), and anatomical sites with high numbers of resident normal plasma cells (i.e., tonsil, lymph node, spleen) would be expected to contain GPRC5D mRNA. Consistent with published data (Smith 2019), expression of GPRC5D in interstitial/tissue-resident plasma cells was confirmed internally in tonsil, lymph node, spleen, bone marrow, salivary glands and gastrointestinal tract (stomach, duodenum and colon) by immunohistochemistry (IHC) and *in situ* hybridisation (ISH) (study reports 10162020 and 06292022; Goldsmith 2021). GPRC5D mRNA and protein expression was also confirmed in hair follicles (hair bulb and shaft) and epithelial cells of eccrine sweat glands of the skin (Goldsmith 2021; study report 06292022). GPRC5D expression was also detected in keratinised structures (filiform papillae) of the human tongue (study report 10162020; Goldsmith 2021) and nailbeds of mice (RNA by ISH; Inoue 2004). Similarly, Smith (2019) reported GPRC5D protein expression in intestinal immune cells, hair follicles, and sweat glands in skin.

Internal efforts did not detect GPRC5D by either IHC or ISH on samples of human normal lung, including airways, alveoli, pleura, and lymphoid tissues (study report 07242020; Goldsmith 2021). This is in apparent conflict with low positive RNA signal for GPRC5D in lung by bulk RNA-sequencing (low levels; Genotype-Tissue Expression project; Human Protein Atlas; study DD17024). However, IHC and ISH expression data provided higher resolution over the bulk quantitative RNA expression measurements (derived from tissue homogenates) because FFPE tissue samples could be pre-screened to confirm anatomical location, tissue quality (eg, proper sampling and handling, appropriate structures present in the sample, and sample suitability for specific IHC/ISH application), and disease-free state. Additionally, the IHC and ISH methods allowed for the examination of specific cell types and subcellular location. No GPRC5D protein was detected by IHC in cerebellum, brainstem (medulla), ependyma or choroid plexus. Low levels of GPRC5D RNA were detected by ISH in the motor neurons of the inferior olivary nucleus in the brainstem (medulla; study report 07242020; Goldsmith 2021). These motor neurons extend axons into the cerebellum, and detection of RNA in these cells could explain very low levels of RNA detection by RT-qPCR in the cerebellum (Pillarisetti 2020). Consistent with this, Smith (2019) reported no GPRC5D protein expression in lung or brain. No GPRC5D RNA or protein expression was detected in other brain regions and nervous system tissues examined as tissue microarray including cerebrum, meninges, corpus callosum, midbrain, thalamus, striatum, spinal cord, dorsal root ganglion, or peripheral nerve.

Effect of JNJ-64407564 on T-cell-dependent cytotoxicity

Treatment with talquetamab led to T cell-mediated cytotoxicity, as measured by % dead cells of fluorophore labelled GPRC5D-positive multiple myeloma cell lines (H929, MM.1R, and OPM-2) after 48-hour incubation at an E:T ratio of 5:1 (determined from fresh and frozen bone marrow samples from subjects with multiple myeloma) with T cells from 6 different healthy donors (**Figure 4**).

Figure 4. Talquetamab-mediated killing of GPRC5D-positive MM cell lines (study report DD17025)



Drug concentrations:

µg/mL	0	0.0003	0.001	0.005	0.020	0.078	0.313	1.250	5.000	20.000	80.000
nM	0	0.0020	0.008	0.032	0.130	0.520	2.078	8.313	33.250	133.000	532.000

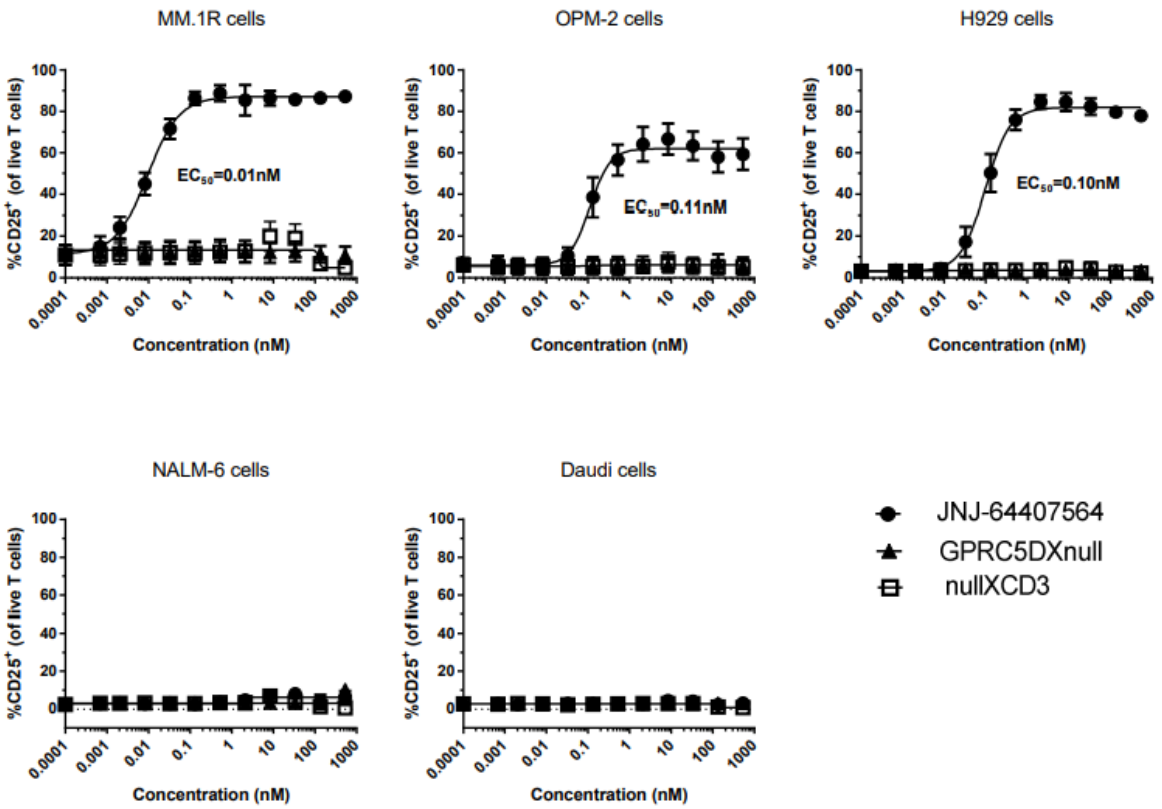
EC50, 50% effective concentration.
Top panel shows cytotoxicity results for three GPRC5D-positve cell lines and lower panel shows results for two GPRC5D-negative cell lines. Data from six T-cell donors was pooled in each graph. Mean ± standard error oKRaf the mean is graphed.

Additionally, the effect of talquetamab on cytotoxicity was tested in an *in vitro* assay, in which whole blood from healthy donors was incubated in the presence of GPRC5D-positive MM H929 cells at an E:T ratio of 5:1 (determined from fresh and frozen bone marrow samples from subjects with multiple myeloma), along with increasing concentrations of talquetamab for 48 hours. Treatment with talquetamab resulted in dose-dependent H929 cytotoxicity. Individual cytotoxicity EC50 (EC20) values from the 6 donors ranged from 0.206 to 0.612 (0.041 to 0.357) nM, producing a mean of 0.389 (0.131) nM (Study report DD17025).

Effect of talquetamab on T-cell Activation and cytokines release

The expression of CD25 was measured as an indicator of the degree of T cell activation in the cytotoxicity assays by talquetamab (**Figure 5**).

Figure 5. T Cell-mediated antibody-dependent T cell activation in MM cell lines (Study report DD17025)



Antibody concentrations:

µg/mL	0	0.0003	0.001	0.005	0.020	0.078	0.313	1.250	5.000	20.000	80.000
nM	0	0.0020	0.008	0.032	0.130	0.520	2.078	8.313	33.250	133.000	532.000

CD3 = cluster of differentiation 3; CD25 = cluster of differentiation 25; EC50 = half-maximal effective concentration; E:T = effector:target; GPRC5D = G Protein-coupled receptor family C group 5 member D; JNJ-64407564 = talquetamab.
Note: Talquetamab and negative control molecules were incubated at increasing concentrations with MM cell lines and healthy donor pan T cells at an E:T ratio of 5:1 (determined from fresh and frozen bone marrow samples from subjects with multiple myeloma) in the presence of fragment crystallizable blocker. After 48 hours of incubation the T cell activation was measured as percent CD25 expressing CD3-positive cells. The data above represent the average of 6 different T cell donors.

Talquetamab did not cause activation of T cells in the absence of target GPRC5D-expressing cells, demonstrating the specificity of T cell activation (Study report DD17026).

Cytokine concentrations were determined from H929 assay and respective values were calculated for each donor. JNJ-64407564 treatment led to the secretion of IFN-γ, TNF-α, IL-1β, IL-2, IL-6, IL-8, IL-10, and IL-13 in the H929 assay (data not shown), consistent with the T-cell activation CD25 expression data. In general, EC50 values for each cytokine were similar across donors, though the maximal values were variable. JNJ-64407564 showed consistent cytokine release upon T-cell activation, with IL-8 being the most responsive cytokine. Mean EC50 (EC20) values were: IFN-γ, 1.120 (0.615) nM; IL-1β, 0.720 (0.462) nM; TNF-α, 1.545 (0.805) nM; IL-2, 1.962 (1.380) nM; IL-4, 1.867 (1.733) nM; IL-6, 0.684 (0.441) nM; IL-8, 0.440 (0.273) nM; and IL-10, 1.082 (0.670) nM

The activation of T cells and the release of cytokines were also determined in a whole blood/H929 model system. Activation was measured as the percentage of T cells (CD3+) that were also positive for activation marker CD25. Treatment with talquetamab resulted in dose-dependent T cell activation as

high as ~50% as. Individual T cell activation EC50 (EC20) from the 6 donors ranged from 0.124 to 0.407 (0.042 to 0.153) nM, producing a mean of 0.236 (0.083) nM.

Cytokine concentrations for IFN-γ, IL-1β, TNF-α, IL-2, IL-6, IL-8, and IL-10 were determined from this normal whole blood spiked-in with H929 cell assay and respective values were calculated for each donor. JNJ-64407564 produced consistent cytokine release upon T-cell activation, with IL-10 being the most responsive cytokine with an EC50 value of 0.107 nM. Mean EC50 (EC20) values were: IFN-γ, 0.639 (0.245) nM; IL-1β, 0.285 (0.160) nM; TNF-α, 0.598 (0.228) nM; IL-2, 0.554 (0.272) nM; IL-4, 0.627 (0.277) nM; IL-6, 0.454 (0.099) nM; IL-8, 0.500 (0.105) nM; and IL-10, 0.107 (0.032) nM (Study report DD17025).

Talquetamab binding, cytotoxicity, and T cell activation assays using subject-derived CD138-positive multiple myeloma bone marrow cells (DD17025)

The ability of talquetamab to induce cytotoxicity using primary multiple myeloma samples (n=6) in co-culture with T cells from healthy donors was assessed by measurement of loss of CD138+ plasma cells. Antibody binding and T cell activation potential were also measured (**Table 2**).

Table 2. Cytotoxicity and T-cell activation EC20, EC50, and EC90 values from MM BM MNCs in a T-cell redirection assay (Study report DD17025)

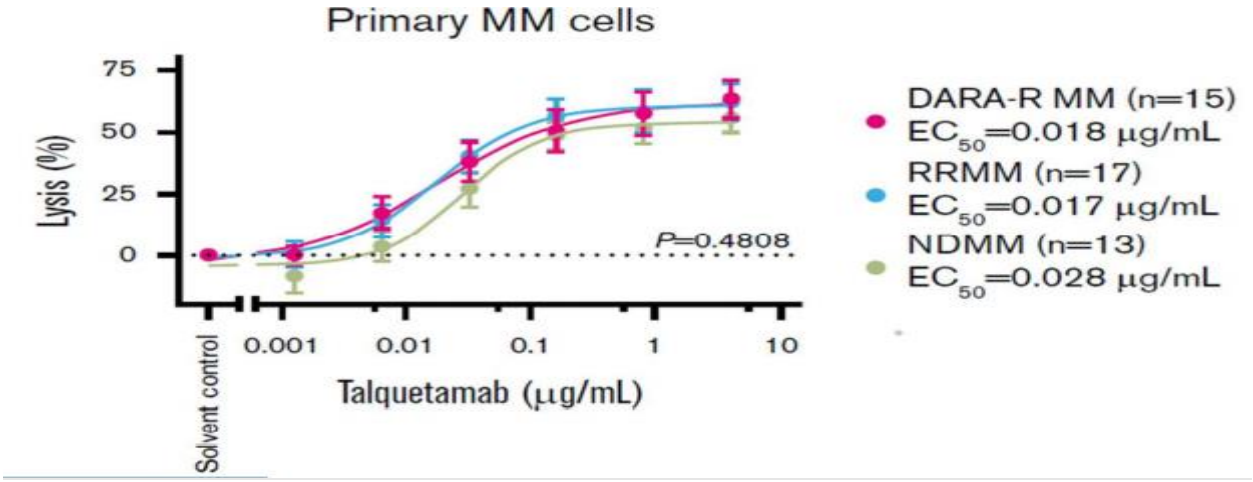
	Donor						
	MM283 BM	MM303 BM	MM305 BM	MM306 BM	MM293 BM	MM296 BM	Mean
				EC_{20} (nM)			
Cytotoxicity	0.007	0.007	0.01	0.004	0.158	0.062	0.041
T-cell activation	0.006	0.007	0.01	0.008	0.027	0.039	0.016
				EC_{50} (nM)			
Cytotoxicity	0.053	0.032	0.029	0.058	0.45	0.14	0.127
T-cell activation	0.022	0.024	0.031	0.027	0.11	0.15	0.061
				EC_{90} (nM)			
Cytotoxicity	0.799	0.245	0.136	1.76	2.398	0.496	0.972
T-cell activation	0.124	0.128	0.164	0.141	1.076	1.299	0.489

EC20, 20% effective concentration; EC50, 50% effective concentration; EC90, 90% effective concentration; MM, multiple myeloma; BM MNC, bone marrow mononuclear cells.
Individual and mean EC20, EC50, and EC90 values for JNJ-64407564-mediated cytotoxicity and T-cell activation from six different MM patient donors are shown.

Talquetamab cytotoxicity assays using autologous CD138-expressing multiple myeloma patient bone marrow cells (Verkleij 2021)

Multiple myeloma cell lysis by talquetamab was analysed in an autologous setting with bone marrow samples from newly diagnosed multiple myeloma, relapsed or refractory multiple myeloma, and relapsed or refractory multiple myeloma plus daratumumab-refractory multiple myeloma (Verkleij 2021). Lysis of CD138high/CD38+ multiple myeloma cells was assessed by flow cytometry (**Figure 6**).

Figure 6. Autologous bone marrow CD138+MM lysis following incubation with talquetamab



Cross-reference: Verkleij 2021
Dara-R MM = daratumumab-refractory multiple myeloma; NDMM = newly diagnosed multiple myeloma; RRMM = relapsed/refractory multiple myeloma; ns = non-significant

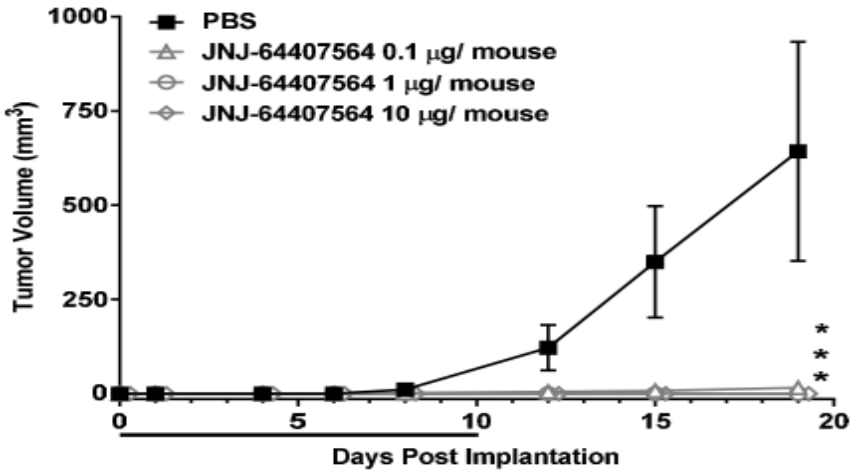
Talquetamab-mediated multiple myeloma cell cytotoxicity was associated with activation (CD25) and degranulation (CD107a) of CD4+ and CD8+ T cells (data not shown).

In vivo pharmacodynamics (study DD17029, 2015-2016)

Efficacy of JNJ-64407564 measured by effect on tumour volume was evaluated in three GPRC5D+ human multiple myeloma (MM) models in non-obese diabetic (NOD) severe combined immunodeficiency (SCID) gamma (NSG) mice engrafted with human peripheral blood mononuclear cells (PBMCs) or human T cells. Treatment was either in a prophylactic model where treatment was initiated at the time of tumour cell implantation (H929, **Figure 7**), or in established models where treatment was initiated after palpable tumours were formed (MM.1S,

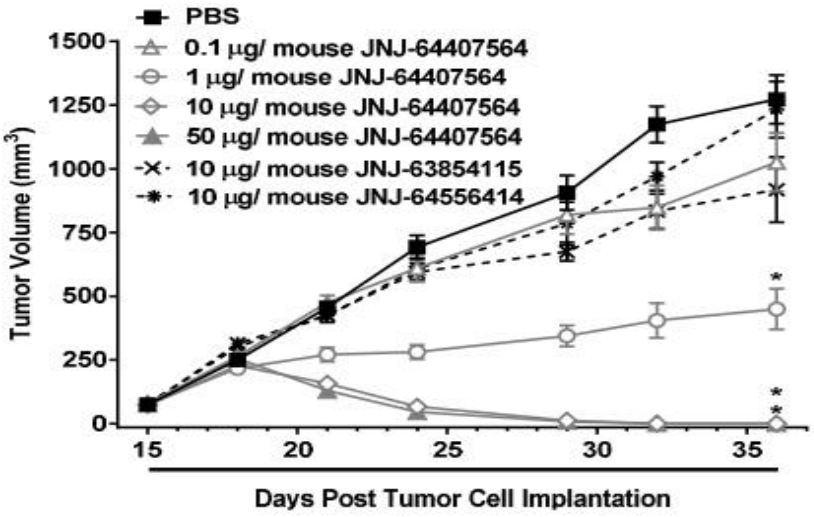
Figure 8 and RPMI-8226,**Figure 9**).

Figure 7. Effect of talquetamab on growth of H29 MM tumours in PBMC-humanised NSG mice - Study ONC2015-137



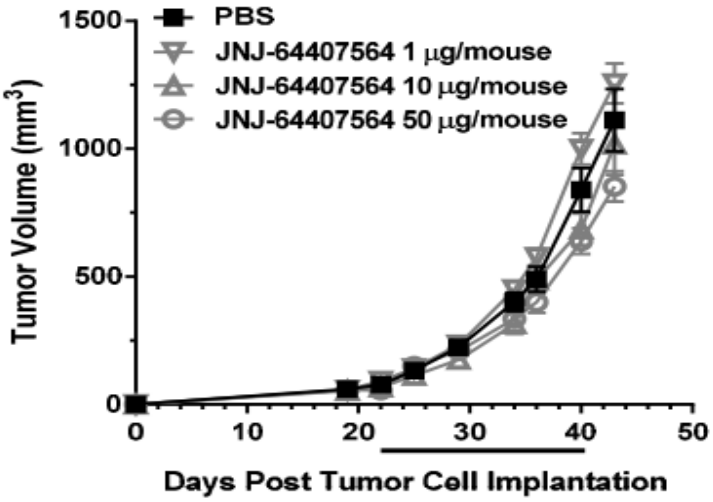
Tumor volumes are graphically represented in mm^3 (mean ± standard error of the mean [SEM]). Bar below the x axis denotes the dosing interval. Statistical significance was evaluated on Day 19 (*p≤0.05, n=6-8/group on Day 19). PBS, phosphate-buffered saline; JNJ-64407564 (GPRC5D x CD3).

Figure 8. Effect of talquetamab on the growth of established MM.1S MM tumours in PBMC-humanised NSG mice - Study ONC2016-159



Tumor volumes are graphically represented as mean ± standard error of the mean (SEM). Bar below the x axis denotes the dosing interval. Statistical significance was evaluated on Day 36 using a 1-way ANOVA with Dunnett's multiple comparisons test (*p≤0.05). PBS, phosphate-buffered saline; JNJ-64407564 (GPRC5D x CD3); JNJ-63854115 (CD3 x Null); JNJ-64556414 (Null x GPRC5D).

Figure 9. Effect of talquetamab on the growth of established RPMI-8226 MM tumours in T-cell-humanised NSG mice - Study ONC2016-067



Tumor volumes are graphically represented as mean ± standard error of the mean (SEM). Bar below the x axis denotes the dosing interval. Statistical significance was evaluated on Day 43 using a 1-way ANOVA with Dunnett's multiple comparisons test ($p \leq 0.05$). PBS, phosphate-buffered saline; JNJ-64407564 (GPRC5D x CD3).

Identification of a pharmacologically relevant species/Rationale for use of a tool molecule

Sequence homology, GPRC5D tissue expression, and molecule binding affinity and functional activity *in vitro* were evaluated to identify a suitable animal species for the nonclinical pharmacokinetics and *general* toxicology evaluation of talquetamab.

Cynomolgus monkey CD3ε has 88% homology in the ECD relative to the human sequence (study report DS-TEC-51663), and talquetamab has similar binding (within approximately 5-fold differential) to human and cynomolgus monkey CD3 when measured on human or cynomolgus monkey T cells (Kd values: human CD3=15.1 nM and cynomolgus monkey CD3=2.8 nM; study report DS-TEC-91511). The tool molecule (JNJ-64024701) was also confirmed to bind to cynomolgus monkey T cells (Kd value: 5.88 nM; study report DS-TEC-91511), which is comparable to the binding of talquetamab to human T cells.

The CD3 epsilon chain (CD3ε) recognised by the CD3 fragment antigen binding arm (derived from parental antibody CD3B219) in talquetamab and in the tool molecule is poorly conserved in other common laboratory species, such as the pig, mouse, guinea pig, and rat with 65%, 63%, 59%, and 57% homology, respectively, relative to the human sequence (study reports DS-TEC-51663 and DS-TEC-51660). Because of the poor homology, neither talquetamab nor the tool molecule would be expected to have any cross-reactivity with these species. Lack of binding to mouse CD3 was demonstrated experimentally with the parental CD3 antibody (CD3B219), and therefore talquetamab was not tested for binding to mouse CD3 (study report DS-TEC-102635).

Full-length hGPRC5D is 94%, 81%, and 96% identical to marmoset, mouse, and cynomolgus/rhesus monkey GPRC5D, respectively, based on amino acid sequence alignments (study report DS-TEC-91511). GPRC5D has 4 extracellular domains; cGPRC5D extracellular loops domains are 88%, 100%, 87%, and 100% identical to those of human. It is not clear whether talquetamab binds to a single

extracellular loop or more than 1 discontinuous loop. GPRC5D expression in cynomolgus monkey exhibits a similar pattern in normal tissues as hGPRC5D; it is primarily expressed in normal plasma cells and keratinised structures such as hair follicles in skin (Smith 2019). The high homology and similar expression pattern make cynomolgus monkey a relevant species for GPRC5D.

Talquetamab binds to hGPRC5D but it binds poorly to cGPRC5D and does not bind to marmoset GPRC5D. Additionally, talquetamab demonstrated approximately 100-fold lower *in vitro* bioactivity (T cell activation and cytotoxicity) against cGPRC5D-expressing cells compared with hGPRC5D-expressing cells. In concordance with the *in vitro* data, talquetamab showed no adverse effects and minimal pharmacodynamic activity in cynomolgus monkeys administered 4 weekly IV doses up to 30 mg/kg confirming poor bioactivity in cynomolgus monkey. Therefore, the cynomolgus monkey is not a relevant species for toxicity assessment of talquetamab, and a tool molecule strategy was pursued for hazard identification.

The tool molecule (GCDB32 GPRC5DxCD3) identified has binding affinity and *in vitro* functional activity against cGPRC5D-expressing cells consistent with the binding affinity and *in vitro* functional activity of talquetamab against hGPRC5D (

Table 3 and **Table 4**). Based on these data, it was considered an appropriate GPRC5DxCD3 tool molecule for hazard identification in cynomolgus monkeys.

Table 3. Binding affinity of talquetamab to human GPRC5D-expressing MM.1R cells and tool molecule (JNJ-64024701) to cynomolgus monkey GPRC5D-expressing HEK cells (Study report DS-TEC-91511)

Antibody	K_d (nM) Human GPRC5D	Kd (nM) Cynomolgus Monkey GPRC5D
Talquetamab	189 (95% CI: 149-240)	Not determined (saturation not achieved)
Tool molecule (JNJ-64024701)	Not measured	280.6 (95% CI: 199.7-394.1)

CI = confidence interval; GPRC5D = G Protein-coupled receptor family C group 5 member D; HEK = human embryonic kidney; Kd = dissociation constant.

Table 4. *In vitro* functional activity of talquetamab and tool molecule (JNJ-64024701) to human and cynomolgus monkey GPRC5D ((Study report DD17027)

Antibody	Assay	Human GPRC5D/ Human T Cells (nM)		Cynomolgus GPRC5D/ Human T Cells (nM)		Cynomolgus GPRC5D/ Cynomolgus T Cells (nM)	
		EC_{50}	EC_{20}	EC_{50}	EC_{20}	EC_{50}	EC_{20}
Talquetamab	Cytotoxicity	0.03	0.01	3.41	1.25	4.01	0.76
	T cell activation	0.03	0.01	3.33	1.65	1.85	0.74
Tool molecule (JNJ-64024701)	Cytotoxicity	0.04	0.02	0.07	0.01	0.12	0.02
	T cell activation	0.03	0.01	0.14	0.05	0.19	0.07

EC20 = 20% maximal effective concentration; EC50 = half-maximal effective concentration; GPRC5D = G Protein-coupled receptor family C group 5 member D; HEK = human embryonic kidney.
Note: Data were generated using recombinant human and cynomolgus monkey GPRC5D-overexpressing HEK cell lines and primary human and cynomolgus monkey T cells. HEK-hGPRC5D cells have a receptor density of 2,226 receptors/cell, and the HEK-cGPRC5D cells have a receptor density of 128,584 receptors/cell.

2.5.2.2. Secondary pharmacodynamic studies

TOX14948: Assessment of the binding profile of GC5B596.009 using a human plasma membrane protein cell array

The GPRC5D binding arm of talquetamab showed high specificity for GPRC5D, its primary target, on both fixed and live cell microarrays, following a screen for binding against fixed HEK293 cells expressing 5861 individual full-length human plasma membrane proteins and cell surface-tethered human secreted proteins, as well as a further 371 human heterodimers.

2.5.2.3. Safety pharmacology programme

Stand-alone safety pharmacology studies were not submitted, in accordance with the provisions of the ICH S6(R1) and S7A guidance documents. However, cardiovascular, respiratory, and observational CNS safety pharmacology endpoints were incorporated into the 1-month GLP repeat dose toxicity study conducted with the tool molecule in cynomolgus monkeys (See section 2.5.4.2). There were no treatment-related effects on the examined cardiovascular (electrocardiograms, blood pressure, heart rate), respiratory (respiration rate), or CNS (clinical observations and body temperature) parameters. Gross and microscopic pathology assessments indicated that there were no treatment-related effects on heart weight or histo-morphological effects on the heart or skeletal muscles.

Although the tool molecule had no effects on the cardiovascular system in this study, hypotension and tachycardia have been observed in cynomolgus monkeys following treatment with other CD3 redirectors, which are possibly related to cytokine release (Saber 2017). However, there were no significant increases in circulating cytokines in cynomolgus monkeys administered talquetamab or the tool molecule.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted.

2.5.3. Pharmacokinetics

Absorption

Talquetamab: Single-dose PK and immunogenicity in cynomolgus monkeys (CP2017PK-002)

The pharmacokinetic profile of talquetamab was evaluated in male cynomolgus monkeys (4/group) after a single IV dose of 0.5 or 5 mg/kg in a recombinant human serum albumin (rHSA) formulation or 0.5 mg/kg in a buffer formulation (**Table 5**).

Table 5. Mean (SD) Serum JNJ-64407564 PK parameter estimates following a single IV dose in male cynomolgus monkeys (N=4 per group), (CP2017PK-002)

Dose (mg/kg)	Formulation		C_{max} (µg/mL)	AUC_{last} (µg·day/mL)	AUC_{inf} (µg·day/mL)	CL (mL/day/kg)	V_z (mL/kg)	$T_{1/2}$ (day)
0.5[a]	rHSA	Mean	12.73	51.23	54.71	9.53	160.76	11.88
		SD	(1.76)	(11.81)	(11.46)	(2.46)	(35.90)	(2.22)
5[b]	rHSA	Mean	133.21	366.82	463.94[c]	10.92	139.19	8.98
		SD	(8.38)	(28.62)	(61.81)	(1.46)	(8.78)	(1.57)
0.5[d]	Formulation buffer	Mean	13.71	57.37	64.08	8.61	137.37	12.07
		SD	(0.90)	(18.50)	(22.47)	(3.09)	(9.71)	(3.77)

Estimated parameters are means of values for 4 males/group.
[a] Talquetamab was quantifiable in serum up to 1176 hours and BQL (<0.16 µg/mL) at the 1344 and 1416 hours.
[b] Talquetamab was quantifiable in serum up to 408 hours and BQL at 576 hours through the last sampling time point of 1416 hours.
[c] For 2 of the 4 animals, the AUCinf was slightly larger than 20% (29% and 37%) than AUClast.

[d] Talquetamab was quantifiable in serum up to the last sampling time point of 1416 hours.

Anti-drug antibodies (ADA) were detected in 2/4 animals receiving a dose of 0.5 in both rHSA and buffer formulations and in all 4 animals receiving the higher 5 mg/kg dose. ADA development likely impacted the pharmacokinetics in animals from the 5 mg/kg in rHSA formulation group; however, it was unusual that all animals in this group demonstrated a sharp serum concentration decrease at the same time point, while the pharmacokinetics in ADA-positive animals from the lower dose group (0.5 mg/kg in rHSA formulation) seemed unaffected.

Talquetamab: Repeat-dose TK in cynomolgus monkeys (T-2016-027, Appendix 12)

In an exploratory 4-week tolerability study, the toxicokinetic profile of talquetamab was assessed in cynomolgus monkeys (2 males and 1 female/group, except 1 male and 1 female in the control group) administered talquetamab weekly by a slow IV bolus at 0, 0.5, 3, 10, or 30 mg/kg on Days 1, 8, 15, and 22 (T-2016-027/App12). Serum samples for toxicokinetic assessment were obtained from blood collected prior to each dose and at time points up to 120 hours after the Day 1 dose and 24 hours after the Day 22 dose (**Table 6**).

Table 6. Mean (SD) serum TK parameter estimates in cynomolgus monkeys administered 4 Weekly IV doses in an exploratory tolerability non-GLP study (T-2016-027) – Individual data

			Following Dose on Day 1		Following Dose on Day 22
Group	Gender	ID	C_{max} (µg/mL)	AUC_{Day1-8} (µg·day/mL)	C_{max} (µg/mL)
Group 2 0.5 mg/kg	Female	2501	15.82	31.77	21.33
	Male	2001	10.93	28.06	18.23
	Male	2002	10.96	20.11	16.56
	Mean		**12.57**	**26.64**	**18.71**
	SD		**2.82**	**5.96**	**2.42**
Group 3 3 mg/kg	Female	3501	78.52	157.47	97.45
	Male	3001	72.47	141.81	102.70
	Male	3002	73.46	133.37	98.65
	Mean		**74.82**	**144.22**	**99.60**
	SD		**3.24**	**12.23**	**2.75**
Group 4 10 mg/kg	Female	4501	246.59	470.12	336.53
	Male	4001	249.27	441.72	364.59
	Male	4002	256.83	488.07	358.24
	Mean		**250.90**	**466.64**	**353.12**
	SD		**5.31**	**23.37**	**14.72**
Group 5 30 mg/kg	Female	5601	621.90	1506.33	893.09
	Male	5001	550.41	1539.09	675.52
	Male	5002	736.57	1574.30	990.93
	Mean		**636.29**	**1539.91**	**853.18**
	SD		**93.91**	**33.99**	**161.45**

Tool Molecule (JNJ-64024701): Repeat-dose TK and immunogenicity in cynomolgus monkeys

- **2-week tolerability study (T-2016-060 Appendix 9)**

An exploratory 2-week tolerability study characterised the toxicokinetic profile of the tool molecule administered at 0, 0.3, 1, or 10 mg/kg by weekly IV slow bolus injection for a total of 2 doses (Days 1 and 8) to cynomolgus monkeys (1/sex/group plus 1 male for the 10 mg/kg group)(**Table 7**).

Table 7. Mean (SD) serum TK parameter estimates in cynomolgus monkeys administered 2 Weekly IV doses in an exploratory tolerability non-GLP study (T-2016-060)

Weekly Dose (mg/kg)	N	Following Dose on Day 1		Following Dose on Day 8		
		C_{max} (µg/mL)	AUC_{Day1-8} (µg·day/mL)	C_{max} (µg/mL)	$AUC_{Day8-15}$ (µg·day/mL)	R_{AUC}
0.3	1 M, 1 F	6.59	15.33	7.73	21.48	1.40
1	1 M, 1 F	18.37	47.87	22.05	59.96	1.23
10	2 M, 1 F	186.65 (52.39)	480.47 (75.31)	233.29 (42.51)	379.95 (74.82)[a]	NR

Sample collection was on Day 1 predose and postdose (2, 24, and 72 hours) and on Day 8 predose and postdose (2 and 24 hours for all groups, 72 and 168 hours for 0.3 and 1 mg/kg groups, and 68 to 70 hours for the 10 mg/kg group).
[a] The partial AUC following the dose on Day 8 was estimated by AUCDay8-10.83 and the accumulation ratio could not be reported

Pivotal 1-month toxicity GLP study (T-2017-009)

A pivotal 1-month toxicity GLP study characterised the toxicokinetic profile of the tool molecule administered at 0, 10, or 30 mg/kg by weekly IV slow bolus injection for a total of 4 doses to cynomolgus monkeys (3/sex/group). Serum samples for toxicokinetic assessment were obtained from blood collected prior to each dosing on Days 1, 8, 15, and 22, on Day 1 up to 96 hours postdose (Day 5), and on Day 22 up to 168 hours postdose (Day 29).

Table 8. Mean (SD) serum toxicokinetic parameter estimates in cynomolgus monkeys administered 4 weekly IV doses in a 1-Month toxicity GLP study (T-2017-009)

Weekly Dose (mg/kg)	N	Following Dose on Day 1		Following Dose on Day 22		
		C_{max} (µg/mL)	AUC_{Day1-8} (µg·day/mL)	C_{max} (µg/mL)	$AUC_{Day22-29}$ (µg·day/mL)	R_{AUC}
10	3/sex	230.64 (14.41)	550.85 (48.19)	196.98 (49.08)	182.95 (323.22)	0.35 (0.63)
30	3/sex	663.85 (67.85)	1753.55 (187.22)	758.31 (134.66)	1471.16 (1074.52)[a]	0.80 (0.55)

Sample collection was Day 1 predose and postdose (1, 24, 48, and 96 hours), Days 8 and 15 predose, and Day 22 predose and postdose (1, 24, 48, 96, and 168 hours).
[a] AUCDay22-29 was estimated based on the data up to Day 23 for 1 female (#2501) or Day 24 for 3 males (#2001, #2002, #2003) since the concentration was below the lowest quantifiable concentration (0.16 µg/mL) toward the end of the dosing period.

Serum samples for ADA assessment were obtained from blood collected on Day 1 predose and on Day 22 predose and 168 hours postdose. ADA was detected in 10 of 12 animals in the 10 and 30 mg/kg dose groups. When compared to ADA-negative animals in the same dose group, all ADA-positive animals exhibited either lower exposure prior to the last dose on Day 22 or faster concentration decrease after the first dose. Additionally, 3 of 6 control animals tested ADA-positive; however, the signals were just slightly above the screen cut-point and the titers were very low. Only 1 sample of the 3 tested for ADA for each control animal was slightly above the method cut-point.

Distribution, metabolism and excretion

Traditional distribution studies were not submitted for talquetamab. Due to its molecular size of approximately 147kD, talquetamab is expected to be primarily confined to the vascular space with only limited distribution to the extracellular space, which is typical of IgG-based antibodies.

As an IgG4 bispecific antibody, talquetamab is generally considered to be catabolised and eliminated by processes involved in the turnover and degradation of endogenous IgGs, and proteolytically

degraded to constituent amino acids. Such compounds are proteolytically degraded to constituent amino acids, which can then be reincorporated into newly synthesised proteins or utilised as an energy source. Because they are not metabolised via CYP systems but are degraded to individual amino acids, no reactive metabolites are generated. Therefore, classical biotransformation studies as performed for small molecule pharmaceuticals are not required for therapeutic antibodies.

Similar to other IgG-based antibodies, talquetamab is presumably eliminated via catabolic pathways that are typically associated with endogenous IgG. Thus, routine studies that attempt to assess mass balance are not expected to be informative.

Pharmacokinetic drug interactions

As an IgG-based bispecific antibody, talquetamab is not expected to undergo any direct metabolism-based small molecule drug interactions and no pharmacokinetic drug interaction studies were submitted.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single-dose toxicity studies were conducted with either talquetamab or the tool molecule. Toxicity, after a single dose, was evaluated as part of the repeat- dose toxicity studies in cynomolgus monkeys. Moreover, safety parameters as physical examination, body weights, body temperature, blood pressure, heart/respiration rates were measured in the single-dose PK study (CP2017PK-002)**.** No adverse findings were reported excepted minor common findings as alopecia, small aera of erythema, minor scabbed areas, bruises/abrasions, coloured faeces and deformity of the eyelids.

2.5.4.2. Repeat dose toxicity

Talquetamab: Repeat-dose TK in cynomolgus monkeys (T-2016-027, Appendix 12).

For description of the study see section 2.5.3 Pharmacokinetics of this report. Intravenous administration of talquetamab as 4 weekly doses was well tolerated in male and female cynomolgus monkeys at doses up to 30 mg/kg with no talquetamab-related adverse findings. Decreases in absolute T-helper and T-cytotoxic lymphocytes cell counts were observed in all animals group including control but at higher incidence in treated groups. These were related to talquetamab binding to CD3 and not considered adverse findings.

Tool Molecule (JNJ-64024701): Exploratory 2-week tolerability non-GLP study in cynomolgus monkeys (T-2016-060) and of 1-month IV toxicity GLP study in cynomolgus monkeys (T-2017-009).

For description of these studies see section 2.5.3 Pharmacokinetics of this report.

The tool molecule was well tolerated in cynomolgus monkeys after weekly intravenous doses up to 30 mg/kg. No treatment-related findings were observed.

2.5.4.3. Genotoxicity and carcinogenicity

Genotoxicity and carcinogenicity studies have not been conducted with talquetamab are not required for biotechnology-derived pharmaceuticals.

2.5.4.4. Reproductive and developmental toxicity

Although fertility studies have not been conducted with talquetamab, potential effects on fertility were evaluated based on the repeat-dose toxicity studies, in accordance with ICH S6(R1) and S9 guidelines. In the repeat-dose IV toxicity studies in cynomolgus monkeys, no adverse effects on reproductive organs and tissues were observed macroscopically or microscopically following 4 weekly doses up to 30 mg/kg (high dose) of talquetamab (JNJ-64407564) or the tool molecule (JNJ-64024701).

Embryo-fetal development or enhanced pre- and postnatal development studies in cynomolgus monkeys with talquetamab or the tool molecule would not be feasible nor further inform pregnancy risk to multiple myeloma patients. The potential risks to the fetus, pregnant mother, and nursing infant are unknown.

2.5.4.5. Toxicokinetic data

See pharmacokinetic section (2.5.3) of this report.

2.5.4.6. Local tolerance

A single-dose SC local tolerability GLP study with talquetamab was performed in New Zealand White rabbits to support change from IV to SC administration in humans.

The New Zealand White rabbit was chosen as the animal model for the local tolerance study because it is a generally accepted species for tolerability/irritancy testing and talquetamab is not sufficiently cross-reactive with common toxicology species. Rabbits are not a pharmacologically relevant species due to poor sequence homology of rabbit CD3 with human CD3; therefore, this study only assessed the tolerability of the formulation. There were no major findings or clinical observations in this study.

2.5.4.7. Other toxicity studies

Talquetamab was assessed in a series of *in vitro* assays to identify binding (and potential sites of toxicity) in a human tissue cross-reactivity study (**Table 9**).

Table 9. Summary of tissue cross-reactivity study, compatibility in human serum, haemolytic potential in human whole blood, and cytokine release

Species/Strain Sex/No. Per Group Study No GLP statut	**Duration of Dosing**	**Doses**	**Noteworthy Findings**
Tissue cross-reactivity T-2016-040/GLP 38 normal human tissues (cryosections) 3 donors/tissue	NA	2, 10 µg/mL biotinylated talquetamab	Membrane and cytoplasm staining of resident, migrating, and/or infiltrating **mononuclear cells** in: - lymphoid tissues (lymph node, spleen, thymus, and tonsil, as well as in gut-associated lymphoid tissue (GALT) in the colon, esophagus, small intestine, and stomach and bronchial-associated lymphoid tissue (BALT) in the lung -non-lymphoid tissues: bladder, breast, Fallopian tube, kidney, liver, ovary, parathyroid, peripheral nerve, pituitary, placenta, prostate, salivary gland, thyroid, ureter, and uterus (cervix, endometrium) CD3 is expressed by T cells; therefore, staining of mononuclear cells (which includes T cells) was anticipated

			All other staining was cytoplasmic in nature and is considered of little to no toxicologic significance.
Serum compatibility T-2017-003/non-GLP Human serum 3 donors	40 min	0.01 to 10 mg/mL	compatible with human serum (no precipitation)
Haemolytic potential T-2017-002/non-GLP Human whole blood 3 donors	40 min	0.01 to 10 mg/mL	compatible with human blood (no haemolysis)
Cytokine release, soluble format assay T-2017-001/non-GLP Human whole blood 16 normal healthy donors (same donors as T-2017-024)	48h	0.0106 to 200 µg/mL (0.068to 1333 nM)	1333 nM: statistically significant, dose-dependent increases (relative to the PBS negative control) in IL-1β, IL-2, IL-6, IL-8, IL-10, IL-13, IFN-γ, and TNF-α. Estimates of population EC20 values of JNJ-64407564 were: IL-1β, 346.39nM; IL-2, 195.49 nM; IL-8,519.20 nM; IFN-γ, 6616.99nM; TNF-α, 859.97 nM. Estimates of EC20 values could not be calculated for IL-6, IL-10, and IL-13 due to lack of 4-parameter curve fit, from either insufficient induction across the dose range or high donor-to-donor variability. IL-4 and IL-12p70 were not different than control.

2.5.5. Ecotoxicity/environmental risk assessment

Talquetamab 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 talquetamab are required.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Talquetamab function requires the formation of a trimolecular complex by the binding to CD3 on T-cells and to tumour associated antigen (GPRC5D) on target cells to elicit pharmacologic activity. The pharmacology characterisation of talquetamab demonstrated the bi-specific binding with high nanomolar affinity to GPRC5D and CD3, and that talquetamab selectively promoted the T-cell dependent elimination of human cells expressing GPRC5D on their surface *in vitro* and *in vivo*. The T-cell mediated cytotoxic effect on GPRC5D-positive MM cells of talquetamab at nanomolar concentrations and induction of cytokine secretion was also demonstrated in physiologically relevant conditions.

In xenograft mice tumour models, 0.005 mg/kg, 0. 5 mg/kg and 2.5 mg/kg talquetamab doses (when delivered IP every 3 or 4 days for 7 total treatments post human PBCMCs implantation) significantly

inhibited the tumour growth by the study D36 of 65% - 100%. The duration of the response was not measured. Significant reduction of tumour growth was also noted in prophylactic xenograft tumour model (H929 GPRC5D+) with lower talquetamab doses, max 0.5 mg/kg. Although talquetamab failed in second therapeutic xenograft tumour model (other MM origin cells and use of human pan T-cell implantation), these studies provided the proof of concept for *in vivo* functionality for this bi-specific Mab.

Cynomolgus monkey was initially selected as a pharmacologically relevant species. hGPRC5D shares 96% sequence homology with cGPRC5D; however, talquetamab was shown not to bind the cynomolgus monkey target molecule cGPRC5D. A tool molecule (JNJ-64024701) was therefore used and presented similar binding to cGPRC5D than talquetamab to hGPRC5D. The functional activities of talquetamab and the tool molecule was demonstrated *in vitro* and were similar. Although the cynomolgus monkey could be considered as a pharmacologically relevant animal species for evaluation of toxicity with the tool molecule administration, results from studies in normal healthy monkeys (in which only very low amounts of GPRC5D cells are present and uncertainty regarding the similarity of GPRC5D expression outside the tumor between monkey an human) may have limited translatability to multiple myeloma patients, and the toxicity data should be interpreted with caution.

The pharmacology of talquetamab has been adequately characterised and enhanced T cell-mediated cytotoxicity through recruitment of CD3-expressing T cells to GPRC5D-expressing cells is reflected in the SmPC.

Pharmacokinetics

The nonclinical pharmacokinetics programme characterised the pharmacokinetic/toxicokinetic profile and an impact of ADA on systemic exposure of talquetamab IV in cynomolgus monkeys following a single dose of 0.5 or 5 mg/kg or 4 weekly doses of 0.5, 3, 10, or 30 mg/kg. In addition, since talquetamab is not pharmacologically active in monkeys, the tool molecule which is expected to be active is also administrated in monkey. No exploratory PK study was performed. The PK parameters of the tool molecule was collected during the two toxicity studies performed after 2 weekly doses of 0.3, 1, or 10 mg/kg or 4 weekly doses of 10, or 30 mg/kg in monkeys.

Serum talquetamab and tool molecule exposure, Cmax and AUC (within 1 dose interval) increased with dose in an approximately dose-proportional manner in cynomolgus monkeys after single or repeated doses. No differences between male and females were observed. The volume of distribution of talquetamab in cynomolgus monkeys in the single-dose pharmacokinetic study ranged from 137.37 to 160.76 mL/kg. The serum half-life of talquetamab was estimated to be 9 to 12 days in cynomolgus monkeys. No half-life was measured for the tool molecule.

Formation of ADA was clearly triggered by talquetamab and tool molecule. ADAs were detected in most of the talquetamab-treated animals (10 out of 12 animals) in pivotal repeated dose toxicology/toxicokinetic study. Development of ADAs resulted in reduced exposure and/or faster concentration decrease after the last dose in treated animals.

Traditional distribution studies were not conducted for talquetamab, which is an antibody with a molecular weight of 147 kDa. Due to its molecular size, talquetamab 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, talquetamab is presumed to be catabolised and eliminated by processes involved in the turnover and degradation of endogenous IgGs.

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

Talquetamab/tool molecule pharmacokinetics/toxicokinetics characterisation is considered sufficient.

Toxicology

Talquetamab and the tool molecule was well tolerated in cynomolgus monkeys up to highest dose tested (30 mg/kg). Indeed, talquetamab did not bind cGPRC5D, a tool molecule was identified which binds cGPRC5D and cCD3 with similar affinity and generated similar *in vitro* PD activity than in humans. Therefore, the tool molecule was administrated in cynomolgus monkey to represent a pharmacologic model. However, the applicant stated that weak PD activity of the tool molecule was observed in 2-week and pivotal 4-week studies. As the model used is healthy animal in which only very low amounts of GPRC5D-positive cells are present, it is not clear which PD activity was expected. Moreover, in 4-week pivotal study raw data on immunophenotyping were not analysed. Indeed, the results was not interpreted or reported due to recorded issues.

The limited PD effect observed in healthy monkey was expected and is not considered as an acceptable argument to omit the 13-week study. However, considering the reduced exposure and/or faster elimination of JNJ-64024701 due to ADA presence in almost all animals at this end of the study, it is obvious that a longer animal study with the tool molecule will add no additional value in the toxicity characterisation profile of talquetamab.

The overall toxicology data package is thus considered adequate.

2.5.7. Conclusion on the non-clinical aspects

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

2.6. Clinical aspects

2.6.1. 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**

StudyID EudraCT Number First Patient First Visit Completion date Study Status	Country(ies)/ Territory (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
64407564MMY1001 Synopsis 2017-002400-26 03 January 2018 NA Ongoing	Belgium, France, Germany, Israel, the Netherlands, Poland, Republic of Korea, Spain, United States 47[a]	Phase 1/2 First-in-human, 3-part, open-label, single-arm, multicenter study Men or women ≥18 years of age with relapsed or refractory multiple myeloma To characterize the safety of talquetamab and identify the proposed RP2D (Part 1); to further characterize the safety of talquetamab at RP2Ds (Part 2); to evaluate efficacy of talquetamab at the RP2Ds (Part 3).	Planned: 580 (Phase 1: 260 Phase 2: 320) Enrolled: 501	Talquetamab: IV or SC Part 1: Dose escalation for talquetamab IV was initiated at 0.0005 mg/kg Q2W. Talquetamab IV was additionally administered at doses ranging 0.001 to 0.00338 mg/kg Q2W and 0.0015 to 0.180 mg/kg weekly. The majority of IV doses were preceded by step-up dosing. Dose escalation for talquetamab SC was initiated at 0.005 mg/kg weekly. Talquetamab SC was additionally administered at doses ranging from 0.015 to 0.8 mg/kg weekly, 0.8 or 1.2 mg/kg Q2W, or 1.6 mg/kg monthly. All SC doses were preceded by step-up dosing. Part 2: Talquetamab SC administered at the putative RP2Ds identified in Part 1: treatment dose of 0.405 mg/kg weekly (preceded by step-up doses of 0.01 and 0.06 mg/kg) on Days 1, 8, and 15 of a 21-day cycle; or a treatment dose of 0.8 mg/kg Q2W (preceded by step-up doses of 0.01, 0.06, and 0.3 mg/kg) on Days 1 and 15 of a 28-day cycle Part 3: Talquetamab SC administered at the 2 RP2Ds confirmed in Part 2: Cohort A and Cohort B: the step-up schedule was talquetamab SC at 0.01 and 0.06 mg/kg The treatment dose schedule was Days 1, 8, 15, and 22 of a 28-day cycle. Cohort C: the step-up schedule was talquetamab SC at 0.01, 0.06, and 0.3 mg/kg. The treatment dose schedule was Days 1 and 15 of a 28-day cycle.

KEYS: IV = intravenous; NA = not applicable; Q2W= every 2 weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous.

a In addition, 3 centres in China treated at least 1 participant in the standalone China cohort

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The PK, pharmacodynamics (PD), and immunogenicity results were derived from Study 64407564MMY1001 (MonumenTAL-1). The number of participants included in the different phases and cohorts of this study is summarised in **Table 10**.

Table 10. Overview of participants and dosing schedules in Study 64407564MMY1001 (MonumenTAL-1)

Type of Study	Study ID	Population	Number of Participants	Dose/Formulation
FIH, open-label, dose escalation (Part 1), dose expansion (Part 2), and Phase 2 (Part 3), multicenter study	64407564MMY1001 (MonumenTAL-1)	Participants with relapsed or refractory multiple myeloma	501 Phase 1 (Part 1 and Part 2) n=236 • IV: n=102 • SC: n=134	Talquetamab, solution: Part 1 • 0.5-180 µg/kg weekly or Q2W IV • 5-800 µg/kg weekly SC • 800-1200 µg/kg Q2W SC • 1600 µg/kg monthly SC Part 2 SC at putative RP2Ds • 405 µg/kg weekly, preceded by step-up doses of 10 and 60 µg/kg • 800 µg/kg Q2W, preceded by step-up doses of 10, 60, and 300 µg/kg
			Phase 2 (Part 3) n=265 • Cohort A: n=122 • Cohort B: n=34 • Cohort C: n=109	Part 3 SC at confirmed RP2Ds Cohort A, B • 400 µg/kg weekly, preceded by step-up doses of 10 and 60 µg/kg Cohort C • 800 µg/kg Q2W, preceded by step-up doses of 10, 60, and 300 µg/kg

FIH=first-in-human; ID=identifier; IV=intravenous; Q2W=every 2 weeks; RP2D=recommended Phase 2 dose; SC=subcutaneous(ly).
Note: Number of participants refers to those participants who received the first dose of talquetamab on or before the clinical cutoff (16 May 2022).

Non-compartmental analysis (NCA) was used to estimate talquetamab PK parameters and descriptive statistics of PK parameters were calculated for each dose levels. For IV and SC administration PK parameters included were AUCtau, Cmax, Tmax, t½, CL and V for IV and apparent clearance or volume (CL/F or Vd/F) for SC.

PK results for the two proposed doses of talquetamab during the treatment phase are summarised in **Table 11** and **Table 12** respectively.

Table 11. PK parameters talquetamab following first treatment dose (with set-up doses) of 400 µg/kg QW SC in Cycle 1 and Cycle 3 in patients with MM

Parameter	Mean(SD), T_{max}: Median (Range) Talquetamab SC, Weekly (µg/kg) 10/60 then 405
Cycle 1 Day 1	
n	21[a]
C_{max}, ng/mL	1568 (1185)
T_{max}, day	2.93 (0.98 – 7.75)
AUC_{tau}, ng.h/mL	178101 (130802)
AUC_{last}, ng.h/mL	173356 (125935)
C_{trough}, ng/mL	178 (124)
$t_{1/2}$, day	7.9
Cycle 3 Day 1	
n	13[b]
C_{max}, ng/mL	3799 (2411)
T_{max}, day	2.01 (0.94 – 5.97)
AUC_{tau}, ng.h/mL	607297 (371399)
AUC_{last}, ng.h/mL	522329 (362478)
C_{trough}, ng/mL	2548 (1308)
CL/F, L/h	0.0773 (0.0409)
V_d/F, L	9.34
$t_{1/2}$, day	4.9
AR_{Cmax}	3.94 (2.79)
AR_{AUCtau}	4.50 (3.85)

Table 12. PK parameters talquetamab following first treatment dose (with set-up doses) of 800 µg/kg Q2W SC in Cycle 1 and Cycle 3 in patients with MM

Parameter	Mean(SD), T_{max}: Median (Range) Talquetamab SC, Q2W (µg/kg) 10/60/300 then 800
Cycle 1 Day 1	
n	33[a]
C_{max}, ng/mL	2507 (1568)
T_{max}, day	2.83 (1.68 – 13.98)
AUC_{tau}, ng.h/mL	675764 (399680)
AUC_{last}, ng.h/mL	595284 (417502)
C_{trough}, ng/mL	597 (437)
$t_{1/2}$, day	10.4 (4.6)
Cycle 3 Day 1	
n	19[b]
C_{max}, ng/mL	4161 (2021)
T_{max}, day	2.85 (0.96 – 7.82)
AUC_{tau}, ng.h/mL	1021059 (383417)
AUC_{last}, ng.h/mL	965885 (399705)
C_{trough}, ng/mL	1831 (841)
CL/F, L/h	0.0641 (0.0341)
V_d/F, L	288
$t_{1/2}$, day	NR[c]
AR_{Cmax}	2.33 (1.79)
AR_{AUCtau}	2.17 (1.78)

Population PK model

Population pharmacokinetics (Pop-PK) modelling (Report EDMS-RIM-736096) was conducted using the nonlinear mixed-effects modelling. This analysis was based on serum concentration data collected from Part 1 (Phase 1 dose escalation), Part 2 (Dose expansion at RP2D), and Part 3 (Phase 2) of the pivotal phase 1/2 Study 64407564MMY1001 (MonumenTAL-1) with the PK data cutoff on 22 April 2022.

A total of 5354 measurable serum talquetamab concentration from 492 patients with relapsed or refractory multiple myeloma who received at least 1 talquetamab dose were used for the nonlinear mixed-effects modelling. This included 100 subjects (1928 PK observations) who received talquetamab IV administration from 0.0005 to 0.00338 mg/kg Q2W and from 0.0015 to 0.18 mg/kg weekly; and 392 patients (3426 PK observations) who received SC administration. Among the subjects who received SC administration, 333 received one of the 2 claimed dosing regimens [0.4 mg/kg weekly or 0.8 mg/kg Q2W] with or without concomitant T cell or bispecific antibody therapy contributing (2538 PK observations)

The observed concentration-time data of talquetamab after SC administration were adequately described by a 2-compartment mammillary model with sequential zero and first-order absorption and 2 parallel and linear time-independent (representing the nonspecific clearance for IgG) and time-dependent (representing changes in capacity of the target-mediated clearance) clearance components. 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 model was parameterised in terms of total clearance at time t=0 (CL0), fraction clearance at steady state described by the time-independent clearance component (CLPCT), first-order decay coefficient of the time-dependent clearance (KDES), volume of distribution of the central compartment (V1), inter-compartmental clearance (Q), volume of distribution of the peripheral compartment (V2), first-order absorption rate constant (Ka), SC bioavailability (F), and input duration of SC administration (D1).

The covariates assessed in the population pharmacokinetic analysis included demographic characteristics (body weight, age, sex, race, region, ethnicity), disease characteristics and biomarkers (baseline total T cells, baseline soluble BCMA, 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, experiencing CRS events or not), 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 [≤4 vs >4]), concurrent use of tocilizumab, prior autologous or allogenic transplantation, use of human Ig).

After the covariate selection procedure, the covariate effects retained in the final model were the effect of body weight BW on CL0 and V1 and myeloma subtype (IgG versus non-IgG) and ISS stage (II and III versus I) on CL0. Other covariates tested were not statistically significant.

The parameters of the final PopPK model with importance resampling results are summarised in **Table 13**.

Table 13. Parameter estimates for the base and final talquetamab population PK model

	Base model (run 021)		Final model (run 029)		
Parameters, unit	**Estimate (RSE%)**	**Shrinkage (%)**	**Estimate (RSE%)**	**Shrinkage (%)**	**SIR Median (95% CI)**
Fixed effect		-			
CL_0 (L/day)[a]	1.63 (4.79)	-	2.08 (6.58)	-	2.08 (1.85, 2.33)
BWT on CL_0	0.621 (27.8)	-	0.672 (20.7)	-	0.682 (0.418, 0.923)
TPMMG on CL_0	-	-	-0.547 (5.43)	-	-0.547 (-0.595, -0.496)
ISS II/III on CL_0	-	-	0.318 (26.3)	-	0.322 (0.175, 0.462)
CL_{PCT}	0.509 (4.45)	-	0.512 (4.32)	-	0.513 (0.472, 0.557)
V_1 (L)[b]	4.32 (2.48)	-	4.30 (2.54)	-	4.30 (4.11, 4.49)
BWT on V1	0.677 (16.8)	-	0.670 (17.0)	-	0.672 (0.504, 0.853)
Q (L/day)	0.989 (6.05)	-	1.01 (6.10)	-	1.01 (0.906, 1.11)
V_2 (L)	5.74 (8.38)	-	5.78 (8.59)	-	5.80 (5.04, 6.64)
K_a (1/day)	0.137 (5.20)	-	0.138 (5.47)	-	0.138 (0.125, 0.152)
F	0.618 (4.76)	-	0.619 (4.58)	-	0.618 (0.564, 0.680)
K_{DES} (1/day)	0.0237 (6.76)	-	0.0229 (7.21)	-	0.0227 (0.0190, 0.0265)
D1 (day)	0.116 (0.242)	-	0.142 (19.6)	-	0.142 (0.115, 0.186)
Inter-individual variability (CV%)					
CL_0	65.3 (5.00)	16.9	51.7 (4.89)	20.0	52.2 (47.6, 57.1)
CL_{PCT}	61.2 (4.40)	23.9	59.7 (4.43)	23.3	59.6 (54.9, 66.2)
V_1	22.2 (8.68)	53.4	22.3 (8.58)	53.2	22.2 (18.8, 26.2)
Q	41.2 (13.0)	65.6	39.4 (13.1)	65.9	39.7 (28.7, 48.4)
V_2	83.0 (9.17)	46.1	82.8 (8.99)	45.1	83.1 (69.9, 97.2)
K_a	63.7 (4.89)	27.4	65.9 (4.79)	25.7	66.1 (59, 72)
F	95.3 (11.0)	44.9	80.8 (11.3)	47.0	80.2 (65.2, 96)
K_{DES}	65.2 (10.4)	53.8	67.4 (10.2)	52.9	67.8 (55.4, 81.8)
D1	128.6 (6.32)	63.1	145.3 (9.98)	60.8	143.4 (124.6, 163.7)
Residual variability					
Proportional error (CV%)	0.221 (0.565)	13.9	0.220 (0.569)	13.9	0.220 (0.216, 0.114)

BWT=baseline body weight in kilograms; CL0=total clearance at time t=0; CLPCT=fraction clearance at steady state described by the time-independent clearance component; CI=confidence interval; CV=coefficient of variation; D1=input duration of subcutaneous administration; F=subcutaneous bioavailability; IgG=immunoglobulin G; ISS=International Staging System; Ka=first-order absorption rate constant; KDES=first-order decay coefficient of the time-dependent clearance;Q=inter-compartmental clearance; RSE=relative standard error; SIR=Sampling Importance Resampling; TPMMG=multiple myeloma type category group (0=IgG,1=Non-IgG); V1=volume of distribution of the central compartment; V2=volume of distribution of the peripheral compartment.

Base model:

$$CL_0(L/day) = 1.63 \times \left(\frac{BWT}{74.8}\right)^{0.621}$$

$$CL = CL_0 * CL_{PCT} + CL_0 * (1 - CL_{PCT}) \times e^{-0.0237 \times Time\ (in\ days)}$$

[b] $$V_1(L) = 4.32 \times \left(\frac{BWT}{74.8}\right)^{0.677}$$

Final model:

[a] $$CL_0(L/day) = 2.08 \times \left(\frac{BWT}{74.8}\right)^{0.672} \times 0.453^{TPMMG=Non-IgG} \times 1.318^{ISS\ II/III}$$

$$CL = CL_0 * CL_{PCT} + CL_0 * (1 - CL_{PCT}) \times e^{-0.0229 \times Time\ (in\ days)}$$

[b] $$V_1(L) = 4.30 \times \left(\frac{BWT}{74.8}\right)^{0.670}$$

To assess the impact of covariates on the systemic exposure of talquetamab for patients in study MonumenTAL-1, subgroup analyses were conducted on predicted systemic exposure based on the individual pharmacokinetic parameters from the final PopPK following the two studied RP2Ds dosing regimens RP2Ds [i.e 0.4 mg/kg weekly SC preceded by step-up dose schedule 0.01 and 0.06 mg/kg on days -4 and -2 respectively before the full dose on day 0, and 0.8 mg/kg Q2W SC preceded by step-up dose schedule 0.01 and 0.06 and 0.3 mg/kg on days -6, -4 and -2 respectively before the full dose on day 0].

No clinically meaningful differences (i.e., <20-30%) in the exposure to talquetamab were observed in subjects with different body weight when talquetamab was administered on the weight-based dosing regimen. Exposure of talquetamab largely overlapped across body weight subgroups, even a tendency of increase on systemic exposure is expected (geometric mean ratio of: 1.2 with CI95%: [1.1-1.4]) in heavier patients with BW > 87.7 kg.

The disease status variables including multiple myeloma type (non-IgG versus IgG) and ISS staging (II versus I and III versus I) affected the systemic exposure of talquetamab. The simulated $C_{avg,4weeks}$ at the two RP2Ds 0.4 mg/kg weekly and 0.8 mg/kg Q2W were 90 and 100% higher in patients with non-IgG subtype of multiple myeloma compared with those with IgG subtype of multiple myeloma, and they were approximately 20 to 30% lower in participants with ISS Stage II/III when comparing with ISS Stage I. With regard to the multiple myeloma subtype, this covariate was later also identified as a significant factor associated with clinical efficacy ORR endpoint and thus confounded with systemic exposures.

Based on the total PK population of n=492 with both IV and SC doses, patients with presence of treatment-emergent anti-drug antibodies (ADAs) (n=91 positive, 18.5%), mild and moderate hepatic impairment (N=76, 15.4% mild and moderate), mild or moderate renal impairment (based on MDRD eGFR, 231 [47%] mild, 142 [28.9%] moderate), age (33 to 86 years old), sex, race and geographical region did not result in clinically meaningful differences (ie, <20%) in exposures.

Absorption

Following SC administration of talquetamab at 400 µg/kg QW Tmax is generally achieved at 2 days with mean Cmax of 3799 ng/mL and mean AUC of 607.3 µg.h/mL.

Following SC administration of talquetamab at 800 µg/kg Q2W Tmax is generally achieved at 2.8 days with mean Cmax of 4161 ng/mL and mean AUC of 1021 µg.h/mL.

SC bioavailability was estimated by calculating the ratio of the mean-dose normalised AUCtau (18.1 ng.h/mL) observed at Cycle 3 Day 1 in the RP2D cohort of 0.405 mg/kg SC QW with the dose normalised AUCtau (24.5 ng.h/mL) at Cycle 3 Day 1 of the cohort IV QW. This resulted in an approximation of the SC bioavailability of 74% for the RP2D cohort.

Based on the PopPK analysis, SC bioavailability was estimated at 62%.

Distribution

Typical mAbs are primarily confined in the vascular system. Based on NCA, at Cycle 3 Day 1 for approximately a 400 µg/kg dose (405 µg/kg), mean Vd/F was 9.34 L, and for a 800 µg/kg dose, 13.1 L. Based on PopPK analysis, typical V_1 was 4.3 L. V_1 increased with body weight with an allometric exponent of 0.67. The typical V_2 was estimated to be 5.78 L.

Elimination

Based on the PopPK analysis, the elimination of talquetamab was described by parallel linear CL_1 and linear CL_t ($CL_t=CL_2 \cdot \exp[-K_{DES} \cdot Time]$, where CL_2 is the time-dependent clearance at time 0. 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, disease severity, or improvement of cancer-related cachexia, as a result of talquetamab treatment, similarly to nivolumab, teclistamab, and daratumumab.

Typical total clearance was 2.08 L/day at initial treatment and 1.06 L/day at steady state for participants with IgG subtype of myeloma and ISS stage I, and K_{DES} was 0.0229 d^{-1}. The median terminal phase $t_{1/2}$ based on the post-hoc parameters of all SC populations (n=392) was 7.56 d at initial treatment, and 12.2 d at steady state.

Dose proportionality and time dependencies

Following talquetamab SC administration, exposure (Cmax and AUC) increased in an approximately dose-proportional manner at Cycle 1 and Cycle 3 across the range of 0.005 mg/kg to 0.8 mg/kg QW and 0.8 mg/kg to 1.2 mg/kg Q2W.

Following SC administration, for weekly dosing schedule in Cycle 3, the mean accumulation ratio of Cmax was 3.9 and 4.5 for AUCtau. For Q2W dosing schedule at Cycle 3, the mean accumulation ratio of Cmax was 2.33 and 2.17 for AUCtau. Steady state seems to be achieved at week 16.

Inter-individual variability

Inter-individual variability (CV%) in CL_0, V1, V2, F and Ka was estimated to be 52%, 22%, 83%, 81% and 66%, respectively, based on PopPK model estimates (**Table 13**).

Special populations

Renal impairment

The effect of renal impairment as defined using the Modification of Diet in Renal Disease formula (normal [n=119, 24.2%], mild [n=231, 47%], moderate [n=142, 24.7%], and severe [n=0, 0%]) was evaluated in Pop-PK analysis and was not identified as significant covariate on talquetamab systemic exposure.

Hepatic impairment

The effect of hepatic impairment as defined using the National Cancer Institute criteria (normal [n=414, 84.1%], mild [n=74, 15.0%], moderate [n=2, 0.4%], and severe [n=0, 0%]) was evaluated in the Pop-PK analysis. Hepatic impairment (mild or moderate) was not identified as a significant covariate on talquetamab systemic exposure.

Gender

The effect of sex on the PKs of talquetamab was evaluated in Pop-PK analysis. Approximately 57.3% of the patients included in the dataset were male (n=282). The covariate analyses showed that sex had no significant effect on PK parameters.

Race

In the Pop-PK analysis, race or ethnicity was not identified to significantly influence the PKs of talquetamab. The composition of patients included in the analysis dataset were White (n=424, 86.2%), Black (n=43, 8.7%), Asian (n=11, 2.2%), or others (n=14, 2.8%).

Weight

In the Pop-PK analysis, BW effect was included as allometric scaling component on the total clearance at start of treatment (CL0) and volume of distribution parameters with estimated exponents of 0.672 and 0.67, respectively.

Elderly

The effect of age (median: 65 years; range: 33 to 86 years) on talquetamab PK was assessed in Pop-PK analysis. The covariate analyses showed that age had no significant effect on the PK parameters.

The number of elderly subjects included in the PK analysis is shown in **Table 14**.

Table 14. Number of older subjects with PK data in study 64407564MMY1001

	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	**181/492**	**73/492**	**1/492**

Pharmacokinetic interaction studies

PBPK model

A PBPK model was developed to evaluate the potential influence of Interleukin 6 (IL-6) serum levels on the exposure of various CYP substrates, including caffeine (CYP1A2), s-warfarin (CYP2C9), omeprazole (CYP2C19), midazolam and cyclosporine (CYP3A4 and CYP3A5), and simvastatin (CYP3A4), for two dosing regimens of talquetamab (400 ug/kg weekly subcutaneous (SC) treatment dose and 800 ug/kg). The study also assessed the time taken to achieve the maximum change in CYP activity due to IL-6, as well as the time required to return to 80% of the baseline enzymatic activity, with Cycle 1 as the reference point. The simulations aimed to analyse the impact of IL-6, resulting from talquetamab administration, on CYP substrates and provide recommendations for clinical monitoring of co-medication of CYP substrates with a narrow therapeutic index in the label.

Based on the results of PBPK modelling and simulation, the highest risk of drug-drug interaction occurs when initiating the step-up dose of talquetamab within 1 to 7 days after the first treatment dose, or during a CRS event, for the 400 ug/kg weekly SC dosing regimen. Similarly, for the 800 ug/kg Q2W SC dosing regimen, the highest risk of drug-drug interaction occurs when initiating the step-up dose of talquetamab within 1 to 9 days after the first treatment dose or during a CRS event.

2.6.2.2. Pharmacodynamics

Mechanism of action

Talquetamab is a novel, humanised IgG4 bispecific antibody designed to target the CD3 receptor complex on T cells and on GPRC5D multiple myeloma cells, resulting in T cell activation and subsequent lysis of GPRC5D-expressing multiple myeloma cells. As a stable bispecific IgG molecule generated through controlled fragment antigen binding arm exchange following the method reported by Labrin 2013, talquetamab is able to draw T cells in close proximity to myeloma cells, without regard to T cell receptor specificity or reliance on major histocompatibility complex Class 1 molecules on the surface of antigen presenting cells for activation.

Primary and secondary pharmacology

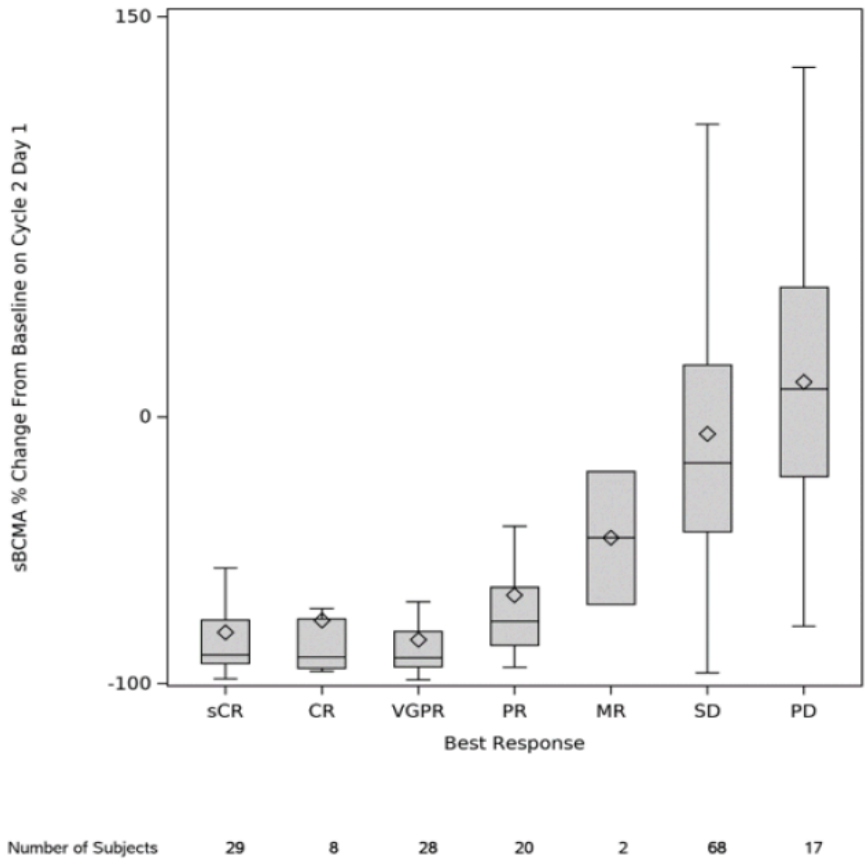
To determine if treatment with talquetamab results in increased antitumor activity by redirected T cell-mediated killing of GPRC5D-expressing multiple myeloma cells and increased activation of cytotoxic T cells, serum and whole blood samples were collected to evaluate sBCMA (as a potential surrogate marker of tumour burden) as well as cytokines and immune cell populations by flow cytometry as pharmacodynamic biomarkers of immune activation.

Soluble B cell maturation antigen

A correlation between reduction of sBCMA and overall best response for the whole treatment was observed in Phase 1. Following talquetamab IV or SC administration in Phase 1, 83 of 85 responders (97.6%) and 52 of 87 non-responders (59.8%) showed a decrease in sBCMA at Cycle 2 Day 1 compared with their respective baseline values. In addition, a greater reduction in sBCMA was

observed in participants with deeper responses to talquetamab (**Figure 10**).

Figure 10. Percentage change from baseline in soluble BCMA at Cycle 2 Day 1 by best response as assessed by investigator (Phase 1) (Study 64407564MMY1001) (Pharmacokinetics analysis set)



CR=complete response; MR=minimal response; PD=progressive disease; PR=partial response; (s)BCMA=(soluble) B cell maturation antigen; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response.

Cytokines

Cytokine induction was observed following initial doses. No statistically significant association was observed between treatment response and maximum fold change in IL-6, IFN γ, TNF-α, IL-10, or soluble IL 2Rα. A trend was observed for higher induction of IL-6, IL-10, and soluble IL 2Rα in responders compared with non-responders.

T cell activation

T cell activation was observed following initial doses of talquetamab in patients treated at the 0.8 mg/kg biweekly dose. No statistically significant association was observed between treatment response and maximum fold change in expression of CD25, CD38, HLA-DR, LAG 3, PD 1, or TIM-3 on CD4+ or CD8+ T cells. A trend was observed for higher induction of LAG-3 or TIM-3 on CD4+ or CD8+ T cells in responders compared to non-responders.

T cell redistribution

For treated participants assigned to the 0.4 mg/kg weekly SC RP2D or 0.8 mg/kg Q2W SC RP2D and treated participants with prior T cell redirection therapies assigned to either RP2D, T-cell redistribution was demonstrated by reduction in peripheral CD4+ and CD8+ T cells after the initial dose of talquetamab.

B cells

No significant changes in CD19+ B cell levels were observed within the first cycle for treated participants assigned to the 0.4 mg/kg weekly SC RP2D or the 0.8 mg/kg Q2W SC RP2D and treated participants with prior T cell redirection therapies assigned to either RP2D. Increased CD19+ B cell levels were noted beginning at Cycle 3 for treated participants assigned to the 0.4 mg/kg weekly SC RP2D and beginning at Cycle 2 for treated participants assigned to the0.8 mg/kg Q2W SC RP2D and treated participants with prior T cell redirection therapies assigned to either RP2D

2.6.3. Discussion on clinical pharmacology

Talquetamab exhibited approximately dose-proportional pharmacokinetics following subcutaneous administration across a dose ranging from 0.005 to 0.8 mg/kg weekly (0.0125 to 2 times the recommended 0.4 mg/kg weekly dose) and from 0.8 mg/kg to 1.2 mg/kg biweekly (1.0 to 1.5 times the recommended 0.8 mg/kg biweekly dose).

The mean accumulation ratio between the 1st and 7th weekly dose of talquetamab 0.4 mg/kg was 3.9- and 4.5-fold for Cmax and AUCtau, respectively. The mean accumulation ratio between the 1st and 5th biweekly dose of talquetamab 0.8 mg/kg was 2.3- and 2.2-fold for Cmax and AUCtau, respectively.

However, the applicant noted that the developed method for the quantification of talquetamab concentration in human serum was not specific and different results may have been observed with selection of a different reagent. Therefore, it is recommended that the applicant develops a specific method of quantification of talquetamab in human serum (by using another tool reagent) as part of its ongoing clinical development programme.

Population PK analysis

The developed Pop-PK model, a two-compartment model with both time-varying and time-independent clearance components, appears to adequately describe the whole features of observed PK data.

Based on the population pharmacokinetic model, the typical value of the bioavailability of talquetamab was 62% when administered subcutaneously relative to intravenous dosing.

At 0.4 mg/kg weekly dose regimen, the median (range) T_{max} of talquetamab after the 1st and 7th treatment doses were 3 (1 to 8) days and 2 (1 to 6) days, respectively.

At 0.8 mg/kg biweekly (every 2 weeks) dose regimen, the median (range) T_{max} of talquetamab after the 1st and 5th treatment doses were 3 (2 to 14) days and 3 (1 to 8) days, respectively.

Based on the population pharmacokinetic model, the typical value of the volume of distribution was 4.3 L (22% CV [coefficient of variation]) for the central compartment, and 5.8 L (83% CV) for the peripheral compartment.

Talquetamab exhibited both linear time-independent and time-dependent clearance. Based on the population pharmacokinetic model and the post hoc parameters of participants receiving SC doses (N=392), the median total clearance is 1.64 L/day at initial treatment and 0.80 L/day at steady state.

The time-dependent clearance accounted for 48.8% of total clearance at initial treatment and then decreased exponentially to < 5% at around Week 16. The concentration-time profile at Week 16 would reach 90% of steady-state concentration for both 0.4 mg/kg weekly and 0.8 mg/kg biweekly regimens. The median terminal phase half-life was 7.56 days at initial treatment, and 12.2 days at steady state.

In addition to the effects of BW on PK, the Pop-PK analysis only found that the type of multiple myeloma (IgG vs non-IgG) and International Staging System score were predictors of talquetamab clearance. The simulated $C_{ave,4weeks}$ at the two RP2Ds 0.4 mg/kg weekly and 0.8 mg/kg Q2W were approximately 90 and 100% higher in patients with non-IgG subtype of multiple myeloma compared with those with IgG subtype of multiple myeloma. Further clinical efficacy subgroup analyses and E-R analyses clarified that instead of systemic exposures, myeloma subtype (non-IgG versus IgG) was the covariate of ORR and therefore no dose adjustment is warranted based on multiple myeloma subtype. Bodyweight is taken into account by the use of mg/kg dosing.

The applicant proposes no dosing adjustment for any special populations. These recommendations are overall acceptable and are justified by the results of the Pop-PK PK analyses, together with exposure-response analyses (see also Clinical Efficacy section of this report). However, it should be noted that only limited data (n=2) is available in participants with moderate hepatic impairment while no data are available in participants with severe hepatic or renal impairment.

Talquetamab is not metabolised via CYP enzymes and is not expected to directly affect CYP enzymes. Therefore, the absence of specific clinical DDI studies could be acceptable. However, cytokine release that occurs during CRS may transiently downregulate CYP enzymes.

PBPK model

A PBPK modelling and simulation was used to evaluate the potential influence of Interleukin 6 (IL-6) serum levels on the exposure of various CYP substrates. The simulations aimed to analyse the impact of IL-6, resulting from talquetamab administration, on CYP substrates and provide recommendations for clinical monitoring of co-medication of CYP substrates with a narrow therapeutic index in the label.

According to the PBPK model results, the impact of talquetamab on the exposure of omeprazole, midazolam, simvastatin, and cyclosporine, which are substrates for CYP2C9, CYP2C19, and CYP3A4/5, was found to be weak to moderate. Additionally, the impact on the exposure of caffeine, which is a substrate for CYP1A2, was minimal.

Talquetamab causes release of cytokines that may suppress activity of cytochrome P450 (CYP) enzymes, potentially resulting in increased exposure of CYP substrates. The highest risk of drug-drug interaction is expected to occur from initiation of talquetamab step-up phase up to 9 days after the first treatment dose and during and after CRS. It is therefore recommended to monitor for toxicity or concentrations of drugs that are CYP (e.g., CYP2C9, CYP2C19, CYP3A4/5, CYP2D6) substrates where minimal concentration changes may lead to serious adverse reactions. The dose of concomitant CYP (e.g., CYP2C9, CYP2C19, CYP3A4/5, CYP2D6) substrate drugs should be adjusted as needed.

2.6.4. Conclusions on clinical pharmacology

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

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

Starting dose rationale

The initial IV dose proposed for the Phase 1 Study 64407564MMY1001 was based on estimation of the minimum anticipated biological effect level (MABEL). This was calculated using the lowest mean concentration associated with the 20% maximal drug effect (EC20) from the T cell activation in the whole blood assay with the multiple myeloma cell line H929 (see also Section 2.5.2 of this report). The identified MABEL (0.083 nM) resulted in a recommended starting dose of 0.0005 mg/kg as an approximately 4-hour infusion Q2W.

Rationale for weekly dosing

Dose escalation for the weekly IV cohorts began at a starting dose level that was already determined to be safe for Q2W IV dosing, and the subsequent dose levels were selected based on a statistical model using all available data to identify safe and tolerable RP2Ds, defined as the dose(s) and schedule(s) of talquetamab for characterisation in Part 2. Preliminary first dose pharmacokinetics results from the first 5 cohorts (dose range 0.0005 to 0.00338 mg/kg) following Q2W IV dosing with talquetamab in Study 64407564MMY1001 showed that talquetamab levels were high at (end of infusion after IV flush) EOI and declined quickly with terminal t1/2 ranging from approximately 2 to 6 days. The pharmacokinetics data from the Q2W cohorts suggested that participants may not have had sufficient talquetamab exposure beyond Day 8 following the first dose with Q2W IV dosing. Thus, increasing the IV dosing frequency from Q2W to weekly allowed for more sustained talquetamab exposure over the intended dosing interval. Based on the safety profile and preliminary pharmacokinetics data, weekly IV dosing with talquetamab was initiated and selected for further exploration.

Rationale for subcutaneous dosing

In Study 64407564MMY1001, SC injection of talquetamab, which is shorter in duration compared with IV administration (IV infusion duration of 2 to 4 hours), as well as having more sustained concentration-time profiles, was evaluated for the convenience of patients and healthcare providers. The systemic exposure of talquetamab is expected to be lower with SC administration than with IV infusion. Preliminary modelling of the available talquetamab pharmacokinetics data following IV infusion, using a 2-compartment model, as well as simulation to predict the exposure following SC administration (assuming 60% F and Tmax at 48 or 72 hours) were conducted to compare the exposure from IV (observed) and SC (simulated) dosing. The simulation demonstrated that the Cmax following a 0.0015 mg/kg SC administration on Day -7 was more than 3-fold lower than the observed Cmax following the 0.0015 mg/kg IV step-up dose. Simulated Cmax following the first SC full dose of 0.005 mg/kg on Day 1 was approximately more than 2-fold lower than the observed Cmax following the first IV full dose of 0.00338 mg/kg on Day 1. Thus, the initial SC dose was a 0.0015 mg/kg step-up dose on Day -7, followed by a full dose of 0.005 mg/kg administered on Days 1, 8, and 15 of a 21-day cycle. This SC dose and schedule was initiated after the 0.005 mg/kg weekly IV cohort was deemed to be safe by the study evaluation team.

Rationale for recommended phase 2 dose

In Phase 1, 0.4 mg/kg weekly SC and 0.8 mg/kg Q2W SC achieved exposures consistently above the maximum EC90, activation of T cells and induction of cytokines, a clinically manageable safety profile, and compelling efficacy. In the SC cohorts, ORR and DOR generally increased up to the RP2Ds of 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC. Although lower doses such as 0.135 mg/kg weekly SC also

showed activity with responses in several participants at these doses, fewer participants achieved VGPR or better, and DOR tended to be shorter at these doses compared with the putative RP2Ds. Efficacy and safety data for higher doses did not support the benefit-risk of further dose escalation. Based on pharmacokinetics, pharmacodynamics, safety, and efficacy data available from Phase 1, the optimised treatment doses for talquetamab monotherapy (0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC, after step-up dosing) were selected as the RP2Ds for further evaluation in Phase 2. Results from Phase 2 further established 0.4 mg/kg weekly SC and 0.8 mg/kg Q2W SC as safe and effective dose regimens for the treatment of relapsed or refractory multiple myeloma.

Exposure-response (E-R) relationship

- Phase 1 Overall Response Rate, Duration of Response, and Progression-free Survival for Participants in Phase 1 (Pooled Phase 1 RP2D and Non-RP2D SC Cohorts)

In Phase 1, the ORR was assessed by the investigator (IMWG 2011 criteria). A positive E-R relationship in Phase 1 participants receiving talquetamab SC (n=134) between ORR and $C_{ave,\ 4\ weeks}$ was observed. ORR increased with talquetamab exposure across SC doses below the RP2Ds and reaching a plateau at or above the RP2Ds (data not shown). Based on the Phase 1 E-R relationship and derived pharmacokinetic exposures, it can be concluded that the RP2Ds are better than below the RP2Ds, and there was no additional increase in response rate using above the RP2Ds. Other pharmacokinetic metrics such as $C_{trough,1stdose}$ showed a similar trend as $C_{ave,4\ weeks.}$(data not shown).

The E-R analyses for DOR and PFS in participants in Phase 1 were conducted. The Kaplan-Meier plots for DOR showed overlapping CIs and no statistically significant relationship with all investigated pharmacokinetic metrics (data not shown). PFS plots showed significant E-R relationship at higher exposures (2^{nd} to 4^{th} quartiles, corresponding to RP2Ds and >RP2Ds) correlating with longer PFS (data not shown). These results support the selection of the two RP2Ds.

- Recommended Phase 2 Doses (0.4 mg/kg weekly SC and 0.8 mg/kg Q2W SC) Overall Response Rate

The ORR E-R relationship for participants without prior T cell redirection therapy at RP2Ds of 0.4 mg/kg weekly SC and 0.8 mg/kg Q2W SC (by IMWG 2016 criteria and by IRC) with at least 3 months follow-up (treated on or prior to 15 February 2022 for 0.8 mg/kg Q2W; n=254) was performed. Responders and non-responders had comparable pharmacokinetic exposures. Near flat E-R relationships were observed between ORR and Cave,4 weeks. Other pharmacokinetic metrics, $C_{trough,1stdose}$, $C_{avg,\ 1stdose}$, $C_{avg,\ 2weeks}$, and $C_{avg,\ 3rd\text{-}4th\ weeks}$, also showed similar near flat E-R relationships (data not shown).

The association between talquetamab pharmacokinetic exposure and ORR was not statistically significant in univariate and multivariate E-R modelling for $C_{avg,\ 4\ weeks}$ and other investigated pharmacokinetic metrics. These results suggest participants had sufficient exposure for achieving response.

Prognostic factors of Ig subtype of myeloma (higher ORR in participants with non-IgG) and extramedullary plasmacytomas (higher ORR in participants without extramedullary plasmacytomas) were identified from subgroup analysis and multivariable analysis as factors that could affect ORR. Of these 2 prognostic factors, the Ig subtype of myeloma was confounding and associated with the change in exposures (higher exposure in participants with non-IgG subtype). Additional E-R analysis stratified by Ig subtype of myeloma showed a plateaued E-R relationship in participants with non-IgG or IgG subtype (data not shown) and clarified that instead of pharmacokinetic exposure values, the subtype of myeloma had an impact on ORR, confirming the results from multivariable E-R analysis.

Of note, E-R analysis did not identify dose schedule (weekly SC vs Q2W SC) as a significant covariate for ORR at the RP2Ds, suggesting comparable ORR resulting from either RP2D dose of 0.4 mg/kg weekly or 0.8 mg/kg Q2W.

The Kaplan-Meier plots show overlapping CIs and no statistically significant relationship with quartiles of all investigated pharmacokinetic metrics (data not shown). These plots indicated a plateaued relationship between pharmacokinetic exposures and DOR/PFS at the RP2Ds.

A Cox proportional hazard model showed that exposure was not associated with OS (data not shown). ISS stage (higher hazard rate for higher ISS stage) and extramedullary plasmacytoma (higher hazard rate) were 2 prognostic factors for OS in the RP2Ds.

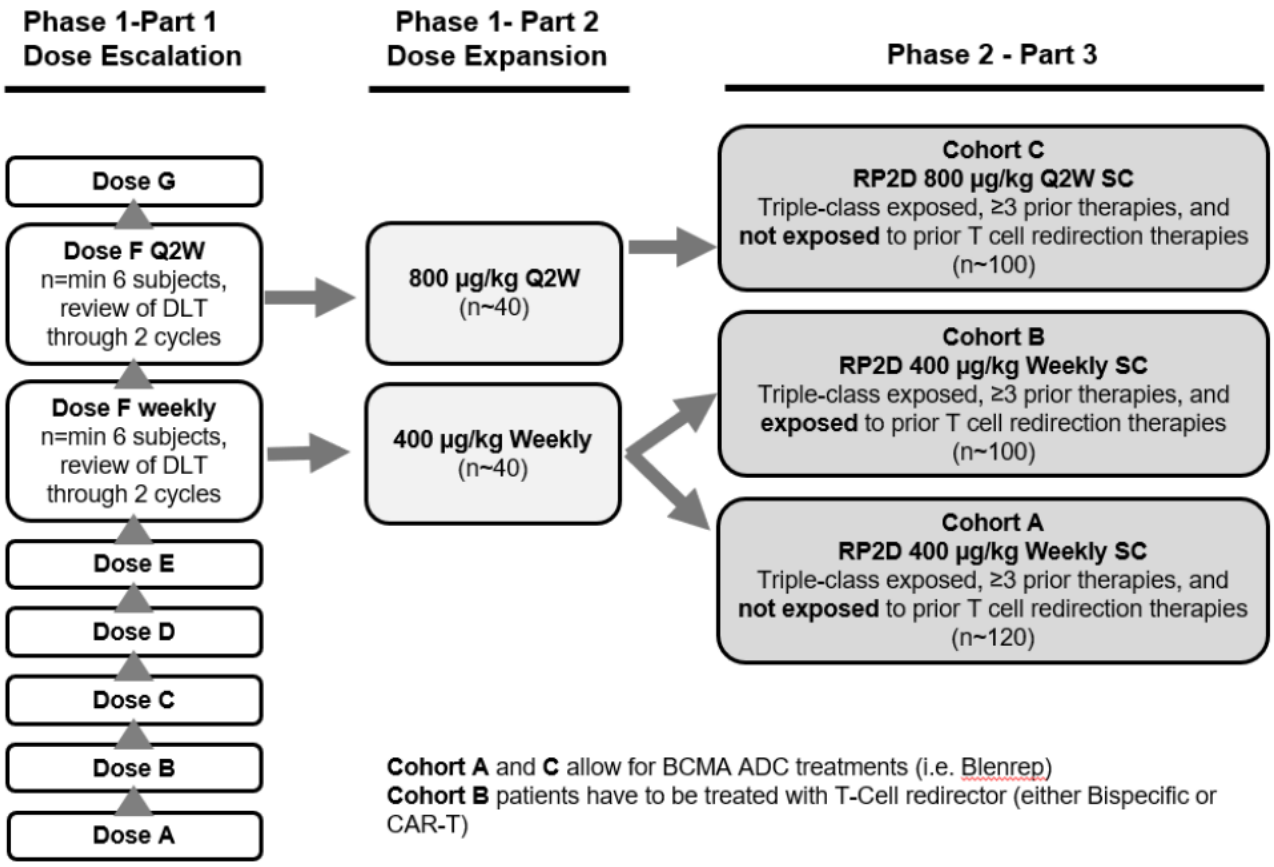
2.6.5.2. Main study

Study 64407564MMY1001 ((MonumenTAL-1): A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanised GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma.

Methods

A diagrammatic representation of the study design is presented in **Figure 11**.

Figure 11. Study 64407564MMY1001 schematic



DLT=dose limiting toxicity; Q2W=every 2 weeks; RP2D=recommended Phase 2 dose; SC=subcutaneous(ly).

- **Study Participants**

Inclusion Criteria

Eligible participants were required to be at least 18 years of age, have a documented diagnosis of multiple myeloma, and have an ECOG Performance Status score of 0 or 1 (Phase 1) or 0 to 2 (Phase 2). All participants were required to have measurable disease, with the following additional criteria in Parts 2 and 3: (1) serum monoclonal paraprotein (M-protein) levels ≥1.0 g/dL or urine M-protein level ≥ 200 mg/24 hours, or (2) light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.

In Phase 2, all participants had previously received at least 3 prior therapies that included at least one PI, one IMiD, and an anti-CD38 monoclonal antibody. Participants in Cohort B were required to have received T cell redirection therapies (such as CAR-T or bispecific antibodies); participants treated with T cell redirection therapies were excluded from Cohorts A and C.

Exclusion Criteria

Participants were not to be enrolled into the study if they had received T cell redirection therapy within 3 months, prior Grade 3 or higher CRS related to any T cell redirection therapy, an allogenic stem cell transplant within the past 6 months, autologous stem cell transplant within 3 months, stroke or seizure within the past 6 months, CNS involvement or clinical signs of meningeal involvement of multiple myeloma, plasma cell leukaemia, active or documented history of autoimmune disease, with the exception of vitiligo, resolved childhood atopic dermatitis, POEMS syndrome, primary light chain amyloidosis and prior Grave's disease that was euthyroid based on clinical symptoms and laboratory testing.

- **Treatments**

In Part 2 (Phase 1 dose expansion), talquetamab was administered SC at the putative RP2Ds identified in Phase 1: a treatment dose of 0.405 mg/kg weekly on Days 1, 8, and 15 of a 21-day cycle (preceded by step-up doses of 0.01 and 0.06 mg/kg before Cycle 1 Day 1); or a treatment dose of 0.8 mg/kg Q2W on Days 1 and 15 of a 28-day cycle (preceded by step-up doses of 0.01, 0.06, and 0.3 mg/kg before Cycle 1 Day 1).

For Part 3 (Phase 2), talquetamab was administered SC at the 2 RP2Ds confirmed in Part 2. In Cohort A and Cohort B, the step-up schedule was talquetamab SC at 0.01 and 0.06 mg/kg, separated by 2 to 4 days and to be completed 2 to 4 days before the first weekly treatment dose of 0.4 mg/kg. In this part of the study, the RP2D dose of 0.405 mg/kg was adjusted to 0.4 mg/kg for operational convenience, with similar exposure to talquetamab; "0.4 mg/kg weekly SC" in this report refers to results for both the Phase 1 dose and the Phase 2 dose. The treatment dose schedule for Cohorts A and B was Days 1, 8, 15, and 22 of a 28-day cycle. In Cohort C, the step-up schedule was talquetamab SC at 0.01, 0.06, and 0.3 mg/kg, each separated by 2 to 4 days and to be completed 2 to 4 days before the first Q2W treatment dose of 0.8 mg/kg. The treatment dose schedule for Cohort C was Days 1 and 15 of a 28-day cycle.

- **Objectives** (**Phase 2 (Part 3))**

Primary Objective

- To evaluate the efficacy of talquetamab at the RP2Ds

Secondary Objectives

- To further assess the efficacy of talquetamab at the RP2Ds
- To evaluate MRD at the RP2Ds
- To further assess the safety and tolerability of talquetamab at the RP2Ds
- To characterise the pharmacokinetics of talquetamab at the RP2Ds
- To assess the immunogenicity of talquetamab
- To assess PROs after treatment with talquetamab
- To evaluate the efficacy of talquetamab in high-risk molecular subgroups

- **Outcomes/endpoints**

The primary efficacy endpoint was objective response rate (ORR), defined as the proportion of participants who achieved a partial response (PR) or better according to the International Myeloma Working Group (IMWG) 2016 response criteria, as assessed by an Independent Review Committee (IRC).

Secondary efficacy endpoints were duration of response (DOR), very good partial response (VGPR) or better rate, CR or better rate, time to response (TTR), progression-free survival (PFS), overall survival (OS), minimal residual disease (MRD) negativity rate, and ORR in participants with high-risk cytogenetics.

DOR was 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, as defined in the IMWG criteria, or death due to progressive disease, whichever occurs first. Relapse from CR was not considered as disease progression. For subjects who have not progressed, data were censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

TTR was 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. For subjects without response, data were censored either at the date of progressive disease, or in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy.

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

OS was defined as the time from the date of first dose of study drug to the date of the subject's death. If the subject was 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.

MRD-negative rate was defined as the proportion of subjects who achieved MRD negative status to a threshold of 10-5 at any timepoint after initial dose of talquetamab and before disease progression or starting subsequent therapy.

- **Sample size**

The sample size planned was 260 subjects in the phase 1 part and 320 subjects in the phase 2 part (120 in cohort A, 100 in cohort B and 100 in cohort C); there was no formal justification of the sample size for the phase 1 part of the trial (dose escalation and expansion). For cohort A, B and C, sample sizes were based on the following targeted clinical responses:

45% ORR observed in cohort A to declare a higher rate than 30% with 90% power ; 35% ORR observed in cohort B to declare a higher rate than 15% with 80% power (in a 2-stage design) – this sample size could be increased to at least 60 subjects to have a more accurate estimate ; 45% ORR observed in cohort C to declare a higher rate than 30% with 85% power – all above null hypotheses were tested with a 2.5% one-sided type-one error.

- **Randomisation and Blinding (masking)**

This was an open label study.

- **Statistical methods**

Overall response rate (ORR) will be tabulated together with its two-sided 95% exact CI. The ORR calculation will include all talquetamab-treated subjects (subjects whose response is not evaluable will be considered as not having responded for the purposes of the ORR calculation).

For the time-to-event endpoints, including DOR, PFS, TTNT, and OS, the Kaplan-Meier method will be used for descriptive summaries.

The analysis of the primary endpoint for Part 3, ORR (PR or better), in Cohort A will be conducted approximately 6 months after 120 subjects in Cohort A have received an initial dose of talquetamab.

The analysis of ORR in Cohort B will be conducted after the response can be assessed for the last subject in Cohort B.

The analysis of the primary endpoint for Part 3, ORR (PR or better), in Cohort C will be conducted approximately 6 months after approximately 100 subjects have received an initial dose of SC talquetamab 800 µg/kg biweekly.

The ORR and its 95% exact CI will be calculated and statistical significance for ORR will be achieved if the lower bound of the confidence interval for ORR in Cohort A and Cohort C is greater than 30% and the lower bound of the 95% confidence interval for ORR in Cohort B is greater than 15%. Analysis of VGPR or better response rate, CR or better response rate, sCR rate, MRD negative rate, DOR, TTR, PFS, TTNT, and OS will be conducted at the same time as the analysis of ORR, and an update of these endpoints will be provided at the end of the study, which is planned to occur 2 years after the last subject has received his or her initial dose of talquetamab or when the last subject has completed the last study assessment in the study, whichever occurs first.

Interim Analysis

In Part 3, Stage 1 analysis was planned to be performed for Cohort B when approximately 21 response evaluable subjects were enrolled in Cohort B and the response for the last patient in Stage 1 can be assessed. Further enrolment may be terminated if 3 or fewer responses are observed in the first stage. Otherwise, additional subjects will be enrolled to ensure 34 response-evaluable subjects with 2 stages combined. Assuming 10% non-response-evaluable rate, a total of 38 subjects will be planned.

Results

- **Participant flow**

Among 143 treated participants (21 in Phase 1 and 122 in Phase 2) without prior T cell redirection

therapy who were assigned to the RP2D of 0.4 mg/kg weekly SC at the clinical cut-off date of 12 September 2022 median duration of follow-up was 14.9 months (range: 0.5 to 29.0). At this clinical cut-off, 64.3% of participants were still in the study and 25.2% were still on talquetamab treatment. The primary reason for treatment discontinuation was progressive disease (56.6%).

In the latest clinical cut-off date of 17 January 2023, among the 106 responders with no prior T cell redirection therapy who were assigned to talquetamab 0.4 mg/kg weekly SC) the median duration of follow-up was 18.9 months (range: 2.7 to 32.9 months).

Among the 145 treated participants (36 in Phase 1 and 109 in Cohort C in Phase 2) without prior T cell redirection therapy who were assigned to talquetamab 0.8 mg/kg Q2W SC median duration of follow-up was 8.6 months (range: 0.2 to 22.5). As of the clinical cut-off of 12 September 2022, 49% of participants were still on talquetamab treatment and 77.2% of participants were still in the study The primary reason for treatment discontinuation was progressive disease (31.7).

In the latest clinical cut-off date of 17 January 2023, among the 104 responders with no prior T cell redirection therapy who were assigned to talquetamab 0.8 mg/kg Q2W SC the median duration of follow-up was 12.9 months (range: 4.1 to 26.1 months).

Among the 33 responders with prior T cell redirection therapy who were assigned to talquetamab 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC and included in the All Treated Analysis set (n=51), the median duration of follow-up was 15.3 months (range: 4.9 to 29.0 months) at the latest clinical cut-off date of 17 January 2023.

- **Recruitment**

First subject enrolled: 03 January 2018

The study is ongoing.

- **Conduct of the study**

Summary of main protocol amendments

There were 15 global amendments to the original protocol. The main changes are summarised below:

Amendment 6 (25 January 2019)

- Added details to start evaluation of the SC administration in study parts 1 and 2

Amendment 11 (23 September 2020)

- Added the phase 2 part of the study

Amendment 13 (17 June 2021)

- Added cohort C to evaluate the alternate 0.8 mg/kg Q2W SC dosing schedule

Amendment 15 (07 December 2021)

- Increased the total number of participants for both cohort B and C

It should be noted that patients with ECOG score of 2 were not allowed for inclusion until amendment 12 (21 January 2021), which is then reflected in the baseline data and limited results in this subgroup.

Protocol deviations

At the first clinical cut-off date of 16 May 2022, protocol deviations occurred for 9.8% of both 0.4mg/kg weekly and prior T-cell redirections therapy groups and 4.8% for 0.8mg/kg Q2W treated patients with no impact on participant safety or data integrity. The most frequent major protocol

deviation was the participants did not meet eligibility criteria before the first dose.

- **Baseline data**

Demographics, disease characteristics and prior multiple myeloma therapies are summarised separately for each claimed dose regimen, and for patients with prior T cell redirection therapy in this section.

0.4mg/kg weekly regimen

Table 15. Summary of demographics and baseline characteristics; All treated analysis set (Study 64407564MMY1001; 400 ug/kg weekly subcutaneous)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	21	122	143
Age, years			
N	21	122	143
Category, n (%)			
< 65 years	13 (61.9%)	52 (42.6%)	65 (45.5%)
65 - <75 years	6 (28.6%)	51 (41.8%)	57 (39.9%)
≥75 years	2 (9.5%)	19 (15.6%)	21 (14.7%)
Mean (SD)	62.0 (9.85)	65.5 (8.73)	65.0 (8.95)
Median	59.0	67.0	67.0
Range	(46; 80)	(47; 86)	(46; 86)
Sex			
N	21	122	143
Female	8 (38.1%)	57 (46.7%)	65 (45.5%)
Male	13 (61.9%)	65 (53.3%)	78 (54.5%)
Race			
N	21	122	143
Asian	0	1 (0.8%)	1 (0.7%)
Black or African American	4 (19.0%)	8 (6.6%)	12 (8.4%)
White	16 (76.2%)	112 (91.8%)	128 (89.5%)
Not reported	1 (4.8%)	1 (0.8%)	2 (1.4%)
Ethnicity			
N	21	122	143
Hispanic or Latino	4 (19.0%)	7 (5.7%)	11 (7.7%)
Not Hispanic or Latino	17 (81.0%)	115 (94.3%)	132 (92.3%)
Weight, kg			
N	21	122	143
Mean (SD)	84.95 (22.067)	73.91 (17.573)	75.53 (18.630)
Median	87.50	69.70	72.00
Range	(41.3; 123.6)	(45.0; 126.0)	(41.3; 126.0)
Height, cm			
N	20	121	141
Mean (SD)	168.97 (9.687)	166.99 (9.225)	167.27 (9.282)
Median	169.50	167.00	167.60
Range	(149.0; 185.4)	(147.0; 192.0)	(147.0; 192.0)
Baseline ECOG score			
N	21	122	143
0	10 (47.6%)	34 (27.9%)	44 (30.8%)
1	11 (52.4%)	75 (61.5%)	86 (60.1%)
2	0	13 (10.7%)	13 (9.1%)

Key: ECOG = Eastern Cooperative Oncology Group; RP2D = recommended Phase 2 dose
Note: N's for each parameter reflect non-missing values.

Table 16. Summary of baseline disease characteristics; All treated analysis set (Study 64407564MMY1001; 400 ug/kg weekly subcutaneous)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	21	122	143
Type of myeloma by immunofixation or serum FLC assay			
N	21	122	143
IgG	9 (42.9%)	67 (54.9%)	76 (53.1%)
IgA	4 (19.0%)	19 (15.6%)	23 (16.1%)
IgM	1 (4.8%)	0	1 (0.7%)
IgD	0	0	0
IgE	0	0	0
Light chain	7 (33.3%)	35 (28.7%)	42 (29.4%)
Kappa	3 (14.3%)	17 (13.9%)	20 (14.0%)
Lambda	2 (9.5%)	17 (13.9%)	19 (13.3%)
FLC-Kappa[a]	1 (4.8%)	1 (0.8%)	2 (1.4%)
FLC-Lambda[b]	1 (4.8%)	0	1 (0.7%)
Biclonal	0	1 (0.8%)	1 (0.7%)
Negative immunofixation	0	0	0
Type of measurable disease per IMWG			
N	21	122	143
Serum only	7 (33.3%)	53 (43.4%)	60 (42.0%)
Serum and urine	2 (9.5%)	21 (17.2%)	23 (16.1%)
Urine only	3 (14.3%)	17 (13.9%)	20 (14.0%)
Serum FLC	6 (28.6%)	30 (24.6%)	36 (25.2%)
Not evaluable	3 (14.3%)	1 (0.8%)	4 (2.8%)
ISS staging[c]			
N	21	122	143
I	11 (52.4%)	51 (41.8%)	62 (43.4%)
II	6 (28.6%)	47 (38.5%)	53 (37.1%)
III	4 (19.0%)	24 (19.7%)	28 (19.6%)
R-ISS staging[d]			
N	19	119	138
I	6 (31.6%)	22 (18.5%)	28 (20.3%)
II	11 (57.9%)	85 (71.4%)	96 (69.6%)
III	2 (10.5%)	12 (10.1%)	14 (10.1%)
Time from multiple myeloma diagnosis to first dose (years)			
N	21	122	143
Mean (SD)	6.02 (2.455)	7.43 (3.818)	7.22 (3.677)
Median	5.62	7.08	6.69
Range	(2.0; 11.2)	(1.4; 20.8)	(1.4; 20.8)
Number of lytic bone lesions			
N	21	122	143
None	4 (19.0%)	19 (15.6%)	23 (16.1%)
1-3	7 (33.3%)	16 (13.1%)	23 (16.1%)
4-10	5 (23.8%)	41 (33.6%)	46 (32.2%)
More than 10	5 (23.8%)	46 (37.7%)	51 (35.7%)
Number of extramedullary plasmacytomas			
N	21	122	143
0	12 (57.1%)	98 (80.3%)	110 (76.9%)
≥1	9 (42.9%)	24 (19.7%)	33 (23.1%)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total
% Plasma cells, bone marrow biopsy/aspirate[e]			
N	20	118	138
<5	11 (55.0%)	43 (36.4%)	54 (39.1%)
≥5 - ≤30	5 (25.0%)	47 (39.8%)	52 (37.7%)
>30 - <60	1 (5.0%)	14 (11.9%)	15 (10.9%)
≥60	3 (15.0%)	14 (11.9%)	17 (12.3%)
% Plasma cells, bone marrow biopsy			
N	14	30	44
<5	5 (35.7%)	7 (23.3%)	12 (27.3%)
≥5 - ≤30	5 (35.7%)	11 (36.7%)	16 (36.4%)
≥30 - <60	1 (7.1%)	4 (13.3%)	5 (11.4%)
≥60	3 (21.4%)	8 (26.7%)	11 (25.0%)
% Plasma cells, bone marrow aspirate			
N	20	116	136
<5	11 (55.0%)	46 (39.7%)	57 (41.9%)
≥5 - ≤30	6 (30.0%)	47 (40.5%)	53 (39.0%)
>30 - <60	2 (10.0%)	12 (10.3%)	14 (10.3%)
≥60	1 (5.0%)	11 (9.5%)	12 (8.8%)
Cytogenetic risk			
N	19	113	132
Standard risk	18 (94.7%)	73 (64.6%)	91 (68.9%)
High risk	1 (5.3%)	40 (35.4%)	41 (31.1%)
del(17p)	0	29 (25.7%)	29 (22.0%)
t(4;14)	1 (5.3%)	11 (9.7%)	12 (9.1%)
t(14;16)	0	5 (4.4%)	5 (3.8%)
Bone marrow cellularity by biopsy			
N	15	32	47
Hypercellular	4 (26.7%)	10 (31.3%)	14 (29.8%)
Normocellular	7 (46.7%)	7 (21.9%)	14 (29.8%)
Hypocellular	2 (13.3%)	7 (21.9%)	9 (19.1%)
Indeterminate	2 (13.3%)	8 (25.0%)	10 (21.3%)
Tumor GPRC5D expression			
N	18	117	135
Mean (SD)	87.52 (11.641)	96.65 (4.792)	95.43 (6.839)
Median	92.80	98.50	98.10
Range	(61.9; 98.7)	(74.7; 100.0)	(61.9; 100.0)

Key: FLC = free light chain; ISS = international staging system; R-ISS = revised international staging system; NE = not evaluable; RP2D = recommended Phase 2 dose; IMWG = international myeloma working group; GPRC5D = G protein-coupled receptor family C group 5-member D

[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 will be derived based on the combination of serum β2-microglobulin and albumin, genetic risk, and the 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 are calculated with the number of subjects in the All Treated Analysis Set as denominator.

Table 17. Summary of prior therapies for multiple myeloma; All treated analysis set (Study 64407564MMY1001; 400 ug/kg weekly subcutaneous)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	21	122	143
Total number of subjects with any prior therapies for multiple myeloma	21 (100.0%)	122 (100.0%)	143 (100.0%)
Number of prior lines of therapy[a]			
N	21	122	143
Category			
2	1 (4.8%)	0	1 (0.7%)
3	3 (14.3%)	22 (18.0%)	25 (17.5%)
4	5 (23.8%)	33 (27.0%)	38 (26.6%)
5	2 (9.5%)	26 (21.3%)	28 (19.6%)
> 5	10 (47.6%)	41 (33.6%)	51 (35.7%)
Mean (SD)	5.7 (2.88)	5.2 (2.00)	5.3 (2.15)
Median	5.0	5.0	5.0
Range	(2; 13)	(3; 13)	(2; 13)
Prior PI	21 (100.0%)	122 (100.0%)	143 (100.0%)
Bortezomib	20 (95.2%)	118 (96.7%)	138 (96.5%)
Carfilzomib	17 (81.0%)	90 (73.8%)	107 (74.8%)
Ixazomib	7 (33.3%)	27 (22.1%)	34 (23.8%)
Prior IMiD	21 (100.0%)	122 (100.0%)	143 (100.0%)
Lenalidomide	21 (100.0%)	121 (99.2%)	142 (99.3%)
Pomalidomide	20 (95.2%)	104 (85.2%)	124 (86.7%)
Thalidomide	6 (28.6%)	66 (54.1%)	72 (50.3%)
Prior anti-CD38	21 (100.0%)	122 (100.0%)	143 (100.0%)
Daratumumab	21 (100.0%)	119 (97.5%)	140 (97.9%)
Isatuximab	0	12 (9.8%)	12 (8.4%)
Prior Selinexor	3 (14.3%)	12 (9.8%)	15 (10.5%)
Prior Melphalan Flufenamide	0	2 (1.6%)	2 (1.4%)
Prior Belantamab	1 (4.8%)	21 (17.2%)	22 (15.4%)
Prior Elotuzumab	7 (33.3%)	7 (5.7%)	14 (9.8%)
Prior Panobinostat	3 (14.3%)	0	3 (2.1%)
Prior PI+IMiD	21 (100.0%)	122 (100.0%)	143 (100.0%)
Prior PI+IMiD+anti-CD38	21 (100.0%)	122 (100.0%)	143 (100.0%)
Prior penta-exposed	17 (81.0%)	88 (72.1%)	105 (73.4%)
Prior transplantation	18 (85.7%)	95 (77.9%)	113 (79.0%)
Autologous	18 (85.7%)	94 (77.0%)	112 (78.3%)
1	15 (71.4%)	68 (55.7%)	83 (58.0%)
≥ 2	3 (14.3%)	26 (21.3%)	29 (20.3%)
Allogenic	2 (9.5%)	7 (5.7%)	9 (6.3%)
Prior radiotherapy	9 (42.9%)	55 (45.1%)	64 (44.8%)
Prior cancer-related surgery/procedure	3 (14.3%)	21 (17.2%)	24 (16.8%)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total

Key: PI = proteasome inhibitor; IMiD = immunomodulatory imide drug; 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.

Table 18. Summary of refractory status to prior multiple myeloma therapy; all treated analysis set (Study 64407564MMY1001; 400 ug/kg weekly subcutaneous)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	21	122	143
Refractory at any point to prior therapy	21 (100.0%)	122 (100.0%)	143 (100.0%)
Refractory status			
Any PI	16 (76.2%)	98 (80.3%)	114 (79.7%)
Any IMiD	20 (95.2%)	113 (92.6%)	133 (93.0%)
Any anti-CD38 antibody	21 (100.0%)	112 (91.8%)	133 (93.0%)
Double (PI+IMiD)	15 (71.4%)	95 (77.9%)	110 (76.9%)
Triple (PI+IMiD+anti-CD38 antibody)	15 (71.4%)	91 (74.6%)	106 (74.1%)
Penta (2 PI, 2 IMiD, anti-CD38 antibody)	5 (23.8%)	37 (30.3%)	42 (29.4%)
Refractory to last line of prior therapy	20 (95.2%)	114 (93.4%)	134 (93.7%)
Refractory to			
Bortezomib	7 (33.3%)	57 (46.7%)	64 (44.8%)
Carfilzomib	14 (66.7%)	74 (60.7%)	88 (61.5%)
Ixazomib	3 (14.3%)	21 (17.2%)	24 (16.8%)
Lenalidomide	16 (76.2%)	98 (80.3%)	114 (79.7%)
Pomalidomide	19 (90.5%)	89 (73.0%)	108 (75.5%)
Thalidomide	0	11 (9.0%)	11 (7.7%)
Daratumumab	21 (100.0%)	106 (86.9%)	127 (88.8%)
Isatuximab	0	12 (9.8%)	12 (8.4%)
Selinexor	2 (9.5%)	11 (9.0%)	13 (9.1%)
Melphalan Flufenamide	0	2 (1.6%)	2 (1.4%)
Belantamab	1 (4.8%)	17 (13.9%)	18 (12.6%)
Elotuzumab	6 (28.6%)	7 (5.7%)	13 (9.1%)
Panobinostat	2 (9.5%)	0	2 (1.4%)

Key: PI = proteasome inhibitor; IMiD = immunomodulatory imide drug; 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.

0.8mg/kg Q2W regimen

Table 19. Summary of demographics and baseline characteristics; all treated analysis set (Study 64407564MMY1001; 800 ug/kg every 2 weeks subcutaneous)

	RP2D: 800 ug/kg Every 2 Weeks Subcutaneous		
	Phase 1	Phase 2 Cohort C	Total
Analysis set: All Treated	36	109	145
Age, years			

	RP2D: 800 ug/kg Every 2 Weeks Subcutaneous		
	Phase 1	Phase 2 Cohort C	Total
N	36	109	145
Category, n (%)			
< 65 years	18 (50.0%)	45 (41.3%)	63 (43.4%)
65 - <75 years	13 (36.1%)	37 (33.9%)	50 (34.5%)
≥75 years	5 (13.9%)	27 (24.8%)	32 (22.1%)
Mean (SD)	64.3 (10.20)	65.4 (10.39)	65.1 (10.32)
Median	65.5	67.0	67.0
Range	(47; 84)	(38; 82)	(38; 84)
Sex			
N	36	109	145
Female	20 (55.6%)	42 (38.5%)	62 (42.8%)
Male	16 (44.4%)	67 (61.5%)	83 (57.2%)
Race			
N	36	109	145
Asian	2 (5.6%)	4 (3.7%)	6 (4.1%)
Black or African American	2 (5.6%)	7 (6.4%)	9 (6.2%)
Native Hawaiian or Other Pacific Islander	0	1 (0.9%)	1 (0.7%)
White	30 (83.3%)	95 (87.2%)	125 (86.2%)
Multiple	0	1 (0.9%)	1 (0.7%)
Unknown	0	1 (0.9%)	1 (0.7%)
Not reported	2 (5.6%)	0	2 (1.4%)
Ethnicity			
N	36	109	145
Hispanic or Latino	4 (11.1%)	13 (11.9%)	17 (11.7%)
Not Hispanic or Latino	31 (86.1%)	96 (88.1%)	127 (87.6%)
Not reported	1 (2.8%)	0	1 (0.7%)
Weight, kg			
N	36	109	145
Mean (SD)	72.25 (18.910)	76.91 (15.061)	75.75 (16.159)
Median	69.00	75.00	74.00
Range	(47.1; 133.6)	(50.0; 112.2)	(47.1; 133.6)
Height, cm			
N	33	108	141
Mean (SD)	164.85 (12.687)	168.86 (9.395)	167.92 (10.352)
Median	165.10	170.00	168.00
Range	(140.0; 193.0)	(148.0; 188.0)	(140.0; 193.0)
Baseline ECOG score			
N	36	109	145
0	19 (52.8%)	37 (33.9%)	56 (38.6%)
1	17 (47.2%)	64 (58.7%)	81 (55.9%)
2	0	8 (7.3%)	8 (5.5%)

Key: ECOG = Eastern Cooperative Oncology Group; RP2D = recommended Phase 2 dose
Note: N's for each parameter reflect non-missing values.

Table 20. Summary of baseline disease characteristics; all treated analysis set (Study 64407564MMY1001; 800 ug/kg every 2 weeks subcutaneous)

	RP2D: 800 ug/kg Every 2 Weeks Subcutaneous		
	Phase 1	Phase 2 Cohort C	Total
Analysis set: All Treated	36	109	145
Type of myeloma by immunofixation or serum FLC assay			
N	36	109	145
IgG	12 (33.3%)	65 (59.6%)	77 (53.1%)
IgA	7 (19.4%)	19 (17.4%)	26 (17.9%)
IgM	0	0	0
IgD	1 (2.8%)	1 (0.9%)	2 (1.4%)
IgE	0	0	0
Light chain	14 (38.9%)	24 (22.0%)	38 (26.2%)
Kappa	4 (11.1%)	11 (10.1%)	15 (10.3%)
Lambda	8 (22.2%)	9 (8.3%)	17 (11.7%)
FLC-Kappa[a]	1 (2.8%)	3 (2.8%)	4 (2.8%)
FLC-Lambda[b]	1 (2.8%)	1 (0.9%)	2 (1.4%)
Biclonal	2 (5.6%)	0	2 (1.4%)
Negative immunofixation	0	0	0
Type of measurable disease per IMWG			
N	36	109	145
Serum only	11 (30.6%)	60 (55.0%)	71 (49.0%)
Serum and urine	3 (8.3%)	9 (8.3%)	12 (8.3%)
Urine only	6 (16.7%)	15 (13.8%)	21 (14.5%)
Serum FLC	13 (36.1%)	25 (22.9%)	38 (26.2%)
Not evaluable	3 (8.3%)	0	3 (2.1%)
ISS staging[c]			
N	35	109	144
I	17 (48.6%)	47 (43.1%)	64 (44.4%)
II	11 (31.4%)	34 (31.2%)	45 (31.3%)
III	7 (20.0%)	28 (25.7%)	35 (24.3%)
R-ISS staging[d]			
N	35	103	138
I	11 (31.4%)	22 (21.4%)	33 (23.9%)
II	21 (60.0%)	65 (63.1%)	86 (62.3%)
III	3 (8.6%)	16 (15.5%)	19 (13.8%)
Time from multiple myeloma diagnosis to first dose (years)			
N	36	109	145
Mean (SD)	6.90 (4.578)	7.54 (4.762)	7.38 (4.710)
Median	6.02	6.45	6.38
Range	(0.8; 21.3)	(1.1; 25.4)	(0.8; 25.4)
Number of lytic bone lesions			
N	36	107	143
None	7 (19.4%)	20 (18.7%)	27 (18.9%)
1-3	12 (33.3%)	19 (17.8%)	31 (21.7%)
4-10	12 (33.3%)	22 (20.6%)	34 (23.8%)
More than 10	5 (13.9%)	46 (43.0%)	51 (35.7%)
Number of extramedullary plasmacytomas			
N	36	109	145
0	25 (69.4%)	81 (74.3%)	106 (73.1%)
≥1	11 (30.6%)	28 (25.7%)	39 (26.9%)

	RP2D: 800 ug/kg Every 2 Weeks Subcutaneous		
	Phase 1	Phase 2 Cohort C	Total
% Plasma cells, bone marrow biopsy/aspirate[e]			
N	34	107	141
<5	11 (32.4%)	26 (24.3%)	37 (26.2%)
≥5 - ≤30	11 (32.4%)	35 (32.7%)	46 (32.6%)
>30 - <60	7 (20.6%)	19 (17.8%)	26 (18.4%)
≥60	5 (14.7%)	27 (25.2%)	32 (22.7%)
% Plasma cells, bone marrow biopsy			
N	27	57	84
<5	10 (37.0%)	11 (19.3%)	21 (25.0%)
≥5 - ≤30	8 (29.6%)	13 (22.8%)	21 (25.0%)
>30 - <60	6 (22.2%)	13 (22.8%)	19 (22.6%)
≥60	3 (11.1%)	20 (35.1%)	23 (27.4%)
% Plasma cells, bone marrow aspirate			
N	31	101	132
<5	11 (35.5%)	31 (30.7%)	42 (31.8%)
≥5 - ≤30	10 (32.3%)	42 (41.6%)	52 (39.4%)
>30 - <60	7 (22.6%)	14 (13.9%)	21 (15.9%)
≥60	3 (9.7%)	14 (13.9%)	17 (12.9%)
Cytogenetic risk			
N	34	94	128
Standard risk	28 (82.4%)	63 (67.0%)	91 (71.1%)
High risk	6 (17.6%)	31 (33.0%)	37 (28.9%)
del(17p)	4 (11.8%)	21 (22.3%)	25 (19.5%)
t(4;14)	3 (8.8%)	11 (11.7%)	14 (10.9%)
t(14;16)	0	6 (6.4%)	6 (4.7%)
Bone marrow cellularity by biopsy			
N	28	47	75
Hypercellular	8 (28.6%)	16 (34.0%)	24 (32.0%)
Normocellular	13 (46.4%)	17 (36.2%)	30 (40.0%)
Hypocellular	2 (7.1%)	5 (10.6%)	7 (9.3%)
Indeterminate	5 (17.9%)	9 (19.1%)	14 (18.7%)
Tumor GPRC5D expression			
N	28	94	122
Mean (SD)	86.26 (11.687)	95.11 (7.695)	93.08 (9.484)
Median	89.65	98.15	96.60
Range	(48.7; 98.7)	(55.4; 100.0)	(48.7; 100.0)

Key: FLC = free light chain; ISS = international staging system; R-ISS = revised international staging system; NE = not evaluable; RP2D = recommended Phase 2 dose; IMWG = international myeloma working group; GPRC5D = G protein-coupled receptor family C group 5-member D

[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 will be derived based on the combination of serum β2-microglobulin and albumin, genetic risk, and the 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 are calculated with the number of subjects in the All Treated Analysis Set as denominator.

Table 21. Summary of prior therapies for multiple myeloma; all treated analysis set (Study 64407564MMY1001; 800 ug/kg every 2 weeks subcutaneous)

	RP2D: 800 ug/kg Every 2 Weeks Subcutaneous		
	Phase 1	Phase 2 Cohort C	Total
Analysis set: All Treated	36	109	145
Total number of subjects with any prior therapies for multiple myeloma	36 (100.0%)	109 (100.0%)	145 (100.0%)
Number of prior lines of therapy[a]			
N	36	109	145
Category			
2	3 (8.3%)	0	3 (2.1%)
3	7 (19.4%)	22 (20.2%)	29 (20.0%)
4	10 (27.8%)	27 (24.8%)	37 (25.5%)
5	3 (8.3%)	14 (12.8%)	17 (11.7%)
> 5	13 (36.1%)	46 (42.2%)	59 (40.7%)
Mean (SD)	5.6 (3.70)	5.3 (1.99)	5.4 (2.52)
Median	4.0	5.0	5.0
Range	(2; 17)	(3; 12)	(2; 17)
Prior PI	36 (100.0%)	109 (100.0%)	145 (100.0%)
Bortezomib	33 (91.7%)	109 (100.0%)	142 (97.9%)
Carfilzomib	28 (77.8%)	73 (67.0%)	101 (69.7%)
Ixazomib	6 (16.7%)	20 (18.3%)	26 (17.9%)
Prior IMiD	36 (100.0%)	109 (100.0%)	145 (100.0%)
Lenalidomide	36 (100.0%)	108 (99.1%)	144 (99.3%)
Pomalidomide	33 (91.7%)	80 (73.4%)	113 (77.9%)
Thalidomide	10 (27.8%)	52 (47.7%)	62 (42.8%)
Prior anti-CD38	36 (100.0%)	109 (100.0%)	145 (100.0%)
Daratumumab	36 (100.0%)	108 (99.1%)	144 (99.3%)
Isatuximab	2 (5.6%)	13 (11.9%)	15 (10.3%)
Prior Selinexor	5 (13.9%)	15 (13.8%)	20 (13.8%)
Prior Melphalan Flufenamide	0	3 (2.8%)	3 (2.1%)
Prior Belantamab	4 (11.1%)	12 (11.0%)	16 (11.0%)
Prior Elotuzumab	7 (19.4%)	24 (22.0%)	31 (21.4%)
Prior Panobinostat	1 (2.8%)	3 (2.8%)	4 (2.8%)
Prior PI+IMiD	36 (100.0%)	109 (100.0%)	145 (100.0%)
Prior PI+IMiD+anti-CD38	36 (100.0%)	109 (100.0%)	145 (100.0%)
Prior penta-exposed	24 (66.7%)	77 (70.6%)	101 (69.7%)
Prior transplantation	28 (77.8%)	86 (78.9%)	114 (78.6%)
Autologous	28 (77.8%)	86 (78.9%)	114 (78.6%)
1	26 (72.2%)	52 (47.7%)	78 (53.8%)
⩾ 2	2 (5.6%)	34 (31.2%)	36 (24.8%)
Allogenic	0	2 (1.8%)	2 (1.4%)
Prior radiotherapy	12 (33.3%)	48 (44.0%)	60 (41.4%)
Prior cancer-related surgery/procedure	5 (13.9%)	18 (16.5%)	23 (15.9%)

	RP2D: 800 ug/kg Every 2 Weeks Subcutaneous		
	Phase 1	Phase 2 Cohort C	Total

Key: PI = proteasome inhibitor; IMiD = immunomodulatory imide drug; 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.

Table 22. Summary of refractory status to prior multiple myeloma therapy; all treated analysis set (Study 64407564MMY1001; 800 ug/kg every 2 weeks subcutaneous)

	RP2D: 800 ug/kg Every 2 Weeks Subcutaneous		
	Phase 1	Phase 2 Cohort C	Total
Analysis set: All Treated	36	109	145
Refractory at any point to prior therapy	36 (100.0%)	109 (100.0%)	145 (100.0%)
Refractory status			
Any PI	27 (75.0%)	93 (85.3%)	120 (82.8%)
Any IMiD	34 (94.4%)	96 (88.1%)	130 (89.7%)
Any anti-CD38 antibody	35 (97.2%)	99 (90.8%)	134 (92.4%)
Double (PI+IMiD)	25 (69.4%)	83 (76.1%)	108 (74.5%)
Triple (PI+IMiD+anti-CD38 antibody)	25 (69.4%)	75 (68.8%)	100 (69.0%)
Penta (2 PI, 2 IMiD, anti-CD38 antibody)	7 (19.4%)	27 (24.8%)	34 (23.4%)
Refractory to last line of prior therapy	33 (91.7%)	104 (95.4%)	137 (94.5%)
Refractory to			
Bortezomib	14 (38.9%)	64 (58.7%)	78 (53.8%)
Carfilzomib	20 (55.6%)	52 (47.7%)	72 (49.7%)
Ixazomib	2 (5.6%)	18 (16.5%)	20 (13.8%)
Lenalidomide	24 (66.7%)	78 (71.6%)	102 (70.3%)
Pomalidomide	31 (86.1%)	67 (61.5%)	98 (67.6%)
Thalidomide	2 (5.6%)	16 (14.7%)	18 (12.4%)
Daratumumab	35 (97.2%)	94 (86.2%)	129 (89.0%)
Isatuximab	0	13 (11.9%)	13 (9.0%)
Selinexor	3 (8.3%)	11 (10.1%)	14 (9.7%)
Melphalan Flufenamide	0	2 (1.8%)	2 (1.4%)
Belantamab	2 (5.6%)	11 (10.1%)	13 (9.0%)
Elotuzumab	5 (13.9%)	20 (18.3%)	25 (17.2%)
Panobinostat	1 (2.8%)	3 (2.8%)	4 (2.8%)

Key: PI = proteasome inhibitor; IMiD = immunomodulatory imide drug; 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.

Prior T cell redirection therapy

Table 23. Summary of demographics and baseline characteristics; all treated analysis set (Study 64407564MMY1001; T-cell redirection therapy)

	RP2D: 400 ug/kg Weekly Subcutaneous		RP2D: 800 ug/kg Every 2 Weeks Subcutaneous	
	Phase 1	Phase 2 Cohort B	Phase 1	Total
Analysis set: All Treated	9	34	8	51
Age, years				
N	9	34	8	51
Category, n (%)				
< 65 years	3 (33.3%)	24 (70.6%)	6 (75.0%)	33 (64.7%)
65 - <75 years	6 (66.7%)	7 (20.6%)	1 (12.5%)	14 (27.5%)
≥75 years	0	3 (8.8%)	1 (12.5%)	4 (7.8%)
Mean (SD)	64.7 (6.78)	60.1 (8.93)	61.5 (9.15)	61.1 (8.64)
Median	68.0	60.0	62.5	61.0
Range	(51; 73)	(38; 78)	(49; 75)	(38; 78)
Sex				
N	9	34	8	51
Female	3 (33.3%)	14 (41.2%)	3 (37.5%)	20 (39.2%)
Male	6 (66.7%)	20 (58.8%)	5 (62.5%)	31 (60.8%)
Race				
N	9	34	8	51
Asian	0	0	1 (12.5%)	1 (2.0%)
Black or African American	0	1 (2.9%)	2 (25.0%)	3 (5.9%)
White	9 (100.0%)	33 (97.1%)	5 (62.5%)	47 (92.2%)
Ethnicity				
N	9	34	8	51
Hispanic or Latino	1 (11.1%)	1 (2.9%)	1 (12.5%)	3 (5.9%)
Not Hispanic or Latino	8 (88.9%)	33 (97.1%)	6 (75.0%)	47 (92.2%)
Not reported	0	0	1 (12.5%)	1 (2.0%)
Weight, kg				
N	9	34	8	51
Mean (SD)	82.64 (17.059)	79.51 (17.518)	72.66 (16.081)	78.99 (17.156)
Median	77.50	76.85	73.25	77.30
Range	(59.0; 121.5)	(51.0; 119.6)	(40.2; 91.0)	(40.2; 121.5)
Height, cm				
N	9	34	8	51
Mean (SD)	171.84 (7.303)	170.30 (10.258)	167.36 (13.898)	170.11 (10.334)
Median	173.60	170.00	168.65	170.00
Range	(161.5; 180.3)	(145.0; 193.0)	(143.0; 186.0)	(143.0; 193.0)
Baseline ECOG score				
N	9	34	8	51
0	5 (55.6%)	15 (44.1%)	2 (25.0%)	22 (43.1%)
1	4 (44.4%)	18 (52.9%)	6 (75.0%)	28 (54.9%)
2	0	1 (2.9%)	0	1 (2.0%)

Key: ECOG = Eastern Cooperative Oncology Group; RP2D = recommended Phase 2 dose
Note: N's for each parameter reflect non-missing values.

Table 24. Summary baseline disease characteristics; all treated analysis set (Study 64407564MMY1001; T-cell redirection therapy)

	RP2D: 400 ug/kg Weekly Subcutaneous		RP2D: 800 ug/kg Every 2 Weeks Subcutaneous	
	Phase 1	Phase 2 Cohort B	Phase 1	Total
Analysis set: All Treated	9	34	8	51
Type of myeloma by immunofixation or serum FLC assay				
N	9	34	8	51
IgG	1 (11.1%)	13 (38.2%)	4 (50.0%)	18 (35.3%)
IgA	2 (22.2%)	6 (17.6%)	1 (12.5%)	9 (17.6%)
IgM	0	0	0	0
IgD	0	0	0	0
IgE	0	0	0	0
Light chain	6 (66.7%)	15 (44.1%)	3 (37.5%)	24 (47.1%)
Kappa	5 (55.6%)	6 (17.6%)	0	11 (21.6%)
Lambda	1 (11.1%)	9 (26.5%)	3 (37.5%)	13 (25.5%)
FLC-Kappa[a]	0	0	0	0
FLC-Lambda[b]	0	0	0	0
Biclonal	0	0	0	0
Negative immunofixation	0	0	0	0
Type of measurable disease per IMWG				
N	9	34	8	51
Serum only	1 (11.1%)	12 (35.3%)	2 (25.0%)	15 (29.4%)
Serum and urine	1 (11.1%)	3 (8.8%)	0	4 (7.8%)
Urine only	4 (44.4%)	8 (23.5%)	1 (12.5%)	13 (25.5%)
Serum FLC	3 (33.3%)	11 (32.4%)	5 (62.5%)	19 (37.3%)
Not evaluable	0	0	0	0
ISS staging[c]				
N	9	34	8	51
I	4 (44.4%)	16 (47.1%)	4 (50.0%)	24 (47.1%)
II	4 (44.4%)	12 (35.3%)	2 (25.0%)	18 (35.3%)
III	1 (11.1%)	6 (17.6%)	2 (25.0%)	9 (17.6%)
R-ISS staging[d]				
N	9	31	7	47
I	4 (44.4%)	3 (9.7%)	1 (14.3%)	8 (17.0%)
II	4 (44.4%)	25 (80.6%)	4 (57.1%)	33 (70.2%)
III	1 (11.1%)	3 (9.7%)	2 (28.6%)	6 (12.8%)
Time from multiple myeloma diagnosis to first dose (years)				

	RP2D: 400 ug/kg Weekly Subcutaneous		RP2D: 800 ug/kg Every 2 Weeks Subcutaneous	
	Phase 1	Phase 2 Cohort B	Phase 1	Total
Number of extramedullary plasmacytomas				
N	9	34	8	51
0	7 (77.8%)	24 (70.6%)	4 (50.0%)	35 (68.6%)
≥1	2 (22.2%)	10 (29.4%)	4 (50.0%)	16 (31.4%)
% Plasma cells, bone marrow biopsy/aspirate[e]				
N	9	29	8	46
<5	2 (22.2%)	9 (31.0%)	6 (75.0%)	17 (37.0%)
≥5 - ≤30	2 (22.2%)	13 (44.8%)	1 (12.5%)	16 (34.8%)
>30 - <60	2 (22.2%)	3 (10.3%)	1 (12.5%)	6 (13.0%)
≥60	3 (33.3%)	4 (13.8%)	0	7 (15.2%)
% Plasma cells, bone marrow biopsy				
N	6	19	4	29
<5	0	5 (26.3%)	3 (75.0%)	8 (27.6%)
≥5 - ≤30	2 (33.3%)	11 (57.9%)	1 (25.0%)	14 (48.3%)
>30 - <60	2 (33.3%)	1 (5.3%)	0	3 (10.3%)
≥60	2 (33.3%)	2 (10.5%)	0	4 (13.8%)
% Plasma cells, bone marrow aspirate				
N	8	23	6	37
<5	3 (37.5%)	8 (34.8%)	5 (83.3%)	16 (43.2%)
≥5 - ≤30	1 (12.5%)	10 (43.5%)	0	11 (29.7%)
>30 - <60	2 (25.0%)	2 (8.7%)	1 (16.7%)	5 (13.5%)
≥60	2 (25.0%)	3 (13.0%)	0	5 (13.5%)
Cytogenetic risk				
N	8	30	6	44
Standard risk	7 (87.5%)	16 (53.3%)	3 (50.0%)	26 (59.1%)
High risk	1 (12.5%)	14 (46.7%)	3 (50.0%)	18 (40.9%)
del(17p)	1 (12.5%)	11 (36.7%)	3 (50.0%)	15 (34.1%)
t(4;14)	0	4 (13.3%)	0	4 (9.1%)
t(14;16)	0	1 (3.3%)	0	1 (2.3%)
Bone marrow cellularity by biopsy				
N	6	20	4	30
Hypercellular	0	5 (25.0%)	1 (25.0%)	6 (20.0%)
Normocellular	4 (66.7%)	7 (35.0%)	3 (75.0%)	14 (46.7%)
Hypocellular	1 (16.7%)	6 (30.0%)	0	7 (23.3%)
Indeterminate	1 (16.7%)	2 (10.0%)	0	3 (10.0%)
Tumor GPRC5D expression				
N	7	29	7	43
Mean (SD)	78.94 (29.152)	83.14 (20.385)	80.04 (12.818)	81.95 (20.616)
Median	86.60	90.90	85.00	86.60
Range	(17.5; 99.8)	(19.8; 99.7)	(55.9; 95.5)	(17.5; 99.8)

Key: RP2D = recommended Phase 2 dose; FLC = free light chain; ISS = international staging system; R-ISS = revised international staging system; NE = not evaluable; IMWG = international myeloma working group; GPRC5D = G protein-coupled receptor family C group 5-member D

[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 will be derived based on the combination of serum β2-microglobulin and albumin, genetic risk, and the 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 are calculated with the number of subjects in the All Treated Analysis Set as denominator.

Table 25. Summary of prior therapies for multiple myeloma; All treated analysis set (Study 64407564MMY1001; T-cell redirection therapy)

	RP2D: 400 ug/kg Weekly Subcutaneous		RP2D: 800 ug/kg Every 2 Weeks Subcutaneous	
	Phase 1	Phase 2 Cohort B	Phase 1	Total
Analysis set: All Treated	9	34	8	51
Total number of subjects with any prior therapies for multiple myeloma	9 (100.0%)	34 (100.0%)	8 (100.0%)	51 (100.0%)
Number of prior lines of therapy[a]				
N	9	34	8	51
Category				
2	0	0	0	0
3	1 (11.1%)	2 (5.9%)	1 (12.5%)	4 (7.8%)
4	1 (11.1%)	6 (17.6%)	0	7 (13.7%)
5	1 (11.1%)	4 (11.8%)	2 (25.0%)	7 (13.7%)
> 5	6 (66.7%)	22 (64.7%)	5 (62.5%)	33 (64.7%)
Mean (SD)	7.0 (3.35)	6.9 (2.96)	7.3 (3.15)	7.0 (3.00)
Median	6.0	6.0	6.5	6.0
Range	(3; 14)	(3; 15)	(3; 12)	(3; 15)
Prior PI	9 (100.0%)	34 (100.0%)	8 (100.0%)	51 (100.0%)
Bortezomib	8 (88.9%)	34 (100.0%)	8 (100.0%)	50 (98.0%)
Carfilzomib	7 (77.8%)	27 (79.4%)	7 (87.5%)	41 (80.4%)
Ixazomib	2 (22.2%)	6 (17.6%)	2 (25.0%)	10 (19.6%)
Prior IMiD	9 (100.0%)	34 (100.0%)	8 (100.0%)	51 (100.0%)
Lenalidomide	9 (100.0%)	34 (100.0%)	8 (100.0%)	51 (100.0%)
Pomalidomide	7 (77.8%)	31 (91.2%)	7 (87.5%)	45 (88.2%)
Thalidomide	2 (22.2%)	12 (35.3%)	2 (25.0%)	16 (31.4%)
Prior anti-CD38	9 (100.0%)	34 (100.0%)	8 (100.0%)	51 (100.0%)
Daratumumab	9 (100.0%)	32 (94.1%)	8 (100.0%)	49 (96.1%)
Isatuximab	0	4 (11.8%)	0	4 (7.8%)
Prior Selinexor	1 (11.1%)	5 (14.7%)	1 (12.5%)	7 (13.7%)
Prior Melphalan Flufenamide	0	0	0	0
Prior CAR-T cell therapy	5 (55.6%)	28 (82.4%)	5 (62.5%)	38 (74.5%)
Prior Belantamab	0	6 (17.6%)	0	6 (11.8%)
Prior bispecific antibody treatment	5 (55.6%)	8 (23.5%)	3 (37.5%)	16 (31.4%)
Prior Elotuzumab	2 (22.2%)	9 (26.5%)	2 (25.0%)	13 (25.5%)
Prior Panobinostat	1 (11.1%)	3 (8.8%)	1 (12.5%)	5 (9.8%)
Prior PI+IMiD	9 (100.0%)	34 (100.0%)	8 (100.0%)	51 (100.0%)
Prior PI+IMiD+anti-CD38	9 (100.0%)	34 (100.0%)	8 (100.0%)	51 (100.0%)
Prior penta-exposed	7 (77.8%)	26 (76.5%)	7 (87.5%)	40 (78.4%)
Prior transplantation	9 (100.0%)	31 (91.2%)	5 (62.5%)	45 (88.2%)
Autologous	9 (100.0%)	31 (91.2%)	5 (62.5%)	45 (88.2%)
1	8 (88.9%)	19 (55.9%)	3 (37.5%)	30 (58.8%)
≥ 2	1 (11.1%)	12 (35.3%)	2 (25.0%)	15 (29.4%)
Allogenic	1 (11.1%)	1 (2.9%)	1 (12.5%)	3 (5.9%)
Prior radiotherapy	4 (44.4%)	15 (44.1%)	3 (37.5%)	22 (43.1%)

	RP2D: 400 ug/kg Weekly Subcutaneous		RP2D: 800 ug/kg Every 2 Weeks Subcutaneous	
	Phase 1	Phase 2 Cohort B	Phase 1	Total
Prior cancer-related surgery/procedure	0	5 (14.7%)	2 (25.0%)	7 (13.7%)

Key: RP2D = recommended Phase 2 dose; PI = proteasome inhibitor; IMiD = immunomodulatory imide drug
[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.

Table 26. Summary of refractory status to prior multiple myeloma treatment; All treated analysis set (Study 64407564MMY1001; T-cell redirection therapy)

	RP2D: 400 ug/kg Weekly Subcutaneous		RP2D: 800 ug/kg Every 2 Weeks Subcutaneous	
	Phase 1	Phase 2 Cohort B	Phase 1	Total
Analysis set: All Treated	9	34	8	51
Refractory at any point to prior therapy	9 (100.0%)	34 (100.0%)	8 (100.0%)	51 (100.0%)
Refractory status				
Any PI	9 (100.0%)	29 (85.3%)	8 (100.0%)	46 (90.2%)
Any IMiD	8 (88.9%)	33 (97.1%)	8 (100.0%)	49 (96.1%)
Any anti-CD38 antibody	9 (100.0%)	32 (94.1%)	8 (100.0%)	49 (96.1%)
Double (PI+IMiD)	8 (88.9%)	28 (82.4%)	8 (100.0%)	44 (86.3%)
Triple (PI+IMiD+anti-CD38 antibody)	8 (88.9%)	27 (79.4%)	8 (100.0%)	43 (84.3%)
Penta (2 PI, 2 IMiD, anti-CD38 antibody)	1 (11.1%)	16 (47.1%)	4 (50.0%)	21 (41.2%)
Refractory to last line of prior therapy	6 (66.7%)	19 (55.9%)	6 (75.0%)	31 (60.8%)
Refractory to				
Bortezomib	7 (77.8%)	23 (67.6%)	6 (75.0%)	36 (70.6%)
Carfilzomib	5 (55.6%)	23 (67.6%)	7 (87.5%)	35 (68.6%)
Ixazomib	1 (11.1%)	5 (14.7%)	0	6 (11.8%)
Lenalidomide	6 (66.7%)	29 (85.3%)	8 (100.0%)	43 (84.3%)
Pomalidomide	7 (77.8%)	28 (82.4%)	4 (50.0%)	39 (76.5%)
Thalidomide	0	4 (11.8%)	1 (12.5%)	5 (9.8%)
Daratumumab	9 (100.0%)	31 (91.2%)	8 (100.0%)	48 (94.1%)
Isatuximab	0	4 (11.8%)	0	4 (7.8%)
Selinexor	1 (11.1%)	5 (14.7%)	1 (12.5%)	7 (13.7%)
Melphalan Flufenamide	0	0	0	0
Belantamab	0	4 (11.8%)	0	4 (7.8%)
CAR-T cell therapy	2 (22.2%)	4 (11.8%)	1 (12.5%)	7 (13.7%)
Elotuzumab	2 (22.2%)	9 (26.5%)	2 (25.0%)	13 (25.5%)
Panobinostat	1 (11.1%)	3 (8.8%)	0	4 (7.8%)
Bispecific antibody treatment	5 (55.6%)	7 (20.6%)	3 (37.5%)	15 (29.4%)

Key: RP2D = recommended Phase 2 dose; PI = proteasome inhibitor; IMiD = immunomodulatory imide drug
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**

Results are presented according to the following 3 participant groupings:

- 0.4 mg/kg weekly SC RP2D: All participants assigned to 0.4 mg/kg weekly SC, either in Phase 1 or in Phase 2 Cohort A, who had not received prior T cell redirection therapy which included 143 treated participants (21 in Phase 1 and 122 in Phase 2)
- 0.8 mg/kg Q2W SC RP2D: All participants assigned to 0.8 mg/kg Q2W SC, either in Phase 1 or in Phase 2 Cohort C, who had not received prior T cell redirection therapy which included 145 treated participants (36 in Phase 1 and 109 in Phase 2)
- Prior T Cell Redirection Therapy: All participants assigned to 0.4 mg/kg weekly SC in Phase 2 Cohort B, or to either 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC in Phase 1, who had received prior T cell redirection therapy which included 51 treated participants (17 in Phase 1 and 34 in Phase 2).

- **Outcomes and estimation**

The applicant initially submitted results with a cut-off date of 12 September 2022. During the procedure an updated analysis was provided with a cut-off date of 17 January 2023. Results presented in this section are from the 17th of January 2023 cut-off date unless otherwise specified.

0.4mg/Kg SC weekly regimen

Primary endpoint: Overall Response Rate

Table 27. Summary of overall best confirmed response based on independent review committee (IRC) assessment; all treated analysis set (Study 64407564MMY1001; 400 ug/kg weekly subcutaneous)

	RP2D: 400 ug/kg Weekly Subcutaneous					
	Phase 1		Phase 2 Cohort A		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: All Treated	21		122		143	
Response category						
Stringent complete response (sCR)	5 (23.8%)	(8.2%, 47.2%)	29 (23.8%)	(16.5%, 32.3%)	34 (23.8%)	(17.1%, 31.6%)
Complete response (CR)	2 (9.5%)	(1.2%, 30.4%)	12 (9.8%)	(5.2%, 16.6%)	14 (9.8%)	(5.5%, 15.9%)
Very good partial response (VGPR)	7 (33.3%)	(14.6%, 57.0%)	30 (24.6%)	(17.2%, 33.2%)	37 (25.9%)	(18.9%, 33.9%)
Partial response (PR)	1 (4.8%)	(0.1%, 23.8%)	20 (16.4%)	(10.3%, 24.2%)	21 (14.7%)	(9.3%, 21.6%)
Minimal response (MR)	0	(NE, NE)	2 (1.6%)	(0.2%, 5.8%)	2 (1.4%)	(0.2%, 5.0%)
Stable disease (SD)	6 (28.6%)	(11.3%, 52.2%)	18 (14.8%)	(9.0%, 22.3%)	24 (16.8%)	(11.1%, 23.9%)
Progressive disease (PD)	0	(NE, NE)	6 (4.9%)	(1.8%, 10.4%)	6 (4.2%)	(1.6%, 8.9%)
Not evaluable	0	(NE, NE)	5 (4.1%)	(1.3%, 9.3%)	5 (3.5%)	(1.1%, 8.0%)
Overall response (sCR + CR + VGPR + PR)	15 (71.4%)	(47.8%, 88.7%)	91 (74.6%)	(65.9%, 82.0%)	106 (74.1%)	(66.1%, 81.1%)

	RP2D: 400 ug/kg Weekly Subcutaneous					
	Phase 1		Phase 2 Cohort A		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
VGPR or better (sCR + CR + VGPR)	14 (66.7%)	(43.0%, 85.4%)	71 (58.2%)	(48.9%, 67.1%)	85 (59.4%)	(50.9%, 67.6%)
CR or better (sCR + CR)	7 (33.3%)	(14.6%, 57.0%)	41 (33.6%)	(25.3%, 42.7%)	48 (33.6%)	(25.9%, 41.9%)

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 are 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 IRC assessment in prespecified subgroups, including demographic and clinical characteristics, number of prior therapies, refractoriness to prior therapies, and cytogenetic risk at baseline and baseline GPRC5D expression. Talquetamab delivered consistent ORR across clinically relevant subgroups, including number of prior lines of therapy, refractoriness to prior therapy, and cytogenetic risk at baseline except among participants with baseline plasmacytomas (data not shown).

Duration of response

Table 28. Duration of response based on independent review committee (IRC) assessment; responders in all treated analysis set (Study 64407564MMY1001; 400 ug/kg weekly subcutaneous)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: Responders in All Treated Analysis Set	15	91	106
Duration of response (months)[a]			
Number of events (%)	8 (53.3%)	57 (62.6%)	65 (61.3%)
Number of censored (%)	7 (46.7%)	34 (37.4%)	41 (38.7%)
Kaplan-Meier estimate (months)			
25th percentile (95% CI)	5.5 (1.4, 19.8)	4.4 (3.4, 6.2)	4.4 (3.4, 6.2)
Median (95% CI)	19.8 (3.1, NE)	8.8 (6.5, 12.7)	9.5 (6.7, 13.3)
75th percentile (95% CI)	NE (19.8, NE)	NE (NE, NE)	NE (19.8, NE)
Range	(1+, 31+)	(1, 19+)	(1+, 31+)
6-month event-free rate % (95% CI)	69.6 (37.8, 87.4)	66.8 (56.1, 75.5)	67.2 (57.2, 75.3)
9-month event-free rate % (95% CI)	61.9 (31.2, 82.1)	49.9 (39.2, 59.7)	51.5 (41.4, 60.6)
12-month event-free rate % (95% CI)	54.2 (25.0, 76.2)	41.9 (31.6, 51.9)	43.5 (33.8, 52.8)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total

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 or death due to any cause.
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).

Minimal residual disease

table 29. summary of overall mrd negativity rate at 10^{-5} in bone marrow; subjects achieving CR or better by independent review committee (IRC) in the all treated analysis set; all treated analysis set (Study 64407564MMY1001; 400 ug/kg Weekly Subcutaneous)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	21	122	143
MRD Negativity Rate (10^{-5})	3 (14.3%)	41 (33.6%)	44 (30.8%)
95% CI[a] of MRD negative rate	(3.0%, 36.3%)	(25.3%, 42.7%)	(23.3%, 39.0%)
MRD Negativity Rate (10^{-6})	2 (9.5%)	28 (23.0%)	30 (21.0%)
95% CI[a] of MRD negative rate	(1.2%, 30.4%)	(15.8%, 31.4%)	(14.6%, 28.6%)
MRD negativity rate[b] in patients achieving CR or sCR	7	41	48
MRD Negativity Rate (10^{-5})[a]	2 (28.6%)	24 (58.5%)	26 (54.2%)
95% CI[b] of MRD negative rate	(3.7%, 71.0%)	(42.1%, 73.7%)	(39.2%, 68.6%)

Key: CI = confidence interval; MRD = minimal residual disease; RP2D = recommended Phase 2 dose
[a] Exact 95% confidence interval.
Note: MRD status result based on next-generation sequencing (NGS).

Time to response

Table 30. Descriptive summaries for time to response based on independent review committee (IRC) Assessment; responders in the all treated analysis set (Study 64407564MMY1001; 400 ug/kg weekly subcutaneous)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: Responders in All Treated Analysis Set	15	91	106
Time to first response (months)[a]			
N	15	91	106
Mean (SD)	1.41 (1.022)	1.53 (1.256)	1.51 (1.222)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total
Median	0.92	1.15	1.15
Range	(0.2; 3.6)	(0.2; 10.9)	(0.2; 10.9)
Time to best response (months)[a]			
N	15	91	106
Mean (SD)	5.17 (4.063)	3.56 (3.242)	3.79 (3.395)
Median	3.61	2.10	2.23
Range	(0.8; 12.4)	(1.1; 12.7)	(0.8; 12.7)
Time to VGPR or better (months)			
N	14	71	85
Mean (SD)	2.44 (1.504)	2.19 (1.606)	2.23 (1.584)
Median	2.23	1.58	1.87
Range	(0.2; 5.1)	(0.2; 10.9)	(0.2; 10.9)
Time to CR or better (months)			
N	7	41	48
Mean (SD)	8.19 (4.109)	4.76 (3.880)	5.26 (4.057)
Median	9.03	2.20	2.64
Range	(1.7; 12.4)	(1.1; 12.2)	(1.1; 12.4)

Key: RP2D = recommended Phase 2 dose; IRC = independent review committee; VGPR = very good partial response; CR = complete response; PR = partial response; IMWG = international myeloma working group
[a] Response PR or better
Note: Response was assessed by IRC, based on IMWG consensus criteria (2016).

Progression-free survival

At time of updated Cut-off date (17 January 2023), median PFS was 7.5 months (95% CI: 5.7, 9.4) in both overall and Phase 2 populations. The 9-month PFS rate was 43.8% (95% CI: 35.3%, 51.9%) overall and 42.6% (95% CI: 33.6%, 51.3%) in the Phase 2 population.

Overall survival

At time of updated Cut-off date (17 January 2023), 66.4% of participants were censored and results for OS were not mature. The estimated OS rate at 6 months was 88.5% (95% CI: 81.9%, 92.8%) overall and 87.6% (95% CI: 80.2%, 92.3%) in Phase 2. The estimated OS rate at 9 months was 81.0% (95% CI: 73.4%, 86.7%) overall and 79.1% (70.7%, 85.4%) in Phase 2. The estimated OS rate at 12 months was 76.4% (95% CI: 68.3%, 82.7%) overall and 73.9% (65.1%, 80.9%) in Phase 2.

0.8mg/kg Q2W SC

Primary endpoint: Overall response rate

Table 31. Summary of overall best confirmed response based on independent review committee (IRC) assessment; all treated analysis set (Study 64407564MMY1001; 800 ug/kg every 2 weeks subcutaneous)

	RP2D: 800 ug/kg Every 2 Weeks Subcutaneous					
	Phase 1		Phase 2 Cohort C		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: All Treated	36		109		145	
Response category						
Stringent complete response (sCR)	9 (25.0%)	(12.1%, 42.2%)	34 (31.2%)	(22.7%, 40.8%)	43 (29.7%)	(22.4%, 37.8%)
Complete response (CR)	3 (8.3%)	(1.8%, 22.5%)	10 (9.2%)	(4.5%, 16.2%)	13 (9.0%)	(4.9%, 14.8%)
Very good partial response (VGPR)	8 (22.2%)	(10.1%, 39.2%)	24 (22.0%)	(14.6%, 31.0%)	32 (22.1%)	(15.6%, 29.7%)
Partial response (PR)	5 (13.9%)	(4.7%, 29.5%)	11 (10.1%)	(5.1%, 17.3%)	16 (11.0%)	(6.4%, 17.3%)
Minimal response (MR)	0	(NE, NE)	0	(NE, NE)	0	(NE, NE)
Stable disease (SD)	10 (27.8%)	(14.2%, 45.2%)	17 (15.6%)	(9.4%, 23.8%)	27 (18.6%)	(12.6%, 25.9%)
Progressive disease (PD)	1 (2.8%)	(0.1%, 14.5%)	8 (7.3%)	(3.2%, 14.0%)	9 (6.2%)	(2.9%, 11.5%)
Not evaluable	0	(NE, NE)	5 (4.6%)	(1.5%, 10.4%)	5 (3.4%)	(1.1%, 7.9%)
Overall response (sCR + CR + VGPR + PR)	25 (69.4%)	(51.9%, 83.7%)	79 (72.5%)	(63.1%, 80.6%)	104 (71.7%)	(63.7%, 78.9%)
VGPR or better (sCR + CR + VGPR)	20 (55.6%)	(38.1%, 72.1%)	68 (62.4%)	(52.6%, 71.5%)	88 (60.7%)	(52.2%, 68.7%)
CR or better (sCR + CR)	12 (33.3%)	(18.6%, 51.0%)	44 (40.4%)	(31.1%, 50.2%)	56 (38.6%)	(30.7%, 47.1%)
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 are calculated with the number of subjects in the All Treated Analysis Set as denominator. Note: Exact 95% confidence intervals are provided.						

The applicant also provided subgroup Analyses on Overall Response Rate Based on IRC Assessment for the All 0.8mg/Kg Q2 W Treated Analysis Set. No clear difference is observed upon subgroups except for patients with extramedullary plasmacytoma (n=39), down to 30.8% (17,0; 47.6%).

Duration of response

Table 32. Duration of response based on independent review committee (IRC) assessment; Responders in all treated analysis set (Study 64407564MMY1001; 800 ug/kg every 2 weeks subcutaneous)

	RP2D: 800 ug/kg Every 2 Weeks Subcutaneous		
	Phase 1	Phase 2 Cohort C	Total
Analysis set: Responders in All Treated Analysis Set	25	79	104
Duration of response (months)[a]			
Number of events (%)	14 (56.0%)	14 (17.7%)	28 (26.9%)
Number of censored (%)	11 (44.0%)	65 (82.3%)	76 (73.1%)
Kaplan-Meier estimate (months)			
25th percentile (95% CI)	3.7 (0.5, 8.7)	NE (7.4, NE)	9.3 (4.6, NE)
Median (95% CI)	10.6 (3.8, NE)	NE (NE, NE)	NE (13.0, NE)
75th percentile (95% CI)	NE (10.7, NE)	NE (NE, NE)	NE (NE, NE)
Range	(0+, 22+)	(1, 14+)	(0+, 22+)
6-month event-free rate % (95% CI)	66.0 (43.3, 81.3)	87.1 (77.3, 92.8)	82.2 (73.2, 88.4)
9-month event-free rate % (95% CI)	56.8 (34.5, 74.1)	82.7 (72.0, 89.6)	76.3 (66.5, 83.7)
12-month event-free rate % (95% CI)	42.6 (22.2, 61.7)	80.0 (68.0, 87.9)	69.3 (57.8, 78.2)

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 or death due to any cause.
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).

Minimal residual disease

Table 33. Summary of averall MRD negativity rate at 10^{-5} in bone marrow; subjects achieving CR or better by independent review committee (IRC) in the all treated analysis set; All Treated Analysis Set (Study 64407564MMY1001; 800 ug/kg weekly subcutaneous)

	RP2D: 800 ug/kg every 2 Weeks Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: Subjects Achieving CR or better by IRC in the All Treated	36	109	145
MRD Negativity Rate (10^{-5})[a]	3 (8.3%)	40 (36.7%)	43 (29.7%)
95% CI[b] of MRD negative rate	(1.8%, 22.5%)	(19.4%, 36.9%)	(14.4%, 28.2%)
MRD negativity rate[b] in patients achieving CR or sCR	12	44	56
MRD Negativity Rate (10^{-5})[a]	3 (25.0%)	21 (47.7%)	24 (42.9%)

95% CI[b] of MRD negative rate	(5.5%, 57.2%)	(32.5%, 63.3%)	(29.7%, 56.8%)

Key: CI = confidence interval; MRD = minimal residual disease; RP2D = recommended Phase 2 dose; CR=complete response; sCR=stringent complete response
[a] Only MRD assessments (10 -5 testing threshold) within 3 months of achieving CR/sCR until death / progression / subsequent therapy (exclusive) are considered
[b] Exact 95% confidence interval.

Time to response

Table 34. Descriptive summaries for time to response based on independent review committee (IRC) Assessment; responders in all treated analysis set (Study 64407564MMY1001; 800 ug/kg every 2 weeks subcutaneous)

	RP2D: 800 ug/kg Every 2 Weeks Subcutaneous		
	Phase 1	Phase 2 Cohort C	Total
Analysis set: Responders in All Treated Analysis Set	25	79	104
Time to first response (months)[a]			
N	25	79	104
Mean (SD)	1.35 (0.801)	1.61 (1.092)	1.55 (1.032)
Median	1.18	1.28	1.25
Range	(0.2; 3.6)	(0.2; 9.2)	(0.2; 9.2)
Time to best response (months)[a]			
N	25	79	104
Mean (SD)	3.47 (3.145)	4.67 (3.289)	4.38 (3.280)
Median	2.23	3.29	3.04
Range	(0.3; 12.5)	(0.3; 12.9)	(0.3; 12.9)
Time to VGPR or better (months)			
N	20	68	88
Mean (SD)	2.46 (1.669)	2.95 (2.143)	2.84 (2.046)
Median	1.41	2.38	2.22
Range	(1.1; 6.7)	(0.3; 12.7)	(0.3; 12.7)
Time to CR or better (months)			
N	12	44	56
Mean (SD)	4.39 (3.156)	5.30 (2.994)	5.11 (3.024)
Median	2.92	5.36	4.68
Range	(1.9; 12.2)	(1.3; 12.2)	(1.3; 12.2)

Key: RP2D = recommended Phase 2 dose; IRC = independent review committee; VGPR = very good partial response; CR = complete response; PR = partial response; IMWG = international myeloma working group
[a] Response PR or better
Note: Response was assessed by IRC, based on IMWG consensus criteria (2016).

Progression-free survival

With a median follow-up of 12.7 months, the 6-month PFS rate was 63.5% overall (95% CI: 54.9%, 70.9%) overall and 67.9% (95% CI: 58.1%, 75.9%) in Phase 2. The 9-month PFS rate was 58.9% (95% CI: 50.2%, 66.6%) overall and 63.8% (95% CI: 53.8%, 72.2%) in Phase 2.

Overall survival

With a median follow-up of 12.7 months overall, 81.4% of participants were censored and results for OS were not mature. The estimated OS rate at 6 months was 85.% (95% CI: 78.2, 90.1 %) overall and 8260% (95% CI: 78.1%, 91.4 %) in Phase 2. The estimated OS rate at 9 months was 83.0% (95% CI: 75.8%, 88.3%) overall and 84.3% (75.9%, 89.9%) in Phase 2.

Prior T Cell redirection therapy

Additionally, the applicant provided results in patients with prior T Cell Redirection Therapy: All participants assigned to 0.4 mg/kg weekly SC in Phase 2 Cohort B, or to either 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC in Phase 1, who had received prior T cell redirection therapy.

Table 35. Summary of overall best confirmed response based on independent review committee (IRC) assessment; all treated analysis set (Study 64407564MMY1001; T-cell redirection therapy)

	RP2D: 400 ug/kg Weekly Subcutaneous				RP2D: 800 ug/kg Every 2 Weeks Subcutaneous			
	Phase 1		Phase 2 Cohort B		Phase 1		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: All Treated	9		34		8		51	
Response category								
Stringent complete response (sCR)	1 (11.1 %)	(0.3%, 48.2%)	13 (38.2 %)	(22.2 %, 56.4%)	1 (12.5 %)	(0.3%, 52.7%)	15 (29.4 %)	(17.5%, 43.8%)
Complete response (CR)	0	(NE, NE)	3 (8.8%)	(1.9%, 23.7%)	0	(NE, NE)	3 (5.9%)	(1.2%, 16.2%)
Very good partial response (VGPR)	4 (44.4 %)	(13.7 %, 78.8%)	4 (11.8 %)	(3.3%, 27.5%)	2 (25.0 %)	(3.2%, 65.1%)	10 (19.6 %)	(9.8%, 33.1%)
Partial response (PR)	0	(NE, NE)	5 (14.7 %)	(5.0%, 31.1%)	0	(NE, NE)	5 (9.8%)	(3.3%, 21.4%)
Minimal response (MR)	0	(NE, NE)	0	(NE, NE)	0	(NE, NE)	0	(NE, NE)
Stable disease (SD)	3 (33.3 %)	(7.5%, 70.1%)	6 (17.6 %)	(6.8%, 34.5%)	5 (62.5 %)	(24.5 %, 91.5%)	14 (27.5 %)	(15.9%, 41.7%)
Progressive disease (PD)	0	(NE, NE)	3 (8.8%)	(1.9%, 23.7%)	0	(NE, NE)	3 (5.9%)	(1.2%, 16.2%)
Not evaluable	1 (11.1 %)	(0.3%, 48.2%)	0	(NE, NE)	0	(NE, NE)	1 (2.0%)	(0.0%, 10.4%)
Overall response (sCR + CR + VGPR + PR)	5 (55.6 %)	(21.2 %, 86.3%)	25 (73.5 %)	(55.6 %, 87.1%)	3 (37.5 %)	(8.5%, 75.5%)	33 (64.7 %)	(50.1%, 77.6%)

	RP2D: 400 ug/kg Weekly Subcutaneous				RP2D: 800 ug/kg Every 2 Weeks Subcutaneous			
	Phase 1		Phase 2 Cohort B		Phase 1		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
VGPR or better (sCR + CR + VGPR)	5 (55.6 %)	(21.2 %, 86.3%)	20 (58.8 %)	(40.7 %, 75.4%)	3 (37.5 %)	(8.5%, 75.5%)	28 (54.9 %)	(40.3%, 68.9%)
CR or better (sCR + CR)	1 (11.1 %)	(0.3%, 48.2%)	16 (47.1 %)	(29.8 %, 64.9%)	1 (12.5 %)	(0.3%, 52.7%)	18 (35.3 %)	(22.4%, 49.9%)

Key: RP2D = recommended Phase 2 dose; 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 are calculated with the number of subjects in the All Treated Analysis Set as denominator.
Note: Exact 95% confidence intervals are provided.

Median DOR for participants with prior T cell redirection therapy who were assigned to talquetamab 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC was 11.9 months (95% CI: 4.8 to Not Estimable), and 93.9% and 81.8% of responders had at least 6 and 9 months of follow-up, respectively. The percentage of participants estimated to be in response at 9 months was 56.6% (95% CI: 37.9%, 71.6%) and at 12 months was 48.2% (95% CI: 29.4%, 64.7%).

With a median follow-up of 14.8 months, 17.6% participants (95% CI: 8.4%, 30.9%) achieved MRD negativity at 10^{5}, and 11.8% (95% CI: 4.4%, 23.9%) achieved MRD negativity at 10^{-6}. Among 18 participants with CR or better by IRC assessment, 33.3% (95% CI: 13.3%, 59.0%) achieved MRD negativity at 10^{-5}.

The median time to first response (PR or better), best response, VGPR or better, and CR or better was 1.1, 2.1, 1.5, and 2.8 months, respectively Median PFS was 5.1 months (95% CI: 3.4, 13.8) overall.

At time of updated Cut-off date (17 January 2023), median PFS based on IRC assessment was 5.1 months (95% CI: 3.4, 12.3) in the All Treated Analysis Set and data are mature. The estimated PFS rate at 12 months was 38.1% (95% CI: 24.8%, 51.2%).

At time of updated Cut-off date (17 January 2023), median OS based on IRC assessment was not yet mature; the estimated OS rate at 9 months was 72.5% (95% CI: 58.0%, 82.7%).

- **Ancillary analyses**

In the absence of a direct comparator in Study 64407564MM1001, an adjusted comparative analysis using the individual participant data from Study 64407564MMY1001 and from LocoMMotion (initiated in 2019) and MoMMent (initiated in November 2021), two prospective, observational studies of real-world physician's choice (RWPC) of treatment and associated outcomes in triple-class exposed patients with relapsed or refractory multiple myeloma has been performed.

Participants included in the comparative effectiveness analyses from the RWPCs were required to satisfy the key inclusion/exclusion criteria for MonumenTAL-1 Phase 2. Propensity-weighting adjustments were applied to control for confounding bias based on prognostic factors identified through literature review and clinical knowledge.

Results reported for Study 64407564MMY1001 are based on the efficacy update with a clinical cut-off of 12 September 2022.

The primary comparative analyses included all participants who received talquetamab at the 0.4 mg/kg weekly SC RP2D in Study 64407564MMY1001 (n=143) and all RWPC patients who met the inclusion criteria for Study 64407564MMY1001 (n=165). Additional comparative analyses included all participants who received talquetamab at the 0.8 mg/kg Q2W SC RP2D in Study 64407564MMY1001 (n=145) and all RWPC patients who met the inclusion criteria for Study 64407564MMY1001 (n=165).

Results from this comparison are summarised below.

Table 36. ATT-weighted results comparing talquetamab vs. real-world physician's choice

Endpoints	**Talquetamab 0.4 mg/kg weekly SC N=143**	**RWPC N=176**	**Response Ratio/ Hazard ratio (95% CI)**	**Talquetamab 0.8 mg/kg Q2W SC N=145**	**RWPC N=176**	**Response Ratio/ Hazard ratio (95% CI)**
ORR (%)	74.1%	28.5%	RR 2.60 (1.86, 3.65)	71.7%	28.3%	RR 2.54 (1.81, 3.56)
DOR (Median months)	9.5	5.8	RR 2.60 (1.86, 3.65)	• Not reached	8.1	HR 0.40 (0.24, 0.67)
PFS (Median months)	7.5	4.1	RR 5.10 (3.15, 8.25)	14.2	4.1	HR 0.40 (0.29, 0.57)
TTNT (Median months)	9.1	4.7	RR 95.53 (7.78,1173.48)	13.3	4.7	HR 0.40 (0.29, 0.54)
OS (Median months)	Not reached	9.3	HR 0.70 (0.45, 1.11)	Not reached	10.3	HR 0.38 (0.24, 0.62)

ATT=average treatment effects on the treated; CR=complete response; ORR=overall response rate; Q2W=every 2 weeks; RR=response ratio; RWPC=real world physician's choice; TTNT=time to next treatment; CI=confidence interval; DOR=duration of response; HR=hazard ratio; OS=overall survival; PFS=progression-free survival

- **Summary of main efficacy results**

The following tables summarise 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 37. Summary of efficacy for trial 64407564MMY1001 (MonumenTAL-1)

Title: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma	
Study identifier	**Study: 64407564MMY1001 (MonumenTAL-1)** **EudraCT Number:2017-002400-26** **ClinicalTrials.gov Identifier**: **NCT03399799, CR108404**
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 11 January 2018 and the study is currently ongoing. 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 has received his or her initial dose of talquetamab or when the last subject has completed the last study assessment in the study, whichever occurs first).
Hypothesis	**Part 1 & 2 (Phase 1):** Objectives: • Part 1: To characterise the safety of talquetamab and recommend the Phase 2 dose(s) and schedule • Part 2: To further characterise the safety of talquetamab at the recommended Phase 2 dose(s) (RP2Ds) Hypothesis: • Part 1 (dose escalation): One or more candidate RP2D(s) of talquetamab can be identified such that <28% of the subjects experience a DLT. • Part 2 (dose expansion): talquetamab is safe and demonstrates preliminary antitumor activity at the putative RP2D(s). **Part 3 (Phase 2):** Objectives: • To evaluate the efficacy of talquetamab at the RP2D: Hypothesis: • Part 3 (Phase 2): talquetamab has anti-myeloma activity and demonstrates efficacy and acceptable safety in 1 or more of the following 3 cohorts of subjects with relapsed or refractory multiple myeloma with unmet medical need: - Cohort A: Treatment with talquetamab will have significant anti-myeloma activity (i.e., the lower limit of the two-sided 95% confidence interval [CI] for ORR in this cohort will be greater than 30%). - Cohort B: Treatment with talquetamab will have meaningful anti-myeloma activity (i.e., the lower limit of the two-sided 95% CI for ORR in this cohort will be greater than 15%). - Cohort C: Treatment with talquetamab will have significant anti-myeloma activity (i.e., the lower limit of the two-sided 95% confidence interval [CI] for ORR in this cohort will be greater	

Treatments groups	**Part 1 -Dose Escalation Intervenus (IV)**	Intravenous (IV) dosing ranging from 0.0005 to 0.00338 mg/kg once every two weeks (Q2W) at start and switched to weekly dosing range of 0.00225 to 0.18 mg/kg. Half of all IV treatment doses were preceded by step-up dosing. Cycles were 21-28 days in length.
	Part 1 -Dose Escalation Subcutaneous (SC)	Subcutaneous (SC) dosing ranging from 0.005 to 0.08 mg/kg weekly dosing, 0.08 to 1.2 mg/kg Q2W, and 1.6 mg/kg monthly. All SC treatment doses were preceded by step-up dosing. Cycles were 21-28 days in length.
	Part 2 – Dose Expansion	Participants were treated at the putative RP2Ds: • 0.405 mg/kg weekly SC on Days 1, 8, and 15 of a 21-day cycle (preceded by step-up doses of 0.01 and 0.06 mg/kg) or • 0.8 mg/kg Q2W SC on Days 1 and 15 of a 28-day cycle (preceded by step-up doses of 0.01, 0.06, and 0.3 mg/kg).

	Part 3 – Phase 2		• Cohort A (0.4 mg/kg weekly SC) was to enrol approximately 120 participants with multiple myeloma who were triple-class exposed (PI, IMiD, and anti-CD38 monoclonal antibody), had previously received treatment with at least 3 prior therapies, and had not been exposed to T cell redirection therapies such as CAR-T or bispecific antibodies. • Cohort B (0.4 mg/kg weekly SC) was to enrol at least 60 and up to approximately 100 participants with multiple myeloma who were triple-class exposed (PI, IMiD, and anti- CD38 monoclonal antibody), had previously received treatment with at least 3 prior therapies, and had been exposed to T cell redirection therapies such as CAR-T or bispecific antibodies. • Cohort C (0.8 mg/kg Q2W SC) was to enrol approximately 100 participants with multiple myeloma who were triple-class exposed (PI, IMiD, and anti-CD38 monoclonal antibody), had previously received treatment with at least 3 prior therapies, and had not been exposed to T cell redirection therapies such as CAR-T or bispecific antibodies.
Endpoints and definitions	Phase 1 (Parts 1 and 2) - Primary endpoint	DLT and Frequency and Severity of AE and SAE and laboratory abnormalities	Part 1 (Dose Escalation): Frequency and type of DLT; frequency and severity of adverse events, serious adverse events, and laboratory abnormalities Part 2 (Dose Expansion): Frequency and severity of adverse events, serious adverse
	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, CR, or 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, as defined in the IMWG criteria, or death due to any cause, whichever occurs first. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.
		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)	Database lock occurred on 14 Mar 2023.
RESULTS AND ANALYSIS	
Analysis description	**Updated primary Analysis (Based on IRC analysis 17 January 2023 Data Cut)**
Analysis population and time point description	A total of 339 participants who received pivotal RP2Ds on or before 20 April 2022 were included in primary efficacy and safety analyses. Primary efficacy data are presented for 143 treated participants with no prior T cell redirection therapy and assigned to the 0.4 mg/kg weekly SC RP2D (21 in Phase 1 and 122 in Cohort A in Phase 2) and 145 treated participants with no prior T cell redirection therapy and assigned to the 0.8 mg/kg Q2W SC (36 in Phase 1 and 109 in Cohort C in Phase 2). In addition, updated data are presented for 51 participants who had received prior T cell redirection therapy, and who were assigned to either the 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC RP2D (17 in Phase 1 and 34 in Phase 2 Cohort B). Efficacy analyses for the primary and key secondary efficacy analyses in these subjects were updated based on a 17 January 2023 clinical cut-off. The updated data provides >8 additional months of follow-up from the initial submission (>4 months of follow-up from the efficacy update based on 12 September 2022 clinical cut-off). The median duration of follow-up was 18.9 months, 12.9 months, and 15.3 months, for the 0.4 mg/kg weekly, 0.8 mg/kg Q2W, and Prior T cell Redirection Therapy analysis sets, respectively.
Descriptive statistics and estimate variability	**Efficacy Analysis Set 0.4 mg/kg weekly (CCO 17 Jan 23)**

Treatment Group	**Efficacy Analysis Set (pooled phase 1 and 2)**
n	143
ORR	106 (74.1%)
95% CI (%)	66.1, 81.1
Stringent complete response (sCR)	34 (23.8%)
95% CI (%)	17.1, 31.6
Complete response (CR)	14 (9.8%)
95% CI (%)	5.5, 15.9
Very good partial response (VGPR)	37 (25.9%)
95% CI (%)	18.9, 33.9
Partial response (PR)	21 (14.7%)
95% CI (%)	9.3, 21.6
Median DOR (months)	9.5 (6.7, 13.3)
Probability of Patients with DOR (%)	At 6 months: 67.2 At 9 months: 51.5 At 12 months: 43.5

	95% CI (%)	At 6 months: 57.2 to 75.3 At 9 months: 41.4 to 60.6 At 12 months: 33.8 to 52.8
	MRD-negativity (at 10^{-5} threshold of sensitivity)	44 (30.8%)
	95% CI (%)	23.3 to 39
	MRD-negativity in patient with CR or better (at 10^{-5} threshold of sensitivity) (%)	26 (54.2%)
	95% CI (%)	39.2 to 68.6
	Time to Response (median months)	Time to first response (PR or better): 1.15 Time to best response: 2.23 Time to VGPR or better: 1.87 Time to CR or better: 2.64
	PFS (median months)	7.5
	95% CI	5.7 to 9.4
	OS (median months)	Not estimable
	95% CI (months)	(25.6, NE)
Descriptive statistics and estimate variability	**Efficacy Analysis Set 0.8 mg/kg Q2W (CCO 17 Jan 23)**	
	Treatment Group	**Efficacy Analysis Set**
	n	145
	ORR (%)	104 (71.7%)
	95% CI (%)	63.7, 78.9%
	Stringent complete response (sCR)	43 (29.7%)
	95% CI (%)	22.4%, 37.8%
	Complete response (CR)	13 (9.0%)
	95% CI (%)	4.9%, 14.8%
	Very good partial response (VGPR)	32 (22.1%)
	95% CI (%)	15.6%, 29.7%
	Partial response (PR)	16 (11.0%)
	95% CI (%)	(6.4%, 17.3%)
	Median DOR (months)	Not estimable

	95% CI (months)	(13.0, NE)
	Probability of Patients with DOR (%)	At 6 months: 82.2 At 9 months: 76.3 At 12 months: 69.3
	95% CI (%)	At 6 months: 73.2, 88.4 At 9 months: 66.5, 83.7 At 12 months: 57.8, 78.2
	MRD-negativity (at 10^{-5} threshold of sensitivity) (%)	43 (29.7%)
	95% CI (%)	(22.4%, 37.8%)
	MRD-negativity in patient with CR or better (at 10^{-5} threshold of sensitivity) (%)	24 (42.9%)
	95% CI (%)	(29.7%, 56.8%)
	Time to Response (median months)	Time to first response (PR or better): 1.25 Time to best response: 3.04 Time to VGPR or better: 2.22 Time to CR or better: 4.68
	PFS (median months)	Not estimable
	95% CI	(9.6, NE)
	OS (median months)	Not estimable
	95% CI	(20.1, NE)
Descriptive statistics and estimate variability	**Participants with Prior T cell Redirection Therapies (CCO 17 Jan 2023)**	
	n	51
	ORR (%)	33 (64.7%)
	95% CI (%)	50.1%, 77.6%
	Stringent complete response (sCR)	15 (29.4%)
	95% CI (%)	17.5%, 43.8%
	Complete response (CR)	3 (5.9%)
	95% CI (%)	1.2%, 16.2%
	Very good partial response (VGPR)	10 (19.6%)
	95% CI (%)	9.8%, 33.1%

	Partial response (PR)	5 (9.8%)
	95% CI (%)	3.3%, 21.4%
	Median DOR (months)	11.9
	95% CI (months)	(4.8, NE)
	Probability of Patients with DOR (%)	At 6 months: 66.3 At 9 months: 56.6 At 12 months: 48.2
	95% CI (%)	At 6 months: 47.4, 79.7 At 9 months: 37.9, 71.6 At 12 months: 29.4, 64.7
	MRD-negativity (at 10^{-5} threshold of sensitivity) (%)	9 (17.6%)
	95% CI (%)	8.4%, 30.9%
	MRD-negativity in patient with CR or better (at 10^{-5} threshold of sensitivity) (%)	6 (33.3%)
	95% CI (%)	13.3%, 59.0%
	Time to Response (median months)	Time to first response (PR or better): 1.12 Time to best response: 2.10 Time to VGPR or better: 1.46 Time to CR or better: 2.81
	PFS (median months)	5.1
	95% CI	(3.4,12.3)
	OS (median months)	Not estimable
	95% CI (months)	(11.6, NE)
Effect estimates per comparison	Not applicable, single-arm study	

2.6.5.3. Clinical studies in special populations

Table 38. Summary of elderly subjects treated with talquetamab in study 64407564MMY1001.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
All Treated	183/501 (36.5%)	73/501 (14.6%)	1/501 (0.2%)
RP2D population, including prior T-cell redirection therapy	121/339 (35.7%)	56/339 (16.5%)	1/339 (0.3%)
RP2D 0.4 mg/kg Weekly (n=143)	57/143 (39.9%)	20/143 (14.0%)	1/143 (0.7%)

RP2D 0.8 mg/kg Q2W (n=145)	50/145 (34.5%)	32/145 (22.1%)	0
Prior T cell redirection therapy (RP2Ds)(n=51)	14/51 (27.5%)	4/51 (7.8%)	0

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The basis of evidence for use of talquetamab monotherapy are the results from the pivotal phase 1/2 Study 64407564MMY1001 (MonumenTAL-1).

Study MMY1001 was an early, uncontrolled, exploratory trial; in principle, B/R evaluations for Marketing Authorisation Application (MAA) procedures would require high-quality confirmatory data from at least one controlled, randomised trial. However, conditional approvals in advanced settings of MM based on promising results from single-arm trials (SAT) are not unprecedented.

Based on this study, the applicant applied for a Conditional Marketing Authorisation for talquetamab, as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression or did not respond to the last therapy.

Considering the poor prognosis and few alternatives for this triple refractory population, this study design could be accepted.

In this report, efficacy assessment will focus on 2 participant grouping, which correspond to both claimed dosing regimens, via SC administration:

- 0.4 mg/kg weekly SC RP2D (patients from phase 1 + cohort A in phase 2), with dosing step up at initiation to mitigate risks of cytokine release syndrome (CRS)

- 0.8 mg/kg Q2W SC RP2D, (patients from phase 1+ cohort C in phase 2), with dosing step up at initiation to mitigate risks of cytokine release syndrome (CRS)

The discussion in this report will be focused on these two dose groups, and especially cohorts A and C which are representative of the targeted indication. Moreover, the applicant included an explorative cohort to study the efficacy of talquetamab in patient with prior T cell redirection therapies (i.e. CAR-T or BCMA/CD3 bispecific antibodies); considering the recently approved therapies, despite limited conclusions based on exploratory data, this cohort is of interest. Data from this "Prior T Cell Redirection Therapy" group (phase 1+ cohort B) will be considered as supportive.

The primary objective in Part 3 (Phase II) of study MMY-1001 was to evaluate the anti-MM activity of talquetamab in terms of ORR using the IMWG response criteria, as assessed by an IRC.

MM is a chronic malignancy with a progressive clinical course: although ORR can be considered an informative endpoint to measure anti MM-activity in advanced disease settings (i.e., when resistance to most active compounds is widespread), clinical benefit is better captured by significant gains in time-to-event endpoints (e.g. PFS, OS). Reliable interpretations of PFS and OS data are, however, hampered by the uncontrolled study design. High ORRs, if supported by meaningful data in terms of response duration, might still be considered supportive of early access in the claimed high unmet medical need setting, provided that no significant uncertainty on internal and external validity is present and high internal consistency is observed in the pivotal study.

The sample size for Phase II Cohort A was determined by assuming that the ORR for talquetamab for subjects in Cohort A is at least 45%. With that assumption, the power to declare that the ORR is higher than 30% at the one-sided significance level of 0.025 was approximately 90% or greater.

The sample size for Phase II Cohort B was determined by using 2-stage design to test the null hypothesis that the ORR is at most 15%, against the alternative that the ORR is at least 35%. With one-sided significance level of 0.025 and a power of 80%, Cohort B needed 34 response-evaluable subjects. Assuming a non-evaluable rate of 10%, the total sample size required for Cohort B was 38 subjects. The sample size will be increased to at least 60 subjects to determine the ORR with more precision.

The sample size for Cohort C was determined by assuming that the observed ORR for talquetamab was at least 45%. With that assumption, the power to declare that the ORR was higher than 30% at the one-sided significance level of 0.025 was greater than 85%.

The secondary endpoints in study MMY-1001 are considered, in principle, adequate to further characterise the efficacy of talquetamab in the target indication. In particular, given the uncontrolled design of the pivotal study, depth and duration of responses are also considered key to support clinical benefit evaluation. The importance of an adequate follow-up to characterise both short- and long-term efficacy is therefore emphasised, and, from a safety perspective, exposure times should be sufficiently long to cover the projected exposure in clinical practice.

During the phase 1 part of the study, the applicant proceeded a dose escalation to determine the RP2D dose regimen; the 0.4 mg/kg weekly SC was first identified. The selected 0.4 mg/kg weekly dose regimen was also supported by the available PK/Pd data: at the RP2D the mean talquetamab concentrations were constantly at or above the identified EC90 value (although some uncertainty remains on the selected EC90 value, see the PK section above). Moreover, T-cell activation markers, including pro-inflammatory cytokines, were sub-optimally induced with doses lower than the RP2D. To enhance treatment compliance and reduce patient discomfort, the applicant also investigated the efficacy of an alternative Q2W administration regimen. However, this suggestion has not been formally tested against the lower weekly dose, for example in a non-inferiority setting. Moreover E-R analysis did not identify dose schedule (weekly SC vs Q2W SC) as a significant covariate for ORR at the RP2Ds, suggesting comparable ORR resulting from either RP2D dose of 0.4 mg/kg weekly or 0.8 mg/kg Q2W. Considering the heavily treated targeted population, the search for more convenient dose regimen is understood. Higher dose regimens did not increase responses substantially and increased the dose reduction frequency. The E-R trend analysis, based on the Phase 1 SC data, suggested that ORR increased with talquetamab exposure across SC doses below the RP2Ds, reaching a plateau at or above the RP2Ds. It should be noted that during the study, for the 0.8 mg/kg Q2W step-up schedule, the third dose was 0.3 mg/kg instead of the proposed 0.4 mg/kg as presented in the SmPC table 1. However, it is unlikely that this discrepancy would impact clinical efficacy, thus recommended step-up schedule is endorsed.

Overall, based on the available data, the clinical rationale supporting the proposed dosing schedules for MA can be considered acceptable.

It is noted that study Amendment 9 introduced the possibility to change the dosing frequency of talquetamab for participants with CR or prolonged non-CR. Overall, the rationale to allow for switching to less frequent administration schedules in responders is understood and considered of possible benefit to patients.

Subjects in Part 3 (Phase 2) Cohorts A and C were requested to have previously received ≥3 prior lines of therapy (including at least one PI, one IMiD, and an anti-CD38 monoclonal antibody) with no previous exposure to T cell redirection therapies such as CAR-T or bispecific antibodies. Subjects were

also required to have documented evidence of progressive disease (as per the IMWG 2016 criteria) on or within 12 months of their last line of therapy, or to have documented evidence of progressive disease within the previous 6 months and to be refractory to their most recent line of therapy. This is overall in line with the final indication and acceptable. However, the majority of subjects who received talquetamab in study MMY-1001 were indeed refractory to their last line of prior therapy 93.7% and 94.5% in the 0.4 mg/kg weekly and 0.8 mg/kg Q2W cohort, respectively.

The CHMP therefore requested that the indication be amended to better reflect refractoriness to the last line of therapy from patients that had "…demonstrated disease progression" to "demonstrated disease progression on the last therapy", which was accepted by the applicant.

Triple-exposed subjects who had also received prior T cell redirection therapy could only be enrolled in the dedicated Cohort B, in order to reduce heterogeneity across the overall study population: this is acceptable and considered of value to provide further support to the efficacy of talquetamab.

Overall, the inclusion criteria in study MMY-1001 can be considerate adequate to define a heterogeneous, heavily pre-treated population representative of an advanced setting of disease. It is noted, however, that patients with severe anaemia (i.e., <8 g/dl), severe renal failure (i.e. GFR <40 ml/min) and high serum calcium levels (i.e. >14 mg/dl) were excluded from trial participation. Since anaemia, renal failure and hypercalcaemia are well known complications of MM, the generalisability of results from study MMY-1001 to patients with severe manifestations of MM is limited. Further, it should be noted that patients with ECOG score of 2 were not allowed for inclusion until amendment 12 (21 January 2021), which is then reflected in the baseline data and limited results in this subgroup.

Protocol deviations occurred for 9.8% of both 0.4mg/kg and prior T-cell redirections therapy groups and 4.8% for 0.8mg/kg Q2W treated patients with no impact on participant safety or data integrity. After the initial protocol have been issued (12 September 2017) the applicant made several amendments to the original study, and this is not unexpected considering the adaptive design and the exploratory nature of study MMY-1001. Most changes were not controversial, being aimed at reflecting the growing information on the efficacy, safety and clinical pharmacology of talquetamab in the study protocol.

Amendment 9 and Amendment 15 both introduced sample size increases to account for the development of the s.c. formulation and to expand the study population in Phase II cohorts B and C. Although, in principle, sample size changes in ongoing, open-label studies conducted for regulatory purposes are not considered acceptable, in this case it is acknowledged that MMY-1001 was designed as an early exploratory study. Although Amendment 15 resulted in an increase of the power of the pre-specified efficacy analyses in the concerned Phase II cohorts, the clinical and regulatory relevance of the efficacy thresholds used in sample size calculations was anyway limited, especially when the high response rates observed with the currently available alternatives in advanced MM (e.g., anti-BCMA CARTs) are taken into account. Therefore, both amendments are not considered to negatively impact on the robustness of the reported results.

Overall, these changes are acknowledged considering the explorative aspect of the trial.

Baseline data are detailed for each claimed dose regimen, and for patients with prior T cell redirection therapy. The demographics and Baseline characteristics were similar between cohort A (0.4 mg/mg QW) and C (0.8 mg/kg Q2W).

Overall, in cohort A and C respectively most subjects were male (53.3% and 61.5%) with a median age of 67 years in both cohorts. Of note, in cohort A, 45.5% of patients were under 65 years, and 14.7% were 75 years old or higher. Moreover, most of the patient were fit with an ECOG score of ≥2 for only 10.7% and 7.3% of the patients respectively, as expected per the inclusion/exclusion criteria previously discussed. This could question on the reliability of the observed results in the real world use,

considering the high selection of patients. Considering that the median age at the time of diagnosis for MM is 70 years with 37% of patients being younger than 65 years of age, patients in this trial are considered younger and fitter than the targeted population, this will be further discussed in comparison with real world data provided by the applicant.

Baseline disease characteristics are also similar between in cohort A and C, patients were around 7 years from diagnosis (7.43 years and 7.54 years respectively) most of them were ISS stage ≤2, R-ISS stage ≤2, and had no extramedullary plasmacytoma (80.3% and 74.3%). Most patients had at least 4 lytic bone lesions (67.9% in cohort A). To be noted, in cohort A and similarly in cohort C, 53.1% of patients had igG MM and 29.4% had light chain MM, which is in line with real world data. Considering prior therapies, 100% of both cohorts patients were triple exposed (PI+IMiD+anti-CD38), as per the inclusion criteria in the protocol, and a majority were penta-exposed (72.1% and 70.6%) and stem cell transplanted (77.9% and 78.9%). Radiotherapy was used on almost half this population (45.1% and 44%). Considering refractory status, 100% of patients were refractory at any point to prior therapy, and a majority of patient were triple refractory (74.6% and 68.8%). Of note, in cohort A, 93.7% of patients were refractory to their last treatment. These data confirm that these relatively young and fit patients were still heavily pre-treated and thus represent the targeted indication.

Of note, demographics and baseline characteristics in the prior T cell redirection therapy subgroup (Cohort B) differ from the other two groups in terms of age (64.7% < 65 years, no patient >80 years) but race, ethnicity, sex ratio and baseline disease are globally in line. Moreover, 64.7% of these patients received more than 5 prior therapies (vs 33.2% and 42.2%), which is expected in this prior T cell redirection therapy subgroup. To be noted, this subgroup of patients has a limited sample size (n=51).

Efficacy data and additional analyses

Results from phase 2 alone, and pooled with phase 1, are discussed below. Of note, taking into account the longer exposure in phase 1 group, and different dose, pooled data could be slightly biased and different from the target population, better represented by phase 2 data. However, pooled data help providing a larger population.

Study 64407564MMY1001 met its pre specified primary endpoint (30% for Cohorts A and C and 15% for cohort B) demonstrating a clinically significant improvement in Overall Response Rate (ORR).

At the latest DCO date (17 January 2023), the median follow-up was 18.8 months of median FU in the RP2D 0.4 mg/kg Weekly SC All Treated Analysis Set and 12.7 months in the RP2D 0.8 mg/kg Q2W SC all treated analysis set. ORR was consistent with 74.1% (95% CI: 66.1% to 81.1%) and 71.7% (95% CI: 63.7% to 78.9%) respectively. CR or better was 33.6% (CI95%:25.9%, 41.9%) and 38.6% (CI95%:30.7%, 47.1%), in the two dosing regimens respectively.

Median DOR for participants assigned to talquetamab 0.4 mg/kg weekly SC was 9.5 months (95% CI: 6.7 to 13.3). Median DOR for participants assigned to talquetamab 0.8 mg/kg Q2W SC remains not reached, and 88.6% of responders had at least 9 months of follow-up; the percentage of participants estimated to be in response at 9 months was 76.3% (95% CI: 66.5%, 83.7%) and at 12 months was 69.3% (95% CI: 57.8%, 78.2%) which is promising.

Median PFS was 7.5 months 95% CI95%: 5.7, 9.4) for the RP2D 0.4 mg/kg Weekly SC analysis set but remains immature for the RP2D 0.8 mg/kg Q2W SC analysis set. Nevertheless, with a median of 12.7 months FU, the estimated 12-month PFS is 54.4% (CI95%: 45.3, 62.6) this is still promising considering the poor prognosis in this heavily pre-treated population. Median OS is still not reached, and OS data are still immature. However, the 12-month overall survival rate (95% CI) was 76.4% (68.3, 82.7) for RP2D 0.4 mg/kg QW SC analysis set and 77.4% (69.1, 83.7) for the RP2D 0.8 mg/kg Q2W SC analysis set, which is promising.

MRD results are comparable between RP2D 0.4 mg/kg Weekly SC and RP2D 0.8 mg/kg Q2W SC, with 30.8% participants (95% CI: 23.3%, 39.0%) and 29.7% participants (95% CI: 22.4%, 37.8%) who achieved MRD negativity at 10^{-5} and 21% (CI95%14.6;28.6) and 20.7% (CI95%: 14.4; 28.2) who achieved MRD negativity at 10^{-6} respectively.

The median time to first response (PR or better), best response, VGPR or better, and CR or better was 1.2, 2.2, 1.9, and 2.6 months in the RP2D 0.4 mg/kg Weekly SC group and 1.3, 3.0, 2.2, and 4.7 months, respectively in the RP2D 0.8 mg/kg Q2W SC. Most participants demonstrated their first response rapidly, by the start of Cycle 2.

ORR and median DOR for participants with prior T cell redirection therapy who were assigned to talquetamab 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC were 64.7% (95% CI:50.1% to 77.6%) and 11.9 months (95% CI: 4.8 to Not Estimable) respectively. Median PFS was 5.1 months (95% CI: 3.4, 13.8) overall and the 9month PFS rate was 40.9% (95% CI: 26.9%, 54.4%). The estimated OS rate at 6 months was 81.1% (95% CI: 66.8%, 89.7%) overall, and the estimated OS rate at 12 months was 59.6% (95% CI: 41.7%, 73.7%) overall, which in this subgroup with highest unmet medical need is promising. However, PFS and OS data are still immature. 17.6% participants (95% CI: 8.4%, 30.9%) achieved MRD negativity at 10^{-5}, and 11.8% (95% CI: 4.4%, 23.9%) achieved MRD negativity at 10^{-6}.

The available data from pivotal study MMY-1001 showed that treatment with talquetamab, in a heavily pre-treated population of patients with RR MM, resulted in high ORRs with a relevant proportion of deeper responses, in line with what observed in similar settings with other T-cell redirection therapies. Uncertainties remain, however, on the generalisability of the results to the targeted population identified by the claimed indication, since less pre-treated patients (e.g. with 2 prior lines of therapy) who received talquetamab in Phase I were included in the pooled efficacy analysis. Furthermore, elderly and frailer patients, that represent a significant fraction of the MM population, might have been under-represented in study MMY-1001.

Overall, despite the significant uncertainties related to the limited sample size, the available data in subjects who had received prior anti-BCMA CAR T cell therapies and bispecific monoclonal antibodies suggested that deep and durable responses can still be obtained with talquetamab. This is of relevance in the context of major therapeutic advantage demonstration when the current treatment options in the claimed indication are considered. In particular, the limited available data can be considered supportive of the possibility of talquetamab to overcome resistance to anti-BCMA T cell engager therapies, at least in a subset of patients.

Comparison of Study 64407564MMY1001 Efficacy Data Using Real World Evidence

To contextualise the efficacy results, namely time to event endpoints, the applicant provided data from two prospective, non-interventional studies (LocoMMotion and MoMMent) in triple-exposed patients treated with real-world (RW) treatment options. Both dosing regimens were compared to the RW data after applying MonumenTAL-1 eligibility criteria, propensity-weighted adjustment and estimating the average treatment effect in the treated population to minimise bias. However, the intrinsic limitations in such matched indirect comparisons are significant especially in the context of disease settings characterised by significant clinical, biological, and treatment-related heterogeneity. Overall, the regulatory relevance of the provided indirect comparisons is considered limited.

Additional efficacy data needed in the context of a conditional MA

To confirm the positive benefit-risk profile that is expected to be established in the still ongoing MonumenTAL-1, the applicant has initiated a confirmatory phase 3 study.

Study 64407564MMY3002 is a multicentre, randomised, open-label, Phase 3 study to determine whether talquetamab in combination with daratumumab and pomalidomide (Tal- DP; Arm A) and

talquetamab in combination with daratumumab (Tal-D; Arm C) have better efficacy respectively than the combination of daratumumab, pomalidomide and dexamethasone (DPd; Arm B) in participants with relapsed or refractory multiple myeloma who have previously received at least 1 prior line of therapy. Approximately 810 patients will be randomised in a 1.1.1 ratio to Tal-DP, Tal-D and DPd.

The proposed confirmatory study is for a different patient population with RRMM in second line and in association, this could be acceptable from an efficacy point of view. Feasibility of this confirmatory study is likely given the different patient population. An interim report from this study is planned for Q2 2027 and the final report in Q2 2030.

2.6.7. Conclusions on the clinical efficacy

The clinical efficacy data submitted in this MAA support the benefit of talquetamab 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 from study 64407564MMY3002 a phase 3 randomised study investigating the efficacy of talquetamab in combination with sc. daratumumab and pomalidomide (Tal-DP) or talquetamab in combination with daratumumab sc (Tal-D) vs. daratumumab sc, pomalidomide and dexamethasone (DPd), in participants with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy should be provided.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The safety data for Study 64407564MMY1001 are summarised by RP2D dose and prior exposure to T cell redirection therapies such as CAR-T or bispecific antibodies, as well as for the total treated population:

-RP2D 0.4 mg/kg weekly SC (n=143): All treated participants assigned to 0.4 mg/kg weekly SC either in Phase 1 (n=21) or Phase 2 Cohort A (n=122), who had not been exposed to T cell redirection therapies.

-RP2D 0.8 mg/kg Q2W SC (n=145): All treated participants assigned to 0.8 mg/kg Q2W SC either in Phase 1 (n=36) or Phase 2 of Cohort C (n=109), who had not been exposed to T cell redirection therapies.

-Prior T cell redirection therapies exposure at RP2Ds (n=51): All treated participants assigned to 0.4 mg/kg weekly SC (either in Phase 1 [n=9] or Phase 2 Cohort B [n=34]) or 0.8 mg/kg Q2W SC (Phase 1 [n=8]), who had been exposed to T cell redirection therapies.

-All treated participants (N=501): All treated participants assigned to any dose cohort, including SC dose regimens lower and higher than the RP2Ds and IV dose regimens, and regardless of prior therapies.

The first clinical cut-off date used for the analysis of safety was 16 May 2022, based on the protocol-specified primary analysis, which was to be conducted approximately 9 months after the 120th participant in Cohort A received his or her initial dose of talquetamab. An updated analysis was provided during the evaluation of the product with a cut-off date of 17th January 2023. Results presented here are for the latest cut-off data unless otherwise specified.

Subject disposition and a summary of the duration of exposure to talquetamab in the All-Treated analysis set are presented in **Table 39** and respectively.

Table 39. Study disposition; all treated analysis set (Study 64407564MMY1001)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		
Analysis set: All Treated	143	145	22	38	51	102	501
Discontinued the study	62 (43.4%)	41 (28.3%)	20 (90.9%)	21 (55.3%)	21 (41.2%)	89 (87.3%)	254 (50.7%)
Reason for discontinuation							
Death	48 (33.6%)	32 (22.1%)	2 (9.1%)	6 (15.8%)	20 (39.2%)	4 (3.9%)	112 (22.4%)
Death - COVID-19	3 (2.1%)	1 (0.7%)	0	0	0	0	4 (0.8%)
Start of subsequent anticancer therapy	4 (2.8%)	2 (1.4%)	16 (72.7%)	13 (34.2%)	0	76 (74.5%)	111 (22.2%)
Withdrawal by subject	6 (4.2%)	5 (3.4%)	2 (9.1%)	1 (2.6%)	0	6 (5.9%)	20 (4.0%)
Lost to follow-up	4 (2.8%)	1 (0.7%)	0	1 (2.6%)	1 (2.0%)	3 (2.9%)	10 (2.0%)

Key: RP2D=recommended phase 2 dose, SC= Subcutaneous, IV= Intravenous.
Note: RP2D includes Phase 1 RP2D treatment groups, Phase 2 Cohort A and Phase 2 Cohort C.
Note: IV includes all IV treatment groups; Non-RP2D(<RP2D) includes 5 ug/kg weekly, 15 ug/kg weekly, 45 ug/kg weekly and 135 ug/kg weekly treatment groups; Non-RP2D(>RP2D) includes 800 ug/kg weekly, 1200 ug/kg bi-weekly and 1600 ug/kg monthly treatment groups; Prior T cell exposures at RP2Ds includes Phase 1 RP2D 400 ug/kg weekly with prior CART or prior bispecific, Phase 1 RP2D 800 ug/kg biweekly with prior CART or prior bispecific and Phase 2 Cohort B treatment groups.
Note: Percentages are based on the number of all treated subjects.
Note: For subjects who discontinue study treatment before disease progression: in Phase I, disease evaluations continued to be performed for up to 16 weeks until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, the subject is lost to follow-up, or the study ends, whichever occurs first; in Phase II, disease evaluations continued until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, the subject is lost to follow-up, or the study ends, whichever occurs first.

Table 40. Summary of treatment months; all treated analysis set (Study 64407564MMY1001)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		
Analysis set: All Treated	143	145	22	38	51	102	501
Distribution of subjects treated in and beyond each month							

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		
>= 1 month	128 (89.5%)	129 (89.0%)	16 (72.7%)	38 (100.0%)	45 (88.2%)	79 (77.5%)	435 (86.8%)
>= 2 months	121 (84.6%)	119 (82.1%)	10 (45.5%)	31 (81.6%)	42 (82.4%)	58 (56.9%)	381 (76.0%)
>= 3 months	110 (76.9%)	112 (77.2%)	10 (45.5%)	28 (73.7%)	35 (68.6%)	47 (46.1%)	342 (68.3%)
>= 4 months	99 (69.2%)	99 (68.3%)	8 (36.4%)	24 (63.2%)	31 (60.8%)	41 (40.2%)	302 (60.3%)
>= 5 months	87 (60.8%)	90 (62.1%)	4 (18.2%)	22 (57.9%)	28 (54.9%)	36 (35.3%)	267 (53.3%)
>= 6 months	79 (55.2%)	85 (58.6%)	4 (18.2%)	21 (55.3%)	24 (47.1%)	33 (32.4%)	246 (49.1%)
>= 7 months	71 (49.7%)	80 (55.2%)	3 (13.6%)	20 (52.6%)	23 (45.1%)	30 (29.4%)	227 (45.3%)
>= 8 months	61 (42.7%)	75 (51.7%)	3 (13.6%)	18 (47.4%)	22 (43.1%)	28 (27.5%)	207 (41.3%)
>= 9 months	57 (39.9%)	69 (47.6%)	3 (13.6%)	17 (44.7%)	21 (41.2%)	26 (25.5%)	193 (38.5%)
>= 12 months	47 (32.9%)	39 (26.9%)	2 (9.1%)	14 (36.8%)	15 (29.4%)	19 (18.6%)	136 (27.1%)
>= 18 months	32 (22.4%)	5 (3.4%)	2 (9.1%)	7 (18.4%)	4 (7.8%)	13 (12.7%)	63 (12.6%)
>= 24 months	5 (3.5%)	1 (0.7%)	2 (9.1%)	4 (10.5%)	0	12 (11.8%)	24 (4.8%)
Total number of treatment months received							
<1	15 (10.5%)	16 (11.0%)	6 (27.3%)	0	6 (11.8%)	23 (22.5%)	66 (13.2%)
1	7 (4.9%)	10 (6.9%)	6 (27.3%)	7 (18.4%)	3 (5.9%)	21 (20.6%)	54 (10.8%)
2	11 (7.7%)	7 (4.8%)	0	3 (7.9%)	7 (13.7%)	11 (10.8%)	39 (7.8%)
3	11 (7.7%)	13 (9.0%)	2 (9.1%)	4 (10.5%)	4 (7.8%)	6 (5.9%)	40 (8.0%)
4	12 (8.4%)	9 (6.2%)	4 (18.2%)	2 (5.3%)	3 (5.9%)	5 (4.9%)	35 (7.0%)
5	8 (5.6%)	5 (3.4%)	0	1 (2.6%)	4 (7.8%)	3 (2.9%)	21 (4.2%)
6	8 (5.6%)	5 (3.4%)	1 (4.5%)	1 (2.6%)	1 (2.0%)	3 (2.9%)	19 (3.8%)
7	10 (7.0%)	5 (3.4%)	0	2 (5.3%)	1 (2.0%)	2 (2.0%)	20 (4.0%)
8	4 (2.8%)	6 (4.1%)	0	1 (2.6%)	1 (2.0%)	2 (2.0%)	14 (2.8%)
9-11	10 (7.0%)	30 (20.7%)	1 (4.5%)	3 (7.9%)	6 (11.8%)	7 (6.9%)	57 (11.4%)
12-17	15 (10.5%)	34 (23.4%)	0	7 (18.4%)	11 (21.6%)	6 (5.9%)	73 (14.6%)
18-23	27 (18.9%)	4 (2.8%)	0	3 (7.9%)	4 (7.8%)	1 (1.0%)	39 (7.8%)
24+	5 (3.5%)	1 (0.7%)	2 (9.1%)	4 (10.5%)	0	12 (11.8%)	24 (4.8%)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		

Key: RP2D=recommended phase 2 dose, SC= Subcutaneous, IV= Intravenous.
Note: RP2D includes Phase 1 RP2D treatment groups, Phase 2 Cohort A and Phase 2 Cohort C.
Note: IV includes all IV treatment groups; Non-RP2D(<RP2D) includes 5 ug/kg weekly, 15 ug/kg weekly, 45 ug/kg weekly and 135 ug/kg weekly treatment groups; Non-RP2D(>RP2D) includes 800 ug/kg weekly, 1200 ug/kg bi-weekly and 1600 ug/kg monthly treatment groups; Prior T cell exposures at RP2Ds includes Phase 1 RP2D 400 ug/kg weekly with prior CART or prior bispecific, Phase 1 RP2D 800 ug/kg biweekly with prior CART or prior bispecific and Phase 2 Cohort B treatment groups.
Note: Percentages are calculated with the number of subjects in the All Treated Analysis Set as denominator.

2.6.8.2. Adverse events

As seen in, all subjects in both the total All Treated Analysis Set and the RP2D group experienced at least 1 TEAE.

Table 41. Overall summary of treatment-emergent adverse events; all treated analysis set (Study 64407564MMY1001)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	P2D 00 ug/kg -weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures a RP2Ds		
Analysis set: All Treated	143	145	22	38	51	102	501
Any TEAE	143 (100.0%)	145 (100.0%)	22 (100.0%)	38 (100.0%)	51 (100.0%)	102 (100.0%)	501 (100.0%)
Study drug-related[a]	143 (100.0%)	142 (97.9%)	19 (86.4%)	37 (97.4%)	51 (100.0%)	97 (95.1%)	489 (97.6%)
Maximum toxicity grade							
Grade 1	4 (2.8%)	1 (0.7%)	0	2 (5.3%)	0	3 (2.9%)	10 (2.0%)
Grade 2	28 (19.6%)	31 (21.4%)	2 (9.1%)	3 (7.9%)	5 (9.8%)	6 (5.9%)	75 (15.0%)
Grade 3	64 (44.8%)	57 (39.3%)	15 (68.2%)	12 (31.6%)	22 (43.1%)	51 (50.0%)	221 (44.1%)
Grade 4	42 (29.4%)	50 (34.5%)	4 (18.2%)	17 (44.7%)	24 (47.1%)	41 (40.2%)	178 (35.5%)
Grade 5	5 (3.5%)	6 (4.1%)	1 (4.5%)	4 (10.5%)	0	1 (1.0%)	17 (3.4%)
Any serious TEAE	76 (53.1%)	70 (48.3%)	15 (68.2%)	17 (44.7%)	29 (56.9%)	37 (36.3%)	244 (48.7%)
Study drug-related[a]	41 (28.7%)	36 (24.8%)	5 (22.7%)	6 (15.8%)	13 (25.5%)	13 (12.7%)	114 (22.8%)
TEAE leading to discontinuation of study drug[b]	7 (4.9%)	12 (8.3%)	2 (9.1%)	2 (5.3%)	4 (7.8%)	4 (3.9%)	31 (6.2%)
TEAE with outcome death[c]	5 (3.5%)	6 (4.1%)	1 (4.5%)	4 (10.5%)	0	1 (1.0%)	17 (3.4%)
Death due to COVID-19	1 (0.7%)	1 (0.7%)	0	0	0	0	2 (0.4%)
COVID-19 TEAEs	16 (11.2%)	38 (26.2%)	0	6 (15.8%)	7 (13.7%)	5 (4.9%)	72 (14.4%)
COVID-19 serious TEAEs	3 (2.1%)	7 (4.8%)	0	0	1 (2.0%)	2 (2.0%)	13 (2.6%)

TEAE=treatment-emergent adverse event; IV = intravenous, SC = subcutaneous, RP2D=recommended Phase 2 dose; RS=cytokine release syndrome; ICANS= immune effector cell-associated neurotoxicity.

Note: RP2D includes Phase 1 RP2D treatment groups, Phase 2 Cohort A and Phase 2 Cohort C.

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 talquetamab 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 42.**

Table 42. Most common (at least 20% in any RP2D group) treatment-emergent adverse events by system organ class, preferred term; all treated analysis set (Study 64407564MMY1001)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		
Analysis set: All Treated	143	145	22	38	51	102	501
Subjects with 1 or more TEAEs	143 (100.0%)	145 (100.0%)	22 (100.0%)	38 (100.0%)	51 (100.0%)	102 (100.0%)	501 (100.0%)
MedDRA system organ class / preferred term							
Nervous system disorders	122 (85.3%)	120 (82.8%)	15 (68.2%)	34 (89.5%)	42 (82.4%)	70 (68.6%)	403 (80.4%)
Dysgeusia	72 (50.3%)	71 (49.0%)	6 (27.3%)	29 (76.3%)	31 (60.8%)	38 (37.3%)	247 (49.3%)
Headache	27 (18.9%)	30 (20.7%)	7 (31.8%)	6 (15.8%)	10 (19.6%)	36 (35.3%)	116 (23.2%)
Ageusia	28 (19.6%)	30 (20.7%)	1 (4.5%)	2 (5.3%)	6 (11.8%)	0	67 (13.4%)
Blood and lymphatic system disorders	97 (67.8%)	109 (75.2%)	17 (77.3%)	31 (81.6%)	40 (78.4%)	87 (85.3%)	381 (76.0%)
Anaemia	64 (44.8%)	66 (45.5%)	12 (54.5%)	18 (47.4%)	25 (49.0%)	59 (57.8%)	244 (48.7%)
Neutropenia	50 (35.0%)	41 (28.3%)	12 (54.5%)	19 (50.0%)	28 (54.9%)	47 (46.1%)	197 (39.3%)
Lymphopenia	40 (28.0%)	42 (29.0%)	1 (4.5%)	17 (44.7%)	9 (17.6%)	53 (52.0%)	162 (32.3%)
Thrombocytopenia	39 (27.3%)	43 (29.7%)	7 (31.8%)	14 (36.8%)	19 (37.3%)	35 (34.3%)	157 (31.3%)
Leukopenia	23 (16.1%)	27 (18.6%)	3 (13.6%)	13 (34.2%)	12 (23.5%)	38 (37.3%)	116 (23.2%)
Gastrointestinal disorders	104 (72.7%)	116 (80.0%)	13 (59.1%)	33 (86.8%)	47 (92.2%)	66 (64.7%)	379 (75.6%)
Dry mouth	38 (26.6%)	58 (40.0%)	2 (9.1%)	19 (50.0%)	26 (51.0%)	8 (7.8%)	151 (30.1%)
Diarrhoea	36 (25.2%)	40 (27.6%)	4 (18.2%)	17 (44.7%)	8 (15.7%)	30 (29.4%)	135 (26.9%)
Nausea	29 (20.3%)	26 (17.9%)	6 (27.3%)	13 (34.2%)	9 (17.6%)	24 (23.5%)	107 (21.4%)
Dysphagia	34 (23.8%)	36 (24.8%)	2 (9.1%)	11 (28.9%)	12 (23.5%)	6 (5.9%)	101 (20.2%)
Constipation	23 (16.1%)	26 (17.9%)	6 (27.3%)	6 (15.8%)	12 (23.5%)	18 (17.6%)	91 (18.2%)
Skin and subcutaneous tissue disorders	117 (81.8%)	120 (82.8%)	10 (45.5%)	32 (84.2%)	45 (88.2%)	42 (41.2%)	366 (73.1%)
Dry skin	32 (22.4%)	48 (33.1%)	2 (9.1%)	12 (31.6%)	17 (33.3%)	5 (4.9%)	116 (23.2%)
Nail disorder	32 (22.4%)	31 (21.4%)	3 (13.6%)	13 (34.2%)	14 (27.5%)	11 (10.8%)	104 (20.8%)

Pruritus	31 (21.7%)	32 (22.1%)	2 (9.1%)	11 (28.9%)	16 (31.4%)	12 (11.8%)	104 (20.8%)
Rash	31 (21.7%)	21 (14.5%)	3 (13.6%)	6 (15.8%)	10 (19.6%)	12 (11.8%)	83 (16.6%)
General disorders and administration site conditions	110 (76.9%)	94 (64.8%)	15 (68.2%)	29 (76.3%)	44 (86.3%)	73 (71.6%)	365 (72.9%)
Pyrexia	56 (39.2%)	40 (27.6%)	7 (31.8%)	14 (36.8%)	16 (31.4%)	35 (34.3%)	168 (33.5%)
Fatigue	35 (24.5%)	40 (27.6%)	6 (27.3%)	13 (34.2%)	23 (45.1%)	39 (38.2%)	156 (31.1%)
Asthenia	39 (27.3%)	16 (11.0%)	4 (18.2%)	4 (10.5%)	5 (9.8%)	5 (4.9%)	73 (14.6%)
Immune system disorders	114 (79.7%)	109 (75.2%)	9 (40.9%)	32 (84.2%)	39 (76.5%)	50 (49.0%)	353 (70.5%)
Cytokine release syndrome	113 (79.0%)	108 (74.5%)	9 (40.9%)	32 (84.2%)	39 (76.5%)	50 (49.0%)	351 (70.1%)
Metabolism and nutrition disorders	77 (53.8%)	97 (66.9%)	14 (63.6%)	26 (68.4%)	29 (56.9%)	66 (64.7%)	309 (61.7%)
Decreased appetite	27 (18.9%)	38 (26.2%)	6 (27.3%)	5 (13.2%)	11 (21.6%)	15 (14.7%)	102 (20.4%)
Hypokalaemia	19 (13.3%)	30 (20.7%)	2 (9.1%)	7 (18.4%)	6 (11.8%)	13 (12.7%)	77 (15.4%)
Infections and infestations	84 (58.7%)	96 (66.2%)	11 (50.0%)	23 (60.5%)	37 (72.5%)	44 (43.1%)	295 (58.9%)
COVID-19	15 (10.5%)	34 (23.4%)	0	6 (15.8%)	6 (11.8%)	4 (3.9%)	65 (13.0%)
Investigations	86 (60.1%)	91 (62.8%)	8 (36.4%)	24 (63.2%)	27 (52.9%)	46 (45.1%)	282 (56.3%)
Weight decreased	59 (41.3%)	60 (41.4%)	3 (13.6%)	13 (34.2%)	15 (29.4%)	12 (11.8%)	162 (32.3%)
Respiratory, thoracic and mediastinal disorders	61 (42.7%)	62 (42.8%)	6 (27.3%)	21 (55.3%)	28 (54.9%)	57 (55.9%)	235 (46.9%)
Cough	28 (19.6%)	28 (19.3%)	2 (9.1%)	8 (21.1%)	16 (31.4%)	37 (36.3%)	119 (23.8%)

Key: RP2D=recommended Phase 2 dose, SC= Subcutaneous, IV= Intravenous; TEAE = treatment-emergent adverse event; CRS = cytokine release syndrome.
Note: RP2D includes Phase 1 RP2D treatment groups, Phase 2 Cohort A and Phase 2 Cohort C.
Note: IV includes all IV treatment groups; Non-RP2D(<RP2D) includes 5 ug/kg weekly, 15 ug/kg weekly, 45 ug/kg weekly and 135 ug/kg weekly treatment groups; Non-RP2D(>RP2D) includes 800 ug/kg weekly, 1200 ug/kg bi-weekly and 1600 ug/kg monthly treatment groups; Prior T cell exposures at RP2Ds includes Phase 1 RP2D 400 ug/kg weekly with prior CART or prior bispecific, Phase 1 RP2D 800 ug/kg biweekly with prior CART or prior bispecific and Phase 2 Cohort B treatment groups.
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 25.0.

Note: Percentages calculated with the number of subjects in the All Treated Analysis Set as denominator.
Note: The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.

Incidence of treatment-emergent adverse events related to talquetamab

The common related TEAE of asthenia occurred at a ≥10% higher frequency in treated participants assigned to 0.4 mg/kg weekly SC (21.7%) than 0.8 mg/kg Q2W SC (6.2%). The common related TEAE of dry mouth occurred at a ≥10% higher frequency in treated participants assigned to 0.8 mg/kg Q2W SC (37.9%) than 0.4 mg/kg weekly SC (21.7%). Although interpretation is limited due to a small sample size (n=51), participants with prior T cell redirection therapies exposure appeared to have relatively higher incidences for several common related TEAEs such as dysgeusia, dry mouth, skin and soft tissue disorders (including pruritis), fatigue, and cytopenia events (including neutropenia, thrombocytopenia, and leukopenia).

RP2D 0.4 mg/kg Weekly SC

The most frequently reported related TEAEs by preferred term (≥20% of participants) were CRS (79.0%), dysgeusia (48.3%), weight decreased (38.5%), neutropenia (28.7%), skin exfoliation (28%), pyrexia (27.3%), anaemia (25.2%), lymphopenia (21.7%), dry mouth (21.7%), asthenia (21.7%), dysphagia (21.0%). nail disorder (21%) and dry skin (20.3%).

RP2D 0.8 mg/kg Q2W SC

The most frequently reported related TEAEs by preferred term (≥20% of participants) were CRS (74.5%), dysgeusia (48.3%), skin exfoliation (38.6%), dry mouth (37.9%), weight decreased (35.9%), dry skin (31.7%), anaemia (24.8%), lymphopenia (24.1%), decreased appetite (24.1%), dysphagia (22.8 %), fatigue (22.1%), neutropenia (20.7%), nail disorder (20.7%) and ageusia (20%).

Participants with Prior T cell Redirection Therapies

The most frequently reported related TEAEs by preferred term (≥20% of participants) were CRS (76.5%), dysgeusia (60.8%), dry mouth (47.1%), neutropenia (45.1%), skin exfoliation (39.2%), fatigue (27.5%), dry skin (31.4%), thrombocytopenia (29.4%), nail disorder (25.5%), weight decreased (25.5%), pruritis (25.5%), anaemia (29.7%), leukopenia (23.5%), and dysphagia (21.6%), lymphopenia (28.3%), neutropenia (20.7%)

All Treated Participants

Investigators considered at least 1 TEAE to be related to study treatment for 97.6% of all treated participants. Higher incidences for several TEAEs were generally observed at doses higher than RP2Ds than those at RP2Ds or doses lower than non- RP2Ds, including CRS (84.2%), dysgeusia (76.3%), dry mouth (47.4%), lymphopenia (39.5%), and skin and subcutaneous tissue disorders such as skin exfoliation (47.4%) and nail disorder (31.6%).

Adverse drug reactions

The ADR analysis of TEAEs was conducted in a stepwise manner:

- Preferred terms representing the same clinical entity (e.g., neutropenia and low neutrophil counts) or closely related events (e.g., tachycardia and sinus tachycardia) were grouped to thoroughly evaluate the true incidence rate of these medical concepts. Grouped terms proposed by the sponsor were added per clinical judgment.
- Inclusion as an ADR of those AEs with an incidence rate of ≥10% (commonly reported) of participants treated with talquetamab and meeting at least 1 specified criterion for ADR classification (ie, evidence of dose response, medical importance, biologic plausibility, class effect, and typical safety concerns such as organ toxicity).
- Inclusion as an ADR of those AEs with an incidence rate <10% meeting at least 1 specified criterion for ADR classification:
  - Reported as serious in ≥2% of participants
  - Clinically relevant and medically important
  - Biologic plausibility.
- Laboratory abnormalities worsening from the baseline in ≥30% of participants following treatment with talquetamab.

Based on the above, the applicant's proposed list of ADRs is summarised in **Table 43.**

Table 43. Adverse reactions in multiple myeloma patients treated with JNJ-64407564 in MonumenTAL-1 with and without prior T-cell redirection therapy - data cut-off 16 May 2022

		RP2D including prior T-cell redirection therapy						
		All (N=339)			Talquetamab SC 400ug/kg QW (N=186)		Talquetamab SC 800ug/kg Q2W (N=153)	
			Incidence (%)		Incidence (%)		Incidence (%)	
System Organ Class	Adverse Reaction	Frequency (all grades)	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Infections and infestations	Upper respiratory tract infection[1]	Very common	70 (20.6%)	5 (1.5%)	48 (25.8%)	2 (1.1%)	22 (14.4%)	3 (2.0%)
	COVID-19[2]	Very common	38 (11.2%)	9 (2.7%)	20 (10.8%)	4 (2.2%)	18 (11.8%)	5 (3.3%)
	Bacterial infection[3]	Very common	36 (10.6%)	9 (2.7%)	19 (10.2%)	3 (1.6%)	17 (11.1%)	6 (3.9%)
	Fungal infection[4]	Very common	34 (10.0%)	1 (0.3%)	23 (12.4%)	1 (0.5%)	11 (7.2%)	0
	Pneumonia[5]	Common	20 (5.9%)	10 (2.9%)	12 (6.5%)	8 (4.3%)	8 (5.2%)	2 (1.3%)
	Viral infection[6]	Common	19 (5.6%)	6 (1.8%)	11 (5.9%)	4 (2.2%)	8 (5.2%)	2 (1.3%)
	Sepsis[7]	Common	15 (4.4%)	13 (3.8%)	10 (5.4%)	8 (4.3%)	5 (3.3%)	5 (3.3%)
Blood and lymphatic system disorders	Anaemia[8]	Very common	144 (42.5%)	94 (27.7%)	82 (44.1%)	56 (30.1%)	62 (40.5%)	38 (24.8%)
	Neutropenia[9]	Very common	116 (34.2%)	101 (29.8%)	70 (37.6%)	65 (34.9%)	46 (30.1%)	36 (23.5%)
	Thrombocytopenia	Very common	96 (28.3%)	67 (19.8%)	54 (29.0%)	42 (22.6%)	42 (27.5%)	25 (16.3%)
	Lymphopenia	Very common	86 (25.4%)	81 (23.9%)	47 (25.3%)	43 (23.1%)	39 (25.5%)	38 (24.8%)
	Leukopenia	Very common	57 (16.8%)	36 (10.6%)	34 (18.3%)	18 (9.7%)	23 (15.0%)	18 (11.8%)
Immune system disorders	Cytokine release syndrome	Very common	257 (75.8%)	5 (1.5%)	146 (78.5%)	4 (2.2%)	111 (72.5%)	1 (0.7%)
Metabolism and nutrition disorders	Decreased appetite	Very common	64 (18.9%)	4 (1.2%)	33 (17.7%)	2 (1.1%)	31 (20.3%)	2 (1.3%)
	Hypokalaemia	Very common	52 (15.3%)	10 (2.9%)	24 (12.9%)	3 (1.6%)	28 (18.3%)	7 (4.6%)
	Hypophosphataemia[10]	Very common	46 (13.6%)	20 (5.9%)	24 (12.9%)	10 (5.4%)	22 (14.4%)	10 (6.5%)
Nervous system disorders	Dysgeusia[11]	Very common	238 (70.2%)	0	133 (71.5%)	0	105 (68.6%)	0
	Headache[12]	Very common	63 (18.6%)	2 (0.6%)	35 (18.8%)	1 (0.5%)	28 (18.3%)	1 (0.7%)
	Encephalopathy[13]	Common	30 (8.8%)	0	19 (10.2%)	0	11 (7.2%)	0
	Immune effector cell-associated neurotoxicity syndrome	Common	25 (9.4%)	4 (1.5%)	14 (9.0%)	2 (1.3%)	11 (10.1%)	2 (1.8%)
Respiratory, thoracic and mediastinal disorders	Cough[14]	Very common	57 (16.8%)	0	35 (18.8%)	0	22 (14.4%)	0
	Dyspnoea[15]	Very common	36 (10.6%)	5 (1.5%)	22 (11.8%)	0	14 (9.2%)	5 (3.3%)
	Oral Pain[16]	Very common	34 (10.0%)	0	19 (10.2%)	0	15 (9.8%)	0
Gastrointestinal disorders	Dry mouth	Very common	114 (33.6%)	0	56 (30.1%)	0	58 (37.9%)	0

		RP2D including prior T-cell redirection therapy						
		All (N=339)			Talquetamab SC 400ug/kg QW (N=186)		Talquetamab SC 800ug/kg Q2W (N=153)	
			Incidence (%)		Incidence (%)		Incidence (%)	
System Organ Class	Adverse Reaction	Frequency (all grades)	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	Dysphagia	Very common	79 (23.3%)	3 (0.9%)	45 (24.2%)	0	34 (22.2%)	3 (2.0%)
	Diarrhoea	Very common	72 (21.2%)	3 (0.9%)	40 (21.5%)	3 (1.6%)	32 (20.9%)	0
	Stomatitis[17]	Very common	62 (18.3%)	4 (1.2%)	40 (21.5%)	3 (1.6%)	22 (14.4%)	1 (0.7%)
	Nausea	Very common	58 (17.1%)	0	33 (17.7%)	0	25 (16.3%)	0
	Constipation	Very common	54 (15.9%)	0	33 (17.7%)	0	21 (13.7%)	0
Skin and subcutaneous tissue disorders	Nail disorder[18]	Very common	168 (49.6%)	0	102 (54.8%)	0	66 (43.1%)	0
	Skin disorder[19]	Very common	139 (41.0%)	1 (0.3%)	73 (39.2%)	0	66 (43.1%)	1 (0.7%)
	Rash[20]	Very common	127 (37.5%)	12 (3.5%)	84 (45.2%)	4 (2.2%)	43 (28.1%)	8 (5.2%)
	Xerosis[21]	Very common	101 (29.8%)	0	51 (27.4%)	0	50 (32.7%)	0
	Pruritus	Very common	66 (19.5%)	1 (0.3%)	40 (21.5%)	0	26 (17.0%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[22]	Very common	146 (43.1%)	11 (3.2%)	90 (48.4%)	7 (3.8%)	56 (36.6%)	4 (2.6%)
General disorders and administration site conditions	Fatigue[23]	Very common	124 (36.6%)	12 (3.5%)	79 (42.5%)	9 (4.8%)	45 (29.4%)	3 (2.0%)
	Pyrexia[24]	Very common	102 (30.1%)	5 (1.5%)	65 (34.9%)	4 (2.2%)	37 (24.2%)	1 (0.7%)
	Pain[25]	Very common	60 (17.7%)	6 (1.8%)	38 (20.4%)	5 (2.7%)	22 (14.4%)	1 (0.7%)
	Oedema[26]	Very common	49 (14.5%)	0	26 (14.0%)	0	23 (15.0%)	0
	Injection site reaction[27]	Very common	44 (13.0%)	0	30 (16.1%)	0	14 (9.2%)	0
Investigations	Weight decreased	Very common	119 (35.1%)	5 (1.5%)	68 (36.6%)	3 (1.6%)	51 (33.3%)	2 (1.3%)
	Transaminase elevation[28]	Very common	42 (12.4%)	11 (3.2%)	20 (10.8%)	5 (2.7%)	22 (14.4%)	6 (3.9%)

Key: RP2D = recommended phase 2 dose, CRS = cytokine release syndrome, ICANS = immune effector cell-associated neurotoxicity syndrome
RP2D includes Phase 1 RP2D treatment group and Phase 2 cohorts A, B and C.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of talquetamab 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 24.1.
Note: The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.
Note: ICANs were only collected for phase 2. Denominators are based on number of subjects in Phase 2: 156 in the 400 ug/kg weekly group and 109 in the 800 ug/kg Bi-weekly group.
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

2.6.8.3. Serious adverse events, deaths, and other significant events

Serious Adverse Events

Serious adverse events At least 1 serious TEAE was reported for 244 subjects (48.7%) in the total All Treated Analysis Set. A summary of the most frequently reported serious TEAEs is provided in **Table 44**.

Table 44. Most common (At Least 2% in any RP2D group) treatment-emergent serious adverse events by system organ class, and preferred term; all treated analysis set (Study 64407564MMY1001)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		
Analysis set: All Treated	143	145	22	38	51	102	501
Subjects with 1 or more serious TEAEs	76 (53.1%)	70 (48.3%)	15 (68.2%)	17 (44.7%)	29 (56.9%)	37 (36.3%)	244 (48.7%)
MedDRAsystem organ class / preferred term							
Infections and infestations	27 (18.9%)	23 (15.9%)	6 (27.3%)	7 (18.4%)	10 (19.6%)	11 (10.8%)	84 (16.8%)
Pneumonia	4 (2.8%)	2 (1.4%)	0	2 (5.3%)	2 (3.9%)	4 (3.9%)	14 (2.8%)
COVID-19	2 (1.4%)	5 (3.4%)	0	0	0	1 (1.0%)	8 (1.6%)
Urinary tract infection	2 (1.4%)	0	2 (9.1%)	0	1 (2.0%)	1 (1.0%)	6 (1.2%)
COVID-19 pneumonia	1 (0.7%)	2 (1.4%)	0	0	1 (2.0%)	1 (1.0%)	5 (1.0%)
Disseminated varicella zoster virus infection	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Escherichia sepsis	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Escherichia urinary tract infection	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Metapneumovirus infection	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Pneumococcal sepsis	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Pneumonia influenzal	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Rash pustular	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Urinary tract infection pseudomonal	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Vascular device infection	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Immune system disorders	24 (16.8%)	15 (10.3%)	3 (13.6%)	4 (10.5%)	6 (11.8%)	9 (8.8%)	61 (12.2%)
Cytokine release syndrome	24 (16.8%)	15 (10.3%)	3 (13.6%)	4 (10.5%)	6 (11.8%)	8 (7.8%)	60 (12.0%)
Haemophagocytic lymphohistiocytosis	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Nervous system disorders	10 (7.0%)	13 (9.0%)	2 (9.1%)	3 (7.9%)	3 (5.9%)	1 (1.0%)	32 (6.4%)
Immune effector cell-associated neurotoxicity syndrome*	5 (4.1%)	4 (3.7%)	-	-	1 (2.9%)	-	10 (3.8%)
Syncope	1 (0.7%)	3 (2.1%)	0	0	1 (2.0%)	0	5 (1.0%)
Parkinson's disease	0	0	0	0	1 (2.0%)	0	1 (0.2%)
General disorders and administration site conditions	11 (7.7%)	8 (5.5%)	0	3 (7.9%)	5 (9.8%)	3 (2.9%)	30 (6.0%)
Pyrexia	8 (5.6%)	7 (4.8%)	0	3 (7.9%)	2 (3.9%)	2 (2.0%)	22 (4.4%)
Pain	1 (0.7%)	0	0	0	2 (3.9%)	0	3 (0.6%)
Chills	0	0	0	0	1 (2.0%)	1 (1.0%)	2 (0.4%)
Gait disturbance	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Injury, poisoning and procedural complications	6 (4.2%)	6 (4.1%)	0	2 (5.3%)	2 (3.9%)	6 (5.9%)	22 (4.4%)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		
Head injury	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Thoracic vertebral fracture	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Gastrointestinal disorders	5 (3.5%)	5 (3.4%)	3 (13.6%)	0	2 (3.9%)	6 (5.9%)	21 (4.2%)
Vomiting	0	0	0	0	1 (2.0%)	1 (1.0%)	2 (0.4%)
Noninfective sialoadenitis	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Musculoskeletal and connective tissue disorders	4 (2.8%)	7 (4.8%)	1 (4.5%)	2 (5.3%)	1 (2.0%)	3 (2.9%)	18 (3.6%)
Bone pain	1 (0.7%)	1 (0.7%)	1 (4.5%)	1 (2.6%)	1 (2.0%)	2 (2.0%)	7 (1.4%)
Respiratory, thoracic and mediastinal disorders	5 (3.5%)	6 (4.1%)	1 (4.5%)	1 (2.6%)	1 (2.0%)	3 (2.9%)	17 (3.4%)
Pleural effusion	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Blood and lymphatic system disorders	6 (4.2%)	3 (2.1%)	2 (9.1%)	1 (2.6%)	3 (5.9%)	1 (1.0%)	16 (3.2%)
Febrile neutropenia	3 (2.1%)	1 (0.7%)	1 (4.5%)	1 (2.6%)	0	0	6 (1.2%)
Neutropenia	0	0	0	0	3 (5.9%)	1 (1.0%)	4 (0.8%)
Leukopenia	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Renal and urinary disorders	3 (2.1%)	2 (1.4%)	1 (4.5%)	3 (7.9%)	1 (2.0%)	4 (3.9%)	14 (2.8%)
Acute kidney injury	1 (0.7%)	1 (0.7%)	0	3 (7.9%)	1 (2.0%)	1 (1.0%)	7 (1.4%)
Cardiac disorders	2 (1.4%)	3 (2.1%)	2 (9.1%)	1 (2.6%)	1 (2.0%)	3 (2.9%)	12 (2.4%)
Atrial fibrillation	1 (0.7%)	2 (1.4%)	0	0	1 (2.0%)	0	4 (0.8%)
Metabolism and nutrition disorders	3 (2.1%)	4 (2.8%)	1 (4.5%)	1 (2.6%)	0	3 (2.9%)	12 (2.4%)
Hypercalcaemia	3 (2.1%)	2 (1.4%)	1 (4.5%)	0	0	2 (2.0%)	8 (1.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.4%)	3 (2.1%)	0	3 (7.9%)	2 (3.9%)	0	10 (2.0%)
Cancer pain	1 (0.7%)	0	0	0	1 (2.0%)	0	2 (0.4%)
Myelodysplastic syndrome	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Skin and subcutaneous tissue disorders	1 (0.7%)	0	1 (4.5%)	1 (2.6%)	1 (2.0%)	1 (1.0%)	5 (1.0%)
Rash maculo-papular	1 (0.7%)	0	1 (4.5%)	0	1 (2.0%)	0	3 (0.6%)
Surgical and medical procedures	4 (2.8%)	0	0	0	1 (2.0%)	0	5 (1.0%)
Bone graft	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Endocrine disorders	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Inappropriate antidiuretic hormone secretion	0	0	0	0	1 (2.0%)	0	1 (0.2%)

Key: TEAE = treatment-emergent adverse event; IV = intravenous, SC = subcutaneous, RP2D=recommended Phase 2 dose; CRS=cytokine release syndrome.
Note: RP2D includes Phase 1 RP2D treatment groups, Phase 2 Cohort A and Phase 2 Cohort C.
Note: IV includes all IV treatment groups; Non-RP2D(<RP2D) includes 5 ug/kg weekly, 15 ug/kg weekly, 45 ug/kg weekly and 135 ug/kg weekly treatment groups; Non-RP2D(>RP2D) includes 800 ug/kg weekly, 1200 ug/kg bi-weekly and 1600 ug/kg monthly treatment groups; Prior T cell exposures at RP2Ds includes Phase 1 RP2D 400 ug/kg weekly with prior CART or prior bispecific, Phase 1 RP2D 800 ug/kg biweekly with prior CART or prior bispecific and Phase 2 Cohort B treatment groups.
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 25.0.
Note: The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.
** ICANs were only collected for phase 2. Denominators are based on number of subjects in Phase 2: 122 in the 400 ug/kg weekly group, 109 in the 800 ug/kg Bi-weekly group, 34 in the Prior T-cell exposures group, and 265 in the Total column.*
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of

talquetamab 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

Table 45. Summary of deaths and cause of death; all treated analysis set (Study 64407564MMY1001)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		
Analysis set: All Treated	143	145	22	38	51	102	501
Total number of subjects who died during study	48 (33.6%)	33 (22.8%)	2 (9.1%)	6 (15.8%)	20 (39.2%)	4 (3.9%)	113 (22.6%)
Primary cause of death							
Adverse event	6 (4.2%)	5 (3.4%)	0	4 (10.5%)	1 (2.0%)	0	16 (3.2%)
Study drug related[a]	0	0	0	0	0	0	0
AE(s) unrelated	6 (4.2%)	5 (3.4%)	0	4 (10.5%)	1 (2.0%)	0	16 (3.2%)
Adverse event - COVID-19	1 (0.7%)	1 (0.7%)	0	0	0	0	2 (0.4%)
Disease progression	28 (19.6%)	25 (17.2%)	1 (4.5%)	1 (2.6%)	19 (37.3%)	2 (2.0%)	76 (15.2%)
Other	14 (9.8%)	3 (2.1%)	1 (4.5%)	1 (2.6%)	0	2 (2.0%)	21 (4.2%)
Other - COVID-19 related	2 (1.4%)	0	0	0	0	0	2 (0.4%)
Total number of subjects who died within 30 days of last study treatment dose	9 (6.3%)	9 (6.2%)	2 (9.1%)	3 (7.9%)	2 (3.9%)	2 (2.0%)	27 (5.4%)
Primary cause of death							
Adverse event	4 (2.8%)	4 (2.8%)	0	2 (5.3%)	0	0	10 (2.0%)
Study drug related[a]	0	0	0	0	0	0	0
AE(s) unrelated	4 (2.8%)	4 (2.8%)	0	2 (5.3%)	0	0	10 (2.0%)
Adverse event - COVID-19	1 (0.7%)	1 (0.7%)	0	0	0	0	2 (0.4%)
Disease progression	4 (2.8%)	5 (3.4%)	1 (4.5%)	0	2 (3.9%)	1 (1.0%)	13 (2.6%)
Other	1 (0.7%)	0	1 (4.5%)	1 (2.6%)	0	1 (1.0%)	4 (0.8%)
Other - COVID-19 related	0	0	0	0	0	0	0
Total number of subjects who died within 60 days of first study treatment dose	8 (5.6%)	8 (5.5%)	1 (4.5%)	0	1 (2.0%)	2 (2.0%)	20 (4.0%)
Primary cause of death							
Adverse event	3 (2.1%)	4 (2.8%)	0	0	0	0	7 (1.4%)
Study drug related[a]	0	0	0	0	0	0	0
AE(s) unrelated	3 (2.1%)	4 (2.8%)	0	0	0	0	7 (1.4%)
Adverse event - COVID-19	0	1 (0.7%)	0	0	0	0	1 (0.2%)
Disease progression	4 (2.8%)	4 (2.8%)	1 (4.5%)	0	1 (2.0%)	1 (1.0%)	11 (2.2%)
Other	1 (0.7%)	0	0	0	0	1 (1.0%)	2 (0.4%)
Other - COVID-19 related	0	0	0	0	0	0	0

Key: AE = adverse event; RP2D = recommended Phase 2 dose, SC= Subcutaneous, IV= Intravenous.
Note: RP2D includes Phase 1 RP2D treatment groups, Phase 2 Cohort A and Phase 2 Cohort C.
Note: IV includes all IV treatment groups; Non-RP2D(<RP2D) includes 5 ug/kg weekly, 15 ug/kg weekly, 45 ug/kg weekly and 135 ug/kg weekly treatment groups; Non-RP2D(>RP2D) includes 800 ug/kg weekly, 1200 ug/kg bi-weekly and 1600 ug/kg monthly treatment groups; Prior T cell exposures

at RP2Ds includes Phase 1 RP2D 400 ug/kg weekly with prior CART or prior bispecific, Phase 1 RP2D 800 ug/kg biweekly with prior CART or prior bispecific and Phase 2 Cohort B treatment groups.
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.

Grade 5 Treatment-emergent Adverse Events

RP2D 0.4 mg/kg Weekly SC

Grade 5 TEAEs within 30 days of the last dose of talquetamab were reported for 5 participants (3.5%), none of which were judged by the investigator to be related to talquetamab:

- In 1 participant (0.7%) with a Grade 5 TEAE (general physical health deterioration), the investigator reported progressive disease was the primary cause of death.
- In the other 4 participants (2.8%), the following Grade 5 TEAEs were reported (one each): COVID 19 pneumonia, septic shock achieved, pulmonary embolism, fungal sepsis

RP2D 0.8 mg/kg Q2W SC

Grade 5 TEAEs within 30 days of the last dose of talquetamab were reported for 6 participants (4.1%), none of which were judged by the investigator to be related to talquetamab:

- In 2 participants (1.4%) with a Grade 5 TEAE, the investigator reported progressive disease was the primary cause of death.
- In the other 4 participants (2.8%), the following Grade 5 TEAEs were reported (one each): basilar artery occlusion, acute respiratory failure, infection and COVID 19 pneumonia.

Participants with Prior T cell Redirection Therapies

Grade 5 TEAE were not reported for any participant.

Adverse events of special interest

Based on the mechanism of action of talquetamab, specifically the activation of T cells, Cytokine Release Syndrome (CRS) and neurotoxicity events were anticipated events in this study. Multiple myeloma as a disease state is associated with cytopenias, hypogammaglobulinaemia, and an increased risk of infection. Other adverse events of clinical interest related to administration of talquetamab include sARRs, injection-site reactions, skin and nail toxicities, and oral toxicities.

Cytokine release syndrome

CRS was graded per American Society of Transplantation and Cellular Therapy (ASTCT) criteria in Phase 2 of Study 64407564MMY1001 and per Lee 2014 grading criteria in Phase 1. Grading of events in Phase 1 was converted during analysis to ASTCT criteria for participants treated at RP2Ds. Symptoms of CRS are presented as such, and not as separate TEAEs, to avoid duplication of events.

RP2D 0.4 mg/kg Weekly SC

At least 1 event of CRS (any grade) was reported for 113 participants (79.0%). Using ASTCT grading, the maximum severity of CRS was Grade 1 (62.2%), Grade 2 (14.7%), or Grade 3 (2.1%). No participant discontinued treatment due to CRS. No additional participants since the initial submission experienced a serious TEAE of CRS.

Per ASTCT criteria, all participants with CRS had at least a symptom of pyrexia. Other symptoms that occurred in ≥5% of participants were hypotension (13.3%), chills (9.1%), and hypoxia (7.7%). As

reported in the initial submission, the maximum severity of most symptoms of CRS was Grade 1 or 2. Grade 3 symptoms of CRS were pyrexia (6.3%) and hypotension (2.8%); no Grade 4 or 5 symptoms were reported.

RP2D 0.8 mg/kg Q2W SC

At least 1 event of CRS (any grade) was reported for 108 participants (74.5%). Using ASTCT grading, the maximum severity of CRS was Grade 1 (57.2%), Grade 2 (16.6%), or Grade 3 (0.7%).

Per ASTCT criteria, all but 1 participant with CRS had at least a symptom of pyrexia. Other symptoms of CRS that occurred in ≥5% of participants were hypotension (13.8%), chills (13.8%), hypoxia (6.2%), headache (5.5%), and tachycardia (5.5%). The maximum severity of most symptoms of CRS was Grade 1 or 2. Grade 3 symptoms of CRS included pyrexia (1.4%), and alanine aminotransferase increased, coagulopathy, dyspnoea, hepatitis, hypotension, hypoxia, and sinus tachycardia (1 participant each; 0.7%), One participant (0.7%) had Grade 4 aspartate aminotransferase increased, and 1 participant had Grade 4 hypotension. No Grade 5 symptoms of CRS were reported

Participants with Prior T cell Redirection Therapies

At least 1 event of CRS (any grade) was reported for 39 participants (76.5%). Using ASTCT grading, the maximum severity of CRS was Grade 1 (52.9%), Grade 2 (21.6%), or Grade 3 (2.0%). No participant discontinued treatment due to CRS.

Per ASTCT criteria, all but 1 participant with CRS had at least a symptom of pyrexia. Other symptoms of CRS that occurred in ≥5% of participants were hypotension (21.6%), chills (17.6%), tachycardia (9.8%), and hypoxia (7.8%). The maximum severity of most symptoms of CRS was Grade 1 or 2, and no Grade 4 or 5 symptoms were reported.

Neurologic adverse events and neurotoxicity

Neurologic adverse events

RP2D 0.4 mg/kg Weekly SC

At least 1 TEAE in the Nervous System Disorders SOC or Psychiatric Disorders SOC was reported for 86.0% of participants. The most commonly reported preferred terms were oral toxicities such as dysgeusia (48.3%), ageusia (19.6%), or taste disorder (7.0%); see Section 2.1.6.8 for a discussion of oral toxicity. Other commonly reported preferred terms (≥5%) for neurologic TEAEs were headache (18.2%), ICANS (10.7%), insomnia (7.0%), and dizziness (5.6%). Incidences for grouped terms were encephalopathy (9.8%), sensory neuropathy (8.4%), and motor dysfunction (3.5%). Grade 3 neurologic TEAEs were reported for 4.9% of participants; ICANS (1.6%) was the only Grade 3 neurologic TEAE reported for more than 1 participant. No Grade 4 or 5 neurologic TEAEs were reported. Serious neurologic TEAEs were ICANS (4.1%), encephalopathy (1.4%), and lethargy, spinal cord compression, and syncope.

RP2D 0.8 mg/kg Q2W SC

At least 1 TEAE in the Nervous System Disorders SOC or Psychiatric Disorders SOC was reported for 80.7% of participants. The most commonly reported preferred terms were oral toxicities such as dysgeusia (46.2%), ageusia (18.6%), or taste disorder (4.1%). Other commonly reported preferred terms (≥5%) for neurologic TEAEs were headache (18.6%), ICANS (10.1%), and dizziness (7.6%). Incidences for grouped terms were encephalopathy (7.6%), sensory neuropathy (4.8%), and motor dysfunction (2.1%). Grade 3 neurologic TEAEs were reported for 6.9% of participants, most commonly syncope (2.1%), ICANS (1.8%), and cerebrovascular accident (1.4%). One participant had Grade 4

basilar artery occlusion on Day 92 that progressed to Grade 5 on Day 94. The investigator considered the event to be unrelated to talquetamab. Serious neurologic TEAEs included ICANS (3.7%), cerebrovascular accident and syncope (each 1.4%), and basilar artery occlusion, nystagmus, and spinal cord compression (each 0.7%).

Participants with Prior T cell Redirection Therapies

At least 1 TEAE in the Nervous System Disorders SOC or Psychiatric Disorders SOC was reported for 84.3% of participants. The most commonly reported preferred terms were oral toxicities such as dysgeusia (60.8%), ageusia (11.8%), or taste disorder (5.9%). Other commonly reported preferred terms (≥5%) for neurologic TEAEs were headache (15.7%) and dizziness (7.8%). Incidences for grouped terms were encephalopathy (9.8%), sensory neuropathy (2.0%), and motor dysfunction (2.0%). A Grade 3 neurologic TEAE of syncope was reported for 1 participant. No Grade 4 or 5 neurologic TEAEs were reported. Serious neurologic TEAEs included ICANS, Parkinson's disease, and syncope, each in 1 participant.

Neurotoxicity

Neurotoxicity included all reported TEAEs in the Nervous System Disorders SOC or Psychiatric Disorders SOC (excluding oral toxicities: dysgeusia, ageusia, hypogeusia, and taste disorder) that were judged by the investigator to be related to talquetamab. Although ICANS is discussed separately in this Section, these events are also included in the discussion of neurotoxicity events.

RP2D 0.4 mg/kg Weekly SC

Neurotoxicity events were reported for 44 participants (30.8%). The most commonly reported preferred terms (≥5%) were ICANS (10.7%) and headache (9.1%). Grade 3 neurotoxicity events were reported for 2 participants (1.4%; both participants had Grade 3 ICANS). No Grade 4 or 5 neurotoxicity events were reported (one fatal ICANS event occurred at the investigational site in China that was outside of the scope of the MAA analyses). Serious neurotoxicity events were reported for 6 participants (4.2%), and included ICANS (4.1%) and encephalopathy (0.7%). Of the neurotoxicity events reported, 34.6% occurred concurrently with CRS (the neurotoxicity event occurred during or within 7 days after the end date of CRS).

At the latest clinical cut-off, 74.4% of neurotoxicity events had resolved, with a median duration of 4 days (range: 1 to 618). Two participants (1.4%) discontinued treatment due to a neurotoxicity event, both due to ICANS.

RP2D 0.8 mg/kg Q2W SC

Neurotoxicity events were reported for 43 participants (29.7%). The most commonly reported preferred terms for neurotoxicity events (≥5%) were ICANS (10.1%), headache (9.0%), and dizziness (6.9%). Grade 3 neurotoxicity events were reported for 4.8% of participants, including 3 participants with ICANS and 1 participant each with dizziness, headache, insomnia, or nystagmus. Grade 4 neurotoxicity was reported for 1 participant (ICANS). No Grade 5 neurotoxicity events were reported. Serious neurotoxicity events were reported for 7 participants (4.8%), and included ICANS (3.7%), and ataxia, dizziness, and nystagmus (each 0.7%). Of the neurotoxicity events reported, 28.4% occurred concurrently with CRS (the neurotoxicity event occurred during or within 7 days after the end date of CRS).

At the latest clinical cut-off, 62.2% of the neurotoxicity events had resolved, with a median duration of 5 days (range: 1 to 321). Two participants (1.4%) discontinued treatment due to a neurotoxicity event, 1 due to ICANS and 1 due to ataxia.

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

Neurotoxicity events were reported for 11 participants (21.6%). The most commonly reported preferred term (≥5%) was headache (9.8%). No Grade ≥3 neurotoxicity event was reported. A serious neurotoxicity event of ICANS was reported for 1 participant. Of the neurotoxicity events reported, 40.0% occurred concurrently with CRS (the neurotoxicity event occurred during or within 7 days after CRS).

At the latest clinical cut-off, 66.7% of neurotoxicity events had resolved, with a median duration of 2.5 days (range: 1 to 24). No participant discontinued treatment due to a neurotoxicity event

ICANS

As Phase 1 for Study 64407564MMY1001 started before the ASTCT consensus criteria for ICANS were implemented, ICANS could not be identified or excluded for participants in Phase 1. Therefore, the incidence and summary of ICANS reported in this section is limited to participants assigned to RP2Ds who were enrolled in Phase 2 of the study (Cohorts A, C, and B).

RP2D 0.4 mg/kg Weekly SC

In Cohort A (n=122), ICANS was reported for 13 participants (10.7%). Grade 3 ICANS was reported for 1.6% of participants; no Grade 4 or 5 ICANS was reported. A serious TEAE of ICANS was reported for 4.1% of participants. Fourteen of 21 ICANS events (66.7%) started concurrently with CRS (during or within 7 days of resolution of CRS).

At the latest clinical cut-off, 85.7% of the ICANS events had resolved. Two participants had unresolved ICANS events (both nonserious Grade 2 events), both of whom died while ICANS was ongoing (1 from multiple organ failure and 1 from progressive disease. 2 participants (1.6%) discontinued treatment due to ICANS (1 with Grade 2 ICANS and 1 with Grade 3 ICANS).

RP2D 0.8 mg/kg Q2W SC

In Cohort C (n=109), ICANS was reported for 12 participants (11.0%). Grade 3 ICANS was reported for 2.8% of participants. Grade 4 ICANS was reported for 1 participant (0.9%). No Grade 5 ICANS was reported. A serious TEAE of ICANS was reported for 3.7% of participants. Ten of 15 ICANS events (66.7%) started concurrently with CRS (during or within 7 days of resolution of CRS).

At the latest clinical cut-off, 80.0% of the ICANS events had resolved, including all Grade 3 events. Two participants had unresolved ICANS events at the updated clinical cut-off, including the participant with Grade 4 ICANS and a participant with a serious Grade 2 event, both of whom died due to progressive disease while ICANS was ongoing. 1 participant discontinued treatment due to ICANS.

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

In Cohort B (n=34), an ICANS event was reported for 1 participant (2.9%) and was concurrent with a CRS event. This was reported as a serious Grade 1 event. No participants discontinued treatment due to ICANS.

Systemic Administration-related Reactions

The frequencies of Systemic Administration-related Reactions (sARRs) in RP2D and other SC doses were low and similar. The switch from IV dosing to SC dosing in dose escalation substantially reduced the incidence of sARRs: at least 1 sARRs event was reported for 19.6% of participants in the IV cohorts).

RP2D 0.4 mg/kg Weekly SC

sARRs events were reported for 3.5% of participants. Pyrexia (2.1%) was the only sARRs event that was reported for more than 1 participant. The median time to onset of sARRs events was 3 days (range: 1 to 4) from the last injection, with a median duration of 3 days (range: 1 to 4).

RP2D 0.8 mg/kg Q2W SC

sARRs events were reported for 2.8% of participants. No sARRs event was reported for more than 1 participant. The median time to onset of sARRs events was 2.0 days (range: 1 to 4) from the last injection, with a median duration of 2.5 days (range: 1 to 6).

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

sARRs events were reported for 7.8% of participants. Pyrexia (3.9%) and rash (3.9%) were reported for more than 1 participant each. The median time to onset of sARRs events was 1.0 days (range: 1 to 2), with a median duration of 2.0 days (range: 1 to 9).

Injection-site Reactions

Injection site reactions (ISRs) reported in treated participants assigned to RP2Ds had a maximum severity of Grade 1 or Grade 2.

RP2D 0.4 mg/kg Weekly SC

ISR events were reported for 13.3% of participants. Injection site erythema (9.1%) and injection site rash (2.8%) were reported for ≥2% of participants. The median time to onset of ISR events was 2 days (range: 1 to 9) from the last injection, with a median duration of 9.5 days (range: 1 to 155).

RP2D 0.8 mg/kg Q2W SC

ISR events were reported for 9.7% of participants. Injection site erythema (5.5%) and injection site reaction (2.1%) were reported for ≥2% of participants. The median time to onset of ISR events was 1 day (range: 1 to 4), with a median duration of 6 days (range: 2 to 50).

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

ISR events were reported for 21.6% of participants. Injection site erythema (7.8%), injection site rash (5.9%), and injection site pruritus (3.9%) were reported for more than 1 participant. The median time to onset of ISR events was of 2 days (range: 1 to 4), with a median duration of 6.5 days (range: 1 to 43).

Hypogammaglobulinaemia

Multiple myeloma as a disease state is associated with hypogammaglobulinaemia (Lancman 2021). The incidence of hypogammaglobulinaemia was assessed based on both AE reporting by investigators (ie, the grouped term hypogammaglobulinaemia, which included the preferred terms hypogammaglobulinaemia, blood immunoglobulin G decreased, and hypoglobulinaemia), as well as by clinical laboratory data (hypogammaglobulinaemia defined as a postbaseline IgG value <500 mg/dL).

RP2D 0.4 mg/kg Weekly SC

Postbaseline IgG values consistent with hypogammaglobulinaemia were reported for 64.3% of participants. A TEAE in the grouped term for hypogammaglobulinaemia was reported for 4 participants (2.8%); the maximum severity of these events was Grade 2. One Grade 1 TEAE of hypogammaglobulinaemia was judged by the investigator as related to talquetamab, and no event of hypogammaglobulinaemia was a serious TEAE. No participant changed dosing or discontinued study

drug due to hypogammaglobulinaemia. Immunoglobulin treatment was administered at any time (before or after receiving talquetamab) in 13.3% of participants.

RP2D 0.8 mg/kg Q2W SC

Postbaseline IgG values consistent with hypogammaglobulinaemia were reported for 60.7% of participants. A TEAE in the grouped term for hypogammaglobulinaemia was reported for 3.4% of participants; the maximum severity of these events was Grade 2. Investigators considered these events to be related to talquetamab treatment but no event of hypogammaglobulinaemia was a serious TEAE. No participant discontinued study drug due to hypogammaglobulinaemia and the dose was reduced for 1 participant. Immunoglobulin treatment was administered at any time (before or after receiving talquetamab) in 9.7% of participants.

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

Postbaseline IgG values consistent with hypogammaglobulinaemia were reported for 66.7% of participants. A TEAE in the grouped term for hypogammaglobulinaemia was reported for 1 participant. The event was judged by the investigator as Grade 1 in severity and related to talquetamab and was not a serious TEAE. The participant did not change dosing or discontinue study drug due to hypogammaglobulinaemia. Immunoglobulin treatment was administered at any time (before or after receiving talquetamab) in 9.8% of participants.

Cytopenias

Events of cytopenia observed during study 64407564MMY1001are summarised in **Table 46**.

Table 46. Summary of treatment-emergent cytopenia; all treated analysis set (Study 64407564MMY1001)

	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Total Phase2 RP2D excluding Prior T-Cell Exposure	Prior T cell exposures
Analysis set: All Treated	143	145	288	51
Number of subjects with cytopenia	97 (67.8%)	107 (73.8%)	204 (70.8%)	39 (76.5%)
Number of subjects with anaemia				
Maximum toxicity grade				
Grade 1	4 (2.8%)	8 (5.5%)	12 (4.2%)	2 (3.9%)
Grade 2	15 (10.5%)	18 (12.4%)	33 (11.5%)	9 (17.6%)
Grade 3	45 (31.5%)	40 (27.6%)	85 (29.5%)	14 (27.5%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Number of subjects with supportive measures to treat anaemia	11 (7.7%)	7 (4.8%)	18 (6.3%)	3 (5.9%)
Granulocyte Stimulating Factor[a]	0	0	0	0
Antibiotics[b]	0	0	0	0
Erythropoietin Agent[c]	7 (4.9%)	4 (2.8%)	11 (3.8%)	2 (3.9%)
Other	4 (2.8%)	3 (2.1%)	7 (2.4%)	1 (2.0%)
Number of subjects with neutropenia				
Maximum toxicity grade				

	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Total Phase2 RP2D excluding Prior T-Cell Exposure	Prior T cell exposures
Grade 1	1 (0.7%)	3 (2.1%)	4 (1.4%)	0
Grade 2	5 (3.5%)	6 (4.1%)	11 (3.8%)	1 (2.0%)
Grade 3	30 (21.0%)	23 (15.9%)	53 (18.4%)	14 (27.5%)
Grade 4	15 (10.5%)	9 (6.2%)	24 (8.3%)	13 (25.5%)
Grade 5	0	0	0	0
Number of subjects with supportive measures to treat neutropenia	30 (21.0%)	22 (15.2%)	52 (18.1%)	18 (35.3%)
Granulocyte Stimulating Factor	29 (20.3%)	21 (14.5%)	50 (17.4%)	18 (35.3%)
Antibiotics[b]	4 (2.8%)	1 (0.7%)	5 (1.7%)	2 (3.9%)
Erythropoietin Agent[c]	0	0	0	0
Other	3 (2.1%)	1 (0.7%)	4 (1.4%)	0
Number of subjects with thrombocytopenia				
Maximum toxicity grade				
Grade 1	4 (2.8%)	10 (6.9%)	14 (4.9%)	3 (5.9%)
Grade 2	6 (4.2%)	6 (4.1%)	12 (4.2%)	1 (2.0%)
Grade 3	15 (10.5%)	13 (9.0%)	28 (9.7%)	8 (15.7%)
Grade 4	14 (9.8%)	14 (9.7%)	28 (9.7%)	7 (13.7%)
Grade 5	0	0	0	0
Number of subjects with supportive measures to treat thrombocytopenia	1 (0.7%)	0	1 (0.3%)	1 (2.0%)
Granulocyte Stimulating Factor	1 (0.7%)	0	1 (0.3%)	1 (2.0%)
Antibiotics	0	0	0	0
Erythropoietin Agent	0	0	0	0
Other	0	0	0	0
Number of subjects with lymphopenia				
Maximum toxicity grade				
Grade 1	1 (0.7%)	1 (0.7%)	2 (0.7%)	0
Grade 2	2 (1.4%)	2 (1.4%)	4 (1.4%)	2 (3.9%)
Grade 3	17 (11.9%)	13 (9.0%)	30 (10.4%)	1 (2.0%)
Grade 4	20 (14.0%)	26 (17.9%)	46 (16.0%)	6 (11.8%)
Grade 5	0	0	0	0
Number of subjects with supportive measures to treat lymphopenia	1 (0.7%)	3 (2.1%)	4 (1.4%)	0
Granulocyte Stimulating Factor	0	1 (0.7%)	1 (0.3%)	0
Antibiotics	1 (0.7%)	2 (1.4%)	3 (1.0%)	0
Erythropoietin Agent	0	0	0	0
Other	0	0	0	0

	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Total Phase2 RP2D excluding Prior T-Cell Exposure	Prior T cell exposures
Key: TEAE = treatment-emergent adverse event; RP2D = recommended Phase 2 dose; Note: Percentages are calculated with the number of subjects in the All Treated Analysis Set as denominator. Note: Adverse events are coded using MedDRA version 25.0. Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of talquetamab or until the start of subsequent anticancer therapy, if earlier.				

Infection

Serious infections, including life-threatening or fatal infections, have been reported in participants treated with talquetamab.

RP2D 0.4 mg/kg Weekly SC

At least 1 TEAE of infection (any grade) was reported for 84 participants (58.7%), The most frequently reported infections (≥5%) were upper respiratory tract infection (12.6%), COVID-19 (10.5%), urinary tract infection (9.8%), nasopharyngitis (9.8%), pneumonia (7.7%), and bronchitis (8.4%).

The maximum severity of infections was Grade 3 or 4 for 19.6% of participants. The following Grade 3 or 4 infections were reported in more than 1 participant each: pneumonia (3.5%), urinary tract infection (2.1%), and COVID-19 and sepsis (each 1.4%), 3 participants (2.1%) had a Grade 5 infection, including 1 participant each with COVID-19 pneumonia, fungal sepsis, and septic shock. Infections were reported as serious TEAEs in 27 participants (18.9%). One participant (0.7%) each discontinued study treatment due to fungal sepsis or pneumonia, reflecting no change since the initial submission.

RP2D 0.8 mg/kg Q2W SC

At least 1 TEAE of infection (any grade) was reported for 96 participants (66.2%). The most frequently reported infections (≥5%) were COVID-19 (23.4%), upper respiratory tract infection (9.0%), nasopharyngitis (6.9%), and pneumonia (6.2%).

The maximum severity of infections was Grade 3 or 4 for 15.9% of participants. The following Grade 3 or 4 infections were each reported in more than 1 participant: COVID-19 and pneumonia (each 2.1%), and cellulitis (1.4%). 2 participants (1.4%) had a Grade 5 infection, including 1 participant each with COVID-19 pneumonia and "infection" (unknown aetiology). Each of these participants had the same preferred term reported as a Grade 3 or 4 event before the Grade 5 event, and neither event was considered related to study drug. Infections were reported as serious TEAEs in 23 participants (15.9%). No participant discontinued study treatment due to an infection.

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

At least 1 TEAE of infection (any grade) was reported for 37 participants (72.5%). The most frequently reported infections (≥5%) were upper respiratory tract infection (17.6%), COVID-19 and urinary tract infection (each 11.8%), rhinovirus infection (7.8%), and pneumonia and respiratory tract infection (each 5.9%).

The maximum severity of infections was Grade 3 or 4 for 27.5% of participants. The following Grade 3 or 4 infections were each reported in more than 1 participant: pneumonia (5.9%), and urinary tract

infection and Escherichia urinary tract infection (each 3.9%). No participant had a Grade 5 infection. Infections were reported as serious TEAEs in 10 participants (19.6%). 1 participant discontinued study treatment due to an infection (rash pustular).

COVID-19

COVID-19 as a grouped term was reported with a higher incidence in participants assigned to 0.8 mg/kg Q2W SC than 0.4 mg/kg weekly SC and participants assigned to RP2Ds with prior T cell redirection therapies (26.2% vs 11.2% and 13.7%, respectively). This may in part be explained by the circulation of more infectious COVID-19 variants (Omicron) at the time that greater numbers of participants were receiving study treatment in the 0.8 mg/kg Q2W SC cohort than the 0.4 mg/kg weekly SC cohort.

RP2D 0.4 mg/kg Weekly SC

As a grouped term, COVID-19 was reported for 16 participants (11.2%). The maximum severity of COVID-19 was Grade 3 for 2 participants and Grade 5 (fatal) for 1 participant. COVID-19 led to skipped doses in 5.6% of participants. No participant discontinued study drug due to COVID-19. Vaccination for COVID-19 was reported for 59.4% of participants.

RP2D 0.8 mg/kg Q2W SC

COVID-19 was reported for 38 participants (26.2%). The maximum severity of COVID-19 was Grade 3 for 2.8% and Grade 5 (fatal) for 0.7% (1 participant). COVID-19 led to skipped doses in 8.3% of participants. No participant discontinued study drug due to COVID-19. Vaccination for COVID-19 was reported for 62.8% of participants.

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

COVID-19 was reported for 7 participants (13.7%). The maximum severity of COVID-19 was Grade 3 for 3.9% and Grade 4 or 5 for no participant. COVID-19 led to skipped doses in 5.9% of participants. No participant discontinued study drug due to COVID-19. Vaccination for COVID-19 was reported for 41.2% of participants.

Opportunistic infections

Opportunistic infections, i.e., those that occur more often or more severely in the setting of immunosuppression, were evaluated as a grouped term.

RP2D 0.4 mg/kg Weekly SC

Opportunistic infections were reported for 5 participants (3.5%). First onset occurred during step-up dosing or the first 4 treatment cycles. As reported in the initial submission, 1 opportunistic infection (fungal sepsis) led to treatment discontinuation and was fatal.

RP2D 0.8 mg/kg Q2W SC

Opportunistic infections were reported for 8 participants (5.5%). First onset to opportunistic infections usually occurred during the first 4 treatment cycles or during later treatment cycles. No opportunistic infection led to treatment discontinuation or was fatal.

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

Opportunistic infections were reported for 3 participants (5.9%). No opportunistic infection led to treatment discontinuation or was fatal.

Herpes Infections

RP2D 0.4 mg/kg Weekly SC

1 participant experienced herpes zoster. In addition, 1 participant experienced oral herpes Most participants received an antiviral medication either prophylactically (88.8%) or concomitantly (91.6%).

RP2D 0.8 mg/kg Q2W SC

1 participant experienced Grade 2 ophthalmic herpes. In addition, 1 participant each experienced herpes zoster, human herpesvirus-6 infection and oral herpes, Most participants received an antiviral medication either prophylactically (82.8%) or concomitantly (87.6%).

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

Two participants experienced oral herpes, and 1 participant experienced herpes zoster. Most participants received an antiviral medication either prophylactically (90.2%) or concomitantly (94.1%).

Infection and neutropenia

RP2D 0.4 mg/kg Weekly SC

Among 84 participants with an infection (any grade) during the study, 11 (13.1%) had the infection concurrently with Grade 3 or 4 neutropenia. Among 31 participants with a Grade 3 or 4 infection during the study, 4 (12.9%) had the infection concurrently with Grade 3 or 4 neutropenia.

RP2D 0.8 mg/kg Q2W SC

Among 96 participants with an infection (any grade) during the study, 3 (3.1%) had the infection concurrently with Grade 3 or 4 neutropenia. Among 23 participants with a Grade 3 or 4 infection during the study, 1 (4.4%) had the infection concurrently with Grade 3 or 4 neutropenia.

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

Among 37 participants with an infection (any grade) during the study, 9 (24.3%) had the infection concurrently with Grade 3 or 4 neutropenia. Among 14 participants with a Grade 3 or 4 infection during the study, 1 (7.1%) had the infection concurrently with Grade 3 or 4 neutropenia.

Tumour lysis syndrome

A TEAE of TLS was reported for 1 participant assigned to 0.8 mg/kg Q2W SC. This was a Grade 3 TEAE of TLS that started on Day 3, after Step-up Dose 1; study drug was interrupted for this event and was not restarted before the participant died of an infection of unknown aetiology on Day 17 that the investigator did not consider to be related to study drug.

Second primary malignancies

The frequencies of second primary malignancy in RP2D and SC doses lower than RP2D were similar; a slightly rate was observed in participants treated at SC doses higher than RP2D (**Table 47**).

Table 47. Summary of second primary malignancies; all treated analysis set (Study 64407564MMY1001)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		
Analysis set: All Treated	143	145	22	38	51	102	501
Subjects with second primary malignancies	5 (3.5%)	4 (2.8%)	0	4 (10.5%)	3 (5.9%)	0	16 (3.2%)
Type / preferred term							
Cutaneous	4 (2.8%)	1 (0.7%)	0	2 (5.3%)	0	0	7 (1.4%)
Basal cell carcinoma	1 (0.7%)	1 (0.7%)	0	0	0	0	2 (0.4%)
Squamous cell carcinoma	0	0	0	2 (5.3%)	0	0	2 (0.4%)
Bowen's disease	1 (0.7%)	0	0	0	0	0	1 (0.2%)
Malignant melanoma	1 (0.7%)	0	0	0	0	0	1 (0.2%)
Squamous cell carcinoma of skin	1 (0.7%)	0	0	0	0	0	1 (0.2%)
Invasive Solid Malignancy	1 (0.7%)	2 (1.4%)	0	1 (2.6%)	1 (2.0%)	0	5 (1.0%)
Hepatic neoplasm	1 (0.7%)	0	0	0	0	0	1 (0.2%)
Hepatocellular carcinoma	0	1 (0.7%)	0	0	0	0	1 (0.2%)
Invasive ductal breast carcinoma	0	1 (0.7%)	0	0	0	0	1 (0.2%)
Neuroendocrine carcinoma	0	0	0	1 (2.6%)	0	0	1 (0.2%)
Prostate cancer metastatic	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Invasive Haematologic Malignancy	0	1 (0.7%)	0	0	1 (2.0%)	0	2 (0.4%)
Acute myeloid leukaemia	0	1 (0.7%)	0	0	0	0	1 (0.2%)
Myelodysplastic syndrome	0	0	0	0	1 (2.0%)	0	1 (0.2%)
Uncoded	0	0	0	1 (2.6%)	1 (2.0%)	0	2 (0.4%)
Missing AETERM	0	0	0	1 (2.6%)	1 (2.0%)	0	2 (0.4%)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		

Key: RP2D=recommended Phase 2 dose, SC= Subcutaneous, IV= Intravenous.
Note: RP2D includes Phase 1 RP2D treatment groups, Phase 2 Cohort A and Phase 2 Cohort C.
Note: IV includes all IV treatment groups; Non-RP2D(<RP2D) includes 5 ug/kg weekly, 15 ug/kg weekly, 45 ug/kg weekly and 135 ug/kg weekly treatment groups; Non-RP2D(>RP2D) includes 800 ug/kg weekly, 1200 ug/kg bi-weekly and 1600 ug/kg monthly treatment groups; Prior T cell exposures at RP2Ds includes Phase 1 RP2D 400 ug/kg weekly with prior CART or prior bispecific, Phase 1 RP2D 800 ug/kg biweekly with prior CART or prior bispecific and Phase 2 Cohort B treatment groups.
Note: Percentages are calculated with the number of subjects in the All Treated Analysis Set as denominator.
Note: Include all second primary malignancies reported during the study.
Note: Adverse events were coded using MedDRA version 25.0.

Weight decreased

RP2D 0.4 mg/kg Weekly SC

A TEAE of weight decreased was reported for 41.3% of participants. The maximum severity for these events was Grade 1 (16.1%), Grade 2 (23.2%), or Grade 3 (2.1%). Most events of weight decreased occurred in Cycle 2 or later. Among the participants with a TEAE of weight decreased, 20.3% had dysgeusia TEAEs, 10.2% had dry mouth, and 8.5% had decreased appetite concurrently (or within 30 days of the end date of weight decreased). A TEAE of weight decreased led to dose modification for 4.9% of participants (all had a dose reduction; 2.8% skipped a dose). One participant discontinued study drug for a TEAE of weight decreased. By the clinical cut-off, 45.5% of weight decreased TEAEs had resolved, with a median duration of 72 days (range: 2 to 568).

RP2D 0.8 mg/kg Q2W SC

A TEAE of weight decreased was reported for 41.4% of participants. The maximum severity for these events was Grade 1 (15.2%), Grade 2 (20.7%), or Grade 3 (5.5%). Most participants experienced weight decreased in Cycle 2 or later. Among the participants with a TEAE of weight decreased, 23.3% had dysgeusia, 10.0% had dry mouth, and 8.3% had decreased appetite concurrently (or within 30 days of the end date of weight decreased). A TEAE of weight decreased led to dose modification for 4.1% of participants (2.8% dose reduction and 0.7% delayed dose). One participant discontinued study drug for a TEAE of weight decreased. By the clinical cut-off, 31.8% of weight decreased TEAEs had resolved, with a median duration of 58 days (range: 1 to 382).

Participants with Prior T cell Redirection Therapies

A TEAE of weight decreased was reported for 29.4% of participants. The maximum severity for these events was Grade 1 (11.8%) or Grade 2 (17.6%). Most participants experienced weight decreased in Cycle 2 or later. Dose modifications for a TEAE of weight decreased included reduced dosing (3.9%) and skipped doses (2.0%). Among the participants with a TEAE of weight decreased, 13.3% had dysgeusia TEAEs, 20.0% had dry mouth, and 13.3% had decreased appetite concurrently. By the clinical cut-off, 38.9% of weight decreased TEAEs had resolved, with a median duration of 64 days (range: 8 to 253). One participant discontinued study drug due to a TEAE of weight decreased.

Skin toxicity

RP2D 0.4 mg/kg Weekly SC

Non-rash skin toxicity TEAEs (skin exfoliation, dry skin, pruritus, or palmar-plantar erythrodysesthesia syndrome) were reported for 80 participants (55.9%). The maximum severity of these events was Grade 1 (30.1%) or Grade 2 (25.9%). 60.0% of skin toxicity events had resolved, with a median duration of 36 days (range: 1 to 685). Two participants discontinued study treatment due to a TEAE of skin exfoliation.

Rash TEAEs were reported for 57 participants (39.9%). The maximum severity of these events was Grade 1 (19.6%), Grade 2 (18.9%), or Grade 3 (1.4%). 88.9% of rash events had resolved, with a median duration of 28 days (range: 1 to 127). No participant discontinued study treatment due to a TEAE of rash.

RP2D 0.8 mg/kg Q2W SC

Non-rash skin toxicity TEAEs were reported for 106 participants (73.1%). The maximum severity of these events was Grade 1 (44.8%), Grade 2 (27.6%), or Grade 3 (0.7%). 57.2% of skin toxicity events had resolved, with a median duration of 39 days (range: 1 to 313). 1 participant discontinued study treatment due to a TEAE of dermatitis exfoliative generalised.

Rash TEAEs were reported for 43 participants (29.7%). The maximum severity was Grade 1 (16.6%), Grade 2 (7.6%), or Grade 3 (5.5%). 72.3% of rash events had resolved, with a median duration of 26 days (range: 1 to 174). No participant discontinued study treatment due to a TEAE of rash.

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

Non-rash skin toxicity TEAEs were reported for 35 participants (68.6%). The maximum severity was Grade 1 (47.1%) or Grade 2 (21.6%). 63.4% of skin toxicity events had resolved, with a median duration of 32 days (range: 4 to 218). No participant discontinued study treatment due to skin toxicity.

Rash TEAEs were reported for 18 participants (35.3%). The maximum severity was Grade 1 (15.7%), Grade 2 (15.7%), or Grade 3 (3.9%). 71.0% of rash events had resolved, with a median duration of 15 days (range: 4 to 183). No participant discontinued study treatment due to a TEAE of rash.

Nail toxicity

RP2D 0.4 mg/kg Weekly SC

Nail disorder TEAEs were reported for 78 participants (54.5%). The maximum severity was Grade 1 (37.1%) or Grade 2 (17.5%). 32.7% of nail disorder events resolved, with a median duration of 88.5 days (range: 1 to 679). 1 participant discontinued study treatment due to a TEAE of nail disorder.

RP2D 0.8 mg/kg Q2W SC

Nail disorder TEAEs were reported for 78 participants (53.8%). The maximum severity was Grade 1 (46.9%) or Grade 2 (6.9%). These events occurred in Cycle 1 or later, with a median onset of 67.5 days (range: 1 to 402) from the initial step-up dose. Various supportive measures were used in 7.6% of participants. No nail disorder led to a dose skip, dose reduction, or dose delay. 25.5% of nail disorder events had resolved, with a median duration of 74 days (range: 14 to 388). No participant discontinued study treatment due to a TEAE of nail disorder.

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

Nail disorder TEAEs were reported for 32 participants (62.7%). The maximum severity was Grade 1 (58.8%) or Grade 2 (3.9%). 31.7% of nail disorder events had resolved, with a median duration of 122.0 days (range: 1 to 461). No participant discontinued study treatment due to a nail toxicity.

Oral toxicity

Dysgeusia and other types of oral toxicity (dry mouth, dysphagia, and oropharyngeal pain) appeared to increase at doses higher than RP2Ds compared with RP2Ds or lower doses, but they rarely led to discontinuation of study treatment.

RP2D 0.4 mg/kg Weekly SC

Dysgeusia TEAEs (ageusia, dysgeusia, hypogeusia, or taste disorder) were reported for 103 participants (72.0%). The maximum severity was Grade 1 (42.7%) or Grade 2 (29.4%), the maximum possible grade by CTCAE. Median time to onset from the initial step-up dose was 20 days (range: 1 to 576). No participant discontinued study treatment for dysgeusia TEAEs. 45.7% of dysgeusia TEAE events had resolved, with a median duration of 95.0 days (range: 4 to 586). Of the 103 participants with dysgeusia TEAEs, concurrent events (during or within 30 days of the end date of the dysgeusia TEAE) included dry mouth for 19.4% and decreased appetite for 10.7%.

A TEAE of dry mouth was reported for 38 participants (26.6%). The maximum severity was Grade 1 (15.4%) or Grade 2 (11.2%); Grade 3 was the maximum possible grade by CTCAE. No participant discontinued study treatment for a TEAE of dry mouth. 50.0% of TEAEs of dry mouth had resolved, with a median duration of 57 days (range: 3 to 263).

A TEAE of decreased appetite was reported for 27 participants (18.9%). The maximum severity was Grade 1 (9.8%), Grade 2 (7.7%), or Grade 3 (1.4%). No participant discontinued study treatment for a TEAE of decreased appetite. 55.2% of TEAEs of decreased appetite had resolved, with a median duration of 71 days (range: 27 to 466).

A TEAE of dysphagia was reported for 34 participants (23.8%). The maximum severity was Grade 1 (13.3%) or Grade 2 (10.5%). No participant discontinued study treatment for a TEAE of dysphagia, 1.4% had a dose interruption, and no participant had a dose reduction.

A TEAE of stomatitis was reported for 19 participants (13.3%). The maximum severity was Grade 1 (3.5%), Grade 2 (9.1%), or Grade 3 (1 participant; 0.7%). No participant discontinued study treatment or had a dose reduction for a TEAE of stomatitis. Three participants (2.1%) had a dose interruption for a TEAE of stomatitis.

RP2D 0.8 mg/kg Q2W SC

Dysgeusia TEAEs were reported for 103 participants (71.0%). The maximum severity was Grade 1 (41.4%) or Grade 2 (29.7%), the maximum possible grade by CTCAE. Median time to onset from the initial step-up dose was 15 days (range: 1 to 340). 2 participants (1.4%) discontinued study treatment due to a dysgeusia TEAE. 30.8% of dysgeusia TEAE events had resolved, with a median duration of 102 days (range: 15 to 504). Of the 103 participants with dysgeusia TEAEs, concurrent events (during or within 30 days) included dry mouth for 15.7% and decreased appetite for 11.8%.

A TEAE of dry mouth was reported for 58 participants (40.0%). The maximum severity was Grade 1 (26.9%) or Grade 2 (13.1%). These events usually occurred in Cycle 1 or later. Various supportive measures were used in 12.4% of participants. No participant discontinued study treatment, 2.1% had a dose reduction, and 1.4% skipped a dose for a TEAE of dry mouth. 31.1% of TEAEs of dry mouth had resolved, with a median duration of 89 days (range: 1 to 317).

A TEAE of decreased appetite was reported for 38 participants (26.2%). The maximum severity was Grade 1 (17.2%), Grade 2 (7.6%), or Grade 3 (1.4%). 42.1% of TEAEs of decreased appetite had resolved, with a median duration of 52 days (range: 3 to 334).

A TEAE of dysphagia was reported for 36 participants (24.8%). The maximum severity was Grade 1 (15.2%), Grade 2 (7.6%), or Grade 3 (2.1%). No participant discontinued study treatment for a TEAE of dysphagia, 1.4% had a dose interruption, and 0.7% had a dose reduction.

A TEAE of stomatitis was reported for 8 participants (5.5%). The maximum severity was Grade 1 (0.7%), Grade 2 (4.1%) or Grade 3 (0.7%). No participant discontinued study treatment, 0.7% had a dose interruption, and no participant had a dose reduction for a TEAE of stomatitis.

Participants Assigned to RP2Ds with Prior T cell Redirection Therapies

Dysgeusia TEAEs (were reported for 39 participants (76.5%). The maximum severity was Grade 1 (51.0%) or Grade 2 (25.5%), the maximum possible grade by CTCAE. No participant discontinued study treatment for dysgeusia TEAEs. 37.0% of dysgeusia TEAE events had resolved, with a median duration of 130 days (range: 8 to 459). Of the 39 participants with dysgeusia TEAEs, concurrent events (during or within 30 days of the end date of the dysgeusia TEAE) included dry mouth for 20.5% and decreased appetite for 2.6%.

A TEAE of dry mouth was reported for 26 participants (51.0%). The maximum severity was Grade 1 (37.3%) or Grade 2 (13.7%). No participant discontinued study treatment for a TEAE of dry mouth. 40.6% of TEAEs of dry mouth had resolved, with a median duration of 58.5 days (range: 8 to 404).

A TEAE of decreased appetite was reported for 11 participants (21.6%). The maximum severity was Grade 1 (11.8%) or Grade 2 (9.8%). No participant discontinued study treatment for a TEAE of decreased appetite. 27.3% of TEAEs of decreased appetite had resolved, with a median duration of 19 days (range: 6 to 79).

A TEAE of dysphagia was reported for 12 participants (23.5%). The maximum severity was Grade 1 (13.7%) or Grade 2 (9.8%). No participant discontinued study treatment for a TEAE of dysphagia, 2.0% had a dose interruption, and 3.9% had a dose reduction.

A TEAE of stomatitis was reported for 7 participants (13.7%). The maximum severity was Grade 1 (5.9%) or Grade 2 (7.8%). No participant discontinued study treatment, 5.9% had a dose interruption, and no participant had a dose reduction for a TEAE of stomatitis.

2.6.8.4. Laboratory findings

Haematology

For the total All Treated Analysis Set, a worsening postbaseline shift of 1 to 2 toxicity grades was commonly observed, and worsening shifts of up to 4 grades from baseline (ie, Grade 0 to Grade 4) were observed for neutrophils, lymphocytes, platelets, and WBC. Similar trends were observed for subjects assigned to RP2D, SC non-RP2D, or IV treatments.

Chemistry

For the total All Treated Analysis Set a worsening postbaseline shift of 1 to 2 toxicity grades was commonly observed. Worsening shifts of 3 or 4 grades from baseline were observed in small numbers of participants for most analytes.

Among treated participants assigned to the RP2Ds, Grade 3 and Grade 4 chemistry laboratory abnormalities were infrequent during treatment, including those related to liver function tests such as ALT, AST, and serum creatinine; no participants met criteria for Hy’s law.

Coagulation

Coagulation was assessed at screening, at each step-up dose, at the first 2 treatment doses, and as clinically indicated thereafter (including if a participant developed CRS). Grade 3 international normalised ratio (INR) increased, activated partial thromboplastin time prolonged, and fibrinogen decreased was observed for <4% of participants who received talquetamab, and a Grade 4 worsening was observed for decreased fibrinogen for 4.3% of participants with prior T cell redirection therapies exposure and 0.9% of treated participants assigned to 0.8 mg/kg Q2W SC. Similar trends were observed for participants assigned to RP2D, SC non-RP2D, or IV treatment.

Vital signs and physical findings

Small fluctuations in vital sign values were observed immediately following administration of study drug; however, no clinically meaningful trends were observed.

Electrocardiograms

Intensive ECG monitoring was conducted in Phase 1. Mean and median changes from baseline in ECG parameters were not considered clinically meaningful.

In Phase 2, 12-lead ECGs were performed only at baseline or when clinically indicated. Two treated participants assigned to 0.4 mg/kg weekly SC (atrial fibrillation, sinus bradycardia) and 6 treated participants assigned to 0.8 mg/kg Q2W SC (sinus tachycardia in 3 participants, and atrial fibrillation, AV block, and loss of consciousness) had a clinically significant abnormality on ECG postbaseline that was not reported at screening. Three participants with prior T cell redirection therapies exposure had a clinically significant abnormality (supraventricular tachycardia, atrial fibrillation, sinus tachycardia) on ECG postbaseline that was not reported at screening.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

- **Pregnant and breastfeeding women**

There is no available data on talquetamab use in pregnant and breastfeeding women.

- **Intrinsic Factors**

Treatment emergent adverse events by age, sex, race, renal and hepatic function and % bone marrow plasma cells are summarised in **Table 48** (RP2D 0.4 mg/kg Weekly SC) and **Table 49** (0RP2D 0.8 mg/kg Q2W).

Table 48. Subgroup analysis on overview of treatment emergent adverse events: all treated analysis set (Study 64407564MMY1001, RP2D 0.4 mg/kg Weekly SC)

	N	TEAE	Serious TEAE	Grade 3 or 4 TEAE	TD due to TEAE [a]	Death due to TEAE [b]
SC RP2D(400 ug/kg weekly)						
All subjects	143	143 (100.0%)	75 (52.4%)	109 (76.2%)	7 (4.9%)	5 (3.5%)
Age:						
<65 years	65	65 (100.0%)	30 (46.2%)	48 (73.8%)	3 (4.6%)	0
65-<75 years	57	57 (100.0%)	32 (56.1%)	43 (75.4%)	1 (1.8%)	1 (1.8%)
>=75 years	21	21 (100.0%)	13 (61.9%)	18 (85.7%)	3 (14.3%)	4 (19.0%)
Sex:						
Male	78	78 (100.0%)	36 (46.2%)	57 (73.1%)	3 (3.8%)	3 (3.8%)
Female	65	65 (100.0%)	39 (60.0%)	52 (80.0%)	4 (6.2%)	2 (3.1%)
Race:						
White	128	128 (100.0%)	67 (52.3%)	97 (75.8%)	6 (4.7%)	5 (3.9%)
Black/African American	12	12 (100.0%)	5 (41.7%)	10 (83.3%)	1 (8.3%)	0
Other	3	3 (100.0%)	3 (100.0%)	2 (66.7%)	0	0
Renal function:						
<30 mL/min/1.73m^2	0	0	0	0	0	0
30- <60 mL/min/1.73m^2	40	40 (100.0%)	25 (62.5%)	34 (85.0%)	2 (5.0%)	4 (10.0%)
60-<90 mL/min/1.73m^2	72	72 (100.0%)	33 (45.8%)	53 (73.6%)	3 (4.2%)	1 (1.4%)
≥ 90 mL/min/1.73m^2	31	31 (100.0%)	17 (54.8%)	22 (71.0%)	2 (6.5%)	0
Hepatic function:						
Normal	120	120 (100.0%)	61 (50.8%)	89 (74.2%)	6 (5.0%)	4 (3.3%)
Impaired	23	23 (100.0%)	14 (60.9%)	20 (87.0%)	1 (4.3%)	1 (4.3%)
Bone Marrow % Plasma cells:						
≤30%	106	106 (100.0%)	56 (52.8%)	80 (75.5%)	5 (4.7%)	2 (1.9%)
>30 - <60%	15	15 (100.0%)	8 (53.3%)	11 (73.3%)	2 (13.3%)	3 (20.0%)
≥ 60%	17	17 (100.0%)	7 (41.2%)	13 (76.5%)	0	0

Table 49. Subgroup analysis on overview of treatment emergent adverse events: all treated analysis set (Study 64407564MMY1001, RP2D 0.8 mg/kg Q2W)

	N	TEAE	Serious TEAE	Grade 3 or 4 TEAE	TD due to TEAE [a]	Death due to TEAE [b]
SC RP2D(800 ug/kg Bi-weekly)						
All subjects	145	145 (100.0%)	59 (40.7%)	101 (69.7%)	9 (6.2%)	6 (4.1%)
Age:						
<65 years	63	63 (100.0%)	25 (39.7%)	46 (73.0%)	5 (7.9%)	3 (4.8%)
65-<75 years	50	50 (100.0%)	22 (44.0%)	38 (76.0%)	2 (4.0%)	2 (4.0%)
>=75 years	32	32 (100.0%)	12 (37.5%)	17 (53.1%)	2 (6.3%)	1 (3.1%)
Sex:						
Male	83	83 (100.0%)	36 (43.4%)	56 (67.5%)	6 (7.2%)	3 (3.6%)
Female	62	62 (100.0%)	23 (37.1%)	45 (72.6%)	3 (4.8%)	3 (4.8%)
Race:						
White	125	125 (100.0%)	48 (38.4%)	82 (65.6%)	8 (6.4%)	5 (4.0%)
Black/African American	9	9 (100.0%)	4 (44.4%)	8 (88.9%)	1 (11.1%)	0
Other	11	11 (100.0%)	7 (63.6%)	11 (100.0%)	0	1 (9.1%)
Renal function:						
<30 mL/min/1.73m^2	0	0	0	0	0	0
30- <60 mL/min/1.73m^2	45	45 (100.0%)	17 (37.8%)	32 (71.1%)	4 (8.9%)	4 (8.9%)
60-<90 mL/min/1.73m^2	68	68 (100.0%)	32 (47.1%)	44 (64.7%)	4 (5.9%)	2 (2.9%)
≥ 90 mL/min/1.73m^2	32	32 (100.0%)	10 (31.3%)	25 (78.1%)	1 (3.1%)	0
Hepatic function:						
Normal	122	122 (100.0%)	46 (37.7%)	81 (66.4%)	8 (6.6%)	5 (4.1%)
Impaired	22	22 (100.0%)	13 (59.1%)	20 (90.9%)	1 (4.5%)	1 (4.5%)
Bone Marrow % Plasma cells:						
≤30%	83	83 (100.0%)	36 (43.4%)	56 (67.5%)	5 (6.0%)	3 (3.6%)
>30 - <60%	26	26 (100.0%)	9 (34.6%)	18 (69.2%)	2 (7.7%)	2 (7.7%)
≥ 60%	32	32 (100.0%)	13 (40.6%)	25 (78.1%)	2 (6.3%)	1 (3.1%)

Table 50 summarises the treatment-emergent adverse events of special interest by cohort and age group.

Table 50. Overall Summary of Treatment-emergent Adverse Events of Special Interest by Cohort and Age Group; All Treated Subjects Who Were at least 65 Years Older (Study 64407564MMY1001)

	400 ug/kg weekly SC				800 ug/kg biweekly SC			
	65=<Age<=74	75<=Age<=84	Age =>85	Total	65=<Age<=74	75<=Age<=84	Age =>85	Total
Analysis set: All Treated	57	20	1	78	50	32	0	82
Number of subjects with CRS	42 (73.7%)	17 (85.0%)	1 (100.0%)	60 (76.9%)	37 (74.0%)	22 (68.8%)	0	59 (72.0%)
Maximum toxicity grade								
Grade 1	34 (59.6%)	13 (65.0%)	1 (100.0%)	48 (61.5%)	27 (54.0%)	17 (53.1%)	0	44 (53.7%)
Grade 2	8 (14.0%)	2 (10.0%)	0	10 (12.8%)	10 (20.0%)	5 (15.6%)	0	15 (18.3%)
Grade 3	0	2 (10.0%)	0	2 (2.6%)	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0	0
Number of subjects with ICANS	5 (8.8%)	4 (20.0%)	1 (100.0%)	10 (12.8%)	5 (10.0%)	3 (9.4%)	0	8 (9.8%)
Maximum toxicity grade								
Grade 1	1 (1.8%)	1 (5.0%)	1 (100.0%)	3 (3.8%)	1 (2.0%)	2 (6.3%)	0	3 (3.7%)
Grade 2	3 (5.3%)	2 (10.0%)	0	5 (6.4%)	1 (2.0%)	1 (3.1%)	0	2 (2.4%)
Grade 3	1 (1.8%)	1 (5.0%)	0	2 (2.6%)	2 (4.0%)	0	0	2 (2.4%)
Grade 4	0	0	0	0	1 (2.0%)	0	0	1 (1.2%)
Grade 5	0	0	0	0	0	0	0	0
Number of subjects with Neurotoxicity	18 (31.6%)	8 (40.0%)	1 (100.0%)	27 (34.6%)	17 (34.0%)	11 (34.4%)	0	28 (34.1%)
Maximum toxicity grade								
Grade 1	12 (21.1%)	4 (20.0%)	1 (100.0%)	17 (21.8%)	8 (16.0%)	6 (18.8%)	0	14 (17.1%)
Grade 2	5 (8.8%)	3 (15.0%)	0	8 (10.3%)	4 (8.0%)	5 (15.6%)	0	9 (11.0%)
Grade 3	1 (1.8%)	1 (5.0%)	0	2 (2.6%)	4 (8.0%)	0	0	4 (4.9%)
Grade 4	0	0	0	0	1 (2.0%)	0	0	1 (1.2%)
Grade 5	0	0	0	0	0	0	0	0
Number of subjects with Skin Toxicity	34 (59.6%)	11 (55.0%)	1 (100.0%)	46 (59.0%)	37 (74.0%)	26 (81.3%)	0	63 (76.8%)
Maximum toxicity grade								
Grade 1	21 (36.8%)	7 (35.0%)	0	28 (35.9%)	20 (40.0%)	15 (46.9%)	0	35 (42.7%)
Grade 2	13 (22.8%)	4 (20.0%)	1 (100.0%)	18 (23.1%)	17 (34.0%)	11 (34.4%)	0	28 (34.1%)
Grade 3	0	0	0	0	0	0	0	0
Number of subjects with Nail Disorder	32 (56.1%)	12 (60.0%)	1 (100.0%)	45 (57.7%)	27 (54.0%)	20 (62.5%)	0	47 (57.3%)
Maximum toxicity grade								
Grade 1	20 (35.1%)	10 (50.0%)	1 (100.0%)	31 (39.7%)	25 (50.0%)	17 (53.1%)	0	42 (51.2%)
Grade 2	12 (21.1%)	2 (10.0%)	0	14 (17.9%)	2 (4.0%)	3 (9.4%)	0	5 (6.1%)
Grade 3	0	0	0	0	0	0	0	0
Number of subjects with Rash	21 (36.8%)	8 (40.0%)	0	29 (37.2%)	15 (30.0%)	11 (34.4%)	0	26 (31.7%)
Maximum toxicity grade								
Grade 1	10 (17.5%)	4 (20.0%)	0	14 (17.9%)	6 (12.0%)	7 (21.9%)	0	13 (15.9%)
Grade 2	10 (17.5%)	3 (15.0%)	0	13 (16.7%)	5 (10.0%)	1 (3.1%)	0	6 (7.3%)
Grade 3	1 (1.8%)	1 (5.0%)	0	2 (2.6%)	4 (8.0%)	3 (9.4%)	0	7 (8.5%)
Number of subjects with Weight Decreased	25 (43.9%)	6 (30.0%)	1 (100.0%)	32 (41.0%)	15 (30.0%)	18 (56.3%)	0	33 (40.2%)
Maximum toxicity grade								
Grade 1	12 (21.1%)	4 (20.0%)	0	16 (20.5%)	7 (14.0%)	7 (21.9%)	0	14 (17.1%)
Grade 2	12 (21.1%)	2 (10.0%)	1 (100.0%)	15 (19.2%)	7 (14.0%)	10 (31.3%)	0	17 (20.7%)
Grade 3	1 (1.8%)	0	0	1 (1.3%)	1 (2.0%)	1 (3.1%)	0	2 (2.4%)
Number of subjects with Dysgeusia	44 (77.2%)	15 (75.0%)	0	59 (75.6%)	35 (70.0%)	25 (78.1%)	0	60 (73.2%)
Maximum toxicity grade								
Grade 1	26 (45.6%)	12 (60.0%)	0	38 (48.7%)	23 (46.0%)	11 (34.4%)	0	34 (41.5%)
Grade 2	18 (31.6%)	3 (15.0%)	0	21 (26.9%)	12 (24.0%)	14 (43.8%)	0	26 (31.7%)
Number of subjects with Cytopenia	40 (70.2%)	12 (60.0%)	1 (100.0%)	53 (67.9%)	36 (72.0%)	20 (62.5%)	0	56 (68.3%)
Maximum toxicity grade								
Grade 1	2 (3.5%)	0	0	2 (2.6%)	1 (2.0%)	2 (6.3%)	0	3 (3.7%)
Grade 2	4 (7.0%)	0	0	4 (5.1%)	6 (12.0%)	4 (12.5%)	0	10 (12.2%)
Grade 3	20 (35.1%)	8 (40.0%)	0	28 (35.9%)	14 (28.0%)	7 (21.9%)	0	21 (25.6%)
Grade 4	14 (24.6%)	4 (20.0%)	1 (100.0%)	19 (24.4%)	15 (30.0%)	7 (21.9%)	0	22 (26.8%)
Grade 5	0	0	0	0	0	0	0	0
Number of subjects with Infection	30 (52.6%)	13 (65.0%)	0	43 (55.1%)	34 (68.0%)	25 (78.1%)	0	59 (72.0%)
Maximum toxicity grade								
Grade 1	3 (5.3%)	1 (5.0%)	0	4 (5.1%)	2 (4.0%)	3 (9.4%)	0	5 (6.1%)

	400 ug/kg weekly SC				800 ug/kg biweekly SC			
	65=<Age<=74	75<=Age<=84	Age =>85	Total	65=<Age<=74	75<=Age<=84	Age =>85	Total
Grade 2	15 (26.3%)	6 (30.0%)	0	21 (26.9%)	19 (38.0%)	18 (56.3%)	0	37 (45.1%)
Grade 3	12 (21.1%)	1 (5.0%)	0	13 (16.7%)	11 (22.0%)	2 (6.3%)	0	13 (15.9%)
Grade 4	0	2 (10.0%)	0	2 (2.6%)	1 (2.0%)	1 (3.1%)	0	2 (2.4%)
Grade 5	0	3 (15.0%)	0	3 (3.8%)	1 (2.0%)	1 (3.1%)	0	2 (2.4%)

Key: TEAE = treatment-emergent adverse event; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome
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: The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.
Note: Percentages are calculated with the number of subjects in each group as denominator.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of talquetamab or until the start of subsequent anticancer therapy, if earlier.
Note: Adverse events are coded using MedDRA version 25.0.
Note: Neurotoxicity events are defined as adverse events in the Nervous System Disorder SOC or Psychiatric Disorders SOC (excluding Dysgeusia, Ageusia, Hypogeusia, Taste disorder) that are considered related by investigator. Skin toxicity events are including Skin exfoliation, Dry skin, Pruritus, Palmar-plantar erythrodysaesthesia syndrome. Nail disorder events are including Nail discolouration, Nail disorder, Onycholysis, Onychomadesis, Onychoclasis, Nail dystrophy, Nail toxicity, Nail ridging. Rash events is including Rash, Rash maculo-papular, Rash erythematous, Erythema. Dysgeusia events are including ageusia, dysgeusia, hypogeusia, and taste disorder. Infection events are defined as adverse events in the Infections and Infestations SOC.

2.6.8.7. Immunological events

RP2D 0.4 mg/kg Weekly SC

A total of 138 participants were ADA evaluable with at least 1 postdose ADA sample, and 85 and 34 participants had evaluable ADA data at ≥6 months and ≥1 year after the first dose of talquetamab, respectively. Anti-talquetamab antibody status for these patients is summarised in **Table 51**.

Table 51. Anti-talquetamab antibody status; talquetamab immunogenicity-evaluable analysis set (Study 64407564MMY1001; 400 ug/kg weekly subcutaneous)

	RP2D: 400 ug/kg Weekly Subcutaneous		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: Talquetamab immunogenicity-evaluable for subjects with appropriate samples[a]	21	117	138
Subjects positive for anti-talquetamab antibodies at baseline[b]	1 (4.8%)	6 (5.1%)	7 (5.1%)
Subjects positive for anti-talquetamab antibodies at baseline who were treatment-boosted for anti-talquetamab antibodies[d]	0	1 (0.9%)	1 (0.7%)
Subjects positive for anti-talquetamab antibodies at baseline who were not treatment-boosted for anti-talquetamab antibodies[d]	1 (4.8%)	5 (4.3%)	6 (4.3%)
Subjects positive for treatment-emergent anti-talquetamab antibodies[b,c]	6 (28.6%)	41 (35.0%)	47 (34.1%)
Subjects negative for anti-talquetamab antibodies[b]	15 (71.4%)	76 (65.0%)	91 (65.9%)

Key: RP2D = recommended Phase 2 dose; SC = subcutaneous
[a] Subjects who received at least one injection of talquetamab SC and had appropriate plasma samples for detection of antibodies to talquetamab (at least 1 sample after the start of the first injection of talquetamab).
[b] Percentages are calculated with the number of subjects with appropriate sample as the denominators.
[c] Includes all subjects who had at least 1 positive subject status at any time after start of treatment, including those who did not have a baseline sample.
[d] Baseline positive subjects were included only if post-treatment sample titers increased by at least 2-fold compared to baseline.

RP2D 0.8 mg/kg Q2W SC

A total of 139 participants were ADA evaluable with at least 1 postdose ADA sample, and 86 and 13 participants had evaluable ADA data at ≥6 months and ≥1 year after the first dose of talquetamab, respectively. Anti-talquetamab antibody status for these patients is summarised in **Table 52**.

Table 52. Anti-talquetamab antibody status; talquetamab immunogenicity-evaluable analysis set (Study 64407564MMY1001; 800 ug/kg every 2 weeks subcutaneous)

	RP2D: 800 ug/kg Every 2 Weeks Subcutaneous		
	Phase 1	Phase 2 Cohort C	Total
Analysis set: Talquetamab immunogenicity-evaluable for subjects with appropriate samples[a]	36	103	139
Subjects positive for anti-talquetamab antibodies at baseline[b]	0	4 (3.9%)	4 (2.9%)
Subjects positive for anti-talquetamab antibodies at baseline who were treatment-boosted for anti-talquetamab antibodies[d]	0	0	0
Subjects positive for anti-talquetamab antibodies at baseline who were not treatment-boosted for anti-talquetamab antibodies[d]	0	4 (3.9%)	4 (2.9%)
Subjects positive for treatment-emergent anti-talquetamab antibodies[b,c]	12 (33.3%)	37 (35.9%)	49 (35.3%)
Subjects negative for anti-talquetamab antibodies[b]	24 (66.7%)	66 (64.1%)	90 (64.7%)

Key: IV = intravenous; SC = subcutaneous
[a] Subjects who received at least one injection of talquetamab and had appropriate plasma samples for detection of antibodies to talquetamab (at least 1 sample after the start of the first injection of talquetamab).
[b] Percentages are calculated with the number of subjects with appropriate sample as the denominators.
[c] Includes all subjects who had at least 1 positive subject status at any time after start of treatment, including those who did not have a baseline sample.
[d] Baseline positive subjects were included only if post-treatment sample titers increased by at least 2-fold compared to baseline.

Participants with Prior T cell Redirection Therapies

A total of 51 participants were ADA evaluable with at least 1 postdose ADA sample, and 25 and 8 participants had evaluable ADA data at ≥6 months and ≥1 year after the first dose of talquetamab, respectively. Anti-talquetamab antibody status for these patients is summarised in

Table 53. Anti-talquetamab antibody status; talquetamab immunogenicity-evaluable analysis set (Study 64407564MMY1001; T-cell redirection therapy)

	RP2D: 400 ug/kg Weekly Subcutaneous		RP2D: 800 ug/kg Every 2 Weeks Subcutaneous	
	Phase 1	Phase 2 Cohort B	Phase 1	Total
Analysis set: Talquetamab immunogenicity-evaluable for subjects with appropriate samples[a]	9	34	8	51
Subjects positive for anti-talquetamab antibodies at baseline[b]	0	3 (8.8%)	0	3 (5.9%)
Subjects positive for anti-talquetamab antibodies at baseline who were treatment-boosted for anti-talquetamab antibodies[d]	0	2 (5.9%)	0	2 (3.9%)
Subjects positive for anti-talquetamab antibodies at baseline who were not treatment-boosted for anti-talquetamab antibodies[d]	0	1 (2.9%)	0	1 (2.0%)
Subjects positive for treatment-emergent anti-talquetamab antibodies[b,c]	1 (11.1%)	8 (23.5%)	1 (12.5%)	10 (19.6%)
Subjects negative for anti-talquetamab antibodies[b]	8 (88.9%)	26 (76.5%)	7 (87.5%)	41 (80.4%)

Key: RP2D = recommended Phase 2 dose; SC = subcutaneous
[a] Subjects who received at least one injection of talquetamab SC and had appropriate plasma samples for detection of antibodies to talquetamab (at least 1 sample after the start of the first injection of talquetamab).
[b] Percentages are calculated with the number of subjects with appropriate sample as the denominators.
[c] Includes all subjects who had at least 1 positive subject status at any time after start of treatment, including those who did not have a baseline sample.
[d] Baseline positive subjects were included only if post-treatment sample titers increased by at least 2-fold compared to baseline.

2.6.8.8. Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been performed with talquetamab.

2.6.8.9. Discontinuation due to adverse events

Treatment-emergent Adverse Events Leading to Treatment Discontinuation

RP2D 0.4 mg/kg Weekly SC

Seven participants (4.9%) experienced TEAEs leading to treatment discontinuation. The only TEAE that led to treatment discontinuation for more than 1 participant was ICANS (1.6%). Investigators considered these TEAEs to be related to study drug for 4.2% of participants.

RP2D 0.8 mg/kg Q2W SC

Nine participants (6.2%) experienced TEAEs leading to treatment discontinuation. The only TEAE that led to treatment discontinuation for more than 1 participant was dysgeusia (1.4%). Investigators considered these TEAEs to be related to study drug for 3.4% of participants.

Participants with Prior T cell Redirection Therapies

Three participants (5.9%) experienced TEAEs leading to treatment discontinuation. No TEAE led to treatment discontinuation for more than 1 participant. Investigators considered these TEAEs to be related to study drug for 3.9% of participants.

All Treated Participants

For the total All Treated Analysis Set, 26 participants (5.2%) experienced TEAEs leading to discontinuation of study treatment. The most frequently reported TEAE by preferred term that led to treatment discontinuation was ICANS (1.1%).

Treatment Modifications Due to Toxicity

Treatment cycle delays, incidence and reason for dose modification is summarised in

Table 54. Summary of treatment cycle delays, incidence and reason for dose modification; all treated analysis set (Study 64407564MMY1001)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		
Analysis set: All Treated	143	145	22	38	51	102	501
Subjects with cycle delays	65 (45.5%)	55 (37.9%)	6 (27.3%)	15 (39.5%)	25 (49.0%)	34 (33.3%)	200 (39.9%)
Reason for cycle delays							
Adverse event	55 (38.5%)	42 (29.0%)	3 (13.6%)	13 (34.2%)	22 (43.1%)	24 (23.5%)	159 (31.7%)
Adverse event - COVID-19	9 (6.3%)	7 (4.8%)	0	2 (5.3%)	3 (5.9%)	2 (2.0%)	23 (4.6%)
Other	23 (16.1%)	13 (9.0%)	5 (22.7%)	4 (10.5%)	8 (15.7%)	24 (23.5%)	77 (15.4%)
Other - COVID-19	3 (2.1%)	2 (1.4%)	3 (13.6%)	0	0	10 (9.8%)	18 (3.6%)
Subjects with dose interruptions[a]	96 (67.1%)	61 (42.1%)	14 (63.6%)	21 (55.3%)	29 (56.9%)	42 (41.2%)	263 (52.5%)
Reason for dose interruptions							
Adverse event	85 (59.4%)	53 (36.6%)	9 (40.9%)	19 (50.0%)	22 (43.1%)	25 (24.5%)	213 (42.5%)
Adverse event - COVID-19	6 (4.2%)	9 (6.2%)	0	0	2 (3.9%)	0	17 (3.4%)
Other	32 (22.4%)	11 (7.6%)	8 (36.4%)	5 (13.2%)	11 (21.6%)	31 (30.4%)	98 (19.6%)
Other - COVID-19	6 (4.2%)	2 (1.4%)	0	0	1 (2.0%)	5 (4.9%)	14 (2.8%)
Subjects with dose delays	18 (12.6%)	24 (16.6%)	8 (36.4%)	9 (23.7%)	3 (5.9%)	17 (16.7%)	79 (15.8%)
Reason for delays							
Adverse event	12 (8.4%)	20 (13.8%)	4 (18.2%)	7 (18.4%)	0	7 (6.9%)	50 (10.0%)
Adverse event - COVID-19	0	1 (0.7%)	0	0	0	0	1 (0.2%)
Other	5 (3.5%)	4 (2.8%)	4 (18.2%)	2 (5.3%)	3 (5.9%)	12 (11.8%)	30 (6.0%)
Other - COVID-19 related	0	0	0	0	0	0	0
Subjects with dose skipped	90 (62.9%)	45 (31.0%)	9 (40.9%)	16 (42.1%)	27 (52.9%)	36 (35.3%)	223 (44.5%)
Reason for skipping							
Adverse event	78 (54.5%)	40 (27.6%)	5 (22.7%)	14 (36.8%)	22 (43.1%)	23 (22.5%)	182 (36.3%)
Adverse event - COVID-19	6 (4.2%)	8 (5.5%)	0	0	2 (3.9%)	0	16 (3.2%)
Other	31 (21.7%)	7 (4.8%)	6 (27.3%)	4 (10.5%)	9 (17.6%)	23 (22.5%)	80 (16.0%)
Other - COVID-19 related	6 (4.2%)	2 (1.4%)	0	0	1 (2.0%)	5 (4.9%)	14 (2.8%)

	SC					IV	Total
	RP2D (400 ug/kg weekly)	RP2D (800 ug/kg Bi-weekly)	Non-RP2D (<RP2D)	Non-RP2D (>RP2D)	Prior T cell exposures at RP2Ds		
Subjects with dose reduced[b]	22 (15.4%)	10 (6.9%)	1 (4.5%)	11 (28.9%)	5 (9.8%)	11 (10.8%)	60 (12.0%)
Reason for reduction							
Adverse event	21 (14.7%)	9 (6.2%)	0	9 (23.7%)	4 (7.8%)	5 (4.9%)	48 (9.6%)
Adverse event - COVID-19	0	0	0	0	0	0	0
Other	3 (2.1%)	1 (0.7%)	1 (4.5%)	4 (10.5%)	1 (2.0%)	8 (7.8%)	18 (3.6%)
Other - COVID-19 related	0	0	0	0	0	0	0

Key: RP2D=recommended phase 2 dose, SC= Subcutaneous, IV= Intravenous.
Note: RP2D includes Phase 1 RP2D treatment group, Phase 2 Cohort A and Phase 2 Cohort C.
Note: IV includes all IV treatment groups; Non-RP2D(<RP2D) includes 5 ug/kg weekly, 15 ug/kg weekly, 45 ug/kg weekly and 135 ug/kg weekly treatment groups; Non-RP2D(>RP2D) includes 800 ug/kg weekly, 1200 ug/kg bi-weekly and 1600 ug/kg monthly treatment groups; Prior T cell exposures at RP2Ds includes Phase 1 RP2D 400 ug/kg weekly with prior CART or prior bispecific, Phase 1 RP2D 800 ug/kg biweekly with prior CART or prior bispecific and Phase 2 Cohort B treatment groups.
[a] Dose interruption includes delays within cycle and dose skipped.
[b] Repeat step-up doses were excluded for dose reduced.

2.6.8.10. Post marketing experience

No post marketing data are available.

2.6.9. Discussion on clinical safety

The safety data available stem from the ongoing first-in human, open-label, multicentre phase 1/2 64407564MMY1001 (MonumenTAL-1) study, in which a total of 501 subjects have been exposed to

talquetamab monotherapy. Of these, 143 and 145 subjects with no prior T cell redirection therapy have been exposed to the RP2D 0.4 mg/kg weekly SC and the RP2D 0.8 mg/kg Q2W SC, respectively and 51 subjects with prior T cell redirection therapy received either one of the RP2Ds (0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC). Of patients with prior T-cell redirection therapy, only 8 participants were assigned to the 0.8 mg/kg Q2W SC regimen.

MonumenTAL-1 is a single-arm trial, with no control group against which the safety profile of talquetamab could be compared, which limits a comprehensive assessment of safety. The median duration of follow-up was 19.0 months for the RP2D 0.4 mg/kg weekly treated participants and 13 months for the RP2D 0.8 mg/kg Q2W treated population. Median follow-up was 15 months for participants with prior T cell redirection therapies. 36.5% of participants assigned to either of the SC regimens discontinued study participation. The most frequent reason for study discontinuation were death. Furthermore, 76.9% and 58.6% of patients assigned to the RP2D 0.4 mg/kg weekly SC and RP2D 0.8 mg/kg Q2W SC, respectively discontinued talquetamab most frequently for progressive disease.

The most common TEAEs were in nervous system disorders, the blood and lymphatic system disorders, general disorders and administration site conditions, immune system disorders, gastrointestinal disorders. In the RP2D 0.4 mg/kg Weekly SC treated participants, the most frequently reported TEAEs were CRS (79.0%), dysgeusia (50.3%), anaemia (44.8%), weight decreased (41.3%), pyrexia (39.2%), neutropenia (35%), lymphopenia (28.0%), thrombocytopenia (27.3%), skin exfoliation (28%), asthenia (27.3%), dry mouth (26.6%), diarrhoea (25.2%), dysphagia (23.8%), fatigue (24.8%), dry skin (22.4%), nail disorder (22.4%), and rash (21.7%).

The type and incidence of common TEAEs were generally similar among participants who received either of the RP2Ds. TEAEs that occurred at a higher frequency in participants assigned to 0.8 mg/kg Q2W than 0.4 mg/kg weekly were dry mouth (40% vs. 26.6%) and skin exfoliation (40% vs. 28%). Although interpretation is limited due to a small sample size (n=51), participants with prior T cell redirection therapies exposure appeared to have relatively higher incidences of several common TEAEs, such as dysgeusia, dry mouth, neutropenia, pruritis, and fatigue, and lower incidences of lymphopenia, diarrhoea, and asthenia than participants without prior T cell redirection therapies exposure.

CRS, cytopenias, dysgeusia, as well as skin exfoliation were the most commonly reported treatment-related TEAEs. Cytopenias, together with infections hypophosphataemia and pneumonia, were the most commonly reported Grade 3 or 4 events.

Hypertension AEs were reported for 9.4% of patients in all treated population, however most cases were either confounded by prior medical history or events resolves on treatment and thus there is no need to include this AE in the SmPC.

As of the clinical cut-off, 15% of subjects in the-all treated analysis set had died. The incidence of deaths during the study was higher for participants with prior T cell redirection therapies exposure (16 subjects (31.4%)) than participants without prior T cell redirection therapies exposure (30 subjects (21.0%) for the RP2D 400 ug/kg weekly and 18 subjects (12.4%) for the RP2D 800 ug/kg Bi-weekly). Progressive disease was the most commonly reported cause of death for participant with prior T-cell exposure (all but one). This may be attributable to differences in disease status at baseline.

The incidence of Grade 5 TEAEs within 30 or 60 days was similar for treated participants assigned to 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC. No participants with prior T cell therapies exposure experienced a Grade 5 TEAE. None of Grade 5 TEAEs within 30 or 60 days were judged by the investigator to be related to talquetamab (one participant each with grade 5 basilar artery occlusion, acute respiratory failure, infection, pulmonary embolism, fungal sepsis, septic shock, 2 participants with COVID-19).

At least 1 serious TEAE was reported for 53.1% of participants assigned to RP2D 0.4 mg/kg Weekly SC and 48.3% of participants assigned to RP2D 0.8 mg/kg Bi-Weekly. The most common events were CRS, pyrexia, ICANS, pneumonia and febrile neutropenia.

Cytokine release syndrome (CRS) was observed in a high proportion of subjects (77% in participants assigned to either of the RP2Ds and regardless of prior T cell exposure). These events were mostly Grade 1 or 2, but 5 subject (1.5%) experienced Grade 3 CRS. One participant discontinued treatment due to CRS. Among participants without prior T cell redirection treated at the 0.4 mg/kg weekly SC dose schedule, CRS rates after the first three doses (step-up Dose 1, step-up Dose 2, and Cycle 1 Day 1) were 33.6%, 49.0% and 26.6% respectively, with a CRS rate of 4.2% after Cycle 1 Day 8. Among participants without prior T cell redirection treated at 0.8 mg/kg Q2W SC dose schedule, CRS rates after the first three doses (step-up Dose 1, step-up Dose 2, and step-up Dose 3) were 26.2%, 40.7% and 34.5%, respectively, with a CRS rate of 13.1% after C1D1.

Events of CRS were generally of a transient nature (median duration was 17 hours when calculated). Multiple CRS events occurred in 30% of participants, with worsening at a subsequent event for 4.4% of participants. Worsening of CRS severity only occurred during step-up dosing or cycle 1 and each event resolved.

Median time to onset of CRS was 2.0 days. In Phase 2, median time to onset of CRS in hours was 26.5 (range: 0.1 to 167.3). Approximately 5% and 8% of CRS events occurring in participants without prior T cell redirection treated with 0.4 mg/kg weekly SC and 0.8 mg/kg Q2W SC started more than 48 hours after talquetamab administration. The majority of these events were of Grade 1. In all Grade 2 cases (n= 4 treated with 0.8 mg/kg Q2W SC), the participants were hospitalised. Only 2 (1.4%) and 3 (2.1%) CRS events started after 72 hours and the majority of these events were Grade 1. In the Grade 2 case (n= 1 treated with 0.8 mg/kg Q2W SC), the participant was hospitalised. As the large majority of the first CRS events occurred in association with the step-up dosing schedule, focusing on this period with more intensive monitoring requirements as recommended in the SmPC is considered appropriate.

Most symptoms of CRS had maximum severity of Grade 1 or Grade 2. Grade 3 symptoms of CRS included pyrexia, hypotension, dyspnoea, hypoxia, and sinus tachycardia. One participant (0.7%) had Grade 4 aspartate aminotransferase increased and one participant had grade 4 hypotension. No Grade 5 symptoms were reported.

Supportive measures, including the use of tocilizumab, were used for management of CRS in a substantial proportion of subjects and the SmPC provides detailed recommendations for the management of these type of events. A Patient Card is also included as an additional risk minimisation measure to further mitigate the risk of CRS, by increasing patient awareness of signs and symptoms requiring medical attention.

Neurotoxicity events attributable to talquetamab were reported in 28.9% of subjects assigned to either RP2Ds regardless of prior T cell exposure, mostly of grade 1 and 2. Six subjects (2.6%) experienced grade 3 or 4 neurotoxicity events. The most common reported neurotoxicity events were ICANS (10%) and headache (9.1%). The most common serious AEs were ICANS. Neurotoxicity events were reported during step-up dosing, in cycle 1, and in later treatment cycles. Anakinra was used to treat neurotoxicity in one participant. By the clinical cut-off, 66% of related neurotoxicity events had resolved, with a median duration of 3.5 days.

Motor dysfunction grouped terms (dysgraphia, dysphonia, gait disturbance, muscle spasms, muscular weakness, and tremor) were reported in 16 (4.7%) participants, considered related to talquetamab by the investigator. Whether bispecific antibodies can cross the blood-brain remains unclear, but GPRC5D expression on cerebellum may be a plausible explanation for the motor dysfunction observed as a

possible GPRC5D off-target toxicity. Therefore, in the absence of controlled data, the role of talquetamab in the onset of motor dysfunction cannot be excluded.

Sensory neuropathy (10%) (grouped term includes: dysaesthesia, hypoaesthesia, hypoaesthesia oral, neuralgia, peripheral sensory neuropathy, sciatica, and vestibular neuronitis), dizziness (12%) (grouped term includes: syncope and vertigo), and motor dysfunction (11%) (grouped term includes: dysgraphia, dysphonia, gait disturbance, muscle spasms, muscular weakness, and tremor) were included as ADR in section 4.8 of the SmPC.

ICANS events were reported for 10% of participants. Serious and Grade 3 ICANS were reported for 3.8% and 2.3% of participants and one Grade 4 ICANS was reported. Importantly, one fatal ICANS event related to talquetamab was reported in MonumenTAL-1 in the China cohort. The subject died due to ICANS syndrome Grade 3 occurring 6 days after the Cycle 1 Day 1 dose of 400 µg/kg SC and concurrently with CRS. The investigator considered the event of ICANS to be very likely related to talquetamab. According to the applicant, a possible deviation in management of this patient could be a potential reason for the fatal outcome.

The median time from last dose of talquetamab to onset of ICANS was 28 hours and thus the recommended 48 hours for patient monitoring and the management of ICANS risk as proposed in the SmPC is considered appropriate. Detailed guidance on the management and mitigation of ICANS is also provided in the SmPC and PL including a warning to indicate the absence of data of use of talquetamab in patients with CNS involvement of myeloma or other clinically relevant CNS pathologies A Patient Card is also included as an additional risk minimisation measure to further mitigate the risk of ICANS, by increasing patient awareness of signs and symptoms requiring medical attention. Finally, all health care professional educational materials who are expected to prescribe or administer talquetamab shall be provided with medical education material to ensure awareness of the risk of neurologic toxicity including ICANS and facilitate identification, management and monitoring of those risks. A survey to measure the effectiveness of the HCP Educational Materials is also planned.

Post baseline IgG values of less than 500 mg/dl consistent with hypogammaglobulinaemia have been reported in reported in 64% of patients treated with talquetamab at the 0.4 mg/kg weekly dose schedule, 66% of patients at the 0.8 mg/kg biweekly dose schedule. Therefore, hypogammaglobulinaemia was included as an ADR and in the SmPC with a reminder that patients should be treated according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement.

Treatment-emergent Grade 3 or 4 neutropenia, febrile neutropenia and thrombocytopenia have been observed in patients who received talquetamab. The majority of cytopenias occurred during the first 8 to 10 weeks. Complete blood counts should be monitored at baseline and periodically during treatment. Supportive care should be provided per local institutional guidelines. Patients with neutropenia should be monitored for signs of infection. Talquetamab treatment should be withheld as described in Section 4.2 of the SmPC.

Serious infections, including life-threatening or fatal infections, have been reported in participants treated with talquetamab. The most frequently reported (≥5%) were upper respiratory tract infection, COVID-19, urinary tract infection, pneumonia, bronchitis, and nasopharyngitis. Infection onset was distributed evenly over the course of study treatment. Among participants treated with either of SC dosages regardless of prior T cell redirection therapy (N=339), Grade 3 or Grade 4 infections occurred in 19% of patients, and fatal infections occurred in 1.5% of patients (5 patients) including 2 participants with COVID-19 pneumonia, and 1 participant each with fungal sepsis, septic shock and "infection" (unknown aetiology).

Patients should be monitored for signs and symptoms of infection prior to and during treatment with talquetamab and treated appropriately. Prophylactic antimicrobials should be administered according to local guidelines. Talquetamab should not be administered in patients with active serious infection and should be withheld as detailed in the SmPC. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur.

Immune response to vaccines may be reduced when taking talquetamab. The safety of immunisation with live viral vaccines during or following talquetamab treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 4 weeks prior to the start of treatment, during treatment, and at least 4 weeks after treatment.

A TEAE of tumour lysis syndrome (TLS) was reported for 1 participant assigned to 0.8 mg/kg Q2W SC. This was a Grade 3 TEAE of TLS considered related to talquetamab. Considering that monitoring, recognition, and treatment of TLS is part of standard oncology medical practice, and that these events could continue to be monitored through routine pharmacovigilance, the inclusion of TLS as an ADR or as a Warning/Precaution specifically for talquetamab in the SmPC is not warranted at this time.

With talquetamab, in all treated population, 16 cases (3.2%) of second primary malignancies were diagnosed. All were considered as not related to talquetamab by investigators. Overall, based on current evidence, it can be agreed that the reporting rate of second primary malignancies is consistent with medical literature. However, the applicant is recommended to continue to monitor the second primary malignancies in the ongoing clinical trials and in the post marketing setting through routine pharmacovigilance and report in upcoming PSUR.

Most events of weight decreased occurred in cycle 2 or later. This AE led to reduced dosing (3.9%) and skipped doses (3.9%). Treatment discontinuation incidence was low (1.2%). In some participants, weight decreased occurred concurrently with dysgeusia, dry mouth, and decreased appetite concurrently. Warning on Weight loss was included in the section 4.2 within the oral toxicity paragraph. Despite management with dose reductions, and modifications, only few AEs of weight decreased (33%) were resolved. However, the low rate of treatment discontinuation due to adverse events of weight decreased may indicate that these events were adequately controlled following institutional guidelines for intervention and with the proposed dose modifications.

Oral toxicity including dysgeusia, dry mouth, dysphagia, oropharyngeal pain, stomatitis and decreased appetite were common AEs and over time significant weight loss occurred. Oral toxicities were often reported concurrently and were managed by dose reductions and skipped doses with supportive care. Appropriate warnings and management guidelines for oral toxicity have included in SmPC.

Skin toxicity including non-rash skin reactions and rash TEAEs, occurred in patients who received talquetamab with either of the RP2Ds. Dose modifications guidelines were included in the SmPC for skin toxicity. Rash TEAEs were reported for 34.8% of participants. The maximum severity was grade 3 (3.5%). In a minority of participants, rash led to dose skips (4%), reductions (<1%), or delays (<1%). By the clinical cut-off date, 88% and 72.3% of rash events had resolved, with a median duration of 28 and 26 days for patients assigned to the weekly and biweekly dosage, respectively. Warnings and precautions related to rash including maculo-papular rash, erythema, and erythematous rash were included in the SmPC which is endorsed.

Non-rash skin toxicity TEAEs (skin exfoliation, dry skin, pruritus, or palmar-plantar erythrodysesthesia syndrome) were reported for 65.1%of participants Adverse events were mostly of Grade 1 and Grade 2, with one event of Grade 3 pruritis reported. Resolution of non-rash skin toxicity occurred in about 50% of participants who experienced these adverse events. The rate of discontinuation of treatment was however very low. Warnings for skin reactions in section 4.4 include non-rash skin toxicity as well as rash toxicity.

Nail disorder TEAEs including brittle nails, cracking nails, painful nails, and loss of nails, were common (reported in 56% treated with talquetamab. Most of these events were Grade 1 and generally not associated with treatment discontinuations. Only 1 participant in the cohort 0.4 mg/kg weekly SC required dose modification. 66.3% and 70.4% of nail disorder events were reported as not recovered or not resolved at 0.4 mg/kg weekly SC and 0.8 mg/kg Q2W SC, respectively. Instructions for dose modifications for nail disorders are also included in the SmPC.

Laboratory values fluctuated within the normal range for most parameters. However, data are limited at later timepoints. Grade 1 to 2 abnormalities in clinical chemistry parameters were common. No participants met criteria for Hy's law.

INR increased, activated partial thromboplastin time prolonged and fibrinogen decreased occurred frequently in the study and have been included as ADRs in the SmPC. Of the 12 thrombotic events (3.5%) in the total RP2Ds analysis set, 3 were concurrent with CRS. Although the inflammation and the cytokines' storm might be involved in thrombotic events, the limited numbers do not allow drawing definitive conclusions and current wording in the product information is considered sufficient.

Treatment emergent related cardiac disorders were reported in 6.3%, 10.3% and 17.6% in participants treated with 0.4 mg/kg weekly, 0.8 mg/kg Q2W SC and in the previously exposed to T cell redirection therapy cohorts respectively. All AEs were Grade 1 or 2, generally concomitant with CRS and all resolved. Available data do not suggest that there is a risk of QT prolongation or cardiac toxicity with talquetamab.

Safety profile seems less favourable for patients with prior CAR-T therapy compared to patients who have received prior bispecific therapy. Numerically higher discontinuations (11.1% vs 0%), COVID-19 TEAEs (19.4% vs 0%), weight decreased AEs (36% vs 16%) and grade 3 CRS (2.7% vs 0%) were observed in participants who received prior CAR-T therapy compared to patients with prior bispecific therapy. Nevertheless, serious AEs were higher among patients who have received prior bispecific therapy than patients with prior CAR-T therapy. Given the low number of subjects in each subgroup, no clear conclusion could be drawn. Safety in patients with prior CART-cell is included as missing information in the RMP and additional information in this subpopulation will be collected through the ongoing study MMY1001.

136 participants in the total All Treated Analysis Set received ≥12 months of study treatment (47 treated participants without prior T cell redirection therapy assigned to 0.4 mg/kg weekly SC, 39 treated participants without prior T cell redirection therapy assigned to 0.8 mg/kg Q2W SC, and 15 participants with received prior T cell redirection therapy). The incidence of TEAEs, TEAE severity, serious TEAEs, and deaths due to TEAEs reported 12 months or more after the start of treatment was lower compared with reporting rates over the full treatment period. However, the incidence of weight decreased events reported 12 months or more after the start of treatment were a higher in participants assigned to 0.8 mg/kg Q2W SC than 0.4 mg/kg weekly SC and participants assigned to RP2Ds with prior T cell redirection therapies (20%, vs 6.4%, vs 15.4%, respectively).

Immunogenicity data is available for 328 subjects treated with any dose of SC talquetamab. 106 of 328 (32.3%) subjects were identified as positive for anti-talquetamab antibodies. There appeared to be a trend for a higher CRS, sARR and ISR in ADA-positive participants than in ADA-negative participants among participant treated RP2D 0.8 mg/kg Q2W SC and with prior T cell redirection therapies. However, the low event rates for sARRs and ISRs, preclude drawing a definite conclusion regarding the effect of the neutralising ADAs on clinical parameters.in combination with the low ADA incidence rate, limited a definitive conclusion regarding the impact of ADAs on these events. In addition, several ADA positive samples were not evaluated for Nab and the applicant justified this due to unevaluable samples exceeding the drug tolerance that was validated at lower talquetamab concentrations than that reached during the drug development. According to the applicant a new assay

to detect neutralizing antibodies to talquetamab has recently been validated and all ADA positive samples tested in Study 4MMY1001 will be re-assessed using this new method. It is recommended that the applicant submits the validation report of the new method together with the samples re-analysis with this new method when available.

Permanent discontinuation of talquetamab was required infrequently (6.7%). The most frequent adverse reactions leading to treatment discontinuation were ICANS (1.1%), weight decreased (0.9%) and dysgeusia (0.7%). The incidence of TEAEs leading to cycle delay or dose modification was high; 71.3% for participants assigned to 0.4 mg/kg weekly SC and 57.2% for participants assigned to 0.8 mg/kg Q2W SC.

The nature of AEs requiring treatment modifications is consistent with the general safety profile of talquetamab, the most common reasons being CRS, pyrexia, Covid-19, upper respiratory tract infection, weight decreased, rash and neutropenia.

There is no available data on talquetamab use in pregnant and breastfeeding women. Human IgG is known to cross the placenta after the first trimester of pregnancy. Therefore, talquetamab has the potential to be transmitted after the first trimester of pregnancy from the mother to the developing foetus. Therefore, talquetamab use is not recommended for women who are pregnant or for women of childbearing potential not using contraception. It is not known whether talquetamab is excreted in human milk. Because the potential for serious adverse reactions in breast-fed infants is unknown for talquetamab, patients should not breast-feed during treatment with talquetamab and for at least 3 months after the last dose.

Additional safety data needed in the context of a conditional MA

As duration of exposure to talquetamab and corresponding follow-up of patients in MMY1001 is relatively short, further data from subsequent data lock-points are expected in order to further characterise the long-term safety of talquetamab and the important identified risks associated with its use. This includes an updated safety report for MMY1001 which is expected to be available by the end of 2024. Additional safety data for the known important identified risks with talquetamab, will be required from the ongoing comparative MMY3002 study which will support eventual conversion to a full MA for Talvey.

2.6.10. Conclusions on the clinical safety

The safety profile of talquetamab monotherapy in relapsed or refractory multiple myeloma, including participants with prior T cell redirection with CAR-T therapy or bispecific antibody treatment 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 as well as the overall short duration of follow-up limit a comprehensive assessment.

The safety profile of talquetamab, seems to be in line with what is expected from bispecific antibody and T cell activation with regards to CRS, cytopenias, and most of the neurological findings, ICANS included. Warnings and recommendations in the product information in conjunction with Patient Card to be distributed to all patients/caregivers who are expected to use talquetamab are expected to minimise those risk. Appropriate guidance for the management of other key risks associated with talquetamab use such as motor dysfunction, infections, skin and nail toxicities and oral toxicity is included in the product information.

The CHMP considers the following measures necessary to address issues related to safety:

-Updated safety data providing a minimum of 2 years of long-term safety data after the last participant for 64407564MMY1001 study (MonumenTAL-1) when available.

-Comprehensive long-term safety data from the ongoing phase 3 study 64407564MMY3002.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of Safety Concerns	
Important Identified Risks	Cytokine release syndrome
	Neurologic toxicity including ICANS
	Serious infections
Important Potential Risks	None
Missing Information	Long-term safety
	Safety in patients with prior CAR-T cell therapy

2.7.2. Pharmacovigilance plan

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
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				
64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma	The primary objective in Part 1 (dose escalation) is to characterise the safety of talquetamab and recommend the Phase 2 dose and schedule. The primary objective in Part 2 (dose expansion) is to further characterise the safety of talquetamab at the recommended Phase 2 dose (RP2D).	CRS Neurologic toxicity including ICANS Serious infections Long-term safety Safety in patients with prior CAR-T cell therapy	Updated Safety Report	Q3 2024

2.7.3. Risk minimisation measures

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

Safety Concern	Risk Minimisation Measures
	• Instructions that talquetamab should be administered by a healthcare professional with adequate medical equipment and personnel to manage severe reactions, including CRS, is included in SmPC Section 4.2. • Instructions for step-up dosing and pretreatment medicinal products (corticosteroids, antihistamines, antipyretics) to reduce the risk of CRS are included in SmPC Section 4.2. • Recommendation that patients should remain close to a healthcare facility and be monitored for 48 hours after administration of all doses within the step-up phase is provided in SmPC Section 4.2. • Recommendations for the management of CRS by severity, and including actions to be taken (eg, withholding, discontinuation) and treatment, are included in SmPC Section 4.2. • Recommendations for the monitoring, evaluation, and treatment of CRS (including hospitalisation, supportive care, medicinal products, etc) is provided in SmPC Section 4.4. • Guidance for patients to recognise symptoms of CRS and get medical help right away are included in PL Sections 2 and 4. • Legal status • 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. Step-up dosing is designed to mitigate the severity of CRS. **Additional risk minimisation measures:** • Patient Card
ICANS	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • PL Section 2 • PL Section 4 • Recommendation that patients should remain close to a healthcare facility and be monitored for 48 hours after administration of all doses within the the step-up phase is provided in SmPC Section 4.2. • Recommendations for the management of ICANS (including neurology consultation/evaluation) by severity, and including actions to be taken (e.g., withholding, discontinuation) and treatment, are included in SmPC Section 4.2. • Recommendations for the monitoring, evaluation, and treatment of ICANS (including neurology consultation, corticosteroids, and anti-seizure medicinal products) is provided in SmPC Section 4.4. • Recommendation for restrictions on driving and operating machines due to the potential for ICANS is provided in SmPC Sections 4.4 and 4.7 and PL Section 2. • Guidance for patients to recognise symptoms of ICANS and get medical help right away are included in PL Sections 2 and 4. • Legal status **Additional risk minimisation measures:**

Safety Concern	Risk Minimisation Measures
	• Patient Card • HCP Educational Materials
Serious infections	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Recommendation that talquetamab should be withheld during the step-up phase until the infection resolves, and should be withheld during the treatment phase until the infection improves to Grade 2 or better, is provided in SmPC Section 4.2. • Recommendation that antiviral prophylaxis should be considered for prevention of herpes zoster virus reactivation, per local institutional guidelines, prior to starting talquetamab is provided in SmPC Section 4.2. • Recommendations for the management and treatment of serious infections, as well as guidance that the stepup dosing schedule should not be administered in patients with active infection, is provided in SmPC Section 4.4. • Guidance that talquetamab should not be administered in patients with active serious infection is provided in SmPC Section 4.4. • Guidance for patients to recognise symptoms of serious infection is included in PL Sections 2 and 4. • Legal status **Additional risk minimisation measures:** • None
Long-term safety	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** • None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. 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 request alignment of the PSUR cycle with the international birth date (IBD-to be determined). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. 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.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Talvey (talquetamab) 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.

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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant is requesting a Conditional Marketing Authorisation (CMA) for talquetamab in the following indication: as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

3.1.2. Available therapies and unmet medical need

The standard of care treatment for multiple myeloma includes regimens from 3 distinct therapeutic classes: proteasome inhibitors (PIs), immunomodulatory imide drugs (IMiDs), and anti-CD38 monoclonal antibodies. During disease course, all patients eventually relapse and become refractory to existing treatments and treatment guidelines for MM do not give specific recommendations after

multiple relapses. Among available therapies, no satisfactory treatment exists in the RR settings of the disease.

In the last decade, a number of new targeted therapies has emerged (anti CD38, anti SLAMF7, anti BCMA), and in conjunction with previous therapies (IMiDs, IP corticosteroids, alkylating agents and anthracyclines) have significantly improved survival for patients and number of various combinations are used in current practice. The recent arrival of T-cell redirection therapies, including CAR-T cells and BCMA/CD3 bispecific antibodies, has added additional treatment options in this condition.

However multiple myeloma is still an incurable and lethal disease for which there is a significant unmet need, especially after refractoriness failure to the three major lines of therapies is achieved (IMiD, IP and anti-CD38). With recent practice to combine multiple treatment, multi-refractoriness emerges on early lines of treatment, creating a new unmet medical need for RRMM patients.

3.1.3. Main clinical studies

The basis of evidence for use of talquetamab monotherapy is derived from efficacy and safety results from a single pivotal phase 1/2 Study 64407564MMY1001 (MonumenTAL-1): A phase 1/2, first-in-human, open-label, dose escalation study of talquetamab in Subjects with R/R MM.

3.2. Favourable effects

ORR according to the 2016 International Myeloma Working Group (IMWG) Response Criteria as assessed by the IRC was 74.1% (CI95%: 66.1%, 81.1%) for the 0.4mg/kg QW and 71.1% (CI95%: 63.7%, 78.9%) for the 0.8mg/kg Q2W analysis group. Median DOR was 9.5 months (CI95%: 6.7, 13.3) for the 0.4mg/kg QW analysis group and not reached (CI95%: 13, NE) for the 0.8 mg/kg Q2W analysis group.

The median TTR was similar in both cohorts (1.2 months (range: 0.2 to 10.9) for the 0.4mg/kg QW and 1.3 months (range: 0.2 to 9.2) for the 0.8mg/kg Q2W.

Median PFS was 7.5 months (CI95%: 5.7, 9.4) 2 in the 0.4mg/kg QW and 14.2 months (95% CI 8.4, NE) in the 0.8mg/kg Q2W cohorts.

The 12-month overall survival rate (95% CI) was 76.4% (68.3, 82.7) for RP2D 0.4 mg/kg QW SC analysis set and 77.4% (69.1, 83.7) for the RP2D 0.8 mg/kg Q2W SC analysis set.

MRD results are comparable between RP2D 0.4 mg/kg Weekly SC and RP2D 0.8 mg/kg Q2W SC, with 30.8% participants (95% CI: 23.3%, 39.0%) and 29.7% participants (95% CI: 22.4%, 37.8%) achieving MRD negativity at 10^{-5} respectively, and 21% (CI95%14.6; 28.6) and 20.7% (CI95%: 14.4;28.2) achieving MRD negativity at 10^{-6} respectively.

Additional subgroup information in patients with prior T-cell redirection therapy were provided, with 62.7% ORR (CI95%: 48.1, 75.9), a median DOR of 12.7 months (95% CI: 3.7, not estimable) and an estimated OS rate at 12 months at 59.6% (95% CI: 41.7%, 73.7%).

3.3. Uncertainties and limitations about favourable effects

Study MMY1001 was an uncontrolled, open-label, exploratory trial whose design is not suitable to provide confirmatory evidence as it is not possible to assess the potential impact of selection bias or interpret meaningfully time to event endpoints.

Subjects in the pivotal study were generally fit, and patients with reduced performance status (baseline ECOG PS score ≥ 2-9% across cohorts) or aged ≥75 years (range 8-22% across cohorts) were underrepresented, and no data are currently available in rare and aggressive forms of MM (e.g., plasma cell leukaemia, MM with meningeal involvement). Furthermore, exclusion criteria in study MMY1001 included known clinical markers of MM progression (i.e., severe hypercalcaemia, renal failure and anaemia), possibly resulting in a selected patient population that might have excluded subjects with rapid/severe clinical progression. High levels of missing data in relevant variables such as cytogenetics further increase the uncertainty around the generalisability of the results.

A trend towards higher rates of response in fitter and less heavily pre-treated subjects (i.e., patients with baseline ECOG PS score 0 and <4 prior lines of therapy) was observed, as well as a trend towards lower ORRs in subjects with ISS/R-ISS stage III, reduced baseline renal function (i.e., ≤60 ml/min), extramedullary plasmacytoma (ORR 42.2 - 47.4% across talquetamab regimen cohorts). Limited sample size in relevant subgroups did not allow, however, to draw robust conclusions. Similarly, the reduced sample size and short follow-up question the robustness of the results observed in subjects who had received prior anti-BCMA CAR T cell therapies and bispecific monoclonal antibodies.

3.4. Unfavourable effects

In the RP2D 0.4 mg/kg Weekly SC treated participants, the most frequently reported TEAEs were CRS (79.0%), dysgeusia (50.3%), anaemia (44.8%), weight decreased (41.3%), pyrexia (39.2%), neutropenia (35%), lymphopenia (28.0%), thrombocytopenia (27.3%), skin exfoliation (28%), asthenia (27.3%), dry mouth (26.6%), diarrhoea (25.2%), dysphagia (23.8%), fatigue (24.8%), dry skin (22.4%), nail disorder (22.4%), and rash (21.7%). The type and incidence of common TEAEs were generally similar among participants who received either of the RP2Ds.

Permanent discontinuation of talquetamab was required infrequently (6.7%). The most frequent adverse reactions leading to treatment discontinuation were ICANS (1.1%), weight decreased (0.9%) and dysgeusia (0.7%). The incidence of TEAEs leading to cycle delay or dose modification was high; 71.3% for participants assigned to 0.4 mg/kg weekly SC and 57.2% for participants assigned to 0.8 mg/kg Q2W SC.

The incidence of Grade 5 TEAEs during the study was similar for treated participants assigned to 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC. No participants with prior T cell therapies exposure experienced a Grade 5 TEAE. None of the Grade 5 TEAEs occurring within 30 or 60 days were judged by the investigator to be related to talquetamab.

Among the 339 patients who were treated with talquetamab at either of the recommended dosing regimen and regardless of prior exposure to T cell redirection therapy, CRS occurred in 77% of patients. Most events were Grade 1 or 2, with Grade 3 events occurring in 1.5% of patients. Neurotoxicity events were reported for 28.9% of patients, mostly of grade 1 and 2, and 2.6% of patients who experienced grade 3 or grade 4 neurotoxicity events.

ICANS occurred in 10% of patients (N=265). Most events were Grade 1 or 2, with Grade 3 and serious events occurring in 2.3% and 3.8% of patients, respectively. In addition, one fatal ICANS event was reported in the China cohort of the study. 68% of ICANS events occurred concurrently with CRS. The median time to onset of ICANS was 28 hours from the last dose, 68% of events started within 48 hours from the last dose, and the median duration of ICANS was 9 hours.

Infections occurred in 64% of patients. Grade 3 or Grade 4 infections occurred in 20% of patients, and fatal infections occurred in 1.5% of patients. All considered unrelated to talquetamab by investigators.

3.5. Uncertainties and limitations about unfavourable effects

The key uncertainty relates to the single-arm nature of the study, and the absence of a control group in a heavily pre-treated patient population, which compromises a comprehensive assessment of the safety associated with talquetamab.

The size of the safety population is currently limited for patients who received prior T-cell redirection therapy (N=51). Long-term safety and safety in patients with prior CART-cell are missing and additional information is expected from the submission of the final study report for Study 64407564MMY1001 and the planned confirmatory phase 3 study (Study 64407564MMY3002).

3.6. Effects Table

Table 55. Effects table for Talvey for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody (data cut-off: 17 January 2023).

Effect	Short Description	Unit	Treatment	Uncertainties/ Strength of evidence	References
Favourable Effects					
ORR	Percentage of participants with a confirmed partial response or better according to the 2016 IMWG Response Criteria by IRC	%	Weekly RP2D: 74.1 (CI95%: 66.1, 81.1) Q2W RP2D: 71.7 (CI95%: 63.7,78.9)	Uncontrolled trial	Study 64407564 MMY1001
Median DOR	Time from first documented evidence of PR or better until the earliest date of documented PD per IMWG, or death due to PD	months	Weekly RP2D: 9.5 (CI95%: 6.7, 13.3) Q2W RP2D: NE (CI95%: 10.6, NE)	Duration of follow-up: 18.8 months (range: 2.7 to 32.9) 12.7 months (range: 4.1 to 26.1)	
Unfavourable Effects					
Cytokine release syndrome	Incidence	%	76.7	≥Grade 3: 1.5% Absence of control arm	Study 64407564M MY1001
Neurotoxicity			29 ICANS: 10*	≥Grade 3: 2.6% (ICANS 2.3%) Absence of control arm	
Infections			64	≥Grade 3: 20% Absence of control arm	

Abbreviations: ORR: objective response rate; Q2W RP2D: 0.8 mg/kg Q2W SC, weekly RP2D: 0.4 mg/kg Weekly SC; CI: confidence interval; DOR: duration of response; PD: progressive disease; IMWG: International Myeloma Working Group; NE=not estimable; ICANS: immune effector cell-associated neurotoxicity.

Notes: Clinical Cut-off for safety: 16 May 2022,
Incidence are based on number of patients treated with talquetamab at either of the recommended dosing regimen and regardless of prior exposure to T cell redirection therapy (N=339) unless otherwise specified
*ICANS were only collected for Phase 2. Denominator is based on number of patients in Phase 2 (N=265)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy data from uncontrolled study MMY-1001 showed that treatment with talquetamab administered at either 0.4 mg/Kg weekly or 0.8 mg/Kg Q2W resulted in high ORRs in a heavily pre-treated population of patients with RRMM. This is considered of clinical relevance in a population characterised by widespread chemoresistance.

Moreover, the durable responses observed with talquetamab, and which are uncommon in such advanced settings of disease, are highly suggestive that talquetamab could provide an important treatment option at least for a subgroup of patients with RRMM. Overall OS and PFS are promising in both proposed dose regimen despite the known limitations in the interpretation of time to event endpoints in single arm trials.

The major risks associated with talquetamab use are CRS and potential fatal ICANS. Despite the high incidence of CRS, these events can be managed adequately with the recommendations and guidance provided in the product information. ICANS occurred in 10% of patients with some patients experiencing grade ≥3. ICANS typically occurred frequently with or few days after CRS events. Like CRS, the risk of ICANS can be managed with detailed warnings and recommendations in the product information. Management of both risks is expected to be further minimised though the Patient card which should enable patients to recognise symptoms easier and seek medical attention promptly.

Serious infections, including life-threatening or fatal infections, have also been reported in patients receiving talquetamab. In the absence however of a control arm in the registrational study, it is difficult to determine the role of talquetamab in the incidence and severity of infection and cytopenias AEs especially considering the high underlying prevalence of these events among patients with MM.

The limited follow-up and the overall limited size of the database also pose uncertainties particularly for assessment of very rare events; as such, the safety profile of talquetamab may still be evolving but will be further characterised through the ongoing MMY-1001 study and the randomised phase 3 study MMY3002.

3.7.2. Balance of benefits and risks

Available efficacy data suggest that talquetamab represent an additional treatment option for heavily pre-treated patients with RRMM. Being the first bispecific monoclonal antibody targeting GPRC5D on MM plasma cells, talquetamab might also retain anti-MM activity in subjects refractory to anti-BCMA agents.

In the intended indication, the safety profile could be considered manageable overall with appropriate risk minimisation measures. However, the limited follow-up and overall size of the safety database particularly for patients with prior T-cell redirection therapy limit a comprehensive assessment of the

risks associated with the use of talquetamab. Severe CRS and ICANS toxicity related to the use of talquetamab remain serious issues that should be carefully considered.

Longer-term safety data, also from appropriately controlled studies, will enable an improved overall contextualisation of the safety profile together with a more comprehensive understanding of efficacy.

In the context of a CMA, the B/R balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, 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.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

To confirm the positive benefit-risk profile, the applicant has initiated a confirmatory phase 3 (study MMY-3002 MonumenTAL-3) study which will provide additional efficacy/safety data. Study MMY-3002 is designed to compare the efficacy and safety of talquetamab in triple combination with daratumumab and pomalidomide or as a "doublet" with daratumumab vs. the approved "triplet" regimen daratumumab, pomalidomide and dexamethasone in subjects with RRMM who have received at least 1 prior line of therapy. Approximately 810 subjects will be randomised in a 1:1:1 ratio, and study completion is expected by April 2027. One interim analysis (IA) for efficacy and safety is planned when approximately 383 PFS events in all 3 arms combined will have been accumulated.

- Unmet medical needs will be addressed.

MM is an in incurable malignancy characterised by a relapsing/remitting behaviour and a progressive clinical course. In earlier settings of relapse, chemoresistance is usually limited, several effective regimens based on the combination of different mechanisms of action are currently available, and treatment choice is guided by patient characteristics/preferences, response to prior lines of therapy and previous toxicity/concomitant comorbidities.

In later MM stages, however, resistance to those drugs that form the backbone of the most active anti-MM regimens (i.e., proteasome inhibitors [PIs], immunomodulators [IMiDs] and anti-CD38 monoclonal antibodies [mAbs]) becomes widespread, refractoriness to treatment is common and responses are usually short-lasting. An unmet need for additional treatment options when "standard" approaches based on combinations of PI, IMiD and anti-CD38 mAbs have exhausted their activity is therefore, recognised.

Recently, preliminary evidence showing high response rates and the possibility for long-lasting disease control in a subset of triple-exposed MM patients has supported the granting of CMA in advanced settings of RRMM for BCMA-targeting T-cell redirection therapies (including e.g., CARTs and bispecific monoclonal antibodies). With the limits intrinsic in such indirect comparisons, a similar response rate is observed with the efficacy data of talquetamab in pivotal study MMY1001 compared to anti-BCMA T-cell recruiting therapies.

Although a trend towards deeper and longer-lasting responses can be observed with ciltacabtagene autoleucel, it is acknowledged that talquetamab would represent an "off-the-shelf" option not requiring the complex manufacturing and long turnaround time of CAR T-cell therapies. Other options within the therapeutic niche with conditional MA include teclistamab, melphalan flufenamide and belantamab mafodotin where talquetamab fulfil the unmet medical need to (at least) the same degree. Limits inherent in indirect comparisons in such a heterogenous condition should be taken into consideration when interpreting such data.

In addition, despite the similar mechanism of action that relies on T-cell recruiting and activation, the different target of talquetamab (GPRC5D) could reduce the risk of cross-resistance with anti-BCMA agents, as suggested by preliminary results from the cohort of subjects previously exposed to T-cell redirection agents who received talquetamab in study MMY-1001. Indeed, results from participants who had received prior T cell redirection therapy such as CAR-T or bispecific antibodies treated with talquetamab at the RP2D showed an ORR of 62.7% (95% CI: 48.1%, 75.9%). Therefore, talquetamab would provide a treatment alternative in a patient population with limited treatment options after failing anti BCMA therapies.

Overall, an unmet medical need for off-the-shelf therapies aimed at non-cross resistant targets in advanced settings of RRMM is acknowledged. Based on the available data, talquetamab could represent an additional off-the-shelf treatment option to answer to this medical need.

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

A substantial number of patients are expected to benefit from treatment with talquetamab over the period between Conditional Marketing Authorisation and full approval. Taking into account the known supply issues for CAR-T therapy, and the short life expectancy under CAR-T alternatives (excluding teclistamab which also has a Conditional Marketing Authorisation), immediate availability is considered of public health interest.

3.8. Conclusions

The overall benefit/risk balance of Talvey is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Talvey is not similar to Darzalex, Imnovid, Farydak, Kyprolis, Ninlaro, Blenrep, Abecma, and Carvykti within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Talvey is favourable in the following indication:

TALVEY is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 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 TALVEY is marketed, all patients/carers who are expected to use talquetamab have access to/are provided with the Patient Card which will inform and explain to patients the risks of CRS and neurologic toxicity including ICANS. The Patient Card also includes a warning message for healthcare professionals treating the patient that the patient is receiving talquetamab.

The Patient Card will contain the following key messages:

- A description of the key signs and symptoms of CRS and neurologic toxicity, including ICANS
- A description of when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS or neurologic toxicity, including ICANS, present themselves
- A reminder that patients should stay close to a healthcare facility for 48 hours after administration of each of the first 3 doses of the step-up dosing schedule
- The prescribing physician’s contact details

HCP educational programme

Prior to the launch of talquetamab in each Member State, the MAH must agree on the content and format of the educational materials with the National Competent Authority.

The MAH shall ensure that in each Member State where talquetamab is marketed, all HCPs who are expected to prescribe or administer talquetamab shall be provided with medical education material to:

- ensure awareness of the risk of neurologic toxicity including ICANS and recommendations to help minimise the risk, including information on frequency, severity, and time to onset observed in patients who received treatment with talquetamab
- facilitate identification of neurologic toxicity including ICANS
- facilitate management of neurologic toxicity including ICANS
- facilitate monitoring of neurologic toxicity including ICANS
- ensure that adverse reactions are adequately and appropriately reported

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 talquetamab 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 or after the last therapy, the MAH shall submit the results of study 64407564MMY3002, a Phase 3 randomised study comparing talquetamab SC in combination with daratumumab SC and pomalidomide (Tal-DP) or talquetamab SC in combination with daratumumab SC (Tal-D) versus daratumumab SC, pomalidomide and dexamethasone (DPd), in participants with relapsed or refractory multiple myeloma.	April 2027
In order to further characterise the 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, and have demonstrated disease progression on or after the last therapy, the MAH shall submit an updated safety report of 64407564MMY1001, a Phase 1/2, first-in-human, open-label, dose escalation study of talquetamab, a humanised GPRC5D x CD3 bispecific antibody, in subjects with relapsed or refractory multiple myeloma	September 2024

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that talquetamab is to be qualified as a new active substance in itself as it is a constituent of a medicinal product previously

authorised within the European Union.