24 March 2022
EMA/594558/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Carvykti

International non-proprietary name: ciltacabtagene autoleucel

Procedure No. EMEA/H/C/005095/0000

Note

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

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List of abbreviations

ADR	adverse drug reaction
AKI	acute kidney injury
ALT	alanine aminotransferase
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
BBB	blood- brain barrier
BCMA	B-cell activating factor
CAR-T	chimeric antigen receptor T cell
CI	confidence interval
Cilta-cel	ciltacabtagene autoleucel
Cmax	concentration maximum
CR	complete response
CRES CAR-T	related encephalopathy syndrome
CRP	C-reactive protein
CRS	cytokine release syndrome
DCO	Data Cut Off
DIC	disseminated intravascular coagulation
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FOIA	Freedom of Information Act
HLH	hemophagocytic lymphohistiocytosis
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
IgG	immunoglobulin G
IL	interleukin
IMiD	immunomodulatory agent
IMP	investigational Medicinal Product
IMWG	International Myeloma Working Group
INR	international normalization rate

IRC	Independent Review Group
IV	intravenous
IVIG	intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
MMY2001	JNN68284528MMY2001 clinical trial (CARTITUDE 1)
MMY2003	JNN68284528MMY2003 clinical trial (CARTUTUDE 2)
MRD	minimal residual disease
MUGA	multiple-gated acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
OOS	out of specification
ORR	overall survival
PBMC	peripheral blood mononuclear cell
PD	Progression of Disease
PFS	progression free survival
PI	proteasome inhibitor
RCL	replication competent lentivirus
sBCMA	soluble B-cell maturation antigen
sCR	stringent complete response
SPM	second primary malignancy
TEAE	treatment-emergent adverse event
TLS	tumour lysis syndrome

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International NV submitted on 29 April 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Carvykti, through the centralised procedure falling within the Article 3(1) and point 1a of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 March 2019

Carvykti was designated as an orphan medicinal product EU/3/20/2252.on 28 February 2020 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 Carvykti 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/medicines/human/EPAR/Carvykti

The applicant applied for the following indication:

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

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ciltacabtagene autoleucel was considered to be a new active substance.

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(s) P/0353/2019 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 request(s) for consideration

1.5.1. Conditional marketing authorisation and accelerated assessment

The applicant applied initially for a full marketing authorisation, but during the assessment, in response to CAT and CHMP concerns on the comprehensiveness of the data, requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004.

The applicant requested accelerated assessment in accordance to Article 14(9) of the same Regulation.

1.5.2. New active substance status

The applicant requested the active substance ciltacabtagene autoleucel 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.

1.5.3. Scientific recommendation on classification

The applicant Janssen-Cilag International NV submitted on 4 May 2018 an application for Scientific recommendation on Classification to the European Medicines Agency (EMA) for Carvykti, which was designated as an Advanced Therapy Medicinal Product in accordance with Regulation (EC) No 1394/2007on 5 July 2018. Carvykti was classified as a gene therapy medicinal product.

1.6. PRIME

Carvykti was granted eligibility to PRIME on 28 March 2019 in the following indication: treatment of adult patients with relapsed or refractory multiple myeloma, whose prior regimens included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on the last regimen.

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

- For patients that are not eligible for ASCT and have progressed following standard therapies (proteasome inhibitor (PI), anti-CD38 and immunomodulatory agent (iMID)), the prognosis is poor and there are few treatment options. Hence, the unmet medical need has been agreed.
- The non-clinical data has shown proof of principle in *in vitro* MM cell lines and *in vivo* models where a dose-dependent anti-tumour activity and prolongation of survival was demonstrated in nude mice.
- In the first phase 1 single arm trial CAR T cells in patients with relapsed/refractory MM (Legend -2), ORR for the total population was 87.8%, with 64% CR and 56.8% MRD negative, VGPR was 10.8%, PR was 12.2%, CR (64%) and ORR (87.8%) in patients that had relapsed following IMiDs and PI treatment. The estimated duration of response was 14.32 months (95%CI: 10.35, NE) and PFS was 14.85 months. In the one patient that was heavily pretreated and received anti-CD38 daratumumab, the patient achieved CR with MRD negativity.
- The magnitude of the effect seems convincing if compared with historical data and the data robust enough to demonstrate a compelling effect on efficacy in terms of ORR. Based on the mechanism of action, it could be cautiously possible to extrapolate the clinical efficacy to patients that have been previously heavily pretreated, depending on their prognostic factors.
- Therefore, it is considered that this product could potentially fulfil the criteria for PRIME

eligibility and address the unmet medical need in patients that have been previously heavily pretreated with chemotherapy, mAb (anti-CD38), PI and/or IMiDs and hence, has the potential to be of major therapeutic advantage over current treatment options.

Upon granting of eligibility to PRIME, Jan Mueller-Berghaus was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 19 June 2019. 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:

- CMC: The EMA recommended that the lentiviral comparability plan should be included in a Scientific Advice request. EMA also recommended that the characterisation testing for both lentiviral vector and drug product should be included in a Scientific Advice request to ensure appropriate release specifications. Furthermore, a Scientific Advice request should be considered in order to clarify the exemption from batch release testing in the EU due to e,g., limited amount of material available or the short shelf life (GMP for ATMPs 11.27) of JNJ-68284528.
- Non-clinical: To follow up on the potential cross-reactivity between JNJ-68284528 and claudin 9, the Sponsor should consider cross-reactivity to other members of the claudin gene family. In addition, the acceptability of the follow up plan should be included as a separate question in the upcoming Scientific Advice request. In said request, the plan to validate/invalidate the binding of JNJ-68284528 to claudin 9, the clinical consequences of this potential off-target cross reactivity and its appropriate monitoring should be discussed.
- Clinical: The proposed clinical data package (~100 patients/single arm study) was considered limited in the context of a full marketing authorisation. The planned six months follow-up foreseen was also considered limited to sufficiently characterize the progression-free survival and durable response of JNJ-68284528. The EMA recommended that Janssen consider submitting the planned clinical pharmacology modelling to Scientific Advice prior to a marketing authorisation application and discuss the comparative evidence strategy including data sources.
  In the context, the applicant was invited to provide the statistical analysis plan for real world evidence, once available.
- Regulatory: In the context of the product-specific waiver EMA recommended to have further discussions with PDCO to identify the extent to which BCMA targeted CAR-T cells could be efficacious in other malignancies.
- EMA recommended that an orphan designation should be filed as soon as possible in order to hold conversations with Janssen regarding the maintenance of the orphan designation and similarity exercise. Furthermore, EMA recommended that Janssen characterize the molecular structural features of the lentiviral vector more fully (not just the features of the CAR) during the similarity assessment against authorised orphan drugs in multiple myeloma and discuss this aspect in a Scientific Advice.
- Post authorisation studies: EMA recommended early planning for development of an appropriate protocol for registries. Early engagement with EBMT, as well as inclusion of EBMT representatives could be considered for participation in future Scientific Advice.

1.7. Scientific advice and protocol assistance

The applicant received scientific advice and protocol assistance on the development relevant for the indication subject to the present application.

The scientific advice and protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- the definition of the plasmids used for lentiviral vector manufacturing, the lentiviral vector, the apheresis material, the CAR T cell pellet as well as on the final cryopreserved medicinal product; drug substance and drug product specification review strategy;
- adherence of the apheresis material to Directive 2002/98/EC and Directive 2004/23/EC;
- comparability study for the clinical manufacturing process to be used in the clinical trials and to be the commercial process;
- the approach to demonstrate analytical comparability between the manufacturing process and the commercial process.
- the strategy to show non-similarity as compared to Orphan medicines (authorised and products under or pending review by the EMA) for the treatment of multiple myeloma;
- process performance qualification of the lentiviral vector (LV) and drug product manufacturing process as well as the accompanying analytical testing strategies and specification setting plan;
- the nonclinical safety package to support a MAA;
- the single arm study (68284528MMY2001) design to support an initial registration and a full MA for the treatment of heavily pre-treated and refractory population of patients with multiple myeloma who have no satisfactory treatment options, together with the use of Real-World data to provide context to the study data, in particular: the intended target population, the proposed target dose, the use of ORR as the primary endpoint and follow-up for the primary analysis; the size of the safety database;
- the Phase 3 study (68284528MMY3002) design to support regulatory approval for an extension of indication in patients with relapsed or refractory multiple myeloma who have been previously exposed to 1 to 3 prior lines of therapy, including prior exposures to PIs and IMiDs, and who are refractory to lenalidomide;
- the use of EORTC QLQ-C30 and qualitative interview to generate results in study MMY2001 being relevant for labelling as well as on the planned approach to define thresholds for meaningfulness of intra-patient changes of EORCT QLQ-C30 subscales.
- studies 68284528MMY2001: the planned analysis to contextualize the single arm clinical trial data using Real-World Data (RWD);
- study 68284528MMY3001: the overall safety management plan for the combination of CAR-T therapy and lenalidomide treatment, including titrating the initial dose of lenalidomide based on haematological recovery, conducting a safety run-in study in a separate cohort, and the implementation of the IDMC; the proposed patient population; the choice of lenalidomide maintenance as control; the choice of PFS as primary efficacy endpoint and proposed statistical design and analyses plan.
- the proposed PASS to evaluate the long-term safety;
- the collection and reporting of the long-term safety data up to 15 years post infusion via a PASS;
- the pooling of data from the prospective CIBMTR registry, the prospective EBMT registry and long-term follow-up study to assess long term safety;
- the study design of the proposed long-term follow-up study (LTFU);
- the collection of second primary malignancies (SPMs), and overall survival to assess long term safety; the measures to monitor the risk of insertional mutagenesis and potential clonality in the ongoing clinical studies; the approach to address the concern of new malignancy within the LTFU study;
- the collection of data items by EBMT to characterize SPMs; the sample size of patients needed across data sources (EBMT and CIBMTR registries) to address long-term follow-up;

- the generation of clinical study report (CSR) for the 68284528MMY4002 study.

1.8. Steps taken for the assessment of the product

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

CAT Rapporteur: Jan Mueller-Berghaus CAT Co-Rapporteur: Marcos Timón

The application was received by the EMA on	29 April 2021
Accelerated Assessment procedure was agreed-upon by CAT and CHMP on	28 January 2021
The procedure started on	20 May 2021
The CAT Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	12 August 2021
The CAT Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	11 August 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	24 August 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CAT during the meeting on	2 September 2021
The CAT agreed on the consolidated List of Questions to be sent to the applicant during the meeting; the assessment timetable was reverted back from accelerated to standard assessment timelines on	10 September 2021
The applicant submitted the responses to the CAT consolidated List of Questions on	11 October 2021
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at Janssen Pharmaceuticals Inc. 1000 U.S. Route 202 South Raritan, NJ, USA 08869 conducted on 05th November 2021. The outcome of the inspection carried out was issued on:	31 January 2022
The CAT/PRAC Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CAT, PRAC and CHMP members on	18 November 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	2 December 2021
The CAT agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	10 December 2021
The applicant submitted the responses to the CAT List of Outstanding Issues on	15 February 2022

The CAT Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	4 March 2022
The CAT, 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 Carvykti on	18 March 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Carvykti on	24 March 2022
The CAT and CHMP adopted a report on similarity of Carvykti with Imnovid, Farydak, Kyprolis, Darzalex, Ninlaro, Blenrep and Abecma on	18/24 March 2022
Furthermore, the CAT and CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	18/24 March 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Claimed therapeutic indication

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

2.1.2. Epidemiology

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

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

2.1.3. Biologic features

Multiple Myeloma is characterised by the increased proliferation of malignant monoclonal plasma cells in the bone marrow, with the subsequent bone marrow failure due to replacement of normal bone marrow haematopoiesis, the over-production of monoclonal immunoglobulins (M-protein, either intact immunoglobulins and/or free light chains [FLC]) which could be detected in the serum or urine, and

finally the presence of systemic symptoms named as CRAB (hyperCalcaemia, 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).

2.1.4. 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, hypercalcaemia, renal insufficiency or failure, and neurological complications (Palumbo 2011). Profound intratumoural 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).

2.1.5. 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 analyzed 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 tumour 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.

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

Ciltacabtagene autoleucel (cilta-cel) consists of autologous T cells genetically modified to express a chimeric antigen receptor (CAR) utilizing a lentiviral vector (LV). The target antigen of the CAR is BCMA, which is expressed on malignant plasma cells. The LV coding sequence is comprised of a human CD8 alpha signal peptide (CD8α SP), BCMA targeting single-domain antibodies (VHH1 and VHH2) designed to confer avidity, human CD8 alpha hinge and transmembrane domain (CD8α hinge+TM), human CD137 cytoplasmic domain (4-1BB), and a human CD3 zeta cytoplasmic domain (CD3ζ). The expression of the LV is driven/controlled by a human elongation factor 1 alpha promoter (hEF1α promoter).

Cilta-cel is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody. Cilta-cel is to be administered in a single

infusion at a target dose of 0.75 x 10^6 CAR-positive viable T cells/kg (range: Patients 100 kg and below: 0.5 - 1.0 x 106 CAR-positive viable T cells/kg body weight. Patients above 100 kg: 0.5 - 1.0 x 108 CAR-positive viable T cells (non-weight based).

Upon binding to BCMA expressing cells which are primarily represented by late-stage B cells, plasma cells, and malignant B-lineage cells, the CAR promotes T-cell activation, expansion, and elimination of target cells.

2.3. Type of application and aspects on development

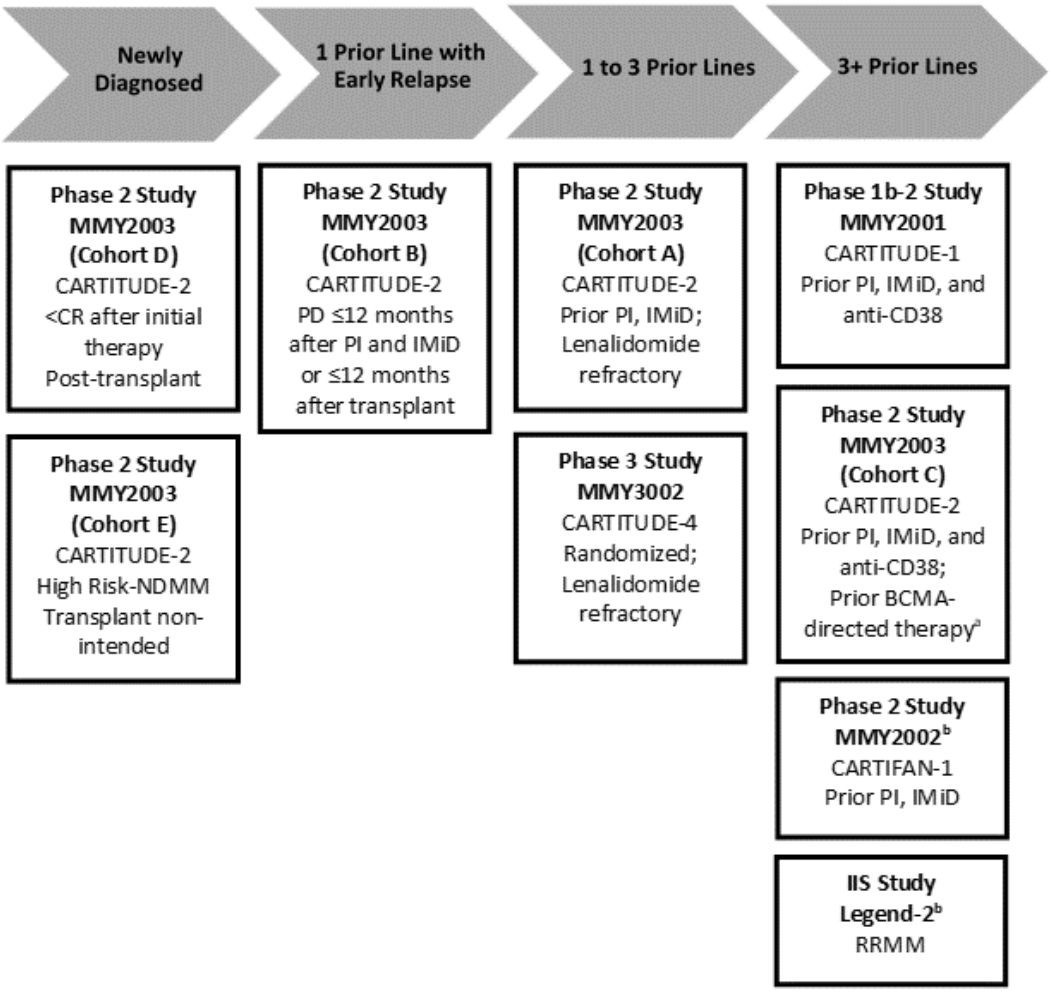
Carvykti has been granted PRIME eligibility.

Clinical development programme

The clinical development programme for cilta-cel consists of one Phase-1 study (LEGEND-2) one Phase 1b-2 study (MMY2001-CARTITUDE-1), one Phase 2 (MMY2002-CARTIFAN-1), one multicohort Phase 2 study (MMY2003-CARTITUDE-2), one Phase 3 randomised study (MMY3002-CARTITUDE-4) and one long term (for up to 15 years) safety follow up study (68284528MMY4002).

The clinical development plan for cilta-cel in the treatment of multiple myeloma is outlined in the following figure 1.

Figure 1. clinical development plan for ciltacabtagene autoleucel



CR=complete response, IMiD=immunomodulatory drug, NDMM=newly diagnosed multiple myeloma, PD=progressive disease,
PI=proteasome inhibitor, RRMM=relapsed or refractory multiple myeloma
[a] Excluding cellular immunotherapy
[b] Study conducted in China

A description of the on-going clinical trials for Carvykti is included in the table below:

Study Protocol Number	Study Title	Participating Countries
68284528MMY2001	A Phase 1b-2, Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Relapsed or Refractory Multiple Myeloma	United States & Japan
68284528MMY2003	A Phase 2, Multicohort Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Multiple Myeloma	United States, Spain, Netherlands, France, Belgium, Israel, Germany
68284528MMY3002	A Phase 3 Randomized Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide-Refractory Multiple Myeloma	Australia, Austria*, Belgium, Denmark, France, Germany, Greece*, Israel, Italy, Japan, Korea, Netherlands, Poland, Spain, Sweden, United Kingdom, United States

* Clinical trial applications under review

Accelerated assessment

The CHMP and CAT 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 the potential of Carvykti to address an unmet need and to provide a valuable further treatment option for patients suffering from relapsed or refractory MM. For this patient population Carvykti thus may represent a therapeutic advantage over available treatment options. However, during the assessment, a GMP inspection and provision of a GMP certificate were considered necessary which did not allow maintenance of the accelerated assessment timetable.

Conditional Marketing Authorisation (applicant claim)

In light of the concerns raised during assessment on the comprehensiveness of the data set 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 in a patient population consistent with the CARTITUDE-1 study.
- It is likely that the applicant will be able to provide comprehensive data by post approval measures as described below:
  - CARTITUDE-1 (MMY2001): A Phase 1b/2, open-label, multicentre study to evaluate the safety and efficacy of JNJ 68284528 in adult subjects with relapsed or refractory multiple myeloma (due date 31 December 2022)
  - CARTITUDE-4 (MMY3002): A Phase 3 randomised study comparing JNJ-68284528, a CAR-T therapy directed against BCMA vs PVd or DPd in subjects with relapsed and lenalidomide-refractory multiple myeloma (due date 31 December 2026).
- Unmet medical needs will be addressed, as:
  - Although satisfactory methods of treatment of the condition have been authorised in the EU, all patients with this disease will eventually relapse after initial response and require further therapy. Newer agents with novel therapeutic strategies that effectively target relevant and specific molecules on the surface of multiple myeloma cells benefit patients with relapsed/refractory multiple myeloma to improve and deepen ORR and prolong PFS and OS. Therefore, the applicant considers that cilta-cel addresses an unmet medical need for those affected by the condition.
  - Major therapeutic advantage over pomalidomide, lenalidomide, bortezomib, carfilzomib, ixazomib, daratumumab, isatuximab, elotuzumab, and panobinostat has been established via the documentation of a favorable response (ORR) with ciltacabtagene autoleucel treatment in patients who had previously failed treatment containing these agents.
  - Major therapeutic advantage over idecabtagene vicleucel, belantamab mafodotin, selinexor, and melphalan flufenamide has been established via indirect methods comparing ORR, CR, and PFS outcomes. Patients treated with cilta cel were more likely to show a favorable response (ORR, CR) and extended survival without disease progression (PFS) compared to patients treated with idecabtagene vicleucel, belantamab mafodotin, selinexor, and melphalan flufenamide.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.
  - With respect to public health, when patients have exhausted the most common classes of

agents used in this setting (PIs, IMiDs, Anti-CD38 Abs), a highly efficacious, one-time treatment, is the best available option for the patient compared to all other existing therapies.

- For these reasons, making cilta-cel available to patients with relapsed or refractory multiple myeloma now is justified with the understanding that more efficacy and safety results from the CARTITUDE-1 and CARTITUDE-4 studies will be provided in due course.

2.4. Quality aspects

2.4.1. Introduction

Carvykti is presented as a dispersion for infusion containing 3.2 x 10^6 to 1 x 10^8 CAR-positive viable T cells of ciltacabtagene autoleucel as active substance. The other ingredient is the cryoprotectant Cryostor® CS5 which contains dimethyl sulfoxide (DMSO). The product is available in ethylene vinyl acetate (EVA) 30 mL or 70 mL infusion bags with sealed addition tube and two available spike ports. Each infusion bag is packed in an aluminium cryo cassette.

2.4.2. Active Substance

The section on the active substance is separated into two parts; part 1 for the lentiviral vector (starting materials) and part 2 for the transduced cells (active substance).

Part 1: Lentiviral Vector starting material

Lentiviral vector - General Information

The lentiviral vector is a third-generation HIV-1-derived replication-incompetent and self-inactivating (SIN) vector pseudotyped with the vesicular stomatitis virus glycoprotein (VSV-G). The vector genome encodes the B cell maturation antigen (BCMA, also known as CD269 and TNFRSF17) specific CAR under the control of a human EF1α promotor. The CAR is comprised of a human CD8α signal peptide, llama-derived single domain antibodies (VHH1 and VHH2) specific for recognizing BCMA antigen followed by a human CD8α hinge and transmembrane domain that is fused to the T cell cytoplasmic signalling domains of 4-1BB and CD3ζ. The packaged vector RNA encodes no viral genes. The LV is a critical starting material used to transduce the autologous T cells to manufacture cilta-cel.

Lentiviral vector – Manufacture and process controls

The LV is manufactured in a 70stage manufacturing process consisting of upstream and downstream steps. The upstream manufacturing process starts with thaw and preculture of a single WCB (working cell bank) vial in a shake flask followed by serial cell expansions in shake flasks and finally transfer to a culture bag. Subsequently, cells are harvested, transferred into bioreactors and transfected with the vector genome carrying transfer plasmid and three packaging and helper plasmids the harvest is pooled and clarified followed by a sterile filtration. Concerning the downstream manufacturing process, the LV undergoes a series of purification steps and finally, the purified bulk LV is filled into vials and stored frozen. Overall, the manufacturing process of the LV is adequately described.

The LV is manufactured in compliance with GMP and manufacturing licenses have been provided for the different manufacturing and test sites.

IPCs, PPs, and CPPs including acceptance criteria, proven acceptable ranges or operating ranges have been defined. The applicant differentiates between IPCs with an acceptance criterion and IPCs with a predefined instruction. IPCs with an acceptance criterion are controls to assess parameters at an in-process sampling location and covers tests for safety. IPCs with predefined instructions are controls that may be used during routine manufacturing Acceptance criteria of the existing IPCs have been sufficiently justified. To identify the CPPs, each PP was evaluated for its potential effect on CQAs considering the degree of knowledge uncertainty.

PARs have been justified based on one-factor-at-a-time (OFAT) studies, design of experiment (DOE) studies and validation studies. In order to confirm the PARs, statistical consideration as well as extrapolated criteria have been used. These extrapolated criteria were derived from retrospective analysis of process characterisation data and represent limits that are expected at the respective manufacturing stage to produce LV, which meets LV release specification after further downstream processing. Furthermore, some process parameters controlled within an operating range have been justified based on manufacturing experience. CQAs have been defined based on the severity of their impact to patient safety as well as finished product efficacy, the degree of knowledge uncertainty for severity and regulatory expectations.

The LV manufacturing process contains seven process intermediates whose hold conditions were evaluated to confirm their biochemical stability at the proposed hold time and temperature. Overall, the provided data support the proposed hold conditions of the process parameters. A cumulative extended hold study has also been performed.

Lentiviral vector – Control of Materials

The applicant provided a tabulated overview for all compendial and non-compendial materials. For the non-compendial materials test methods and acceptance criteria have been specified. A two-tiered cell banking system has been generated to ensure continuous supply of the vector production cell line. The overall testing strategy for the cells banks is adequately described. The applicant accepted a recommendation to qualify and perform an additional identity test on the WCB. Suitable stability programs for the MCB and WCB have been provided and the preparation of future WCBs has been described.

The LV is manufactured by transient transfection using a 3rd generation packaging system comprising a transfer plasmid encoding the CAR transgene and three helper plasmids Development history, plasmid maps, manufacturing process for plasmid MCBs and plasmid DNAs, release specifications, summary of methods used to control the plasmids, and stability testing have been described. Stability data are presented supporting the proposed shelf life when stored frozen at the recommended storage condition. The applicant committed to implement recommendations related to the cell bank specification used to manufacture the plasmids.

Lentiviral vector - Process validation

For process validation of the commercial LV manufacturing process, commercial scale batches were manufactured and evaluated for CPPs, IPCs and release specifications. Moreover, data have been provided confirming the capability of the manufacturing process to consistently remove process-related impurities including those derived from media, buffers and process additives. Results of several further parameters that are not analysed routinely during commercial manufacturing has been additionally provided for these three validation batches as part of process characterisation. Generally, these data support consistent manufacturing. Some process parameters had been controlled during validation but are not controlled at the commercial process which has been sufficiently justified by the applicant. The applicant´s approach for the validation studies for the mixing equipment is considered acceptable.

Initial validation and routine revalidation of aseptic manufacturing deems in accordance with the requirements. To provide on-going assurance that the process remains in a state of control during commercial manufacture, continuous process verification that includes monitoring of release tests, IPCs and PPs is planned. The proposed programme on continuous process verification is considered acceptable.

Adequate shipping qualification data has been provided. Qualification programme of future LV shipping systems has been sufficiently described and a temperature logger is used for shipment.

Lentiviral vector – Manufacturing process development

The initial changes implemented to the plasmids were designed to increase the safety of the vector. This included changing from a 2nd/3rd generation LV construct used in the First-in-Human study to a 3rd generation LV packaging system. During further clinical development, the antibiotic resistance gene of the plasmids was changed to further improve patient safety. To increase manufacturing capacity for clinical and commercial demands further changes were introduced late in development leading to the commercial process.

Several studies were conducted to support comparability of the respective LV products from the different designs, processes and sites.

Initially a Major Objection was raised in view of the observed differences for some CQAs and the low number of batches used for the comparability exercise even though more batches had been manufactured. Comparability of the clinical and commercial processes was not considered confirmed The applicant subsequently provided further data and statistical analysis to support the comparability assessment. This included justification for differences observed which were not expected to have a significant impact on the efficacy and safety of the final CAR-T finished product which was accepted.

Lentiviral vector – Characterisation

Characterisation of the lentiviral vector was performed during development and release of the lentiviral vector. The characterisation tests are performed for a more detailed understanding of the LV for process monitoring purposes. The assays were used to confirm the full vector sequence and integrity of the integrated proviral sequence in transduced T-cells together with additional analysis of LV composition. Respective characterisation tests have been described by the applicant.

All impurities are controlled at batch release and their removal has been analysed during process validation. Recommendations were made for the applicant to continue characterisation of the LV.

Lentiviral vector - Specifications, analytical procedures, reference standards, batch analysis, and container closure

Release specifications cover tests for safety, potency, identity, genomic integrity, quantity, general characteristics, and purity and are in line with the expectations given in Ph. Eur. 5.14. Acceptance criteria are considered sufficiently justified.

The analytical procedures used for release testing of the LV have been adequately described. Validation of the non-compendial analytical procedures are generally in line with ICH Q2(R1) and compendial methods have been verified as appropriate. System suitability requirements have been described for each analytical procedure. For analytical procedures performed at different sites, co-validation have been performed and equivalence analysed.

Batch data was provided from commercial batches and representative clinical batches including details such as manufacturing site, manufacturing date, scale and use. The analytical procedures used for release control have been provided. In general, the provided batch data support consistent

manufacturing of LV. Recommendations were made for the applicant continue to characterise appropriate reference materials to support LV.

The primary container closure system is a preassembled, single use vial and stopper which is received ready to use. The container closure components meet the requirements for the corresponding Ph. Eur. monographs and container closure integrity was demonstrated. Leachable and extractable studies were performed.

Lentiviral vector - Stability

Long term stability studies are ongoing on multiple batches including those manufactured using the commercial process and supportive lots manufactured by the clinical manufacturing process considered representative of the commercial process. Test methods used for the stability study are a subset of those used for release testing which is in line with the expectations. Acceptance criteria are the same as for release.

During review a concern was raised regarding the availability of data to support the shelf-life claim in line with the requirements of ICH Q1A_R2. In response the applicant provided predictive estimates to further support the shelf-life claim which was accepted. The applicant committed to provide additional stability data (meeting acceptance criteria to further support the assigned shelf life once available

A post-approval stability programme was submitted and is considered adequate.

Part 2: CAR-T active substance

2.4.2.1. General information

Ciltacabtagene autoleucel (cilta-cel) is an engineered autologous T cell immunotherapy by which a patient´s own T cells are harvested and engineered ex vivo by lentiviral transduction of a chimeric antigen receptor (CAR) construct encoding an anti-BCMA CAR, which consists of two llama-derived single domain antibodies fused to CD137 (4-1BB) and CD3ζ intracellular signalling domains. The applicant has provided sufficient information concerning the CAR domains, architecture and function. Cilta-cel was designed to bind specifically to cells expressing BCMA and induce BCMA-dependent, CAR-T mediated cytolysis.

2.4.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The ciltacabtagene autoleucel finished product (FP) manufacturing process is a continuous process. First, fresh autologous peripheral blood mononuclear cells (PBMCs) procured by apheresis are cryopreserved centrally (Germany) or locally at cryopreservation sites spatially associated with the apheresis centres.

Next the cryopreserved PBMCs are shipped to the AS (Active substance) and FP manufacturing site Janssen Pharmaceuticals, Inc, 1000 Route 202 South Raritan, New Jersey 08869, USA. A major objection was raised due to the lack of valid EU GMP certificate and an inspection took place during assessment and a certificate issued. Batch certification to the EU market is performed by Janssen Biologics, Leiden, The Netherlands and a valid MIA was provided.

Upon cryopreservation, the frozen cell material is transported to the commercial AS/FP where manufacture of the final FP is continued in a 5-stage continuous manufacturing process. The

manufacture starts with the acceptance and thawing of the apheresis material and T cell enrichment. Enriched T cells are then activated and transduced with LV and cells are expanded. At the end of the culture period cells are harvested, washed and cryopreserved.

Manufacture and control of the FP have been sufficiently described and a continuous flow-scheme with all manufacturing and unit operations, hold-steps (intermediates) as well as IPCs/PPs/CPPs (in-process controls/ process parameters /critical process parameters) has been indicated. IPCs, PPs, and CPPs including acceptance criteria, proven acceptable ranges or operating ranges have been defined, justified and are deemed appropriate to assure sufficient process control.

To provide justification to the proposed PARs (proven acceptable ranges), OFAT and/or DoE studies have been performed using healthy donor (HD) and/or surplus patient apheresis material in a qualified reduced-scale (RSM) model.

Acceptance criteria used for the establishment of PARs during development studies are based on clinical assay specification at the time of study execution, which also meet the commercial specification. Hence, it is assured that specification compliant finished product can be manufactured at conditions that represent the PAR extremities.

Control of materials

Apheresis starting material

Patient material is collected at apheresis sites assessed by the applicant according to FACT, JACIE and EBMT standards and in accordance with Directives 2004/23/EC, 2002/98/EC and 2006/17/EC.

Acceptance criteria have been established for procured patient material, which is considered acceptable to not exclude patients, whose apheresis may not meet existing release criteria but may give rise to a successfully manufactured product.

After procurement at the apheresis site, the fresh apheresis material is transported to cryopreservation facilities for formulation and cryopreservation. Hold time data supporting the transport and defined cryopreservation processes have been provided and are based on clinical manufacturing experience. Upon receipt at the cryopreservation facility the cell count is adjusted to an appropriate target range for formulation into cryopreservation media based on historical patient data as well as CPC (cryopreservation centre) and FP manufacturing capabilities Overall, the apheresis formulation and cryopreservation process has been adequately described.

PARs have been proposed for relevant PPs in process characterisation studies for the impact on key process performance post-thaw attributes, such as cell counts, viability and cell phenotype.

Concerning the control of materials used for apheresis formulation and cryopreservation, an impact assessment of the patient apheresis material and the cryoprotectant on pre-defined critical apheresis quality attributes has been provided.

To lend support to the established apheresis starting material control strategy, information was compiled on multiple cryopreserved patient apheresis batches manufactured across several CPC sites, with regards to quality of apheresis as measured by process performance attributes (PPAs) Data presented suggests an overall robust manufacture of apheresis starting material using the established process across the involved CPC sites.

Thermal shipper qualification and distribution studies have been performed that demonstrate the suitability of the transportation of fresh apheresis material to the cryopreservation sites within the EU.

Compendial and non-compendial raw materials

The applicant provided a tabulated overview for all compendial and non-compendial materials including product-contacting consumables. For the non-compendial materials, acceptance criteria for test methods that are performed in addition to the testing performed by the vendor according to their certificates of analysis (CoAs) have been specified. Reference to the respective monographs (USP, JP and Ph. Eur.) has been provided for the compendial raw materials. The manufacturers of the raw materials and product-contacting consumables have been specified. Confirmation has been provided by the applicant that internal procedures do not require verification of compendial test methods.

More information on raw human/animal derive materials can be found in the Adventitious agents section below.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the cita-cel active substance manufacturing process is given.

CPPs and final FPs CQAs have been identified using a risk-based approach, taking into account the potential impact on safety and efficacy as well as the degree of knowledge uncertainty. Hold conditions for all AS/FP process intermediates have been qualified in a cumulative hold study for compliance with established IPCs, CPPs and FP release specifications.

Process validation

For process validation of the commercial AS/FP manufacturing process consecutive commercial scale batches were manufactured using multiple lots of cellular starting material and LV.

All PV batches manufactured were within the specified acceptance limits for all PPs/CPPs and IPCs for apheresis thaw and T cell enrichment, T cell activation, T cell transduction and expansion, T cell harvest and wash manufacturing step and the final formulation, fill and cryopreservation. Any results not in compliance with the release specifications were justified by the applicant and subject to corrective actions as appropriate These data supported by further data from multiple clinical batches manufactured at the commercial FP facility, suggest that the commercial process is consistently delivering a FP of defined quality, lending substantial support towards a successfully validated commercial manufacturing process.

Process performance attributes (PPAs) have been defined for process stages 1-5, iAlert limits have been established for some but not all PPAs to indicate potential drift from clinical experience, Adequate justification has been provided for those parameters for which no alert limits are foreseen.

It is noted that the applicant has made adjustment to IPCs and process parameters post-validation. While the changes to the IPCs are considered minor or improve the overall process, some of the process parameters for the commercial process are widened in contrast to the process validation ranges, and are supported by process development studies. Although performed after formal process validation, this was considered to be acceptable.

Studies to qualify hold conditions for all process intermediate hold steps have been performed for the commercial manufacturing process challenging the maximum pre-defined hold-times for each intermediate (cumulative hold times). The presented FP release data are compliant with established FP release specifications, demonstrating that under worst-case hold conditions, FP of sufficient quality can be manufactured.

Electronic and paper-based systems have been implemented to control, review, track and record the patient CoI/CoC (Chain of Identity / Chain of Custody). Validation data has been presented for both systems demonstrating their capability to ensure bidirectional tracking of cells contained in Carvykti in

accordance with provisions contained in the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.

Risks to FP and/or patients safety stemming from polymeric materials used for apheresis, cryopreservation as well as LV and FP manufacture have been assessed in a risk analysis Apheresis centres are qualified by JACIE/EBMT standards using appropriately qualified materials for patient material procurement.

The applicant´s control strategy to assure control of the final FP´s QAs is deemed overall well in agreement with the provisions contained in ICH Q11.

Final FP CQAs have been identified using a risk-based approach, taking into account the potential impact on safety and efficacy as well as the degree of knowledge uncertainty

To provide sufficient control to raw and starting materials as well as consumables entering the manufacturing process, the applicant confirmed that raw materials are controlled according to the provisions provided in Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products and Ph. Eur. 5.2.12. Raw materials are produced in compliance with applicable GMP and controlled through routine release at least for identity, sterility and endotoxin. Raw materials have been assigned to risk categories and the underlying risk factors associated with the material, the vendor and/or utilisation of the material within the process justified.

IPCs implemented to control for manufacturing consistency and final FP quality, together with their respective action or acceptance limits have been summarised. Action/acceptance limits have been justified based on available process development data and/or manufacturing experience.

Process- and product-related impurities introduced during the AS/FP manufacturing process have been categorised during development regarding criticality in a risk assessment by calculating the safety margin separating the theoretical exposure limit from the predetermined safety level.

Robust and sufficient depletion of critical process- and product-related impurities has been demonstrated for a sufficient number of patient batches using the commercial manufacturing process.

Manufacturing process development

Concerning manufacturing history, tabular summaries of process changes introduced during process development have been provided together with the rationales for changes. Commercial production will be performed at Janssen Pharmaceuticals, Raritan, USA.

Changes to the AS/FP manufacturing process and site of manufacture have been introduced through clinical development.

changes have also been made to the apheresis or LV starting materials used for FP manufacturing.

To address the impact of changes implemented during development, a series of process development and formal comparability studies have been conducted, which were designed to demonstrate comparable process performance and FP quality after the changes were implemented.

Common to all studies is parallel manufacturing using split-apheresis of variable number of healthy and/or patient apheresis lots, which was endorsed. In-process data as well as final FP release and characterisation data have been gathered for the individual study arms and assessed with regard to compliance with established in-process and/or release criteria, historical data (where established) and similarity based on side-by-side comparisons. Although the presented data appear to suggest some degree of comparability of the FP, it is noted however, that the applicant has not been able to define clear comparability criteria, based on which an unbiased decision on comparability of pre- and post-change FP can be made. Due to unavailability of meaningful comparability criteria, comparability of the

different vector starting materials and FP manufacturing processes is being assessed following a scientific approach based on the available in-process and release data. Hence, no further comparability criteria are requested.

Changes to the analytical methods used for FP release testing have been summarised and are for the most part deemed minor with respect to assay comparability throughout development.

In conclusion based on the information available, FP comparability for the different sites and vector starting materials could not be conclusively demonstrated. However, the presentation of further comparability data is not deemed to be required to resolve this issue as differences in batch release data from the different manufacturing processes should be clinically evaluated, when taking into account the autologous nature of the therapy and the characteristics of living cells which are expanding in vivo and are altering their therapeutic potential depending on tumour cell abundance as CAR-T cell stimulus. The applicant has further agreed to reconfirm to provide safety and efficacy updates on commercial-LV-treated patients, after marketing authorisation, as part of the ongoing clinical development of cilta-cel in study MMY2003, cohort A (2Q 2023) and study MMY3002.

Characterisation

Final FP batches manufactured by the commercial manufacturing process have been analysed for lymphocyte composition, T cell phenotype and in-vitro effector function. Batches investigated displayed a substantial uniformity with regard to T cell purity/lymphocyte composition.

The effector function of FP has been studied in-vitro in co-culture experiments, suggesting BCMA-specific cytokine induction and T cell proliferation.

See also discussion on impurities in the process validation section above.

The potential presence of nitrosamine impurities has been evaluated considering the raw materials and excipients used as well as the clearance capability of the manufacturing process. Based on the risk evaluation provided, a low likelihood for presence of nitrosamine impurities is concluded.

2.4.2.3. Specification

Manufacture of Carvykti is a continuous process and thus, the respective information is provided in section (Finished medicinal product) below.

2.4.2.4. Stability

Manufacture of Carvykti is a continuous process and thus, the respective information is provided in section (Finished medicinal product) below.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Carvykti FP is composed of CD3-positive T cells that have been transduced by a lentiviral vector encoding a CAR for BCMA, formulated with a cryoprotectant containing 5% DMSO. The finished product consists of 3.2 x 10e6 - 1 × 10e8 CAR+ viable cells which are formulated in either 30 mL or 70 mL CryoStor CS5 freezing medium depending on the total viable cell count. The target dose has been indicated as 0.75 x 10e6 CAR+ viable T cells/kg patient weight with a specification range of 0.5 – 1.0 x

10e6 CAR+ viable T cells/kg patient weight for patients weighing 100.0 kg or below. The FP target dose for patients weighing above 100.0 kg is 0.75 x 10e8 CAR+ viable T cells with a specification range of 0.5 – 1.0 x 10e8 CAR+ viable T cells. The dose specification is set as a range to allow for variability during the formulation / fill finish process.

The target dose is calculated based on the CAR+ expression percentage, patient weight, total viable cell concentration and bag volume.

The only excipient used in the formulation of the finished product is CryoStor CS5, which is a cryoprotectant and cell stabilizer.

Depending on the final volume, the final product is either filled in a 30 mL (50 mL bag) or 70 mL (250 mL freezing bag. Samples for release testing are filled in 1 mL cryovials. Equivalence of both bag sizes and the cryovials has been addressed using healthy donor material including provision of Stability data This approach is considered acceptable.
The suitability of the container closure system including discussion of extractables and leachables has been demonstrated.

Pharmaceutical development activities included an evaluation of FP stability under accelerated conditions and use of FP from patients or healthy donors. In-use stability and FP compatibility were demonstrated up to 3.5 hrs when stored at RT in a bracketing approach using healthy donor apheresis material manufactured with the commercially-representative manufacturing process in-use study have been provided and generally support an in-use shelf life of 2.5 hrs as per the SmPC: "The medicinal product should be administered immediately after thawing and the infusion should be completed within 2.5 hours of thawing".

The applicant committed to perform further in use stability study to assess additional quality attributes the intended in-use time of 2.5 hrs.

2.4.3.2. Manufacture of the product and process controls

As the manufacturing process is considered to be continuous, the complete manufacturing process and the involved manufacturing and test sites are described in the drug substance part.

For shipment of the finished product, a qualification study, a real-time transportation study and a finished product simulated transport study using apheresis material as surrogate, shipped under worst-case long-term transit conditions, have been performed. The shipper is qualified to maintain temperature A temperature logger is used in every FP shipment.

2.4.3.1. Product specification

Since the manufacturing process from receipt of the apheresis starting material to final product is continuous and no active substance is isolated, it is considered acceptable that specifications have only been defined for the finished product. The FP specifications include tests for appearance, identity, viability, quantity, safety and potency. The testing time point and kind of testing sample been indicated for each method. A recommendation was made for the applicant to provide further data demonstrating the representativeness of testing in process samples for a subset of the release tests.

FP specifications were derived from multiple batches manufactured at the commercial manufacturing site that met the release specification. Most quantitative FP attributes were evaluated with a statistical approach. An exemption of retesting upon importation was requested and justified by the insufficient volume available for retesting. The strategy is in line with the Guideline on good manufacturing

practice specific to Advanced Therapy Medicinal Products, 11.17 and the Q&A document on the exemption from batch controls carried out on ATMPs imported into the European Union from a third country (EMA/354272/2019) and is accepted.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

A description and summary of validation as well as complete validation reports has been provided for each analytical procedure. System suitability requirements have been described for each assay. For test performed at different sites, co-validations have been performed using the same test material.

A Major Objection was raised regarding the suitability of the proposed potency test (tumour killing).

Further information was provided by the applicant in response but as there were several remaining concerns with regard to the commercial tumour killing assay the applicant proposed to replace it with an IFN-γ secretion assay as the commercial potency assay. The method has been adequately validated and a specification limit set based on statistical analysis of data from clinical batches available retains samples and clinical experience. With the introduction of the IFN-γ potency assay and associated data submitted the Major Objection was considered resolved. The applicant commits to re-evaluate the specification limit for the IFN-γ secretion assay following further manufacturing of commercial batches.

Batch analysis

Batch analysis data for batches manufactured throughout development have been provided. Results for multiple batches were submitted covering the various manufacturing process versions including batches manufactured using the commercial LV. The majority of batches are within the specifications set at the time of production and comply also with the proposed commercial specifications. OOS batches and the respective OOS parameters were indicated.

Container closure system

The primary container closure system is commercially available and consists of CE marked ethylene vinyl acetate (EVA) 50 mL and 250 mL cryostorage bags specifically designed for storage of blood and blood components freezing bags are sterilised by gamma radiation.

Reference materials

The preparation and qualification of cells used as a positive control have been adequately described.

2.4.3.1. Stability of the product

The applicant proposes a shelf life for the finished product of 9 months at ≤-120°C

FP stability has been investigated using low and high concentrations of viable cells in long-term studies for storage at -120°C and in a temperature excursion study. The finished product lots used in primary and supportive stability studies are representative of the commercial process. For the process validation and commercial batches, 9-month data are currently available. The provided data support a FP shelf life of 9 months at ≤-120°C.

Some deviations from the intended timepoints to the real testing timepoints in this study were apparent but have been appropriately justified. Omission of monthly testing for the first three months as required by ICH Q5C is justified by limited material availability. Currently, 9 months stability data are available for batches manufactured with the commercial process and no OOS results or trends have been observed, the data provided for the early time points are considered sufficient.

No further batches are intended to be placed on stability. This is considered acceptable.

2.4.3.2. Post approval change management protocol

The applicant has provided a post approval change management protocol in relation to the manufacturing production process of the LV and analytical methods used for the LV and finished product. In general, this approach is considered acceptable.

2.4.3.3. Adventitious agents

Donors of the T cells are of autologous origin, therefore, defined selection criteria with regard to CJD do not apply according to Directive 2006/17/EC. The manufacturing process of the lentiviral vector (LV) as well as of the T cells to manufacture ciltacabtagene autoleucel are both serum-free. Furthermore, both manufacturing processes are devoid of the usage of animal-derived materials. The cell bank used to manufacture the LV has also been produced without animal-derived materials, as these cells have been adapted to serum-free medium and to grow in suspension before generation of the cell banks.

A number of materials of biological origin are used throughout the manufacturing process. Furthermore, Raw materials of animal or human origin are used in the manufacture of cilta-cel. The cryo-protectant medium is the only excipient and it is not of animal origin. TSE/BSE statements have been provided for all LV or ciltacabtagene autoleucel contact equipment. In summary, compliance with the TSE guideline for all raw materials has been sufficiently demonstrated and with EU directives for human derived materials.

The autologous PBMCs are obtained from the patients by leukapheresis. Each patient/PBMC donor is tested according to EU guidelines 2002/98/EC, 2004/23/EC and their daughter directives as well as national and local guidelines, policies, and procedures. The testing procedure for a second apheresis, if needed, is also performed in compliance with Dir 2006/17/EC. Since HIV-positive patients are allowed for treatment with Carvykti, the risk of recombination and trans-complementation and thus reactivation of the LV in T cells derived from these patients has been discussed. Despite the fact that the risk cannot be finally excluded, there are several measures in place for risk minimisation, including the design of the LV and testing of the finished product for replication competent lentiviruses (RCL). Furthermore, there is a medical need for treating also HIV-positive patients with Carvykti and patients are advised to continue antiretroviral therapy following Carvykti treatment. Finally, due to the current missing experience with manufacturing Carvykti for patients testing positive for HIV, active HBV, or active HCV, the applicant will impose additional pharmacovigilance activities into the risk-management system for such patients as conditions to the marketing authorisation.

The LV is produced by transient transfection. The cell line genealogy has been sufficiently described and the master cell bank (MCB), the working cell bank (WCB) as well as an End-of-production (EOP) cell bank have been generated and tested sufficiently for adventitious viruses according to Eur. Ph. 5.2.3 and ICH Q5A. All tests failed to demonstrate the presence of any viral contaminant Study reports or certificates of analysis for all tests were provided. The testing strategy for any future WCBs has also been described and is found to be sufficient. The LV harvest will be tested routinely according to Eur. Ph. 5.14 and 2.6.16.

No trypsin or bovine serum has been used for cell banking or is used in the LV manufacture. A fully established traceability system for plasma-derived products from individual donations to the plasma-derived product via the ciltacabtagene autoleucel finished product and finally to the patient and vice versa is implemented. No other materials of human origin and no materials of animal origin are used in

the LV and Carvykti T cell manufacturing processes. The only excipient is also not of animal or human origin.

No adventitious virus testing is done on the finished product and no virus inactivation steps are implemented in the ciltacabtagene autoleucel manufacturing process due to the nature of the product which consists of living cells and which is in line with current guidelines. Virus safety, therefore, relies on the selection, qualification, testing and control of the starting and raw materials. In summary, virus safety of Carvykti has been demonstrated.

In particular to the current Covid-19 pandemics, detailed risk assessments have been performed that demonstrate low contamination risk for LV and ciltacabtagene autoleucel finished product by SARS-CoV-2.

2.4.3.4. GMO

Environmental risk associated with cilta-cel is considered to be negligible.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

During the assessment, 3 Major Objections were raised related to lack of EU GMP certificate, comparability and potency assay. All of them were successfully addressed during assessment with some recommendations in place to address aspects not affecting the benefit-risk of this product.

In general, Module 3 of the dossier is of an acceptable quality standard. The cilta-cel manufacturing process has been adequately described and process-parameters as well as in-process controls established to provide sufficient process control. Acceptable ranges have been justified based on relevant process development studies.

Raw materials are overall appropriately controlled. Immediate starting material for cilta-cel manufacturing are the patient apheresis material and the LV to genetically modify the cells.

The manufacturing process of the LV starting material is sufficiently described. During clinical development several changes have been introduced to the design of the LV, its manufacturing process and the site of manufacturing. Several studies were conducted to analyse comparability, which could not be fully established between the different vector processes (further information and recommendation below). The applicant subsequently provided further data and statistical analysis to support the comparability assessment. This included justification for differences observed which were not expected to have a significant impact on the efficacy and safety of the final CAR-T finished product which was accepted.

After procurement by apheresis, the cellular starting material is formulated and cryopreserved either at a central cryopreservation site or at local cryopreservation sites, which are spatially closely associated with the apheresis centres.

The commercial AS/FP manufacturing process is considered sufficiently validated based on the available in-process and release data for clinical batches manufactured, which demonstrate consistent manufacture of specification-compliant final product.

In the course of pharmaceutical and clinical development, several changes have been implemented to the AS/FP manufacturing process, the starting materials and the equipment. The impact of these changes on product quality and process performance has been assessed in a series of process development and formal comparability studies. Further evaluation will be pursued on a clinical level.

For FP release the method for determination of potency has been changed from a tumour killing assay

to an IFN-γ secretion assay, which is considered suitable assay. The commercial specification limit has been defined based on statistical analysis and clinical experience from retain samples.

Some FP release tests are performed prior to cryopreservation. The applicant was therefore recommended to further demonstrate that the data obtained with material pre-formulation are indicative for the final product after cryopreservation

The TSE and virus safety of cilta-cel has been sufficiently shown.

Overall, based on the review of the data on quality, the marketing authorisation application for Carvykti is considered approvable from the quality point of view, taking into account the applicant's commitments.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendations for future quality development

The CAT/CHMP recommends some points for investigation as described above.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical programme for cilta-cel comprises literature-based assessment of the BCMA expression profile, *in vitro* functional characterisation studies, *in vivo* pharmacology and safety studies, literature-based evaluation of biodistribution, oncogenicity studies by Lentiviral vector (LVV) insertion site analysis, and *in vitro* safety studies by cytokine independent growth assay.

During product development, the LVV has evolved. In the initial nonclinical studies, the second and third generation LV developed by Legend has been used. Later on, the third-generation LV Amp has been further developed. Final adaption of the LVV included replacement of the Amp resistance gene by the Kan resistance gene (LV Kan). Moreover, the LVV manufacturing process has been changed from using adherent to in suspension cell cultures. In the non-clinical package, CAR T cells from different LV manufacturing developmental stages have been used (refer to Section 2.4.2.). In all cases, the CAR expressed by the CAR-T cells is identical.

In nonclinical studies with cilta-cel, the drug product (test article) is identified as JNJ-68284528 for studies conducted or sponsored by Janssen and as CAR-T cells developed with the second/third generation hybrid or third generation LV for studies conducted or sponsored by Legend.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The presented *in vitro* and *in vivo* non-clinical primary pharmacodynamics data support expression of the BCMA CAR on transduced T-cells, specific activation of BCMA CAR T cells upon binding to the target BCMA antigen, and functional activity of the BCMA CAR T cells against target cells.

In the *in vitro* and *in vivo* studies, BCMA CAR T cells have been used, which were generated by lentiviral transduction of T cells derived from both, healthy donors and MM patients. These data, together with characterisation data presented in the quality part of the dossier revealed cell viability, proliferation capacity, CAR T cell activation transduction efficiency, and potent cytotoxicity against BCMA-positive relevant target cells.

For the cytotoxicity and cytokine release assays two different BCMA-positive cell lines have been used: Raji cells, which were shown to have a low expression level of BCMA, and RPMI8226 cells, which were shown to express BCMA at higher levels. The observed response of BCMA CAR T cells against Raji cells was of lower magnitude as compared to responses observed against RPMI8226 cells.

In the *in vivo* proof-of concept studies, a multiple myeloma xenograft model of NCG mice was used.

A single dose of $4x10^6$ cilta-cel cell per mouse showed a statistically significant tumour inhibition and an increase in the survival of animals. In the dose-escalation study (2.46×10^4, 1.25×10^5, or 6.257×10^5 CAR-positive cells per animal) dose-effect relationship was observed as well as CAR expansion and persistence demonstrated.

In the *in vitro* studies BCMA-dependent CAR T cell activation and cytotoxicity have been demonstrated using CAR T cells manufactured with the second, second/third generation hybrid and third generation LV developed by Legend or using JNJ-68284528. Thereby, a comparable CAR T cell activation and cytotoxic potential has been demonstrated. In the *in vivo* dose-escalation study CAR-T cells manufactured with the second, second/third gen hybrid and third generation LV developed by Legend, respectively, were shown to have comparable anti-tumour activity. None of the pharmacology studies used JNJ-68284528 manufactured using the commercial manufacturing process. However, comparability data suggest that the anti-tumour activity of JNJ-68284528 manufactured using the commercial manufacturing process will not be reduced as compared to JNJ-68284528 manufactured using the same process as used for the in vitro study.

2.5.2.2. Secondary pharmacodynamic studies

The absence of secondary pharmacodynamics studies is acceptable based on the nature of the product and the limitations of the available animal models. The restricted expression pattern of BCMA suggests on-target/off-tumour effects of cilta-cel on normal B cells. Such an on-target/off-tumour effect resulting in B-cell aplasia has been observed in the clinical study MMY2001.

2.5.2.3. Safety pharmacology programme

The applicant provided data, which shows that the LAB003-His, a recombinant protein containing the targeting domain, do not bind to mouse BCMA (data not shown). Therefore, the safety effects observed in mice would not be translatable to humans. The absence of safety pharmacology studies is therefore, acceptable.

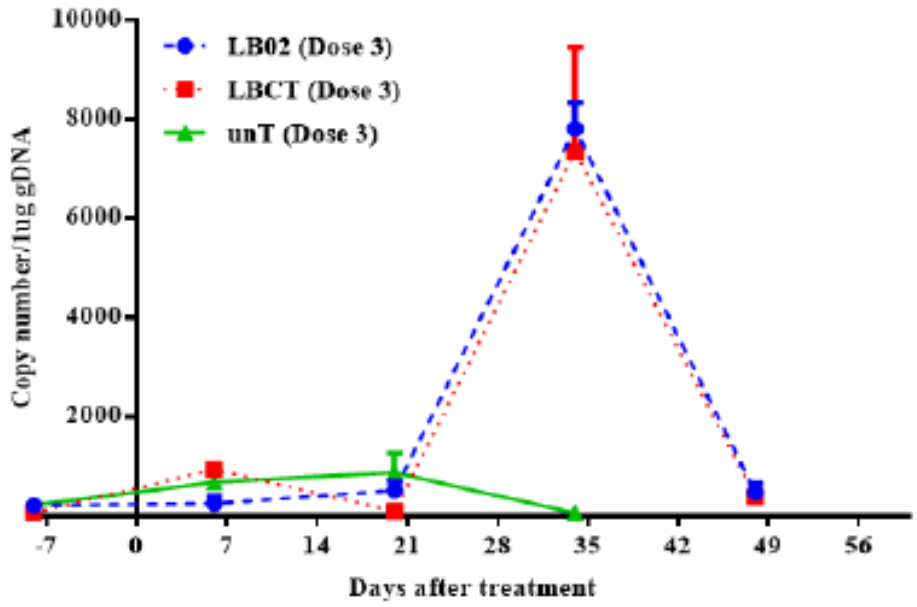
2.5.2.4. Pharmacodynamic drug interactions

Due to the lack of a pharmacologically relevant animal model for cilta-cel and the autologous nature of the cilta-cel product, the lack of pharmacodynamic drug interaction studies is acceptable.

2.5.3. Pharmacokinetics

According to the regulatory guidance for gene therapy medicinal products (GTMPs) (Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products, EMA/CAT/80183/2014), conventional pharmacokinetics studies evaluating ADME are not applicable to cilta-cel. Instead, it is acceptable to evaluate the *in vivo* persistence of cilta-cel, which depends on the dosing and the BCMA-dependent activation and proliferation *in vivo*. Due to the lack of a pharmacologically relevant animal model, the applicant evaluated the persistence of CAR-T cells manufactured with second/third generation hybrid LV developed by Legend in the PD dose escalation study using NCG mice bearing BCMA-expressing tumour cells. A quantitative polymerase chain reaction (qPCR) assay was used for the quantification of CAR gene copy number in mouse whole blood samples collected as part of a primary pharmacology study that evaluated the efficacy, as well as expansion and persistence, of cilta-cel following a single intravenous dose in a model of multiple myeloma with immune-deficient mice. This qPCR assay was developed for research use only. CAR gene copy number showed increases after Day 20 and peaked on Day 34, followed by decreases to baseline levels at study termination on Day 48 (Figure 2). The control group (un-transduced T cells) did not demonstrate statistically significant increases in CAR gene copy number.

Figure 2: cilta-cel CAR Gene Copy Number in Mouse Whole Blood



cilta-cel CAR gene copy number was quantified using qPCR.

CAR-T cell batches: LB02 generated from a healthy donor in the US; LBCT generated from a

relapsed/refractory multiple myeloma patient by Legend in China.

LB02 dose 3 = a single dose of 6.257 x 105 CAR-positive cells/animal

LBCT (DNR47) dose 3 = a single dose of 6.633 x 105 CAR-positive cells/animal.

Data shown is representative of technical triplicates from 3 female and 3 male mice per treatment cohort.

CAR = chimeric antigen receptor; cilta-cel = ciltacabtagene autoleucel; qPCR = quantitative polymerase chain reaction; unT = un-transduced T cells;

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

The applicant performed one in vivo non-GLP toxicology pilot study in Cynomolgus monkeys using autologous CAR-T cells manufactured with the second/ third generation hybrid LV developed by Legend.

Preparation of NHP Cilta-cel

NHP cilta-cel was manufactured from autologous Cynomolgus monkey peripheral blood samples following a similar manufacturing method that would be used for human T cells. T cells were isolated from monkey peripheral blood samples and then pre-activated with a NHP T Cell Activation/Expansion Kit and human IL-2. The pre-activated T cells were transduced with the second/ third generation hybrid LV developed by Legend, followed by expansion for an additional 8 days. Frozen NHP cilta-cel was then administered to the animals.

Study Design

Three days prior to IV infusion of NHP cilta-cel, the 2 monkeys were pre-treated with cyclophosphamide at a single dose of 22.3 mg/kg body weight by IV injection to mimic patient pre-conditioning. On the day of CAR-T treatment (Day 0), NHP cilta-cel was thawed in a 37°C water bath by gentle swirling and within 5 minutes administered by IV infusion. Animals were infused with all available cells present at the end of manufacturing; the percentage of CAR-positive cells was not determined. One male received 5×10^6 cells/kg, while the other male received 40×10^6 cells/kg. Neither T-cell viability, T-cell purity, nor the percent of T cells expressing the CAR was determined. In addition, neither proliferation nor persistence of the T cells postdose was evaluated. Both monkeys were monitored prior to dosing and for 30 days post infusion for body temperature (Days -3 and 0 to 7, and then generally every 3 days), body weight (Days -3, 0, 3, 6, 19, and 30), and complete blood counts and serum chemistry (Days -13, -2, 3, 6, 19, and 30).

Results

Both animals survived to study completion on Day 30. There were no significant changes in body temperature or body weight. Transient and mild decreases in white blood cell, red blood cell, and hemoglobin counts in both animals and platelet count in 1 animal following NHP cilta-cel IV infusion were considered non-adverse. It is unclear if changes in complete blood counts were related to cyclophosphamide pretreatment or NHP cilta-cel because the study did not include cyclophosphamide only and/or vehicle control groups.

2.5.4.2. Repeat dose toxicity

No repeat dose toxicity has been performed given there is no relevant nonclinical species and that cilta-cel is administered as a single dose to patients and is anticipated to undergo expansion and persistence following administration.

2.5.4.3. Genotoxicity

No classical genotoxicity studies have been performed. However, integration studies have been carried out by shearing extension primer tag selection ligation-mediated PCR (S-EPTS/LM-PCR) and bioinformatics analysis including integration site analysis, diversity measurements, common integration site analysis, analysis of integration sites in proximity to cancer-related genes, and comparison of the

vector integration profile with historical datasets. A study has been performed using final drug product derived from 6 MM patients and 3 healthy donors. For analysis, different viral vectors, such as clinical LV or proposed commercial LV, were used for transduction. The results from the study demonstrate a high degree of polyclonality and an integration pattern typical for lentiviruses. Based on this study, the risk of insertional oncogenicity is expected to be very low (data not shown). In addition, clonal dominance might be regarded as an early step in the development of insertional oncogenesis and it is expected that additional steps are needed for T cell transformation.

2.5.4.4. Carcinogenicity

Carcinogenicity studies were not performed for cilta-cel. As indicated in the ICH S9 guidance, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat advanced cancer. In addition, cilta-cel is a human specific CAR-T cell product and lacks cross reactivity to mouse BCMA precluding the conduct of traditional rat and mouse bioassays.

The lack of carcinogenicity studies is acceptable.

2.5.4.5. Reproductive and developmental toxicity

No non-clinical reproductive and developmental toxicity studies have been conducted, which is acceptable based on the type of product and the BCMA expression pattern. In addition, no inadvertent germline transmission studies have been conducted. According to the Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors, EMEA/273974/2005, this is acceptable.

2.5.4.6. Toxicokinetic data

Not applicable.

2.5.4.7. Local tolerance

Not applicable.

2.5.4.8. Other toxicity studies

The applicant addressed the risk of on-target toxicity by a literature survey. Since literature data show that the expression of BCMA is highly restricted to B cells, on-target/off-tumour effects of cilta-cel on normal B cells are expected. Such an on-target/off-tumour effect resulting in B-cell aplasia or hypogammaglobulinaemia has been observed in the clinical study MMY2001.

Potential off-target toxicity was investigated in two studies using CAR-T cells manufactured with the third generation LV developed by Legend or JNJ-68284528 in a human membrane surface protein array covering 4,955 or 5,647 full human membrane proteins. In the first study using CAR-T cells manufactured with third generation LV developed by Legend, none of the proteins presented in this array except BCMA were identified to interact with the CAR. However, in the later study using the CAR-T manufactured by Janssen binding of the CAR was detected not only to BCMA but also to claudin-9 (CLDN9). Although some members of the claudin family, such claudin-6 and claudin-4, show a high degree of homology with CLDN9 in the extracellular domain (ECD), no binding interaction was seen with other members of the claudin family. Amino acid sequence alignment of CLDN9 with BCMA identified 3 regions in CLDN9 with up to 55% sequence identity, one of which partially overlaps with

the binding epitope in BCMA of cilta-cel. This overlapping region is even shared with CLDN6, CLDN4, and CLDN3, which nevertheless did not interact with cilta-cel.

In subsequent orthogonal studies using FACS analysis, the applicant evaluated the binding of LAB003a recombinant protein containing the targeting domain or JNJ-68284528 to monocytes, dendritic cells, basophils, eosinophils, and neutrophils, all of which express CLDN9 endogenously, or cell lines exogenously expressing CLDN9. In addition, T, B, and NK cells have been analyzed for binding interaction to CLDN9, which do not express CLDN9. The data demonstrated that the binding domains in LAB003 and JNJ-68284528 bind only to cell lines that were engineered to express CLDN9 but do not interact with endogenously expressed CLDN9 on primary cells. The possible cause for the observed difference between endogenously and exogenously expressed CLDN9 is explained with reference to published studies showing that engineered protein overexpression can cause cellular defects which can result in overload of translation and folding, post-translational modifications (PTMs), and promiscuous protein-protein interactions (Andrell and Tate, 2013 Moriya 2015).

Finally, *in vitro* studies were conducted to determine the potential for uncontrolled T cell proliferation after lentiviral transduction of T cells derived from 6 MM patients or 3 healthy donors. There was no evidence for IL-2 independent T cell proliferation after vector transduction when compared to untransduced T cells. The applicant demonstrated statistically significant mean differences in the proliferation of JNJ-68284528 (i) obtained from healthy donors or MM patients and (ii) generated with adherent or suspension LVV. These differences, however, were not considered relevant. This is agreed to based on (i) the low number of healthy donors included in the study and the different manufacturing processes used for production of the samples and (ii) the fact that a difference in proliferation has also been detected in donor matched untransduced T cells.

2.5.5. Ecotoxicity/environmental risk assessment

The risk for the environment in general and for transmission to third parties associated with the genetically modified T cells is considered negligible, as genetically modified cells cannot survive in the environment. If transmitted to third parties through direct contact the genetically modified cells are expected to be recognised by the immune system and cleared rapidly. A residual risk for the environment and third parties might only be associated with residual infectious viral particles present in the final cell suspension and/or replication-competent lentiviruses (RCL) contaminating the viral vector suspension or being generated following mobilisation of the integrated provirus. However, it has been shown that the amount of residual infectious particles in CARVIKTY will be reduced to negligible concentrations during manufacturing. Moreover, the absence of RCL has been confirmed at different stages of the manufacturing process. In addition, the risk of RCL formation during manufacturing is considered negligible due to the absence of the majority of the parental lentiviral sequence in the vector and the necessity of several independent recombination events for the generation of a functional RCL.

Therefore, Carvykti is considered to have an overall negligible environment impact.

2.5.6. Discussion on the non-clinical aspects

The presented *in vitro* and *in vivo* non-clinical primary pharmacodynamics data support expression of the BCMA CAR on transduced T-cells, specific activation of BCMA CAR T cells upon binding to the target BCMA antigen, and functional activity of the BCMA CAR T cells against target cells.

In the *in vitro* and *in vivo* studies, BCMA CAR T cells have been used, which were generated by lentiviral transduction of T cells derived from both, healthy donors and MM patients. These data,

together with characterisation data presented in the quality part of the dossier demonstrated acceptable cell viability, acceptable transduction efficiencies, BCMA-induced CAR T cell activation and proliferation capacity, and potent cytotoxicity against BCMA-positive relevant target cells.

The limited evidence on the efficacy of the BCMA CAR T cells in the setting of low BCMA expression, which was restricted to the use of Raji cells in an *in vitro* assay, is accepted based on the available clinical data.

In addition to the in vitro studies, the applicant performed in vivo proof-of concept studies with CAR T cells manufactured with second/third generation or third generation LV from Legend in a multiple myeloma xenograft model using NCG mice. Despite the known limitations of this model such as the unspecific xenogenic response of the CAR T cells or lacking interactions between the CAR T cells and the murine immune cells, the animal model is considered adequate to assess in vivo efficacy against BCMA expressing tumour cells.

None of the pharmacology studies used JNJ-68284528 manufactured using the commercial manufacturing process. However, based on the comparability data provided, it is expected that the anti-tumour activity of the commercial JNJ-68284528 batches will not be reduced as compared to JNJ-68284538 batches from earlier manufacturing processes. Clinical data of the later cohorts of Study MMY2001 (CARTITUDE-1) dosed with JNJ-8284528 representative of commercial batches are expected to confirm this post approval in the context of the imposed SOB.

The provided non-clinical pharmacokinetic investigations focused on the *in vivo* persistence of CAR-T cells manufactured with the second/ third generation hybrid LV developed by Legend in NCG mice bearing BCMA-expressing tumour cells within the PD dose escalation study. However, the results of this study are not considered translatable to humans since the tumour load in patients and thus in vivo proliferation of the CAR T cells are expected to differ as compared to the animal situation. In addition, human-derived CAR-T cells in mice respond to xeno-antigens, do not bind to mouse BCMA, and do not interact with the murine immune system, which very likely alters pharmacokinetics and persistence of human T cells in mice. The absence of biodistribution, metabolism and excretion studies are acceptable. Cilta-cel is a genetically modified cell-based therapy for which traditional pharmacokinetic studies are not suitable. Such studies would have very limited translatability to the clinical scenario since no animal species can be considered responsive to the product administration from a pharmacological standpoint. Despite this limitation, the nonclinical pharmacokinetic evaluation of cilta-cel is considered acceptable.

Similar to the pharmacokinetic evaluation, the non-clinical safety evaluation of cilta-cel was limited due to the lack of a relevant animal model. Therefore, no GLP-compliant formal toxicology studies were performed. The lack of repeat-dose toxicity studies is acceptable based on the fact that cilta-cel will be administered as a single IV infusion, and since cilta-cel is a patient specific product which is not appropriate to administer to immune competent animals. Nevertheless, the applicant performed one *in vivo* (non-GLP) safety study in Cynomolgus monkeys using autologous CAR-T cells manufactured with third generation LV developed by Legend. However, since LAB003 has been shown to not bind to Cynomolgus BCMA, the Cynomolgus monkey model is not considered relevant to evaluate potential safety risks of cilta-cel in humans. Due to the lack of a relevant animal model that could be used in toxicology studies, no other non-clinical safety evaluation has been performed *in vivo*.

The applicant addressed the risk of on-target/off-tumour toxicity by literature-based assessment and the risk of off-target toxicity by various *in vitro* studies. Since BCMA expression is highly restricted to B cells, on-target/off-tumour effects of cilta-cel are expected only on normal B cells. Such an on-target/off-tumour effect resulting in B-cell aplasia or hypogammaglobulinaemia has been observed in the clinical study MMY2001. To minimise those risks, guidance on the required monitoring of blood counts and immunoglobulin levels is provided in Section 4.4 of the SmPC.

Potential off-target toxicity was investigated in two studies using CAR-T cells manufactured with the second/ third generation hybrid LV developed by Legend or JNJ-68284528 in a human membrane surface protein array.

Data demonstrated different binding results for CAR-T cells manufactured with the second/third generation hybrid LV developed by Legend or JNJ-68284528 as JNJ-68284528 was also able to bind to CLDN9. Further analysis indicate that the binding domains in LAB003 and JNJ-68284528 bind only to cell lines that were engineered to express CLDN9 but do not interact with endogenously expressed CLDN9 on primary cells. Based on these findings, the risk of off-target functional consequence in treated patients by cilta-cel is expected to be low. The review of serious adverse events reported with the use of JNJ-68284528 in clinical studies was also not indicative of obvious CLDN9 off-target effects.

In addition to the on- or off-target toxicity studies, the risk of insertional oncogenicity resulting from LVV integration into the T cell genome has been evaluated by integration analysis. In these studies, final drug product derived from 6 MM patients and 3 healthy donors has been used. Although the use of *ex vivo* cilta-cel would have been more suitable for the detection of dominant cell clones, the use of final product for integration analysis is considered acceptable based on the high resistance of mature T cells to oncogene transformation, which is well documented in the literature. For analysis, different viral vectors using clinical and proposed commercial processes were used for transduction. The results from the study demonstrate a high degree of polyclonality and an integration pattern typical for lentiviruses. Based on this study, the risk of insertional oncogenicity is expected to be very low. In addition, clonal dominance might be regarded as an early step in the development of insertional oncogenesis and it is expected that additional steps are needed for T cell transformation. Thus, although clonal dominance after cilta-cel administration cannot be unequivocally excluded, the clinical experience with CAR T cells so far still suggests that the incidence of T cell transformation resulting from insertional mutagenesis would be a very rare event. Despite the expected low likelihood, a risk monitoring approach is being used in clinical trials and the post-approval setting to characterize adverse events such as secondary malignancies (see section 4.4. of the proposed text of the SPC).

Furthermore, the risk of uncontrolled CAR T cell proliferation has been evaluated by an *in vitro* study using cilta-cel derived from 6 MM patients or 3 healthy donors. There was no evidence for IL-2 independent T cell proliferation after vector transduction when compared to untransduced T cells.

In addition to the potential toxicities of cilta-cel, that are dependent either on the cross-reactivity of the chosen CAR with non-target antigens or on the insertion site of the vector, there are expected risks, that are associated with the general mode of action of CAR T cells, such as tumour lysis syndrome (TRS), cytokine release syndrome (CRS) and macrophage activation syndrome (MAS). These toxic effects have not been investigated in non-clinical studies which is acceptable considering that these effects are general effects of CAR T cells and that the extent of these expected toxicities are largely based on patient-specific parameters such as the individual tumour load.

The lack of any non-clinical reproductive and developmental toxicity studies is acceptable based on the type of product, the expression pattern of the target antigen and the lack of a relevant animal model. The risk of inadvertent germline transmission of the cilta-cel has not been addressed by the applicant. However, the Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors, EMEA/273974/2005, indicates that the risk of germline transmission associated with the administration of genetically modified human cells is considered low and, since animal testing of human cells may be difficult or not meaningful, non-clinical germline transmission studies of human genetically modified cells are not recommended. In addition, the proposed text in section 4.6 of the SPC provides a thorough explanation of the potential risks to fertility, pregnancy and lactation including the recommendation of assessment of immunoglobulin levels in newborns of mothers treated with CARVIKTY.

Carvykti is considered to have an overall negligible environment impact.

The CHMP endorses the CAT discussion on the non-clinical aspects as described above.

2.5.7. Conclusion on the non-clinical aspects

Cilta-cel can be granted a marketing authorisation from a non-clinical point of view.

The CHMP endorses the CAT conclusions on the non clinical aspects as described above.

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**

Data are presented from the pivotal open-label, single-arm, multicentre, Phase 1b-2 Study 68284528MMY2001 (indicated as MMY2001 elsewhere in this document).

Table 2. Summary of Key Study Design Elements for Study 68284528MMY2001

Study ID / First Patient First Visit / Study Status	Phase / Study Population / Efficacy Endpoints	Number of Subjects Apheresed/ Number of Subjects Treated (by Study Phase)	Dose Regimen / Duration of Treatment / Duration of Follow-up
68284528MMY2001 Ph 1b: 05 JULY 2018 Ph 2: 25 APRIL 2019 Primary analysis completed, study ongoing The primary analysis population for all efficacy summaries was the All Treated analysis set, which included all 97 subjects who received a cilta-cel infusion at the targeted RP2D dose level at the time of the clinical cutoff.	Phase: 1b-2 Eligible subjects are ≥18 years of age and had a documented diagnosis of multiple myeloma according to IMWG diagnostic criteria and an Eastern Cooperative Oncology Group (ECOG) Performance Status Grade of 0 or 1. Subjects had measurable disease at screening; had received at least 3 prior multiple myeloma lines of therapy or were double refractory to a PI and an IMiD; received a PI, an IMiD, and anti-CD38 antibody; and had documented disease progression during, or within 12 months, of their most recent anti-myeloma therapy. ORR is the primary endpoint. MRD negativity rate, CBR, DoR, TTR, PFS, and OS are secondary endpoints. HRQol will also be evaluated.	Apheresed: Phase 1b: n=35 Phase 2: n= 78 Total: N= 113 Treated with cilta-cel: Phase 1b: n=29 Phase 2: n=68 Total N= 97 [a, b]	Conditioning regimen consisted of cyclophosphamide (300 mg/m^2) IV and fludarabine (30 mg/m^2) IV in 3 daily doses. The dose of cilta-cel is 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1.0 x 10^6 CAR-positive viable T cells/kg) derived from the subject's T cells. Subjects received a single IV infusion of cilta-cel on Day 1 (5 to 7 days after the start of the conditioning regimen). The median duration of follow-up for subjects who received cilta-cel was 12.4 months (range: 1.5 months to 24.9 months) at clinical cutoff.

[a] As of the data cut off of 1 September 2020, one subject was retreated with cilta-cel.
[b] An additional cohort of 9 subjects is ongoing in Japan. These subjects are not in scope for this SCE document.
CBR= clinical benefit rate; DoR=duration of response; ECOG= Eastern Cooperative Oncology Group; ID= identification; IMiD= immunomodulatory agent; IMWG= International Myeloma Working Group: IRC=Independent Review Committee; IV= intravenous; HRQol= Health-Related Quality of Life; MRD= minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PI= proteasome inhibitor; RP2D= recommended Phase 2 dose; SCE= summary of clinical efficacy; TTR=time to response

2.6.2. Clinical pharmacology

Clinical pharmacology data are presented from the Study 68284528MMY2001.

2.6.2.1. Pharmacokinetics

Methods

A validated sensitive method on the MSD platform was used to detect serum antibodies to cilta-cel in Study MMY2001. This assay was developed and validated to screen, confirm, and titer anti-drug antibody (ADA) to recombinant-expressed version of the extracellular BCMA-binding domain of cilta-cel in human serum samples. The screening method was used to detect potentially positive ADA to cilta-cel in human serum samples. The specificity (confirmation) method was used to determine whether potentially positive samples were either ADA positive or ADA negative. Positive samples were evaluated in a titration method to provide a quasi-quantitative assessment of ADA reactivity in serum samples.

All PK parameters were calculated using conventional non-compartmental methods using actual times of sampling, unless otherwise stated in the clinical study report. Population PK analysis used a nonlinear mixed-effects approach to generate the PK parameters.

Model evaluation/qualification assessed various goodness-of-fit measures, including parameter estimates relative standard error (RSE), standard diagnostic plots, and visual predictive check (VPC) based on 1,000 replicates. The final model should be consistent with the existing knowledge of CAR-T PK, provided a good description of the observed data with no apparent trend in the relevant goodness-

of-fit diagnostics. Because SAEM method was used, the typical criteria of successful FOCEI covariance step in NONMEM and condition number less than 1,000 were not applicable.

For calculation of the individual PK parameters, cilta-cel CAR transgene and CD3+CAR+ cell levels below the LLOQ were treated as being zero in case of occurrence before the first or after the last measurable concentration. When more than half (>50%) of the individual blood and bone marrow concentrations of cilta-cel transgene, blood and bone marrow concentrations of CD3+CAR+ cells, and serum concentrations of sBCMA for a given time point were below the LLOQ, the mean, minimum, and median were reported as BQL while SD, coefficient of variation (%CV), and geometric mean were not reported. For graphical analysis, blood concentration values of cilta-cel CAR transgene, CD3+CAR+ cells, and serum concentrations values of sBCMA below LLOQ were treated as being zero for the linear plots and as missing for the semi-logarithmic plots.

For values presented in boxplots the solid line in the box is the median. The boundaries of the box represent the 25th and 75th percentiles. The whiskers indicate the entire range of values. Any points beyond these values are outliers and are drawn individually.

Pharmacokinetics

Cilta-cel PK was characterised by transgene levels and CAR-positive cells in peripheral blood and bone marrow. The key PK findings for the study overall (Phase 1b and Phase 2 combined and comparisons between the phases) are based on transgene level data. In general, PK measurements using both transgene and cellular levels were concordant and showed similar expansion and persistence profiles. Following a single infusion, cilta-cel exhibited an initial expansion phase followed by a rapid decline and then a slower decline with both transgene and cellular persistence over months.

The median time to reach peak levels of cilta-cel expansion in peripheral blood was 12.7 days (range: 8.7 to 54.6 days) post-infusion. After cell expansion, the persistence phase of the cilta-cel levels was observed for all subjects. The median time to last measurable (non-below quantification limit [BQL]) cilta-cel transgene level included all 97 subjects and was comparable in Phase 1b (95.9 days [range: 26.2 to 438.0 days]) and Phase 2 (99.7 days [range: 20.0 to 240.0 days]). Among 57 out of 97 subjects who had cilta-cel transgene levels returned to the predose baseline level of BQL at the time of the data cut-off, the median time to return to BQL was shorter in Phase 1b than Phase 2, but ranges were overlapping. Overall, the median time to return to BQL was 79.7 days (range: 27.0 to 275.0 days) post-infusion.

Cilta-cel transgene exposure parameters maximum observed analyte concentration (C_{max}), area under the analyte concentration-time curve (AUC) from time 0 to 28 days ($AUC_{0\text{-}28d}$), AUC from time 0 to 6 months ($AUC_{0\text{-}6m}$), and AUC from time 0 to time of last measurable (non-BQL) analyte concentration ($AUC_{0\text{-}last}$) showed higher mean values in Phase 2 than in Phase 1b, but with high interindividual variability (%CV: 49.8%-123.6%) and different sample sizes (29 in Phase 1b and 68 in Phase 2). Overall, the mean (SD) cilta-cel transgene values was 48501 (27362) copies/µg genomic DNA for C_{max}, 504561 (385428) copies*day/µg genomic DNA for $AUC_{0\text{-}28d}$, 1036998 (1348041) copies*day/µg genomic DNA for $AUC_{0\text{-}6m}$, and 990124 (1182015) copies*day/µg genomic DNA for $AUC_{0\text{-}last}$. Detectable cilta-cel transgene exposures in bone marrow indicate a distribution of cilta-cel from systemic circulation to bone marrow.

The observed cilta-cel CAR transgene PK-time data were adequately described by a 2-compartment model (with a fast and a slow decline rate from each compartment, respectively) and a chain of 4 transit compartments with a lag time empirically representing the process from infused CAR-T cell to measurable CAR transgene.

None of the covariates explored and tested in the population PK model had a statistically significant effect on CAR transgene systemic level. Therefore, the base model was also the final model. The model

predicted individual CAR transgene systemic level, C_{max} and $AUC_{0\text{-}28d}$ were also compared across different strata for covariates of interest (a subset of all tested covariates), as shown in the figures below.

Figure 3. Forest Plot of CAR Transgene C_{max} (Population PK Final Model)

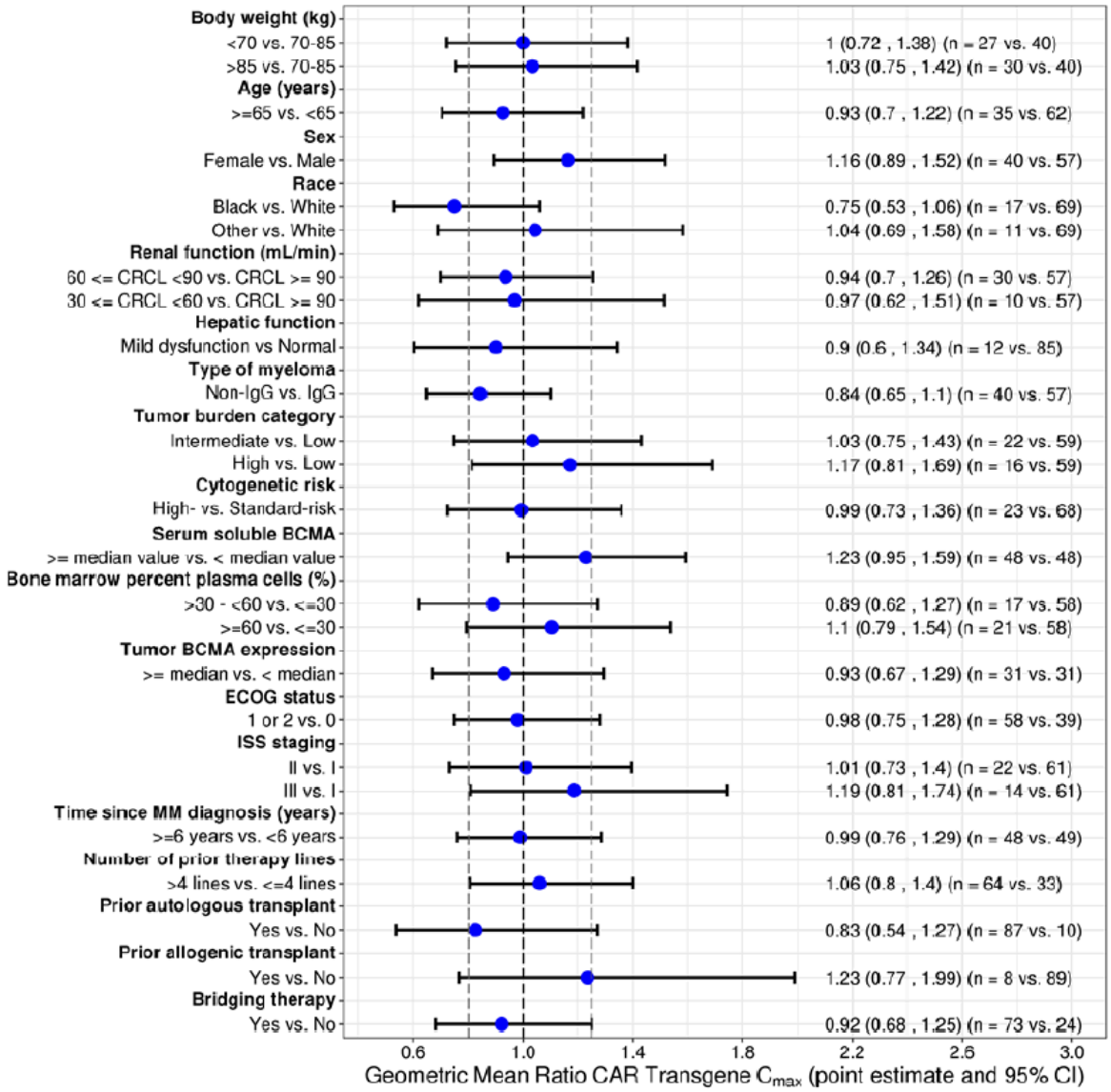
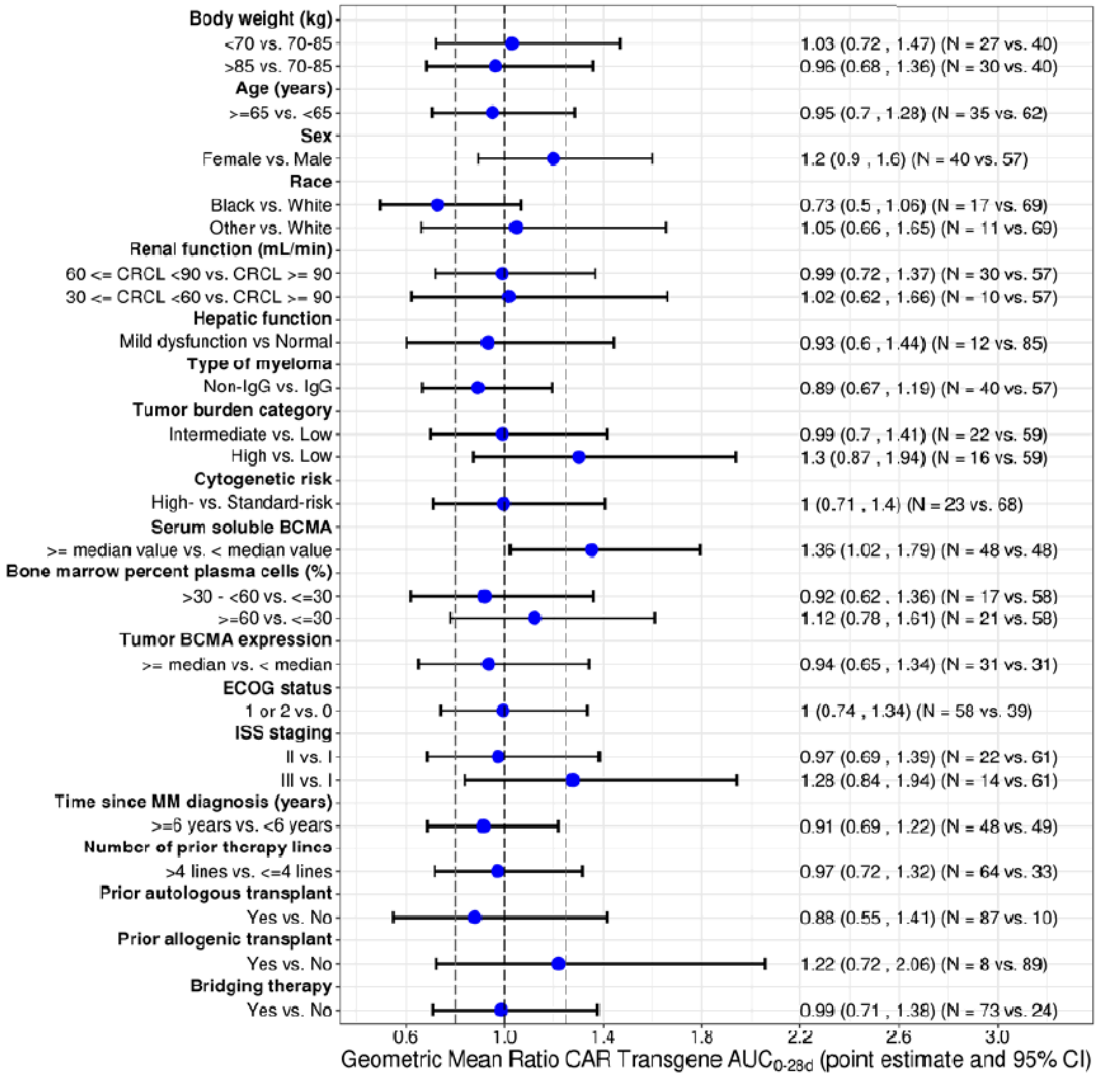


Figure 4. Forest Plot of CAR Transgene $AUC_{0\text{-}28d}$ (Population PK Final Model)



Hepatic Impairment

No dedicated hepatic impairment study was planned as cilta-cel is a genetically modified cell-based therapy and major changes in cilta-cel exposure are not anticipated in subjects with hepatic insufficiency. Population PK analysis confirmed that cilta-cel CAR transgene C_{max} and $AUC_{0\text{-}28d}$ in subjects with mild hepatic dysfunction (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase > ULN or ULN < total bilirubin ≤ 1.5 x ULN) were similar to subjects with normal hepatic function.

Renal Impairment

No dedicated renal impairment study was planned as cilta-cel is a genetically modified cell-based therapy and major changes in cilta-cel exposure are not anticipated in subjects with renal insufficiency. Population PK analysis confirmed that cilta-cel CAR transgene C_{max} and $AUC_{0\text{-}28d}$ in subjects with mild renal dysfunction (60 mL/min ≤ creatinine clearance [CRCL] < 90 mL/min) were similar to subjects with normal renal function (CRCL ≥ 90 mL/min).

Other Intrinsic/Extrinsic Factors

Cilta-cel CAR transgene PK parameters were similar across age groups and across races. There was no apparent relationships between CAR transgene Cmax and AUC0-28d and manufactured product characteristics (percent CD4+ cells, percent CD8+ cells, CD4/CD8 ratio, transduction efficiency, CAR expression, percent CAR+ naïve, percent CAR+ effector, percent CAR+ central memory, percent CAR+ effector memory, percent CAR- naïve, percent CAR- effector, percent CAR- central memory, percent CAR- effector memory, percent CD3+ cells, CD3+ viability, in vitro tumour kill assay, vector copy number, viable nucleated cells, and post-thaw viability).

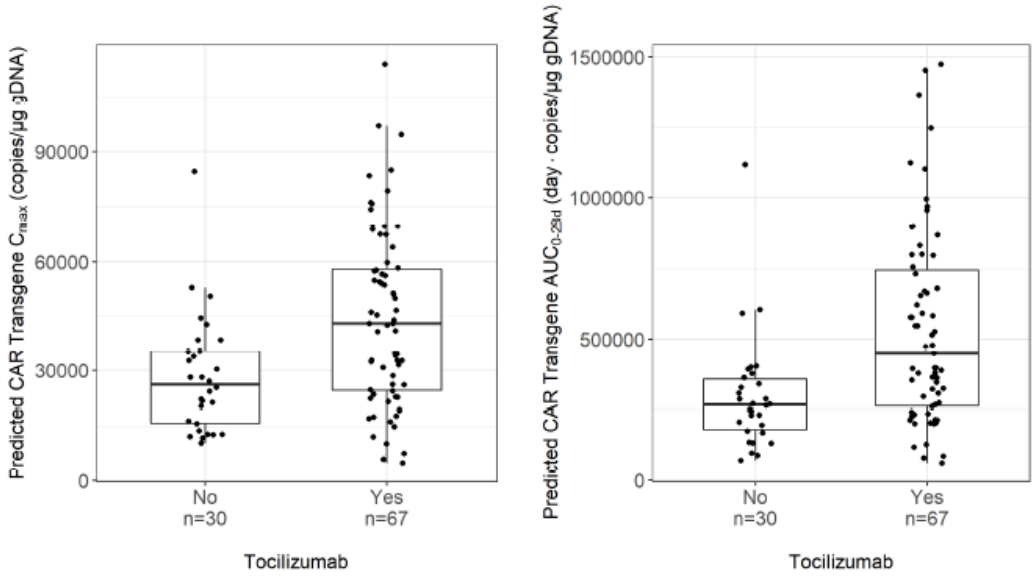
Drug-Drug Interactions

No dedicated drug-drug interaction studies were performed for cilta-cel. As cilta-cel is a single dose cell therapy treatment, no interactions with concomitant medications are expected.

Tocilizumab, Corticosteroids, and Anakinra

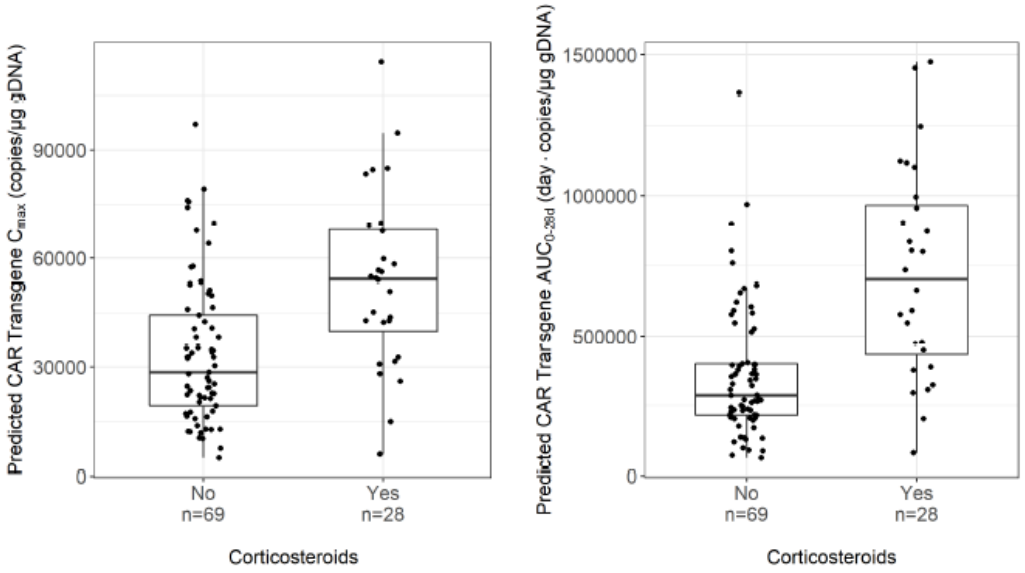
Median CAR transgene C_{max} and $AUC_{0\text{-}28d}$ were higher among subjects who received tocilizumab, corticosteroids, or anakinra for CRS or ICANS management. Subjects treated with tocilizumab (n=67) had median C_{max} and $AUC_{0\text{-}28d}$ 65% and 67% higher, respectively, compared with subjects who did not receive tocilizumab (n=30). Subjects treated with corticosteroids (n=28) had median C_{max} and $AUC_{0\text{-}28d}$ 90% and 144% higher, respectively, compared with subjects who did not receive corticosteroids (n=69). Similarly, subjects treated with anakinra (n=20) had median C_{max} and $AUC_{0\text{-}28d}$ 35% and 72% higher, respectively, compared with subjects who did not receive anakinra (n=77). However, no conclusion regarding the effect of tocilizumab, corticosteroids, or anakinra on cilta-cel PK can be drawn due to the confounding concurrence of CRS and overlapping exposure range.

Figure 5. Relationship between CAR Transgene Exposure and Tocilizumab.



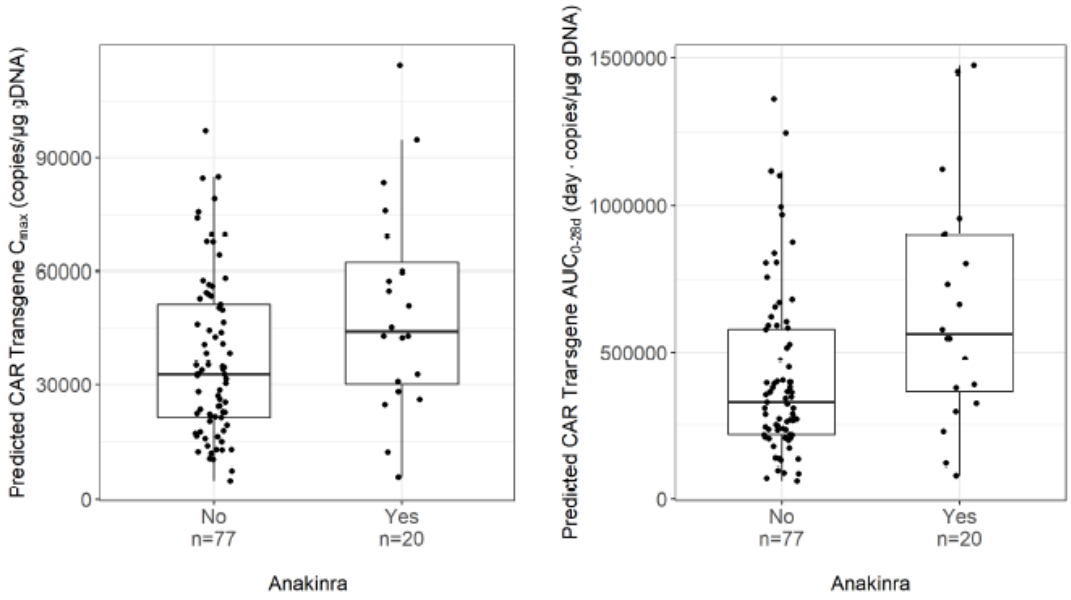
AUC$_{0\text{-}28d}$=area under the CAR transgene systemic level-time curve from the first dose to Day 28; CAR=chimeric antigen eceptor; C_{max}=maximum CAR transgene systemic level; gDNA=genomic DNA.

Figure 6. Relationship Between CAR Transgene Exposure and Corticosteroids



$AUC_{0\text{-}28d}$=area under the CAR transgene systemic level-time curve from the first dose to Day 28; CAR=chimeric antigen receptor; C_{max}=maximum CAR transgene systemic level; gDNA=genomic DNA.

Figure 7. Relationship between CAR Transgene Exposure and Anakinra



$AUC_{0\text{-}28d}$=area under the CAR transgene systemic level-time curve from the first dose to Day 28; CAR=chimeric antigen receptor; C_{max}=maximum CAR transgene systemic level; gDNA=genomic DNA.

Absorption, Distribution, Elimination

Studies investigating cilta-cel adsorbtion, distribution, elimination/ excretion/ metabolism/ inter-conversion/ metabolites/ genetic polymorphism have not been conducted.

2.6.2.2. Pharmacodynamics

Mechanism of action

Carvykti is a BCMA-directed, genetically modified autologous T cell immunotherapy, which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR)

that identifies and eliminates cells that express BCMA. BCMA is primarily expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. The Carvykti CAR protein features two BCMA-targeting single domain antibodies designed to confer high avidity against human BCMA, a 4-1BB co-stimulatory domain and a CD3-zeta (CD3ζ) signaling cytoplasmic domain. Upon binding to BCMA expressing cells, the CAR promotes T-cell activation, expansion, and elimination of target cells.

Primary and Secondary pharmacology

Primary pharmacology

soluble B-cell maturation antigen (sBCMA) in Serum

After a single cilta-cel infusion, sBCMA decreased in all subjects with mean serum concentrations reaching nadir levels around the lower quantifiable concentration (LLOQ) value at Day 78 in Phase 1b and at Day 100 in Phase 2. Increases from nadir were seen in some subjects, but levels remained lower than baseline sBCMA. This reversal of sBCMA levels may reflect a reproduction of BCMA positive plasma cells.

Cytokine Profiling

Across all subjects, levels of interleukin (IL)-6, IL-10, interferon-gamma, and IL-2 receptor alpha increased post-infusion and peaked at Days 7–14. The serum levels of all cytokines generally returned to baseline levels within 2 months post-infusion.

Minimal residual disease (MRD) Negativity

MRD was monitored in subjects using next generation sequencing (NGS) of bone marrow samples DNA (Adaptive clonoSeq, version 2.0). At the time of the clinical cut-off (01 September 2020), 57 of the 97 treated subjects (58.8%) had evaluable bone marrow samples for MRD analysis at the 10^{-5} level of sensitivity using next-generation sequencing (NGS). Evaluable samples were defined as those that passed calibration or quality control and included sufficient cells for evaluation at the respective testing threshold. Of the 57 evaluable subjects, 53 subjects (93.0%) were MRD negative in bone marrow at a sensitivity level of 10^{-5}.

Secondary pharmacology

Replication-competent Lentivirus (RCL)

At the time of the clinical cut-off date 80, 55 and 15 subjects had evaluable samples for RCL analysis at 3, 6 and 12 months, respectively. No positive samples for RCL had been detected in any subjects at any of the collection timepoints.

Immunogenicity

Among the 97 subjects with samples (29 subjects in Phase 1b and 68 subjects in Phase 2), 15 subjects (15.5%) were observed to be positive for treatment-emergent anti-cilta-cel antibodies (ADA; 9 subjects [31.0%] in Phase 1b and 6 subjects [8.8%] in Phase 2). For the ADA-positive subjects, titers of anti-cilta-cel antibodies started to be detectable around the Day 100 visit. Based on the current data, there was no clear evidence to suggest an association between ADA and cilta-cel exposure, efficacy, or safety.

Exposure-Response Relationships

The exposure-response (E-R) relationship for ORR was evaluated according to 2 exposure metrics, CAR transgene Cmax and AUC0-28d. Given that the majority of treated subjects were responders (ORR=96.9%), it was not feasible to draw a conclusion on the E-R relationship between systemic cilta-

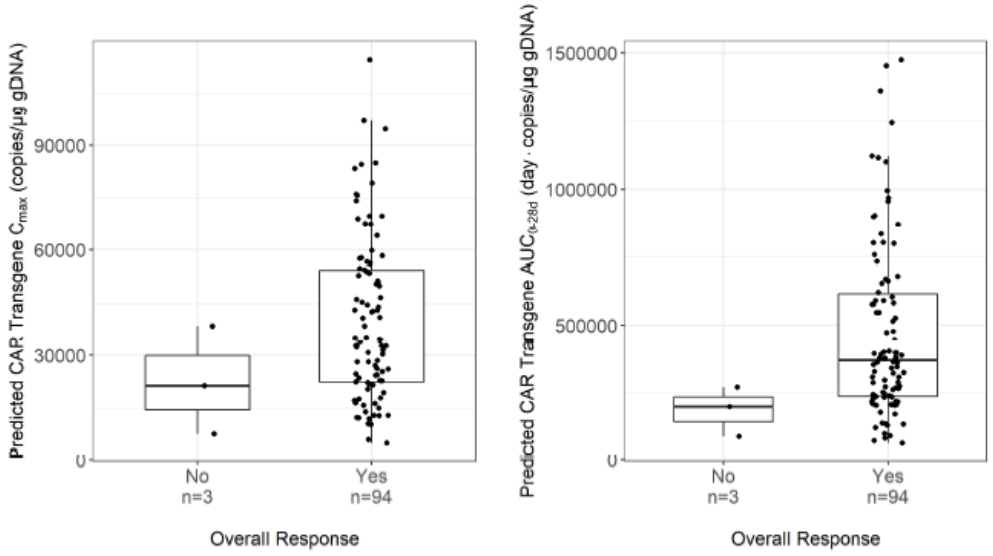
cel CAR transgene level and ORR. Similarly, the E-R relationship between systemic cilta-cel CAR transgene level and disease progression, as measured by DOR, PFS, and OS, could not be readily evaluated due to the limited number of subjects and events (deaths or disease progression).

A trend of higher median systemic cilta-cel CAR transgene levels (Cmax and AUC0-28d) was observed in subjects with CRS or CAR-T cell neurotoxicity (ICANS and other neurotoxicities [including movement and neurocognitive treatment-emergent adverse events]) compared with subjects without these adverse events. However, given the overlapping CAR transgene levels across adverse event categories, this observation needs to be interpreted with caution. No apparent trend with the infused cilta-cel total dose (over the narrow target dose range) was observed for any of these safety endpoints.

Exposure-efficacy

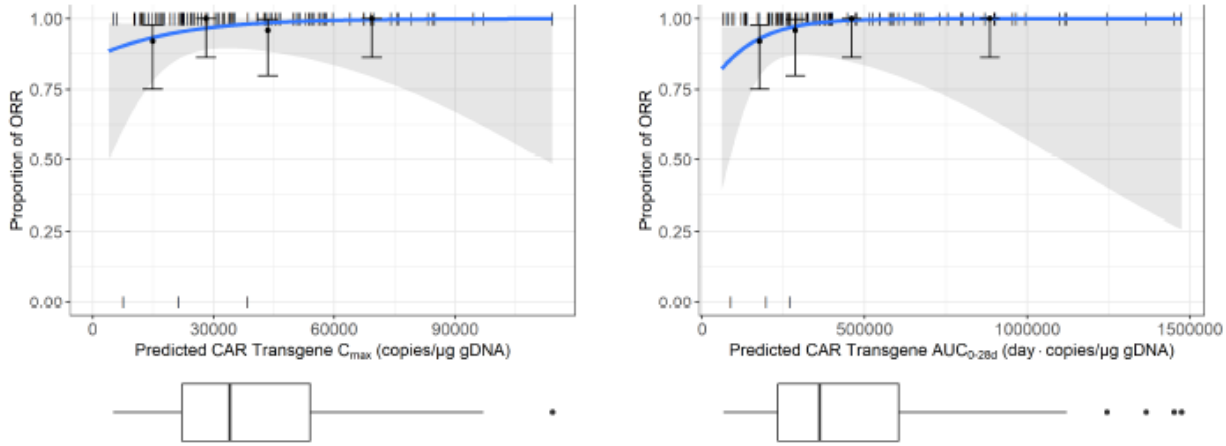
The median predicted cilta-cel transgene Cmax in responders (n=94) was 61% higher compared with the corresponding level in non-responders (n=3) (34,298 [range: 5,088-114,244] versus 21,341 [range: 7,639-38,543] copies/µg genomic DNA). The median predicted cilta-cel transgene AUC0-28d in responders (n=94) was 87% higher compared with the corresponding level in non-responders (n=3) (369,827 [range: 64,886-1,475,249] versus 197,433 [range: 88,249-270,032] days·copies/µg genomic DNA).

Figure 8: Comparison of Predicted CAR Trangene Exposure with the Overall Response



$AUC_{0\text{-}28d}$=area under the CAR transgene systemic level-time curve from the first dose to Day 28; CAR=chimeric antigen receptor; C_{max}=maximum CAR transgene systemic level; gDNA=genomic DNA.

Figure 9. ORR as a Function of CAR Transgene Exposure



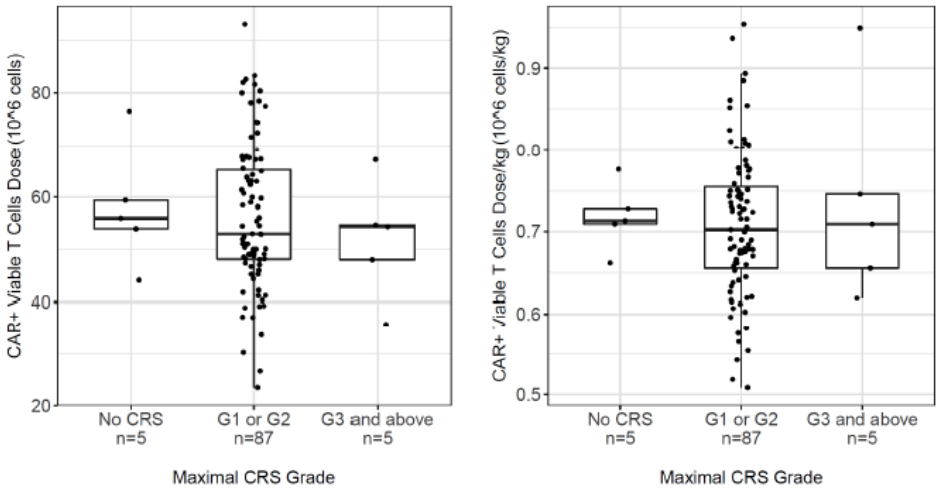
$AUC_{0\text{-}28d}$=area under the CAR transgene systemic level-time curve from the first dose to Day 28; CAR=chimeric antigen receptor; CI=confidence interval; C_{max}=maximum CAR transgene systemic level; gDNA=genomic DNA; ORR=overall response rate.
Line represents model fitting with generalized linear model binomial probability of ORR (partial response or better) as a function of CAR transgene C_{max} (left) or $AUC_{0\text{-}28d}$ (right). Solid points are observed response proportions and the associated 95% CI in groups defined by quartiles of CAR transgene C_{max} (left) or $AUC_{0\text{-}28d}$ (right). Short vertical lines at horizontal lines of 0 and 1 at Y-axis are predicted CAR transgene C_{max} or $AUC_{0\text{-}28d}$ corresponding to non-response and response, respectively. Blue solid lines and shaded areas represent the logistic regression slope model and 95% CI. The horizontal boxplots at the bottom show the overall distribution of the predicted CAR transgene C_{max} (left) or $AUC_{0\text{-}28d}$ (right).

Exposure-safety

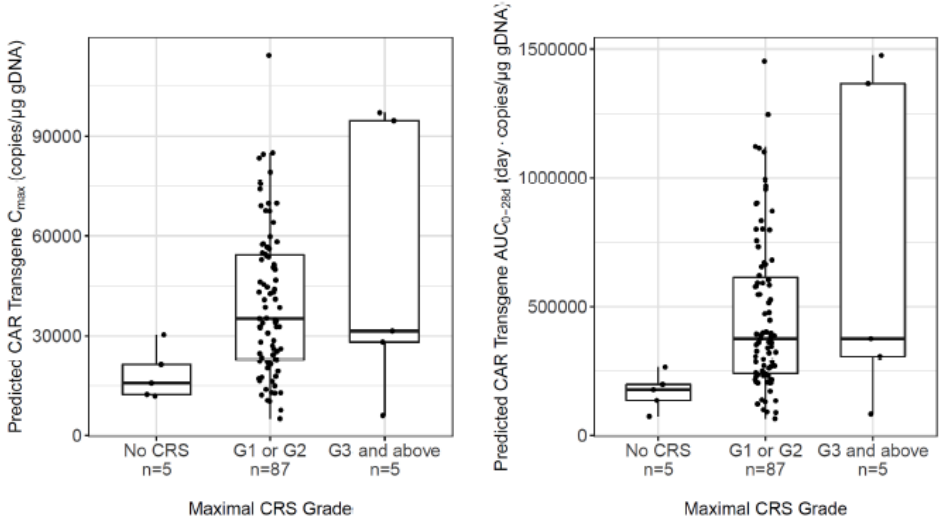
The median systemic CAR transgene levels (Cmax and AUC0-28d) in subjects with CRS, ICANS, or other neurotoxicities (including movement and neurocognitive TEAEs) were generally higher than that in subjects without CRS, ICANS, other neurotoxicities (including movement and neurocognitive TEAEs), or movement and neurocognitive TEAEs, respectively. Given the overlapping systemic CAR transgene levels across AE categories and the small number of subjects with Grade ≥3 CRS (n=5) or Grade ≥3 ICANS (n=2), any trend observed needs to be interpreted with caution.

Figure 10. Comparison of Total Number of CAR-Positive Viable T-cells Administered (With or Without Body Weight Normalisation), Predicted CAR Transgene C_{max} and AUC_{0-28d} Between Subjects with Different Maximal CRS Grade

A: CAR+ T cells Total Dose

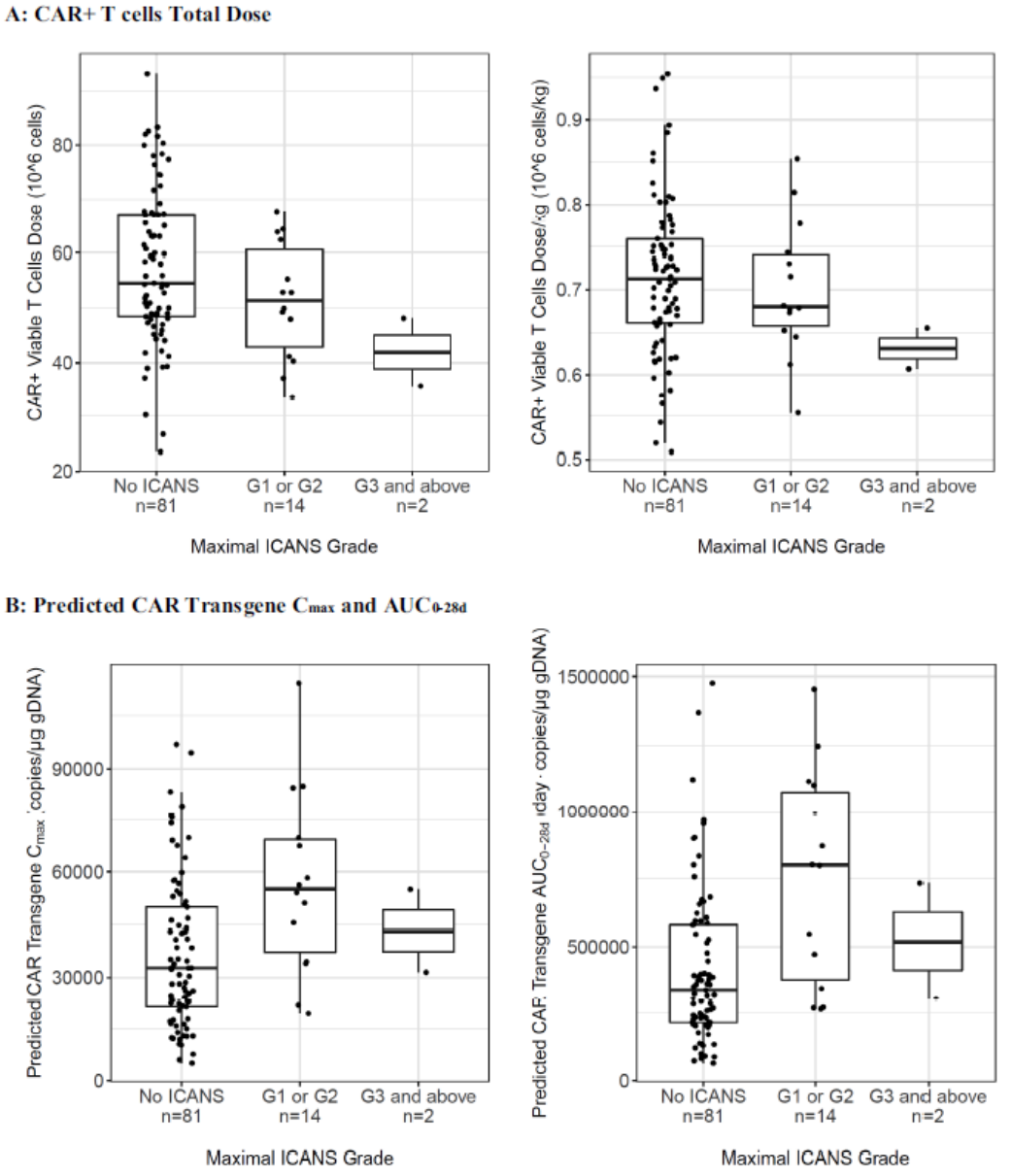


B: Predicted CAR Transgene C_{max} and AUC_{0-28d}



AUC_{0-28d}=area under the CAR transgene systemic level-time curve from the first dose to Day 28; CAR=chimeric antigen receptor; C_{max}=maximum CAR transgene systemic level; CRS=cytokine release syndrome; G=adverse event grade; gDNA=genomic DNA.

Figure 11. Comparison of Total Number of CAR-Positive Viable T-cells Administered (With or Without Body Weight Normalisation), Predicted CAR Transgene C_{max} and AUC_{0-28d} Between Subjects with Different Maximal ICANS Grade



AUC_{0-28d}=area under the CAR transgene systemic level-time curve from the first dose to Day 28; CAR=chimeric antigen receptor; C_{max}=maximum CAR transgene systemic level; ICANS=immune effector cell-associated neurotoxicity syndrome. G=adverse event grade; gDNA=genomic DNA.

2.6.3. Discussion on clinical pharmacology

Clinical pharmacology data are presented from the Study 68284528MMY2001.

PK.

The analytical methods used for PK represent standard methods used in the field. Sampling frequency carried out during the clinical trial is considered adequate. Certain aspects of the PK model still need some clarifications (results of the bootstrap analysis, the large residual error).

PK transgene and cellular levels in peripheral blood and bone marrow are concordant and expansion and persistence profiles are shown to be similar. The kinetic of expansion and persistence indicate an initial expansion phase followed by a rapid decline and then a slower decline with both transgene and cellular persistence over months. The median time to reach peak levels of cilta-cel expansion in peripheral blood was 12.7 days (range: 8.7-54.6 days) post-infusion. After the cell expansion, the persistence phase of the cilta-cel transgene levels was observed for all subjects.

Intraindividual variability is not testable, since cilta-cel is administered as a single dose. For the tested parameters, high interindividual variability was found.

Covariate analysis indicate that none of the investigated subject demographics, baseline characteristics, or manufactured product characteristics had a statistically significant effect on population PK model parameters. Individual outlayers may have influenced some of the findings (e.g. influence of prior allogenic transplant, race, tumour burden); however, due to the low number of patients treated these discrepancies cannot be further addressed at this stage. Generally, the low number of patients treated leaves uncertainties, which could only be answered at higher patient numbers. Post marketing data will further provide data to fill in such gap.

No dedicated renal and hepatic impairment study was planned as cilta-cel is a genetically modified cell-based therapy and major changes in cilta-cel exposure are not anticipated in subjects with renal and hepatic insufficiency. Patients with inadequate renal or hepatic functions were excluded from the clinical trial. Mild hepatic or renal dysfunction had no negative impact on PK parameters in the Pop PK analysis. These aspects are all indicated in the SmPC. Gender, race, weight or age did not impact PK parameters. Cilta-cel is only indicated to treat adults; therefore, investigations in children are not required.

The median systemic CAR transgene levels in subjects with CRS, ICANS, other neurotoxicities (including movement and neurocognitive TEAEs), and movement and neurocognitive TEAEs was higher than in subjects without CRS, ICANS or movement and neurocognitive TEAEs. These findings are expected and similar to previous observations in the literature (Pabst et al, 2020; Milone and Bhoj, 2018. Additionally, median CAR transgene C_{max} and $AUC_{0\text{-}28d}$ were higher among subjects who received tocilizumab, corticosteroids, or anakinra for CRS or ICANS management. Based on the above correlation, this is also expected. Patients having higher CAR+ cell concentrations tend to have CRS of higher grades, which then would correlate with the number of patients requiring rescue medications.

No dedicated drug-drug interaction studies were performed for cilta-cel.

The PK data provided are therefore considered adequate for the developed product

PD

Cilta-cel targets BCMA, which is only expressed on B-cells, plasma cells and malignant B-lineage cells. The experiments support the proposed MoA, ensuring a highly specific therapeutic approach.

The cytolytic mechanism of action of cilta-cel relies on antigen-dependent activation and proliferation of anti-BCMA CAR-T-cells via engagement of BCMA expressed on the cell surface of normal or tumour plasma cells.

Expansion of CAR-positive T cells coincided with decreases of serum sBCMA, serum M-protein, and/or free light chains. Several serum cytokines (eg, IL-6, IL-10, and IFN-gamma) increased, coinciding with expansion of cilta-cel and the onset of CRS. Concentrations of sBCMA in serum slowly decreased as a function of time, with mean serum BCMA concentrations reaching nadir levels around the LLOQ value (ie, <0.25000 µg/L) at Day 78 in Phase 1b and at Day 100 in Phase 2.

Across all subjects, levels of IL-6, IL-10, INF-gamma, and IL-2 receptor alpha (IL-2Ra) increased post-infusion and peaked at Days 7 to 14. The serum levels of all cytokines generally returned to baseline levels within 2 to 3 months post-infusion.

Of the 57 evaluable subjects, 53 subjects (93.0%) were MRD negative in bone marrow at a sensitivity level of 10^{-5}.

The overall incidence of antibodies to cilta-cel was 15.5%. Based on the current data, there was no clear evidence to suggest an association between ADA and cilta-cel kinetics of initial expansion and persistence, efficacy, or safety.

At the time of the clinical cut-off date, no positive samples for RCL had been detected in any subjects at any of the collection timepoints.

Since cilta-cel was administered in a single dose, findings on E-R are somewhat limited. Given that the majority of treated subjects were responders (ORR=96.9%), it was not feasible to draw a conclusion on the E-R relationship between systemic cilta-cel CAR transgene level and ORR and, considering the limited number of subjects and events, disease progression, as measured by DOR, PFS, and OS could not be readily evaluated.

A trend of higher systemic median cilta-cel CAR transgene level was observed in subjects with CRS or CAR-T cell neurotoxicity (ICANS and other neurotoxicities [including movement and neurocognitive TEAEs]) compared with subjects without these AEs.

The PD data provided are therefore considered adequate for the developed product and are considered suitable for the SmPC.

2.6.4. Conclusions on clinical pharmacology

The observed biological activity of cilta-cel supports the proposed mechanism of action. The data confirm a strong pharmacological rationale. The product can be approved on Pharmacology grounds.

The CHMP endorses the CAT assessment regarding the conclusions on the Clinical pharmacology as described above.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

Phase 1b Study 8284528MMY2001/CARTITUDE-1 (Study MMY001)

Objective	Endpoint
Primary	
• To characterize the safety of JNJ-68284528 and establish the dose (RP2D) (Phase 1b)	• Incidence and severity of adverse events

Sample size

A minimum of 24 and up to 50 subjects were planned to receive treatment to confirm treatment safety and provide information to be used in the selection of a recommended dose level (RP2D) for further investigation in the Phase 2 part of the study.

With 24 treated subjects, if the true incidence rate of certain adverse events identified as potential risks was 10%, the probability of observing at least one subject experiencing the event would be more than 90%.

Finally, the Phase 1b part included 29 subjects who received treatment.

Treatment

Each subject received a conditioning regimen of intravenous (IV) cyclophosphamide 300 mg/m2 and fludarabine 30 mg/m2 at 3 daily doses. The planned conditioning regimen lead to lymphodepletion and help promote CAR-T cell expansion in the subject.

Cilta-cel (JNJ-68284528) was administered as a single infusion (Study Day 1) 5 to 7 days after the start of the conditioning regimen (the first day of conditioning is Day -7 to Day -5, and the day of JNJ-68284528 infusion is Day 1).

A staggered dosing strategy was initially used in Phase 1b, whereby an observation period was required between dosing of each of the first 4 subjects: an observation period of 4 weeks was implemented between the first and second subjects followed by a 2-week observation period between the second and third subjects and between the third and fourth subjects.

No observation periods were mandated after the fourth subject received JNJ-68284528.

A Safety Evaluation Team (SET) was established to ensure safety monitoring and Sponsor oversight during the Phase 1b portion and confirmation of the RP2D.

The SET reviewed all available treatment-emergent data (e.g., pharmacokinetic, pharmacodynamics, safety, efficacy) at predefined enrolment milestones to evaluate the need for dose level escalation or de-escalation.

For the first 24 subjects enrolled, SET evaluation was required after every 6 subjects had received treatment at a given cilta-cel dose level and had been monitored for a 21-day dose de-escalation evaluation period. During this period, any observed dose limiting toxicities (DLT) may result in dose de-escalation for future subjects.

Confirmation of the RP2D was to follow SET review of data from at least 24 subjects.

Dose Level

Subjects received the JNJ-68284528 (cilta-cel) infusion at one of the following three dose levels:

- Dose Level 1: 0.75×10^6 CAR-positive viable T-cells/kg (range: $0.5\text{-}1.0\times10^6$)
- Dose Level -1: 0.3×10^6 CAR-positive viable T-cells/kg (range: $0.1\text{-}<0.5\times10^6$)
- Dose Level 2: not to exceed 2.25×10^6 CAR-positive viable T-cells/kg (range: ±30%)

Rationale of Dose and Administration Schedule Selection

Cyclophosphamide 300 mg/m2 and fludarabine 30 mg/m2 before cilta-cel (JNJ-68284528) infusion (Day 1) is consistent with the lymphodepletion regimen used in the marketed CAR-T products Kymriah and Yescarta.

JNJ-68284528 (cilta-cel) was administered at a targeted infused dose of 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1.0 x 10^6 CAR-positive viable T cells/kg with a maximum total dose of 1.0 x 10^8 CAR-positive viable T cells) for this Phase 1b-2 study.

This dose was informed by the Legend-2 clinical study (see section 3.8, supportive studies) performed at 4 study sites across China and in which a different manufacturing process was used with differences potentially leading to an altered activity of the product. The number of viable CAR-positive T cells prepared for the 74 subjects from the Legend-2 study ranged from 0.07 to 2.10 x 10^6 CAR-positive viable T cells/kg (mean 0.642 x10^6 cells/kg, median 0.513 x10^6 cells/kg).

Across all 74 subjects, the safety profile supports doses up to 1.5 x10^6 cells/kg with regards to occurrence of CRS. Analysis of the safety of doses above 1.5 x10^6 in the Legend-2 study is not possible due to the very small number of subjects who received a dose above this concentration.

As stated above, the JNJ-68284528 (cilta-cel) drug product expresses the same CAR protein but is produced using a modified manufacturing process relative to the drug product used in the Legend-2 study so that differences in clinical activity and safety profiles due to the updated manufacturing process are possible. Thus, the targeted infused dose (post-freeze) of 0.75 x 10^6 CAR-positive viable T cells/kg proposed for JNJ-68284528 was reduced to half of the prepared dose (pre-freeze) of 1.5 x 10^6 cells/kg supported by the safety analysis summarised in the following table:

Table 3. Summary of CRS Grade by Weight-adjusted Total CAR-positive T Cell Dose (Legend-2 Study)

	Weight-adjusted total CAR+ cells dose range (x10^6 cells/kg)			
	≤0.5	>0.5to ≤1	>1<to ≤1.5	>1.5
Cytokine release syndrome toxicity grade				
N	34	27	8	5
Grade 0 (No CRS)	4 (11.8%)	2 (7.4%)	0	0
Grade 1	20 (58.8%)	12 (44.4%)	3 (37.5%)	2 (40.0%)
Grade 2	8 (23.5%)	12 (44.4%)	4 (50.0%)	1 (20.0%)
Grade 3	1 (2.9%)	1 (3.7%)	1 (12.5%)	2 (40.0%)
Grade 5	1 (2.9%)	0	0	0

Key: CRS = Cytokine Release Syndrome

At 3 of the 4 sites (65 of 74 subjects) in the Legend-2 study, the dose was split into more than 1 infusion, the most common regimen was 3 infusions given over 7 days. At the 4th site, 9 subjects received CAR-T cells manufactured with the second and third generation LV developed by Legendas a single administration on Day 1. Review of safety (occurrence of CRS) and efficacy data from the 9 subjects who received a single infusion of CAR-T cells manufactured with the second and third generation LV developed by Legend did not discern a meaningful difference between split doses versus single dose administration. Single dose administration is consistent with the dosing regimens of the 2 currently approved CAR-T products (Kymriah, Yescarta), and bb2121 (Abecma).

Based on totality of the Legend-2 clinical data, the applicant proposed a target starting dose of 0.75 x 10^6 CAR-positive viable T cells/kg for JNJ-68284528 in single administration for testing in the clinic. As an added safety precaution (for the study as a whole), a dose de-escalation was planned to be performed in subjects in the event of excess toxicity being observed following dosing in the first 6 subjects. Additionally, a dose escalation was considered if specified safety criteria were met.

Dose de-escalation

The dose de-escalation evaluation period was defined as 21 days after the infusion of JNJ-68284528. Toxicities that were considered at least possibly related to JNJ-68284528 and that occurred during the dose de-escalation evaluation period were considered for dose limiting toxicity (DLT) assessment.

Table 4. Dose Limiting Toxicity Criteria

Toxicities for Dose De-escalation	
CRS	Grade 4 CRS not improved to Grade 2 or lower within 72 hours
Neurotoxicity	Grade 3 or 4 neurotoxicity not improved to Grade 2 or lower within 72 hours
Other non-hematologic toxicity	Grade 3 or 4 non-CRS toxicity of heart, liver, lungs, kidney that does not resolve to Grade 2 or lower within 7 days
Hematologic and non-hematologic toxicity	Any Grade 5 toxicity

If >1 out of the first 6 subjects at any dose level met DLT criteria during the 21-day evaluation period, a dose de-escalation to a target dose (dose level -1) of 0.3 x 106 CAR-positive viable T cells/kg (range: 0.1-0.5 x 106 cells/kg) for following subjects was mandated as determined by the SET. For the duration of the Phase 1b portion of the study, a dose de-escalation was mandated if, at the time of the SET meeting, DLT criteria are met for ≥20% of subjects for any dose level reaching the evaluation milestone (e.g., 6, 12, or 18 subjects).

Adverse events were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 5.0), with the exception of CRS and CAR-T cell-related neurotoxicity (e.g., ICANS). CRS was evaluated according to the ASBMT consensus grading (Lee 2019). CAR-T cell-related neurotoxicity (e.g., ICANS) was graded using the ASBMT consensus grading.

Assessments for immune effector cell-associated encephalopathy (ICE) were performed as specified in the Time and Events Schedule in both the Phase 1b and Phase 2 portions of the study.

Dose Escalation

At the time of the SET meeting, if fewer than 20% of subjects enrolled in the study at the target starting dose (dose level 1) met DLT criteria during the 21-day dose de-escalation evaluation period described above, a dose escalation (dose level 2) could be approved by the SET.

Target dose level and range for dose level 2 did not exceed 3 times dose increase from initial target dose (2.25 x 10^6 viable CAR-positive T cells / kg [range: ±30%, depending on the target dose chosen for dose level 2]). No dose increased beyond dose level 2. After dose increase, the same criteria for dose decrease previously described were used for mandatory reduction back to 0.75 x 10^6 cells / kg (dose level 1).

The RP2D was confirmed by the SET after evaluation of safety, preliminary efficacy, pharmacokinetic, and pharmacodynamic data from at least 24 Phase 1b subjects. The RP2D was a dose level examined in Phase 1b at which <20% of subjects experienced a DLT.

2.6.5.2. Main study

Title of Study

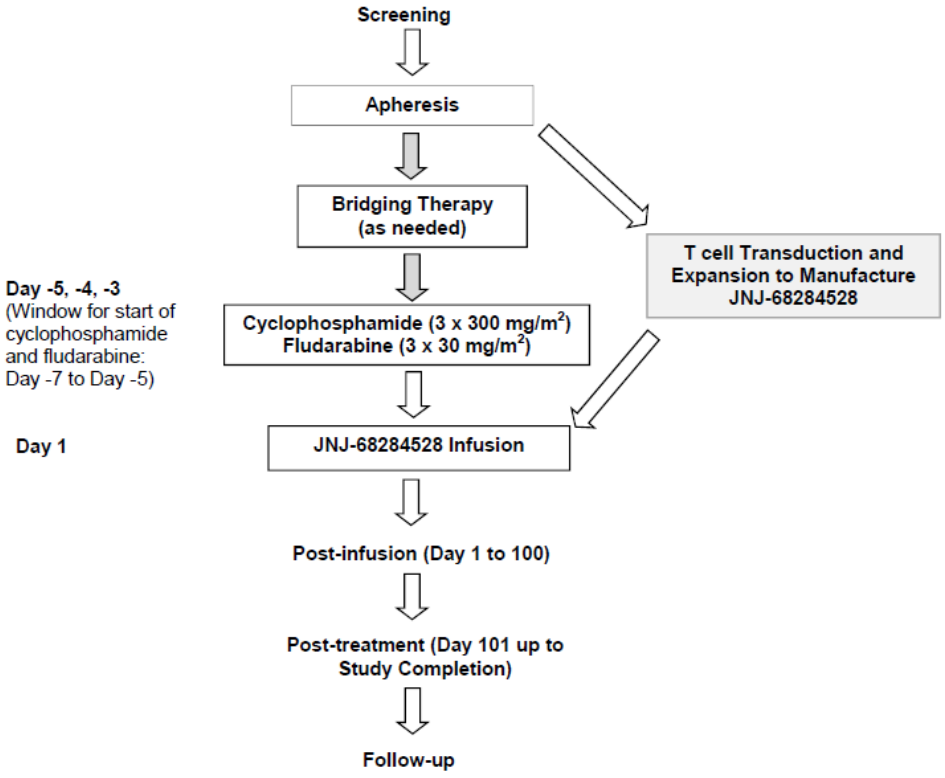
A Phase 1b-2, Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Relapsed or Refractory multiple myeloma (68284528MMY2001)

- ***Methods***

Subjects who satisfied all study inclusion and exclusion criteria during the Screening Phase were considered eligible for the study. Study intervention then comprised 3 steps: apheresis for collection of peripheral blood mononuclear cells, conditioning with cyclophosphamide and fludarabine, and infusion of cilta-cel. Subjects were considered enrolled at the time of apheresis and were assessed before each of these steps to ensure that he or she remained eligible to continue intervention.

Eligible subjects underwent apheresis for collection of peripheral blood mononuclear cells (PBMC) on the day of study enrolment. Subjects could receive bridging therapy if clinically indicated to maintain disease stability while cilta-cel manufacturing was underway. After notification by the sponsor that manufacture and quality testing of cilta-cel had been completed, eligible subjects received a conditioning regimen of intravenous (IV) cyclophosphamide 300 mg/m2 and fludarabine 30 mg/m2 in 3 daily doses. Five to 7 days after the start of the conditioning regimen, cilta-cel was administered as a single infusion with a total targeted dose of 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1.0 x 10^6 CAR-positive viable T cells/kg).

A schematic overview of the study flow chart is presented in **Figure 12**:



- **Study Participants**

Main Inclusion Criteria

1. ≥18 years of age.
2. Documented diagnosis of multiple myeloma according to IMWG diagnostic criteria.
3. Measurable disease at Screening as defined by any of the following:
   - Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
   - Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.
4. Received at least 3 prior multiple myeloma treatment lines of therapy or are double refractory to an IMiD and PI (refractory multiple myeloma as defined by IMWG consensus criteria29). Note: induction with or without haematopoietic stem cell transplant and with or without maintenance therapy is considered a single line of therapy.

- Undergone at least 1 complete cycle of treatment for each line of therapy, unless PD was the best response to the line of therapy.

5. Received as part of previous therapy a PI, an IMiD, and an anti-CD38 antibody (prior exposure can be from different monotherapy or combination lines of therapy).
6. Subject must have documented evidence of progressive disease based on investigator's determination of response by the IMWG criteria on or within 12 months of their last line of therapy. Confirmation may be from either central or local testing. Also, subjects with documented evidence of progressive disease (as above) within the previous 6 months and who are refractory or non-responsive to their most recent line of therapy afterwards are eligible.
7. ECOG Performance Status grade of 0 or 1.

Main Exclusion Criteria

1. Prior treatment with CAR-T therapy directed at any target.
2. Any therapy that is targeted to BCMA.
3. Diagnosed or treated for invasive malignancy other than multiple myeloma, except:
    - Malignancy treated with curative intent and with no known active disease present for ≥2 years before enrolment; or
    - Adequately treated non-melanoma skin cancer without evidence of disease.
4. Prior antitumour therapy as follows, prior to apheresis:
    - Targeted therapy, epigenetic therapy, or treatment with an investigational drug or used an invasive investigational medical device within 14 days or at least 5 halflives, whichever is less.
    - Monoclonal antibody treatment for multiple myeloma within 21 days.
    - Cytotoxic therapy within 14 days.
    - Proteasome inhibitor therapy within 14 days.
    - Immunomodulatory agent therapy within 7 days.
    - Radiotherapy within 14 days. However, if the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.
5. Toxicity from previous anticancer therapy must resolve to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy.
6. The following cardiac conditions:
    - New York Heart Association (NYHA) stage III or IV congestive heart failure
    - Myocardial infarction or coronary artery bypass graft (CABG) ≤6 months prior to enrolment
    - History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
    - History of severe non-ischemic cardiomyopathy
    - Impaired cardiac function (LVEF <45%) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan (performed ≤8 weeks of apheresis).
7. Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 7 days prior to apheresis
8. Received either of the following:
    - An allogenic stem cell transplant within 6 months before apheresis. Subjects who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease (GVHD).
    - An autologous stem cell transplant ≤12 weeks before apheresis
9. Known active, or prior history of central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of multiple myeloma.

10. Stroke or seizure within 6 months of signing ICF.
11. Plasma cell leukemia at the time of screening (>2.0 x 10^9/L plasma cells by standard differential), Waldenström's macroglobulinaemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary AL amyloidosis.
12. Seropositive for human immunodeficiency virus (HIV).
13. Vaccinated with live, attenuated vaccine within 4 weeks prior to apheresis.
14. Hepatitis B infection as defined according to Attachment 8. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status.
15. Hepatitis C infection defined as (anti-hepatitis C virus [HCV] antibody positive or HCV-RNA positive) or known to have a history of hepatitis C. For subjects with known history of HCV infection, confirmation of sustained virologic response [SVR] is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.

- **Treatments**

The cilta-cel pre-treatment/treatment phase included apheresis, bridging therapy (optional) and lymphodepletion chemotherapy (conditioning regimen: Cy-Flu) and cilta-cel infusion.

Apheresis

Eligible subjects underwent apheresis for collection of peripheral blood mononuclear cells (PBMC) on the day of study enrollment. Apheresis was to be performed according to institutional standards, with a collection target of 6 x 10^9 PBMCs (range: 2 to 20 x 10^9 PBMCs); 2 apheresis collections could be performed to attain this target. The apheresis product was then shipped to the sponsor or designated facility for manufacture of cilta-cel.

Bridging therapy

Subjects could receive bridging therapy (anti-plasma cell directed treatment between apheresis and the first dose of the conditioning regimen) if clinically indicated to maintain disease stability while cilta-cel manufacturing was underway. Bridging therapy required preapproval from the sponsor and must have been a short-term treatment which previously generated at least a response of stable disease for the subject. If a subject reached CR after bridging therapy, they were considered no longer eligible to receive cilta-cel.

Conditioning therapy

After notification by the sponsor that manufacture and quality testing of cilta-cel had been completed, eligible subjects received a conditioning regimen of intravenous (IV) cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 in 3 daily doses.

Cilta-cel administration

Cilta-cel was administered as a single infusion 5 to 7 days after the start of the conditioning regimen (the first day of conditioning occurred on Day -7 to Day -5; cilta-cel infusion occurred on Day 1). On the day of cilta-cel infusion, subjects were premedicated with diphenhydramine (or the equivalent) 50 mg and acetaminophen (or the equivalent) 650 to 1,000 mg. This was followed by a single infusion of cilta-cel at a targeted infused dose of 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1.0 x 10^6 CAR-positive viable T cells/kg with a maximum total dose of 1.0 x 10^8 CAR-positive viable T cells; Patients 100 kg and below: 0.5 - 1.0 x 10^6 CAR-positive viable T cells/kg body weight. Patients above 100 kg: 0.5 - 1.0 x 10^8 CAR-positive viable T cells (non-weight based)).

Retreatment

Subjects could be considered for retreatment with cilta-cel if the following pre-specified criteria were met, in addition to continuing to meet all inclusion and exclusion criteria, and obtaining approval from the sponsor:

- Progressive disease after best response of minimal response (MR) or better.
- No ongoing Grade 3 or higher haematologic toxicity.
- No ongoing Grade 2 non-haematologic toxicity (with the exception of nausea, vomiting, hair loss, and constipation).
- At least 6 months between first cilta-cel infusion and detection of PD.

Permitted Medications

The following are examples of supportive therapies that may have been used during the study:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor [H2] antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease) and therapies intended to treat CAR-T cell related toxicity (ie, CRS) as clinically indicated, according to institutional standards and as deemed necessary by the investigator.

- Bisphosphonates may be initiated (if not already being administered) unless contraindicated within 1 week prior to the first dose of study treatment and continued until disease progression is established. In the case of severe adverse events such as hypercalcaemia, bisphosphonates may be administrated as clinically indicated, according to institutional standards and as deemed necessary by the investigator.

- Haematopoietic growth factor support and transfusions (irradiated blood products) are permitted to treat symptoms or signs of neutropenia, anaemia or thrombocytopenia according to local standards of care. Non-pegylated myeloid growth factors are permitted up to 1 day prior to the start of the conditioning regimen.

- Documented infectious complications should be treated with oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator, according to standard institutional practice.

- Chemotherapy agents used to treat CAR-T cell-related toxicities are permitted upon consultation with the sponsor.

Prohibited Therapies

The following medications were prohibited during the study.

- Corticosteroid use should be avoided, except for the treatment of CRS or CAR-T cell-related neurotoxicity (eg, ICANS). Alternative therapies, if feasible, should be given prior to corticosteroids.

- Any chemotherapy, anticancer immunotherapy (other than cilta-cel), or experimental therapy, except as described in Section 3.1 (bridging therapy), or protocol- specific therapies which may be used in conjunction with cilta-cel.

- While in follow-up, emergency orthopaedic surgery or radiotherapy is generally prohibited, but may be allowed in the absence of disease progression. Cases must be discussed and approved by the sponsor. Such emergency radiotherapy may consist of localised radiotherapy for pain control or for stabilisation of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues.

- Nonsteroidal anti-inflammatory agents should be avoided to minimize the risk of exacerbation of potential sub-clinical myeloma-related kidney disease. Based on the investigator's clinical judgement, low-dose aspirin may be continued for thromboprophylaxis.

- Other immunosuppressant agents unless used as protocol-specified pre- or post-treatment medications to treat an adverse event (eg, CRS).

- Vaccination with live, attenuated vaccine after signing consent and in the ≤4 weeks prior to the infusion of cilta-cel, and for 100 days after infusion of cilta-cel.

- The use of IV contrast infusions should be avoided to prevent myeloma-related kidney disease. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.

- **Objectives**

Primary objectives

1. To characterize the safety of cilta-cel and establish the dose (RP2D) (Phase 1b)
2. To evaluate the efficacy of cilta-cel (Phase 2)

Secondary objectives

1. To characterize the safety of cilta-cel (Phase 2)
2. To characterize the pharmacokinetics and pharmacodynamics of cilta-cel
3. To assess the immunogenicity of cilta-cel
4. To further characterize the efficacy of cilta-cel
5. To compare the patient-reported outcomes (PRO) after treatment to subject's reported health state prior to treatment and to assess the sustained benefit of subject's perceived health related quality of life (HRQoL) (Phase 2 only)

- **Outcomes/endpoints**

Primary endpoints

1. Incidence and severity of adverse events.
2. ORR (at least a partial response [PR] or better) as defined by the International Myeloma Working Group (IMWG) response criteria as assessed by the Independent Review Committee (IRC).

Secondary endpoints

1. Incidence and severity of adverse events.
2. Pharmacokinetic and pharmacodynamic markers including but not limited depletion of BCMA expressing cells, circulating soluble BCMA, systemic cytokine concentrations, and markers of CAR-T cells,
3. T cell expansion (proliferation), and persistence via monitoring CAR-T positive cell counts and CAR transgene level.
4. Presence of anti- cilta-cel antibodies.
5. Very good partial response (VGPR)/complete response (CR)/stringent complete response (sCR) rate, minimal residual disease (MRD) negative rate as defined by the IMWG response criteria, clinical benefit rate (CBR; CBR = ORR (sCR + CR + VGPR + PR) + MR (minimal response)]), duration of and time to response (DOR and TTR), progression-free survival (PFS), overall survival (OS).

- **Sample size**

For the Phase 1b part of the study at least 24 and up to approximately 50 patients were planned to be treated in order to assess safety. The probability of detecting at least one subject experiencing a certain adverse event under the assumed true incidence rate based on plausible sample sizes is as follows:

Table 5. Sample Size Scenarios in Phase 1b

Sample Size in Phase 1b	True incidence rate of the adverse event	Probability of observing at least one subject experiencing the adverse event
24	10%	92%
40	6%	91.6%
50	5%	92.3%

For the Phase 2 part of the study a sample size of 60 subjects were planned. With an assumed overall response rate of at least 50%, there were approximately 90% power to declare the ORR to be higher than 30% at the 1-sided significance level of 0.025.

- **Randomisation and Blinding (masking)**

Randomisation was not used in this study, and subjects were to receive study treatment if all inclusion and exclusion criteria were met. The use of a randomised study design was considered impractical given that the study population included subjects who had largely exhausted available treatment options leaving no available comparator to ensure equipoise.

As this was an open-label study, blinding procedures were not employed.

- **Statistical methods**

The ITT population was defined as all patients enrolled. The mITT population was defined as all subjects who received a JNJ-68284528 infusion at the targeted RP2D dose. The all treated analysis set consisted of subjects who received JNJ-68284528 infusion. This set was planned for the primary analysis set for safety summaries.

The primary efficacy endpoint for the Phase 2 study was planned to be ORR. The first analysis was planned to be conducted 6 months after the last subject has received the initial dose of JNJ-68284528, based on the mITT analysis set. The response rate and its 95% Clopper-Pearson exact confidence interval (CI) were planned to be calculated based on binomial distribution. The null hypothesis were planned to be rejected if the lower bound of the confidence interval exceeds 30%. Analysis of VGPR or better response rate, DOR, PFS, and OS were planned to be conducted at the same cutoff as the ORR, and an update of these endpoints were planned to be provided at approximately 9-12 months after the last subject has received his or her initial dose of JNJ-68284528 and at the end of the study, which was defined as 2 years after the last subject has received his or her initial dose of JNJ-68284528.

Sensitivity analyses for the primary efficacy analysis were planned to be performed on the mITT analysis set using disease response based on the computerised algorithm and investigator assessment according to the IMWG response criteria. The prevalence-adjusted-bias-adjusted kappa (PABAK) statistics1 and 95% CI were calculated for agreement between IRC assessment and computerised algorithm assessment for response (response [PR or better] vs. no response). Further sensitivity analysis of ORR analysis were planned on all enrolled analysis set, on all treated analysis set, and on subjects in the mITT set who received the JNJ-68284528 product that met all the pre-specified release criteria.

The intercurrent event of subsequent antimyeloma therapy or retreatment with JNJ-68284528 were handled with the while on treatment strategy, meaning that responses after these intercurrent events

were not considered for the primary endpoint. There was no imputation planned for missing efficacy endpoints, however, patients with no post-baseline data were considered as non-responders. There was no plan for the correction for the type I error and no plan for interim analyses. Subgroup analyses were planned to be performed by descriptive summaries and forest plots.

Secondary efficacy endpoints were analysed as follows: Response rates (VGPR, MRD status, clinical benefit rate etc) were planned according to ORR. The distribution (median and Kaplan-Meier curves) of time to event endpoints (DOR, time to response, PFS, OS, etc) were planned to be provided using Kaplan-Meier estimates for subjects who achieved response during the study. Similar analysis were planned to be performed for OS, PFS, and TTR for the mITT analysis set.

Results

- **Participant flow**

Figure 13. Subject Study Disposition as of the Clinical Cutoff Date (01 September 2020); Study 68284528MMY2001

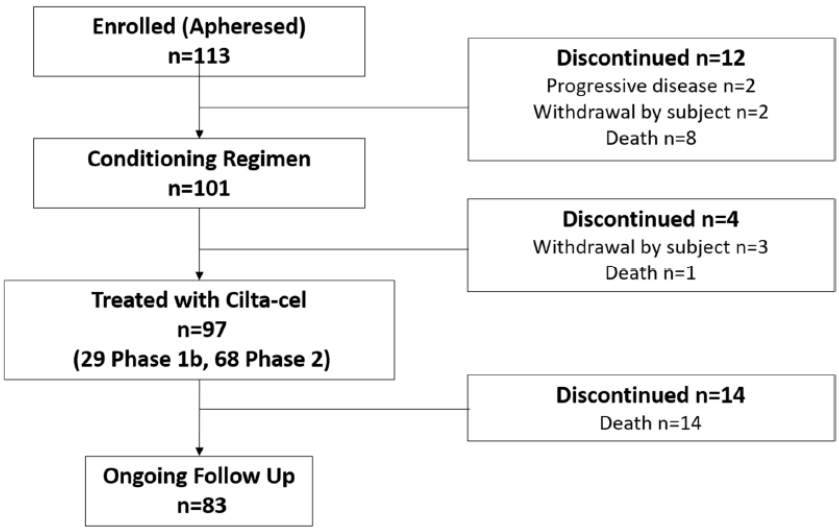


Table 6. Summary of Subject Study Disposition; All Enrolled Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all enrolled	35	78	113
Discontinued the study	11 (31.4%)	19 (24.4%)	30 (26.5%)
After apheresis and prior to the start of conditioning regimen	5 (14.3%)	7 (9.0%)	12 (10.6%)
Reason for discontinuation			
Progressive disease	0	2 (2.6%)	2 (1.8%)
Withdrawal by subject	1 (2.9%)	1 (1.3%)	2 (1.8%)
Death	4 (11.4%)	4 (5.1%)	8 (7.1%)
After the start of conditioning regimen and prior to JNJ-68284528 infusion	1 (2.9%)	3 (3.8%)	4 (3.5%)
Reason for discontinuation			
Withdrawal by subject	1 (2.9%)	2 (2.6%)	3 (2.7%)
Death	0	1 (1.3%)	1 (0.9%)
After JNJ-68284528 infusion	5 (14.3%)	9 (11.5%)	14 (12.4%)
Reason for discontinuation			
Death	5 (14.3%)	9 (11.5%)	14 (12.4%)
Ongoing in follow-up	24 (68.6%)	59 (75.6%)	83 (73.5%)

Note: Percentages are calculated with the number of subjects in the all enrolled analysis set as denominator.

Table 7. Summary of Study Treatment; All Enrolled Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all enrolled	35	78	113
Subjects received cyclophosphamide infusion	30 (85.7%)	71 (91.0%)	101 (89.4%)
Subjects received fludarabine infusion	30 (85.7%)	71 (91.0%)	101 (89.4%)
Subjects received JNJ-68284528 infusion	29 (82.9%)	68 (87.2%)	97 (85.8%)
Subjects received retreatment of JNJ-68284528 infusion	1 (2.9%)	0	1 (0.9%)

Note: Percentages are calculated with the number of subjects in the all enrolled analysis set as denominator.

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- **Recruitment**

DATE STUDY INITIATED: 05 July 2018 (Date first subject signed informed consent)
DATE STUDY COMPLETED: Not applicable, study is ongoing
DATE OF DATA CUT-OFF: 1 September 2020 (Date of last observation recorded as part of the database for the primary analysis)

- **Conduct of the study**

The original protocol was dated 11 April 2018.

There were 4 global amendments to the original protocol (Table below).

Table 8. Overall Reasons for Study 68284528MMY2001 Protocol Amendments

Amendment 1 20 August 2018 (n=2)	Added collection of additional safety information and added clarity to targeted sections of the protocol.
Amendment 2 11 March 2019 (n=21)	Expanded the number of subjects enrolled in the Phase 1b portion, updated cytokine release syndrome (CRS) and neurotoxicity management guidelines, updated the CRS and neurotoxicity grading system to align with ASTCT guidelines published in 2019, and added clarity to targeted sections of the protocol.
Amendment 3 30 July 2019 (n=64)	The overall reason for the amendment was to transition the study into the Phase 2 portion, describe the role of the Independent Review Committee (IRC), add the Medical Resource Utilization (MRU) assessment, and to add clarity to targeted sections of the protocol.
Amendment 4 20 March 2020 (n=113)	The overall reason for the amendment is to add other neurotoxicities as a safety risk and implement additional monitoring and risk minimization measures for JNJ-68284528.
COVID-19 Appendix 30 April 2020 (n=113)	The overall reason for this appendix is to provide guidance on study conduct as a result of the COVID-19 pandemic.

ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; IRC=Independent Review Committee; MRU=medical resource utilization; N= Number of subjects enrolled in the study on the date of the protocol amendment.

- **Baseline data**

Demographics

Table 9. Summary of Demographics and Baseline Characteristics; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Age, years			
N	29	68	97
Category, n (%)			
< 65	21 (72.4%)	41 (60.3%)	62 (63.9%)
65 – 75	8 (27.6%)	19 (27.9%)	27 (27.8%)
> 75	0	8 (11.8%)	8 (8.2%)
Mean (SD)	60.9 (6.42)	62.5 (9.09)	62.0 (8.38)
Median	60.0	62.0	61.0
Range	(50; 75)	(43; 78)	(43; 78)
Sex			
N	29	68	97
Male	14 (48.3%)	43 (63.2%)	57 (58.8%)
Female	15 (51.7%)	25 (36.8%)	40 (41.2%)
Race			
N	29	68	97
American Indian or Alaska native	1 (3.4%)	0	1 (1.0%)
Asian	1 (3.4%)	0	1 (1.0%)
Black or African American	5 (17.2%)	12 (17.6%)	17 (17.5%)
Native Hawaiian or other Pacific islander	0	1 (1.5%)	1 (1.0%)
White	20 (69.0%)	49 (72.1%)	69 (71.1%)
Multiple	0	0	0
Not reported	2 (6.9%)	6 (8.8%)	8 (8.2%)
Ethnicity			
N	29	68	97
Hispanic or Latino	2 (6.9%)	4 (5.9%)	6 (6.2%)
Not Hispanic or Latino	25 (86.2%)	60 (88.2%)	85 (87.6%)
Not reported	2 (6.9%)	4 (5.9%)	6 (6.2%)
Weight, kg			
N	29	68	97
Mean (SD)	84.6 (16.68)	76.9 (16.29)	79.2 (16.69)
Median	83.1	76.6	78.3
Range	(55; 121)	(39; 126)	(39; 126)

Height, cm			
N	29	68	97
Mean (SD)	169.5 (9.67)	169.8 (9.06)	169.7 (9.20)
Median	171.4	170.2	170.2
Range	(150; 185)	(150; 188)	(150; 188)
Body surface area (BSA), m^2			
N	29	68	97
Mean (SD)	1.99 (0.218)	1.90 (0.232)	1.92 (0.231)
Median	1.98	1.88	1.94
Range	(1.5; 2.3)	(1.3; 2.5)	(1.3; 2.5)
ECOG score prior to JNJ-68284528 infusion[a]			
N	29	68	97
0	12 (41.4%)	27 (39.7%)	39 (40.2%)
1	14 (48.3%)	40 (58.8%)	54 (55.7%)
2	3 (10.3%)	1 (1.5%)	4 (4.1%)

Key: ECOG = Eastern Cooperative Oncology Group.
[a] The last non-missing ECOG score on or prior to date of JNJ-68284528 infusion is used. All patients met the inclusion criteria of ECOG score of 0 or 1 during screening.
[TSIDEM01.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TSIDEM01.SAS] 23OCT2020, 13:20

Baseline Disease Characteristics

The baseline value is defined as the closest non-missing value before the initial dose of cilta-cel, with exception of parameters associated with disease-related efficacy assessment for which the baseline value is defined as the non-missing value closest to the start of conditioning regimen and before cilta-cel infusion.

Table 10. Summary of Baseline Disease Characteristics; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: All treated	29	68	97
Type of myeloma by immunofixation, n (%)			
N	29	68	97
IgG	16 (55.2%)	41 (60.3%)	57 (58.8%)
IgA	2 (6.9%)	6 (8.8%)	8 (8.2%)
IgM	1 (3.4%)	1 (1.5%)	2 (2.1%)
IgD	1 (3.4%)	1 (1.5%)	2 (2.1%)
IgE	0	0	0
Light chain	8 (27.6%)	16 (23.5%)	24 (24.7%)
Kappa	5 (17.2%)	10 (14.7%)	15 (15.5%)
Lambda	3 (10.3%)	6 (8.8%)	9 (9.3%)
Biclonal	1 (3.4%)	3 (4.4%)	4 (4.1%)
Negative immunofixation	0	0	0
Type of measurable disease, n (%)			
N	29	68	97
Serum only	14 (48.3%)	35 (51.5%)	49 (50.5%)
Serum and urine	2 (6.9%)	4 (5.9%)	6 (6.2%)
Urine only	2 (6.9%)	9 (13.2%)	11 (11.3%)
Serum FLC only	11 (37.9%)	19 (27.9%)	30 (30.9%)
Not evaluable	0	1 (1.5%)	1 (1.0%)
ISS staging at study baseline [a], n (%)			
N	29	68	97
I	20 (69.0%)	41 (60.3%)	61 (62.9%)
II	9 (31.0%)	13 (19.1%)	22 (22.7%)
III	0	14 (20.6%)	14 (14.4%)
Time since initial MM diagnosis to enrollment, years			
N	29	68	97
Mean (SD)	6.16 (3.525)	7.11 (3.644)	6.82 (3.617)
Median	5.05	6.65	5.94
Range	(1.6; 16.3)	(1.6; 18.2)	(1.6; 18.2)
Number of lytic bone lesions			
N	29	68	97
None	12 (41.4%)	16 (23.5%)	28 (28.9%)
1-3	5 (17.2%)	13 (19.1%)	18 (18.6%)
4-10	4 (13.8%)	11 (16.2%)	15 (15.5%)
More than 10	8 (27.6%)	28 (41.2%)	36 (37.1%)
Presence of extramedullary plasmacytomas, n (%)			
N	29	68	97
Yes	4 (13.8%)	9 (13.2%)	13 (13.4%)
No	25 (86.2%)	59 (86.8%)	84 (86.6%)
Presence of evaluable bone marrow assessment			
N	29	68	97
Yes	29 (100.0%)	67 (98.5%)	96 (99.0%)
No	0	1 (1.5%)	1 (1.0%)
% Plasma cells, bone marrow biopsy/aspirate [b]			
N	29	67	96
≤ 30	17 (58.6%)	41 (61.2%)	58 (60.4%)
> 30 – < 60	5 (17.2%)	12 (17.9%)	17 (17.7%)
≥ 60	7 (24.1%)	14 (20.9%)	21 (21.9%)

% Plasma cells, bone marrow biopsy			
N	24	59	83
≤ 30	14 (58.3%)	36 (61.0%)	50 (60.2%)
> 30 – < 60	3 (12.5%)	12 (20.3%)	15 (18.1%)
≥ 60	7 (29.2%)	11 (18.6%)	18 (21.7%)
% Plasma cells, bone marrow aspirate			
N	28	62	90
≤ 30	19 (67.9%)	49 (79.0%)	68 (75.6%)
> 30 – < 60	6 (21.4%)	6 (9.7%)	12 (13.3%)
≥ 60	3 (10.7%)	7 (11.3%)	10 (11.1%)
Bone marrow cellularity by biopsy			
N	24	61	85
Hypercellular	9 (37.5%)	16 (26.2%)	25 (29.4%)
Normocellular	12 (50.0%)	23 (37.7%)	35 (41.2%)
Hypocellular	1 (4.2%)	15 (24.6%)	16 (18.8%)
Indeterminate	2 (8.3%)	7 (11.5%)	9 (10.6%)
Cytogenetic risk at study baseline [c]			
N	29	68	97
Standard risk	22 (75.9%)	46 (67.6%)	68 (70.1%)
High risk	7 (24.1%)	16 (23.5%)	23 (23.7%)
Del17p	4 (13.8%)	15 (22.1%)	19 (19.6%)
T(4;14)	1 (3.4%)	2 (2.9%)	3 (3.1%)
T(14;16)	2 (6.9%)	0	2 (2.1%)
Unknown	0	6 (8.8%)	6 (6.2%)
Tumor BCMA expression (%)			
N	20	42	62
Mean (SD)	73.7 (20.28)	77.6 (14.36)	76.3 (16.44)
Median	81.4	79.0	79.9
Range	(20; 95)	(39; 98)	(20; 98)
≥50%	18 (90.0%)	39 (92.9%)	57 (91.9%)

Key: FLC = free light chain; ISS = International Staging System; MM = multiple myeloma.
[a] ISS staging is derived based on serum β2-microglobulin and albumin.
[b] Maximum value from bone marrow biopsy and bone marrow aspirate is selected if both the results are available. One subject with non-evaluable bone marrow biopsy/aspirate.
[c] Cytogenetic risk abnormalities are based on central fluorescence in situ hybridization (FISH) testing, or local FISH and karyotype testing if central FISH not available.

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Neurologic Medical History at Baseline

Seventy-two subjects (74.2%) had 1 or more preferred term associated with neurologic disorders reported in their medical history. Note that subjects with known active, or prior history of central nervous system (CNS) involvement and those who exhibited clinical signs of meningeal involvement of multiple myeloma, were excluded from the study.

Table 11. Summary of Neurologic History by MedDRA System Organ Class, Preferred Term, and Toxicity Grade; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b + Phase 2						
	Ongoing at Study Entry						
	Yes					No	Total
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	All Grades	All Grades
Analysis set: all treated							97
Total number of subjects with 1 or more neurological history	64 (66.0%)	54 (55.7%)	10 (10.3%)	0	0	14 (14.4%)	72 (74.2%)
Peripheral sensory neuropathy	60 (61.9%)	51 (52.6%)	9 (9.3%)	0	0	6 (6.2%)	66 (68.0%)
Headache	7 (7.2%)	6 (6.2%)	1 (1.0%)	0	0	3 (3.1%)	9 (9.3%)
Migraine	5 (5.2%)	5 (5.2%)	0	0	0	2 (2.1%)	7 (7.2%)
Seizure	0	0	0	0	0	3 (3.1%)	3 (3.1%)
Peripheral motor neuropathy	1 (1.0%)	1 (1.0%)	0	0	0	1 (1.0%)	2 (2.1%)
Syncope	0	0	0	0	0	2 (2.1%)	2 (2.1%)
Dizziness	1 (1.0%)	1 (1.0%)	0	0	0	0	1 (1.0%)

Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator.
Note: Medical history is reported using MedDRA version 23.0.
[TSIMH02PART3OF3.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TSIMH02.SAS] 23OCT2020, 13:24

Prior therapy

To be eligible for this study, subjects must have received at least 3 prior multiple myeloma treatment lines of therapy or have been double refractory to an IMiD and PI as defined by the IMWG consensus criteria.

All subjects (100%) received at least 3 prior lines of multiple myeloma therapy, median of 6 prior lines (range: 3-18). A majority (49 subjects [50.5%]) received 5 or more. Seventeen subjects (17.5%) received exactly 3 prior lines of therapy.

- All subjects (100%) received prior PI, IMiD, corticosteroids, and anti-CD38 antibody therapy.
- Eighty-one subjects (83.5%) were penta-exposed (received prior treatment with at least 2 PIs, at least 2 IMiDs, and at least 1 anti-CD38 antibody).
- Eighty-seven (89.7%) subjects received one or more autologous stem cell transplantation (ASCT) and 8 subjects (8.2%) received allogenic transplantation.

Note that eligibility for a subsequent ASCT was not collected in this study.

The most commonly reported (≥20% of subjects) prior systemic therapies for multiple myeloma included the following:

- Antineoplastic agents
  - Daratumumab: 94 subjects (96.9%),
  - Bortezomib: 92 subjects (94.8%),
  - Carfilzomib: 83 subjects (85.6%),
  - Melphalan: 80 subjects (82.5%),
  - Cyclophosphamide: 63 subjects (64.9%),
  - Ixazomib: 29 subjects (29.9%),

- Etoposide: 28 subjects (28.9%),
- Doxorubicin: 27 subjects (27.8%),
- Cisplatin: 24 subjects (24.7%),
- Elotuzumab: 23 subjects (23.7%),

- Corticosteroids for systemic use
  - Dexamethasone: 97 subjects (100%)
- Immunomodulatory drugs (IMiDs)
  - Lenalidomide: 96 subjects (99.0%)
  - Pomalidomide: 89 subjects (91.8%)
  - Thalidomide: 21 subjects (21.6%)

Ninety-six subjects (99.0%) were refractory to their last line of prior therapy. Eighty-five subjects (87.6%) were refractory to the 3 major classes of therapeutic agents for multiple myeloma (PI, IMiD, and anti-CD38 monoclonal antibody therapy), referred to as "triple-refractory." Forty-one subjects (42.3%) were refractory to 5 or more agents (including at least 2 PIs, at least 2 IMiDs, and at least 1 anti-CD38 antibody therapy), referred to as "penta-refractory."

Table 12. Summary of Refractory Status to Prior Multiple Myeloma Therapy; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Refractory at any point to prior therapy	29 (100.0%)	68 (100.0%)	97 (100.0%)
Refractory Status			
PI+IMiD+anti-CD38 antibody	25 (86.2%)	60 (88.2%)	85 (87.6%)
Any PI	25 (86.2%)	62 (91.2%)	87 (89.7%)
Any IMiD	28 (96.6%)	67 (98.5%)	95 (97.9%)
Any anti-CD38 antibody	29 (100.0%)	67 (98.5%)	96 (99.0%)
At least 2 PIs + at least 2 IMiDs + 1 anti-CD38 antibody	9 (31.0%)	32 (47.1%)	41 (42.3%)
Refractory to last line of prior therapy	28 (96.6%)	68 (100.0%)	96 (99.0%)
Refractory to			
Bortezomib	15 (51.7%)	51 (75.0%)	66 (68.0%)
Carfilzomib	21 (72.4%)	42 (61.8%)	63 (64.9%)
Ixazomib	7 (24.1%)	20 (29.4%)	27 (27.8%)
Lenalidomide	22 (75.9%)	57 (83.8%)	79 (81.4%)
Pomalidomide	22 (75.9%)	59 (86.8%)	81 (83.5%)
Thalidomide	1 (3.4%)	7 (10.3%)	8 (8.2%)
Daratumumab	27 (93.1%)	67 (98.5%)	94 (96.9%)[b]
Isatuximab	2 (6.9%)	5 (7.4%)	7 (7.2%)
TAK-079[a]	1 (3.4%)	0	1 (1.0%)
Elotuzumab	1 (3.4%)	18 (26.5%)	19 (19.6%)
Panobinostat	3 (10.3%)	5 (7.4%)	8 (8.2%)

Key: IMiD = Immunomodulatory agent; PI = proteasome inhibitor.
[a] TAK-079 is an investigational anti-CD38 antibody.
[b] Two additional subjects were refractory to other anti-CD38 antibodies
Note: Refractory to each medication refers to refractory to any medication-containing line.
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator.
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Bridging Therapy

Bridging therapy was administered for 73 subjects (75.3%) between the time of apheresis and the first

dose of the conditioning regimen. Proteasome inhibitors were used in 44 subjects (45.4%), IMiDs in 26 subjects (26.8%) and Anti-CD38 antibodies in 15 subjects (15.5%). The most common agents used as bridging therapies (≥20% of subjects in the All Treated population) included:

- Dexamethasone: 62 subjects (63.9%),
- Bortezomib: 26 subjects (26.8%),
- Cyclophosphamide: 22 subjects (22.7%), and
- Pomalidomide: 21 subjects (21.6%).

Among the 73 patients received any bridging therapy, 33 subjects (45.2%) had a transient decrease in tumour burden (defined as change in serum M-protein, urine M-protein, or difference between involved and uninvolved free light chain [dFLC]) between screening and cilta-cel infusion. Among those subjects who experienced a tumour burden decrease, 15 subjects (20.5%) experienced a decrease of >50%. However, despite the decrease in tumour burden in some subjects, no subjects achieved CR while on bridging therapy.

Thirty-six of the subjects (49.3%) who received bridging therapy experienced an increase in tumour burden with 25 subjects (34.2%) experiencing an increase ≥25%. Two of the subjects (2.7%) who received bridging therapy did not experience a change in tumour burden as a result of bridging therapy any and additional 2 subjects (2.7%) were not evaluable for assessment of change in tumour burden.

Thirty-seven subjects (38.1%) experienced adverse events related to bridging therapy with 31 subjects (32.0%) experiencing Grade 3 or 4 adverse events.

Apheresis

Out of 143 subjects consented, 113 completed apheresis and were thus considered enrolled into the study. One hundred nine subjects (96.5%) required a single apheresis attempt to meet the collection target (6 x 10^9 PBMC). Three subjects (2.7%) required 2 apheresis attempts and 1 subject (0.9%) required 3 attempts at apheresis. The median duration of apheresis was 239 minutes (range: 127 to 378 minutes), with a median of 185.5 mL collected (range 80 to 349 mL).

Exposure to Study Treatment

Cyclophosphamide and Fludarabine Conditioning

Prior to cilta-cel infusion, subjects were to receive a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and IV fludarabine 30 mg/m^2 in 3 daily doses beginning on Day -7 to Day -5. The median cumulative dose of cyclophosphamide infusion was 897.8 mg/m2 (range; 748 to 946 mg/m^2). The median cumulative dose of fludarabine infusion was 89.6 mg/m^2 (range; 45 to 95 mg/m2).

Table 13. Summary of Conditioning Regimen Infusions; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Cumulative dose of cyclophosphamide infusion (mg/m^2)			
N	29	68	97
Mean (SD)	894.3 (20.69)	889.7 (25.44)	891.1 (24.10)
Median	900.0	894.3	897.8
Range	(825; 943)	(748; 946)	(748; 946)
Cumulative dose of fludarabine infusion (mg/m^2)			
N	29	68	97
Mean (SD)	89.7 (1.50)	87.9 (6.46)	88.4 (5.52)
Median	90.0	89.1	89.6
Range	(84; 93)	(45; 95)	(45; 95)

Note: Cumulative dose over the 3-day conditioning regimen administration is presented.

[TSIEX02.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TSIEX02.SAS] 23OCT2020, 13:22

Cilta-cel Infusion

Cilta-cel infusion occurred on Day 1, which was 5 to 7 days after the start of the conditioning regimen. The median time from initial apheresis to cilta-cel infusion was 47 days (range: 41 to 167 days). Receipt to release (R2R) is calculated from the day after the receipt of leukapheresis material at the manufacturing facility up to, and inclusive of the day on which the CAR-T product is released for shipment to the clinical trial site. R2R for cilta-cel is a median 29 days (range: 23-64 days). The median total number of CAR-positive viable T cells infused was 54.30 x 10^6 (range: 23.5 x 10^6 to 93.1 x 10^6 cells) with a median of 0.709 x10^6 cells/kg administered (range: 0.51 x 10^6 to 0.95 x10^6 cells/kg). The median duration of cilta-cel infusion was 19.0 minutes (range: 5 to 71 minutes).

Table 14. Summary of JNJ-68284528 Infusion; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Time from initial apheresis to JNJ-68284528 Infusion (days)			
N	29	68	97
Mean (SD)	52.2 (17.74)	52.3 (19.74)	52.2 (19.07)
Median	44.0	47.0	47.0
Range	(42; 120)	(41; 167)	(41; 167)
Interquartile range	(43.0; 49.0)	(43.0; 51.0)	(43.0; 51.0)
Time from apheresis to JNJ-68284528 Infusion (days)[a]			
N	29	68	97
Mean (SD)	49.0 (15.00)	52.3 (19.74)	51.3 (18.44)
Median	44.0	47.0	46.0
Range	(41; 120)	(41; 167)	(41; 167)
Interquartile range	(43.0; 47.0)	(43.0; 51.0)	(43.0; 50.0)
≤ 46 days	18 (62.1%)	31 (45.6%)	49 (50.5%)
Duration of JNJ-68284528 infusion (minutes)			
N	29	68	97
Mean (SD)	21.2 (6.29)	20.3 (11.86)	20.6 (10.48)
Median	20.0	17.0	19.0
Range	(14; 38)	(5; 71)	(5; 71)
Total volume infused (mL)			
N	29	68	97
Mean (SD)	66.6 (10.45)	69.1 (16.28)	68.4 (14.77)
Median	70.0	70.0	70.0
Range	(30; 70)	(30; 140)	(30; 140)
Total CAR-positive viable T cells infused (x10E6 cells)			
N	29	68	97
Mean (SD)	59.81 (13.409)	54.69 (13.696)	56.22 (13.744)
Median	59.00	51.45	54.30
Range	(35.7; 82.0)	(23.5; 93.1)	(23.5; 93.1)
JNJ-68284528 dose formulated (x10E6 cells/kg) [b]			
N	29	68	97
Mean (SD)	0.698 (0.0844)	0.694 (0.0821)	0.695 (0.0823)
Median	0.709	0.687	0.693
Range	(0.54; 0.88)	(0.52; 0.94)	(0.52; 0.94)
Interquartile range	(0.673; 0.754)	(0.642; 0.745)	(0.648; 0.747)
JNJ-68284528 dose administered (x10E6 cells/kg) [c]			
N	29	68	97
Mean (SD)	0.710 (0.0877)	0.710 (0.0904)	0.710 (0.0892)
Median	0.722	0.707	0.709
Range	(0.52; 0.89)	(0.51; 0.95)	(0.51; 0.95)

[a] The apheresis that resulted in complete manufacturing of JNJ-68284528 is used if there are multiple apheresis attempts.
[b] CAR-positive viable T cells adjusted by weight at apheresis.
[c] CAR-positive viable T cells adjusted by weight at JNJ-68284528 infusion (on or within 1 day prior to JNJ-68284528 infusion day).
Note: Duration of infusion includes both actual infusion time and interruption time, if any.
Modified from: [TSIEX03.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TSIEX03.SAS] 23OCT2020, 13:22

- **Numbers analysed**

A total of 113 subjects, 35 in Phase 1b and 78 in Phase 2, were enrolled and underwent apheresis. A majority of enrolled subjects (97 subjects; 85.8%) were able to receive a cilta-cel infusion. Note that as all 97 treated subjects received the RP2D, the all-treated analysis set is equivalent to the modified

Intent-to-Treat Analysis set. This analysis set was the primary population used for safety and efficacy analyses.

Table 15. Number of Subjects in Each Analysis Set; All Consented Subjects (Study 68284528MMY2001)

Analysis set	Phase 1b	Phase 2	Phase 1b + Phase 2
All consented [a]	40	103	143
All enrolled [b]	35	78	113
All treated [c]	29	68	97
Modified intent-to-treat (mITT)[d]	29	68	97
Pharmacokinetic [e]	29	68	97
Immunogenicity [f]	29	68	97

[a] Includes subjects who have signed informed consent form.
[b] Includes subjects who underwent apheresis.
[c] Includes subjects who received a JNJ-68284528 infusion.
[d] Includes subjects who received a JNJ-68284528 infusion at the targeted recommended phase 2 dose (RP2D) level.
[e] Includes subjects who received a JNJ-68284528 infusion and have at least 1 post-baseline pharmacokinetic sample value.
[f] Includes subjects who received a JNJ-68284528 infusion and have at least 1 post-baseline immunogenicity sample value.
[TSIDEM02.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TSIDEM02.SAS] 23OCT2020, 13:20

Twelve subjects (10.6%) discontinued between apheresis and the start of conditioning regimen; 8 subjects (7.1%) discontinued due to death, 2 subjects (1.8%) due to PD and 2 subjects (1.8%) due to withdrawal of consent. Four subjects (3.5%) received conditioning regimen but did not receive JNJ-68284528 infusion. Two of them refused future study treatment, one withdrew due to adverse event and one died. No subjects discontinued due to manufacturing failure.

- **Outcomes and estimation**

Efficacy results are presented using a data cutoff date of 1 September 2020, which corresponds to a time point 6 months after the last subject received his or her initial dose of cilta-cel. At the time of clinical cut-off, the median duration of follow-up for all subjects was 12.42 months. Additional key efficacy data with a longer follow-up using a data cutoff of 11 February 2021 was submitted as a separate document. As of the 11 February 2021 cut-off, the median duration of follow-up was 18.0 months.

Primary efficacy endpoint

Overall Response Rate

The ORR (PR or better) as assessed by the IRC based on IMWG Criteria was:

- All Treated population (n=97): 96.9% (95% CI: 91.2% to 99.4%)
- All Enrolled population (n=113): 83.2% (95% CI: 75.0% to 89.6%) (Tables below).

Table 16. Overall Best Response Based on Independent Review Committee (IRC) Assessment; <u>All Treated Analysis Set</u> (Study 68284528MMY2001) (data cut off 1 September 2020)

	Phase 1b		Phase 2		Phase 1b + Phase 2	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: all treated	29		68		97	
Best response						
Stringent complete response (sCR)	25 (86.2%)	(68.3%, 96.1%)	40 (58.8%)	(46.2%, 70.6%)	65 (67.0%)	(56.7%, 76.2%)
Complete response (CR)	0	(NE, NE)	0	(NE, NE)	0	(NE, NE)
MRD-negative CR/sCR [a]	14 (48.3%)	(29.4%, 67.5%)	19 (27.9%)	(17.7%, 40.1%)	33 (34.0%)	(24.7%, 44.3%)
Very good partial response (VGPR)	3 (10.3%)	(2.2%, 27.4%)	22 (32.4%)	(21.5%, 44.8%)	25 (25.8%)	(17.4%, 35.7%)
Partial response (PR)	1 (3.4%)	(0.1%, 17.8%)	3 (4.4%)	(0.9%, 12.4%)	4 (4.1%)	(1.1%, 10.2%)
Minimal response (MR)	0	(NE, NE)	0	(NE, NE)	0	(NE, NE)
Stable disease (SD)	0	(NE, NE)	0	(NE, NE)	0	(NE, NE)
Progressive disease (PD)	0	(NE, NE)	1 (1.5%)	(0.0%, 7.9%)	1 (1.0%)	(0.0%, 5.6%)
Not evaluable (NE)	0	(NE, NE)	2 (2.9%)	(0.4%, 10.2%)	2 (2.1%)	(0.3%, 7.3%)
Overall response (sCR + CR + VGPR + PR)	29 (100.0%)	(88.1%, 100.0%)	65 (95.6%)	(87.6%, 99.1%)	94 (96.9%)	(91.2%, 99.4%)
P-value					<0.0001	
Clinical benefit (Overall response + MR)	29 (100.0%)	(88.1%, 100.0%)	65 (95.6%)	(87.6%, 99.1%)	94 (96.9%)	(91.2%, 99.4%)
VGPR or better (sCR + CR + VGPR)	28 (96.6%)	(82.2%, 99.9%)	62 (91.2%)	(81.8%, 96.7%)	90 (92.8%)	(85.7%, 97.0%)
CR or better (sCR + CR)	25 (86.2%)	(68.3%, 96.1%)	40 (58.8%)	(46.2%, 70.6%)	65 (67.0%)	(56.7%, 76.2%)

Keys: CI = confidence interval.
[a] MRD-negative CR/sCR. Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death / progression / subsequent therapy (exclusive) are considered.
Note: Response was assessed by independent review committee (IRC), based on International Myeloma Working Group (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.
Note: One-sided p-value from exact binomial test for the null hypothesis of overall response rate ≤30% is presented.
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A sensitivity analysis of ORR in the All Treated population was conducted via computerised algorithm that combined all pertinent laboratory results and the results of imaging, as assessed by the investigator, for each patient and derived the outcome in accordance with IMWG Criteria (Palumbo 2016). Assessment by computerised algorithm demonstrated an ORR of 92.8% (95% CI: 85.7% to 97.0%). This assessment demonstrates a high degree of concordance between the IRC assessment and assessment by computerised algorithm, as indicated by Prevalence Adjusted and Bias Adjusted Kappa (PABAK)=0.92 (95% CI: 0.84 to 1.00) and observed agreement of 95.9%.

A sensitivity analysis of ORR was conducted based upon investigator assessment demonstrating an ORR of 96.9% (95% CI: 91.2% to 99.4%). This is consistent with the primary analysis using IRC assessment according to IMWG response criteria.

<u>At the 11 February 2021 data cutoff date</u> treatment of these subjects with cilta-cel resulted in an overall response rate (ORR) of 97.9% with 95 of 97 subjects in the All-treated analysis set achieving a partial response (PR) or better as assessed by Independent Review Committee (IRC) (based on International Myeloma Working Group [IMWG] criteria). Notably, the stringent complete response (sCR) rate was 80.4%. The ORR for the 113 subjects in the All Enrolled analysis set (includes 16 subjects who did not receive a cilta-cel infusion) was 84.1%, with a sCR rate of 69.0%.

Table 17. Overall Best Response Based on Independent Review Committee (IRC) Assessment; All Treated Analysis Set cutoff 1 February 2021 (Study 68284528MMY2001)

	Phase 1b + Phase 2	
	n (%)	95% CI for %
Analysis set: all treated	97	
Best response		
Stringent complete response (sCR)	78 (80.4%)	(71.1%, 87.8%)
Complete response (CR)	0	(NE, NE)
MRD-negative CR/sCR[a]	42 (43.3%)	(33.3%, 53.7%)
Very good partial response (VGPR)	14 (14.4%)	(8.1%, 23.0%)
Partial response (PR)	3 (3.1%)	(0.6%, 8.8%)
Minimal response (MR)	0	(NE, NE)
Stable disease (SD)	0	(NE, NE)
Progressive disease (PD)	1 (1.0%)	(0.0%, 5.6%)
Not evaluable (NE)	1 (1.0%)	(0.0%, 5.6%)
Overall response (sCR + CR + VGPR + PR)	95 (97.9%)	(92.7%, 99.7%)
P-value	<0.0001	
Clinical benefit (Overall response + MR)	95 (97.9%)	(92.7%, 99.7%)
VGPR or better (sCR + CR + VGPR)	92 (94.8%)	(88.4%, 98.3%)
CR or better (sCR + CR)	78 (80.4%)	(71.1%, 87.8%)

Keys: CI = confidence interval.
[a] MRD-negative CR/sCR. Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death / progression / subsequent therapy (exclusive) are considered.
Note: Response was assessed by independent review committee (IRC), based on International Myeloma Working Group (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.
Note: One-sided p-value from exact binomial test for the null hypothesis of overall response rate ≤30% is presented.
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Cross reference: Mod2.7.3Update/Tab1

Table 18. Overall Best Response Based on Independent Review Committee (IRC) Assessment; All Enrolled Analysis Set cutoff 1 February 2021 (Study 68284528MMY2001)

	Phase 1b + Phase 2	
	n (%)	95% CI for %
Analysis set: all enrolled	113	
Best response		
Stringent complete response (sCR)	78 (69.0%)	(59.6%, 77.4%)
Complete response (CR)	0	(NE, NE)
MRD-negative CR/sCR [a]	42 (37.2%)	(28.3%, 46.8%)
Very good partial response (VGPR)	14 (12.4%)	(6.9%, 19.9%)
Partial response (PR)	3 (2.7%)	(0.6%, 7.6%)
Minimal response (MR)	0	(NE, NE)
Stable disease (SD)	0	(NE, NE)
Progressive disease (PD)	1 (0.9%)	(0.0%, 4.8%)
Not evaluable (NE)	17 (15.0%)	(9.0%, 23.0%)
Did not received JNJ-68284528	16	
Overall response (sCR + CR + VGPR + PR)	95 (84.1%)	(76.0%, 90.3%)
Clinical benefit (Overall response + MR)	95 (84.1%)	(76.0%, 90.3%)
VGPR or better (sCR + CR + VGPR)	92 (81.4%)	(73.0%, 88.1%)
CR or better (sCR + CR)	78 (69.0%)	(59.6%, 77.4%)

Keys: CI = confidence interval.
[a] MRD-negative CR/sCR. Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death / progression / subsequent therapy (exclusive) are considered.
Note: Response was assessed by independent review committee (IRC), based on International Myeloma Working Group (IMWG) consensus criteria (2016).
Note: Percentages are calculated with the number of subjects in the all enrolled analysis set as denominator.
Note: Exact 95% confidence intervals are provided.
Modified from :[TEFRESP01A1.RTF] [JNJ-68284528\MMY2001\DBR_4MSU\RE_EFU\PROD\TEFRESP01A1.SAS] 06APR2021, 18:41
Cross reference: Mod5.3.5.2/68284528MMY2001Update/Tab11

Major Secondary Analyses

VGPR or Better Rate

Very good partial response (VGPR) or better rate was defined as the proportion of subjects who achieved a sCR, CR, or VGPR according to IMWG response criteria.

The overall response of VGPR or better as assessed by the IRC was:

- All Treated population (n=97): 92.8% (95% CI: 85.7% to 97.0%)
- All Enrolled population (n=113): 79.6% (95% CI: 71.0% to 86.6%)

Duration of Response

Duration of response (DOR) will 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 PD, as defined in the IMWG Criteria. Most responders' DOR data (74.5% of subjects with PR or better) was censored at the time of clinical cut off, which resulted in a median DOR not reached based on IRC review.

Table 19. Duration of Response Based on Independent Review Committee (IRC) Assessment; Responders in All Treated Analysis Set (Study 68284528MMY2001) (data cut of 1 September 2020)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: responders in all treated	29	65	94
Duration of response			
Number of events (%)	9 (31.0%)	15 (23.1%)	24 (25.5%)
Number of censored (%)	20 (69.0%)	50 (76.9%)	70 (74.5%)
Kaplan-Meier estimate (months)			
25% quantile (95% CI)	12.0 (6.0, NE)	10.3 (4.5, NE)	11.1 (6.0, NE)
Median (95% CI)	NE (15.9, NE)	NE (NE, NE)	NE (15.9, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
6-month event-free rate % (95% CI)	93.1 (75.1, 98.2)	80.7 (68.5, 88.5)	84.6 (75.4, 90.6)
9-month event-free rate % (95% CI)	86.2 (67.3, 94.6)	77.4 (64.8, 85.9)	80.2 (70.4, 87.0)
12-month event-free rate % (95% CI)	72.1 (51.8, 85.0)	71.9 (54.8, 83.4)	68.2 (54.4, 78.6)

Key: CI = confidence interval; NE = not estimable.

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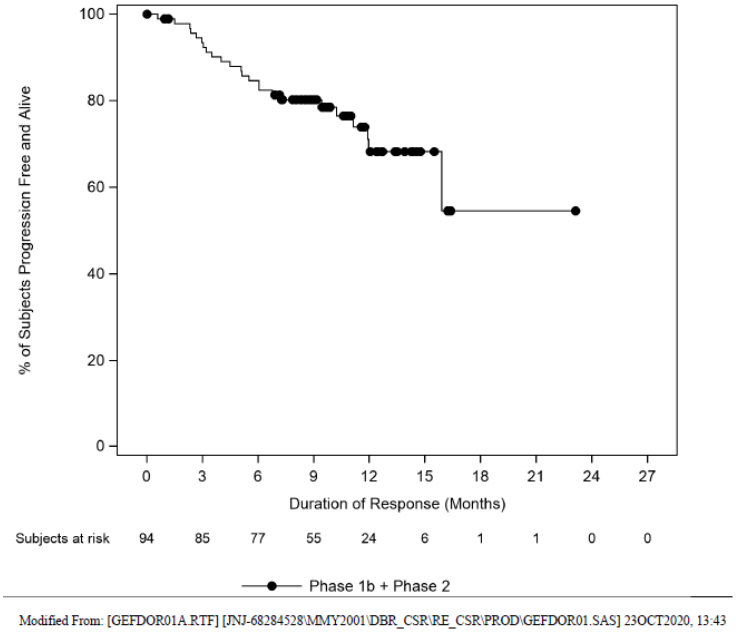
Figure 14. Kaplan-Meier Plot for Duration of Response Based on Independent Review Committee (IRC) Assessment; Responders in All Treated Analysis Set (Study 68284528MMY2001) (data cut off 1 September 2020)



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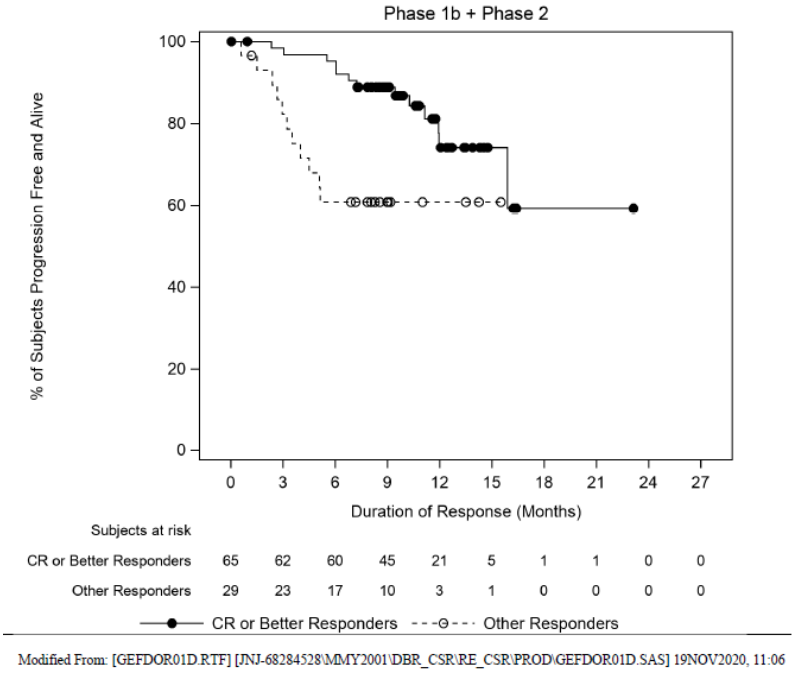
Assessment of DOR based on IRC assessment of best response achieved is presented graphically in Figure 15 below. DOR for those with CR or better as the best response appears to be longer compared to those subjects with PR/VGPR as the best response, although neither group reached median duration of response (mDOR) at the time of data cut off.

Figure 15. Kaplan-Meier Plot for Duration of Response Based on Independent Review Committee (IRC) Assessment: Responders Achieving Complete Response (CR) Versus Other Responders; Responders in All Treated Analysis Set (Study 68284528MMY2001) (data cut off 1 September 2020)



At the 11 February 2021 data cutoff date deep and durable responses were induced by cilta-cel as demonstrated by a very good partial response (VGPR) or better rate of 94.8% in the All-treated analysis set. Seventy-eight subjects (80.4%) achieved a sCR. At a median follow-up of 18.0 months, median duration of response (DOR) was 21.8 months (95% CI: 21.8 months, not estimable [NE]) at the time of the clinical cutoff. The probabilities of the responders remaining in response at 9 months and 12 months were 79.7% (95% CI: 70.0%, 86.5%) and 72.9% (95% CI: 62.6%, 80.9%), respectively. The median DOR for subjects achieving CR/sCR has not yet reached.

MRD Negativity Rate

Subjects were (or will be) assessed for MRD negativity by next-generation sequencing (NGS) (clonoSEQ version 2.0) at baseline, 28 days, 6 months, 12 months, 18 months, and 24 months post cilta-cel infusion and for subjects with suspected CR at the time of CR and then yearly for subjects that remain on study up to disease progression. At the time of clinical cutoff (1 September 2020), 95 subjects (97.9%) had bone marrow samples available for MRD evaluation. However, not all baseline samples were evaluable. Identification of the clone at the baseline sample failed in 25 subjects (26.3%) and samples from 2 subjects had an unsuccessful assay run.

Fifty-three subjects (54.6%) achieved MRD negativity at the 10^{-5} threshold of sensitivity with 33 subjects (34.0%) also achieving CR/sCR. Note that for MRD negative CR/sCR, only MRD assessments (10 -5 testing threshold) within 3 months of achieving CR/sCR until death, progression, or subsequent therapy (exclusive) are considered.

At the 11 February 2021 data cutoff date, 96 subjects (99.0%) had samples available for MRD evaluation (baseline and post-baseline sample). Of the 61 subjects with evaluable samples (ie, subjects with identifiable clone at baseline and had sufficient cells to be tested at sensitivity level of 10^{-5} in post treatment samples), 56 (91.8%) achieved MRD negativity in bone marrow at a sensitivity level of 10^{-5}. Among the 78 subjects who achieved sCR/CR, 47 subjects have evaluable samples. Of

these 47 subjects, 42 (89.4%) achieved MRD negativity at a sensitivity level of 10^{-5}. In the context of the all treated set MRD negativity Rate is 57.7% (N=56; 95% CI: (47.3, 67.7)) with MRD MRD negative patients with sCR of 43.3% N=42; 95% CI: 33.3, 53.7) and in the context of all Leukapheresed the MRD negativity Rate is 49.6% (N= 56; 95% CI: 40.0, 59.1) and the MRD negative patients with sCR is 37.2% (N=42; 95% CI: 28.3, 46.8.

Time to Response

Table 20. Descriptive Summaries for Time to Response Based on Independent Review Committee (IRC) Assessment; Responders in All Treated Analysis Set (Study 68284528MMY2001) (data cut off 1 September 2020)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: responders in all treated	29	65	94
Time to first response[a] (months)			
N	29	65	94
Mean (SD)	1.14 (0.455)	1.39 (1.425)	1.32 (1.214)
Median	0.95	0.95	0.95
Range	(0.9; 2.8)	(0.9; 8.5)	(0.9; 8.5)
Time to best response (months)			
N	29	65	94
Mean (SD)	4.12 (3.712)	3.52 (2.863)	3.70 (3.142)
Median	2.60	2.56	2.56
Range	(0.9; 14.5)	(0.9; 10.6)	(0.9; 14.5)
	Phase 1b	Phase 2	Phase 1b + Phase 2
Time to CR or better (months)			
N	25	40	65
Mean (SD)	4.09 (3.893)	3.66 (3.294)	3.83 (3.512)
Median	2.56	1.84	1.87
Range	(0.9; 14.5)	(0.9; 10.6)	(0.9; 14.5)

Key: CR = complete response.
[a] Response PR or better.

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At the 11 February 2021 data cutoff date, the median time to response was rapid, occurring after 1 month of treatment. The median time to first response was 0.95 months (range: 0.9 to 10.7 months), median time to best response was 2.6 months (range: 0.9 to 15.2 months), and median time to CR or better was 2.63 months (range:0.9 to 15.2 months).

Progression-free Survival

In the all-treated population, 74.2% of subjects' PFS data was censored at the clinical cut off (1 September 2020), which resulted in a median PFS not reached for assessment based on IRC review. As of clinical cut off the 12-month PFS rates are as follows:

- All Treated population (n=97): 76.6% (95% CI: 66.0% to 84.3%)
- All Enrolled population (n=113): 70.7% (95% CI: 60.9% to 78.5%).

Table 21. Progression-Free Survival Based on Independent Review Committee (IRC) Assessment; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Progression-free survival			
Number of events (%)	9 (31.0%)	16 (23.5%)	25 (25.8%)
Number of censored (%)	20 (69.0%)	52 (76.5%)	72 (74.2%)
Kaplan-Meier estimate (months)			
25% quantile (95% CI)	13.73 (6.93, NE)	11.17 (5.42, NE)	12.02 (6.97, NE)
Median (95% CI)	NE (16.79, NE)	NE (NE, NE)	NE (16.79, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
6-month progression-free survival rate % (95% CI)	93.1 (75.1, 98.2)	85.3 (74.4, 91.8)	87.6 (79.2, 92.8)
9-month progression-free survival rate % (95% CI)	86.2 (67.3, 94.6)	77.8 (65.9, 86.0)	80.3 (70.9, 87.0)
12-month progression-free survival rate % (95% CI)	82.8 (63.4, 92.4)	72.6 (56.5, 83.6)	76.6 (66.0, 84.3)
18-month progression-free survival rate % (95% CI)	57.7 (25.9, 79.9)	NE (NE, NE)	54.2 (26.4, 75.4)

Key: CI = confidence interval; NE = not estimable.

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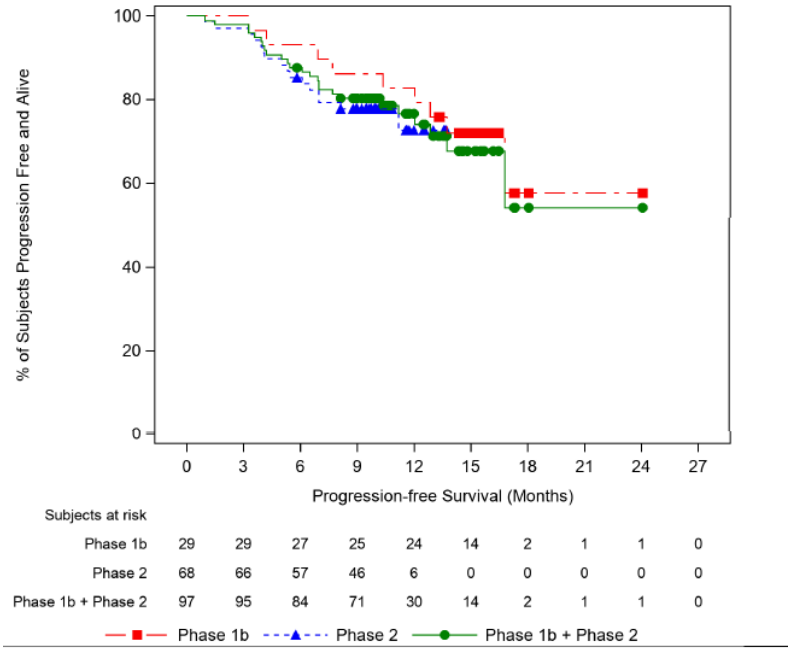
Figure 16. Kaplan-Meier Plot for Progression-Free Survival Based on Independent Review Committee (IRC) Assessment; All Treated Analysis Set (Study 68284528MMY2001)



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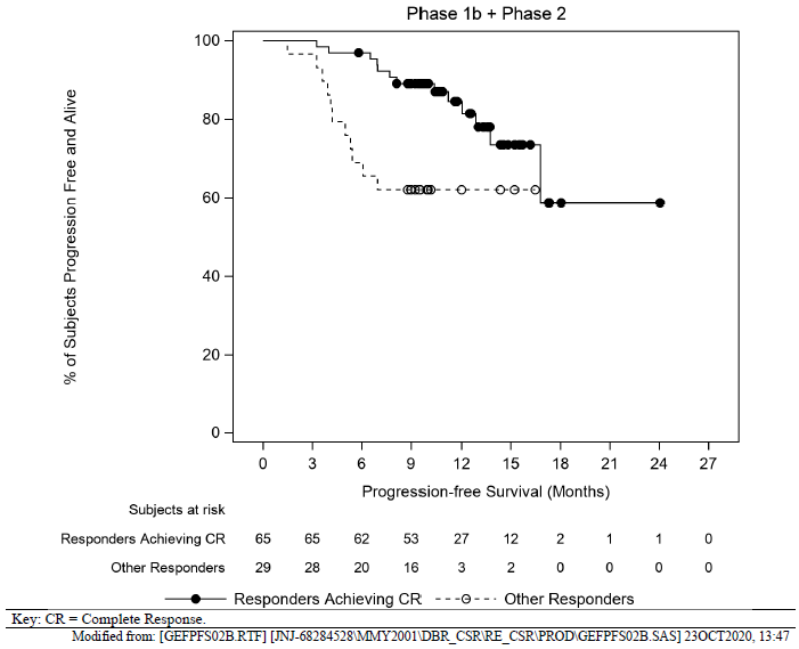
Seventeen subjects (17.5%) had PD. The most common reason for disease progression was the development/increase in plasmacytomas (8 subjects [47.1%]), the development of new or worsening lytic disease (7 subjects [41.2%]) or an increase in serum or urine paraproteins (7 subjects [41.2%]).

While data continue to mature, available data suggests that there may be a positive association between depth of response and PFS. Participants achieving CR or better had a 6-month PFS rate of 96.9% (95% CI: 88.3 to 99.2) versus 69.0% (95%CI: 48.8 to 82.5) for other responders.

Figure 17. Kaplan-Meier Plot for Progression-Free Survival Based on Independent Review Committee (IRC) Assessment: Responders Achieving Complete Response (CR) Versus Other Responders; Responders in All Treated Analysis Set (Study 68284528MMY2001)



All 72 subjects with data censored for PFS analysis in the All Treated analysis set are due to the timing of the clinical data cut off. No subjects have been lost to follow-up.

At the 11 February 2021 data cutoff date, at a median duration of follow-up of 18.0 months, median progression-free survival (PFS) was 22.8 months (95% CI: 22.8, NE) and the median PFS for subjects who achieved CR/sCR was not yet reached. At 12 months post ciltacel infusion, 76.3% of subjects (95% CI: 66.5% to 83.6%) remained progression free.

Overall Survival

At the time of clinical cut off (1 September 2020), 14 subjects (14.4%) had died in the all-treated population. Overall survival data are yet to be mature enough to provide a reliable estimate for median OS. However, the estimated OS rates at 12 months were:

- All Treated population (n=97): 88.5% (95% CI: 80.2% to 93.5%)

- All Enrolled population (n=113): 81.3% (95% CI: 72.6% to 87.6%).

Table 22. Overall Survival; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Overall survival			
Number of events (%)	5 (17.2%)	9 (13.2%)	14 (14.4%)
Number of censored (%)	24 (82.8%)	59 (86.8%)	83 (85.6%)
Kaplan-Meier estimate (months)			
25% quantile (95% CI)	19.12 (13.73, NE)	NE (NE, NE)	19.12 (19.12, NE)
Median (95% CI)	22.80 (19.12, NE)	NE (NE, NE)	22.80 (19.12, NE)
75% quantile (95% CI)	NE (22.80, NE)	NE (NE, NE)	NE (22.80, NE)
6-month overall survival rate % (95% CI)	96.6 (77.9, 99.5)	92.6 (83.2, 96.9)	93.8 (86.7, 97.2)
9-month overall survival rate % (95% CI)	93.1 (75.1, 98.2)	89.7 (79.5, 94.9)	90.7 (82.8, 95.0)
12-month overall survival rate % (95% CI)	93.1 (75.1, 98.2)	86.5 (75.7, 92.7)	88.5 (80.2, 93.5)
18-month overall survival rate % (95% CI)	89.7 (71.3, 96.5)	NE (NE, NE)	85.8 (75.4, 92.1)

Key: CI = confidence interval; NE = not estimable.

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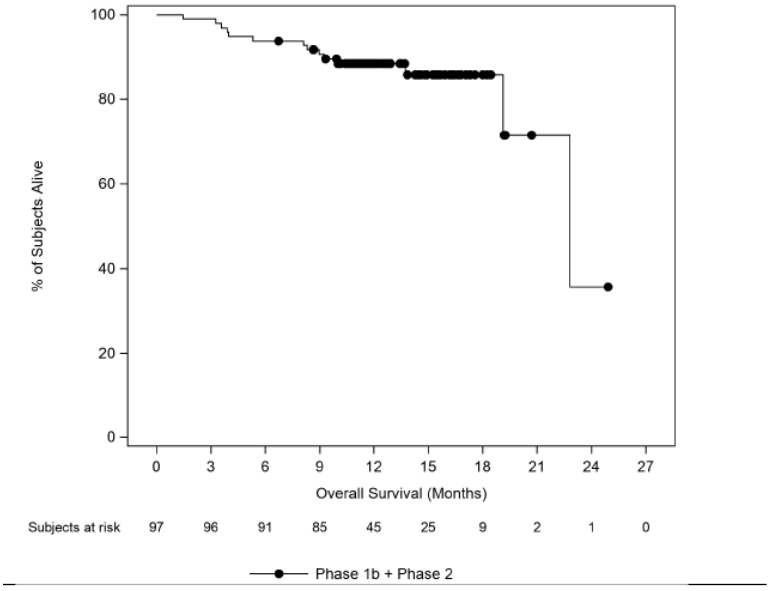
Figure 18. Kaplan-Meier Plot for Overall Survival; All Treated Analysis Set (Study 68284528MMY2001)



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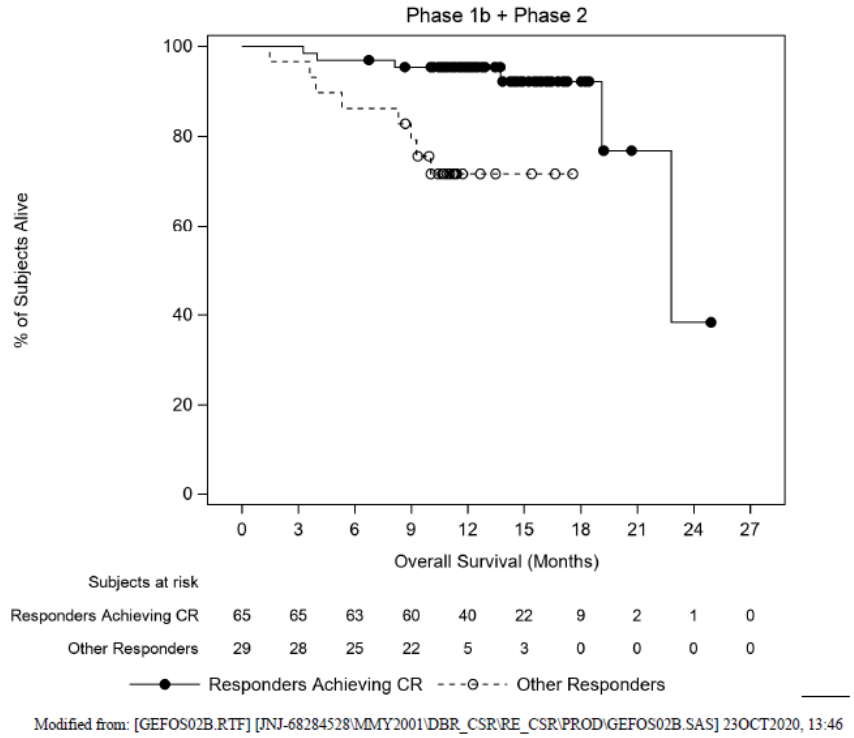
As reported by (Kapoor 2013), depth of response is prognostic of patients' long-term outcome.

Similar trend appears to be true based on limited OS events observed in this study.

Figure 19. Kaplan-Meier Plot for Overall Survival by Response Assessed by Independent Review Committee (IRC): Responders Achieving CR Versus Other Responders; Responders in All Treated Analysis Set (Study 68284528MMY2001).



At the 11 February 2021 data cutoff date, median overall survival (OS) has not been reached. The 12-month OS rate was 87.6% (95% CI: 79.2% to 92.8%). While data continue to mature, available data suggests that there may be a positive association between depth of response and favorable PFS and OS.

Efficacy Following Retreatment

At the time of clinical cut off (1 September 2020), one subject received retreatment with cilta-cel. This subject initially progressed 511 days after the first cilta-cel infusion. The retreated subject developed new and worsening lytic disease and was diagnosed with PD 32 days after retreatment.

Subsequent Anti-myeloma Therapy

Seventeen subjects (17.5%) had PD after cilta-cel infusion. Eleven of these subjects received subsequent anti-myeloma therapy after disease progression.

Table 23. Summary of Subsequent Anti-myeloma Therapies by Preferred ATC Class and Drug; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Subjects with 1 or more subsequent anti-myeloma therapies	5 (17.2%)	6 (8.8%)	11 (11.3%)
Standardized procedure name/Reported procedure name			
Radiotherapy	1 (3.4%)	1 (1.5%)	2 (2.1%)
Radiation therapy	0	1 (1.5%)	1 (1.0%)
Radiotherapy – left leg	1 (3.4%)	0	1 (1.0%)
Preferred ATC class/Drug			
Glucocorticoids	5 (17.2%)	5 (7.4%)	10 (10.3%)
Dexamethasone	5 (17.2%)	5 (7.4%)	10 (10.3%)
Other antineoplastic agents	4 (13.8%)	4 (5.9%)	8 (8.2%)
Selinexor	3 (10.3%)	3 (4.4%)	6 (6.2%)
Carfilzomib	2 (6.9%)	2 (2.9%)	4 (4.1%)
Bortezomib	1 (3.4%)	1 (1.5%)	2 (2.1%)
Nitrogen mustard analogues	4 (13.8%)	3 (4.4%)	7 (7.2%)
Cyclophosphamide	4 (13.8%)	2 (2.9%)	6 (6.2%)
Melphalan	1 (3.4%)	1 (1.5%)	2 (2.1%)
Platinum compounds	3 (10.3%)	2 (2.9%)	5 (5.2%)
Cisplatin	3 (10.3%)	2 (2.9%)	5 (5.2%)
Podophyllotoxin derivatives	3 (10.3%)	2 (2.9%)	5 (5.2%)
Etoposide	3 (10.3%)	2 (2.9%)	5 (5.2%)
Anthracyclines and related substances	2 (6.9%)	1 (1.5%)	3 (3.1%)
Doxorubicin	2 (6.9%)	0	2 (2.1%)
Daunorubicin	0	1 (1.5%)	1 (1.0%)
Other immunosuppressants	2 (6.9%)	1 (1.5%)	3 (3.1%)
Pomalidomide	1 (3.4%)	1 (1.5%)	2 (2.1%)
Thalidomide	1 (3.4%)	0	1 (1.0%)
Monoclonal antibodies	2 (6.9%)	0	2 (2.1%)
Daratumumab	1 (3.4%)	0	1 (1.0%)
Isatuximab	1 (3.4%)	0	1 (1.0%)
Investigational drug	0	1 (1.5%)	1 (1.0%)
Bfcr 4350a	0	1 (1.5%)	1 (1.0%)
Nitrosoureas	1 (3.4%)	0	1 (1.0%)
Carmustine	1 (3.4%)	0	1 (1.0%)
PyrIMiDine analogues	1 (3.4%)	0	1 (1.0%)
Cytarabine	1 (3.4%)	0	1 (1.0%)

Key: ATC = Anatomical therapeutic chemical.
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator.
Note: WHO drug dictionary, 2020-03-01 version.
[TSISAT01.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TSISAT01.SAS] 23OCT2020, 13:24

Health-related Quality of Life

Subjects in the Phase 2 portion of the study completed PRO measures related to their Health-Related Quality of Life (HRQoL). This included assessment of disease-related symptoms, functioning, and general wellbeing using 5 PRO measures: EORTC QLQ-C30, items from the EORTC QLQ-MY20, EQ-5D-5L, Patient Global Impression of Change (PGIC), and the Patient Global Impression of Severity (PGIS). Compliance for the EORTC QLQ-C30 was 92.6% at baseline, 83.1% at Day 100, and declined in the post-treatment, follow-up phase. The rationale for the majority of questionnaires not completed was due to restrictions associated with the COVID-19 pandemic.

EORTC QLQ-C30

Table 24. Meaningful Change (Anchor-Based) in EORTC QLQ-C30 Scales; All Treated Analysis Set (Study 68284528MMY2001)

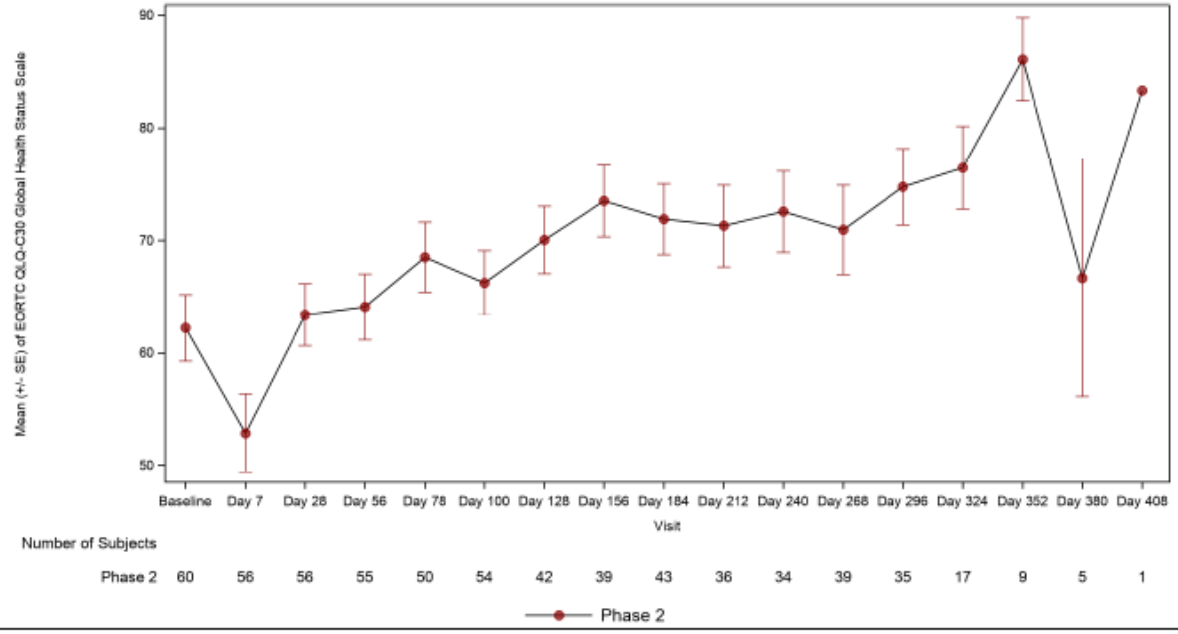
	Phase 2							
	Day 28		Day 56		Day 78		Day 100	
	N	Achieved Meaningful Change, n (%)	N	Achieved Meaningful Change, n (%)	N	Achieved Meaningful Change, n (%)	N	Achieved Meaningful Change, n (%)
Analysis set: all treated	56		55		50		54	
Physical functional scale	56	13 (23.2%)	55	31 (56.4%)	50	28 (56.0%)	52	30 (57.7%)
Global health status scale	56	28 (50.0%)	55	35 (63.6%)	50	33 (66.0%)	54	29 (53.7%)
Pain symptom scales	56	28 (50.0%)	55	22 (40.0%)	50	23 (46.0%)	54	39 (72.2%)
Fatigue symptom scales	56	21 (37.5%)	55	29 (52.7%)	50	32 (64.0%)	52	28 (53.8%)

Key: MID = minimum importance difference.
Note: For anchor-based MID, PGIC is used as an anchor and MID is estimated as the mean change score for the subjects who improved by one point on the PGIC ("A little better now") from prior to JNJ-68284528 infusion to each visit during the post-infusion period.
Note: Percentages are based on the number of subjects with non-missing prior to JNJ-68284528 infusion and post JNJ-68284528 infusion assessment.
[TPROQLQ07C.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TPROQLQ07C.SAS] 23OCT2020, 18:14

Global Health Status (GHS) subscale:

The Phase 2 subjects' assessment of their GHS demonstrated similar results to what was observed clinically; a decrement in health status at Day 7 consistent with the onset of cilta-cel adverse events, followed by improvements starting around Day 28 with overall continued improvement over time.

Figure 20. Mean (+/- SE) of EORTC QLQ-C30 Global Health Status Scale Over Time; All Treated Analysis Set (Study 68284528MMY2001)

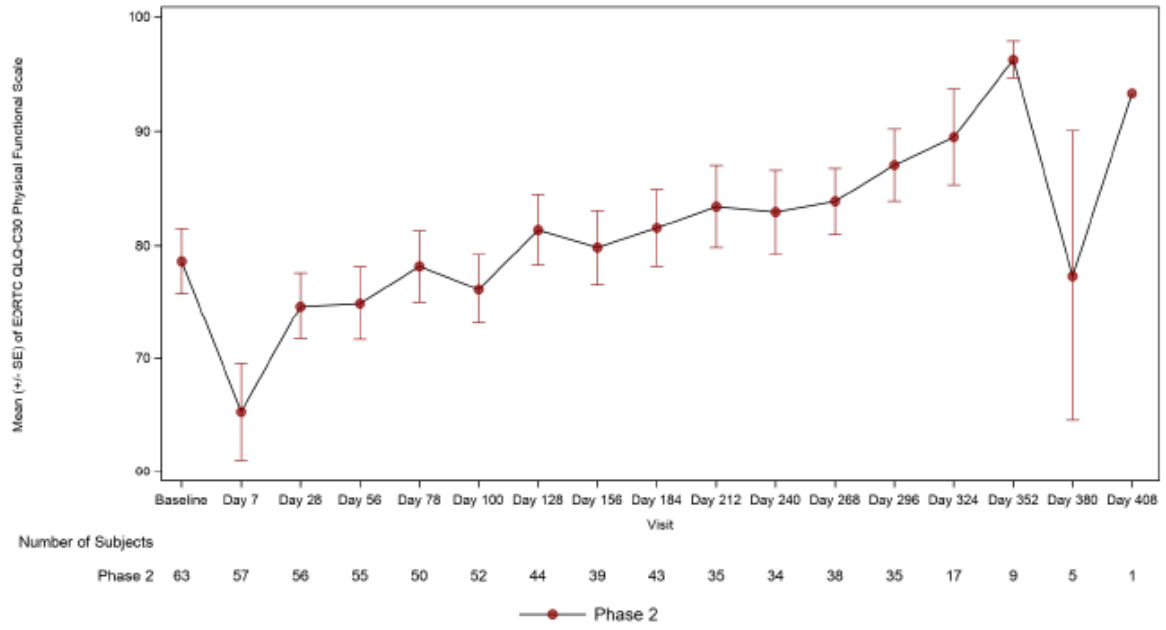


Note: All the scores are presented in the range of 0-100 after linear transformation from raw scores (in the range of 1-4). A higher score indicates better health on the global health and functional scales (physical, role, emotional, cognitive, and social) and greater symptom severity on the symptom scales (fatigue, nausea/vomiting, pain).
[GPROQLQ01A.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\GPROQLQ01A.SAS] 23OCT2020, 15:08

Physical Functional subscale:

Subjects' assessment of their physical function followed a similar trend as GHS. After an initial decline in physical functional scores between Day 1 and Day 7, a steady increase is seen through Day 352.

Figure 21. Mean (+/- SE) of EORTC QLQ-C30 Physical Functional Scale Over Time; All Treated Analysis Set (Study 68284528MMY2001)



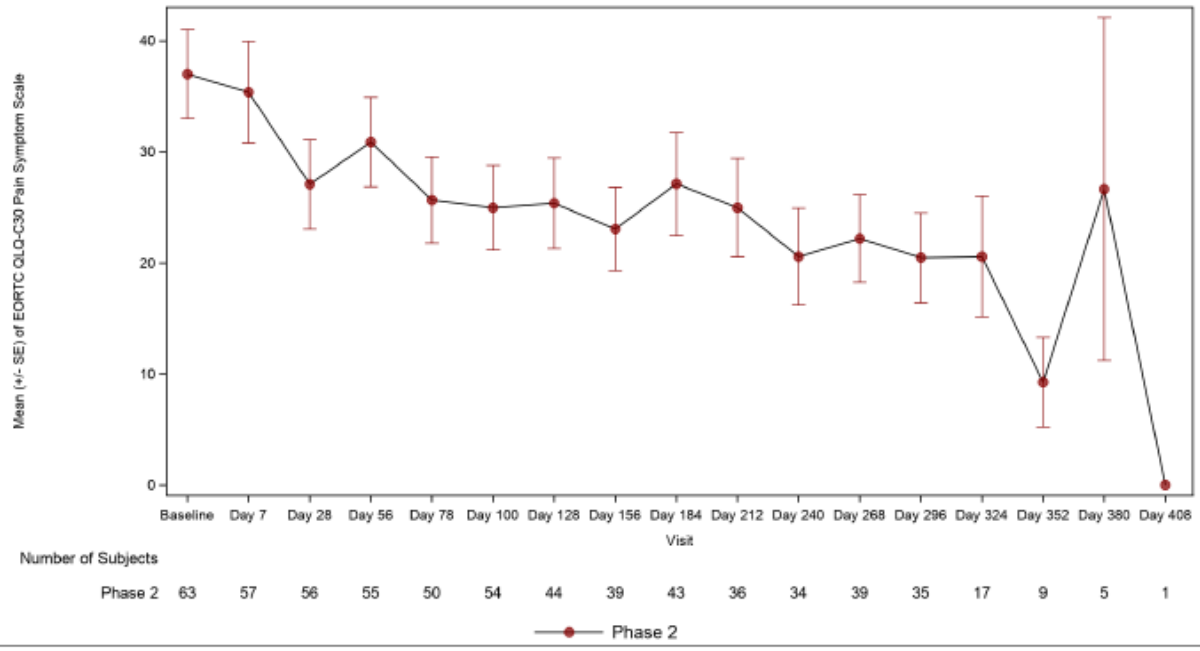
Note: All the scores are presented in the range of 0-100 after linear transformation from raw scores (in the range of 1-4). A higher score indicates better health on the global health and functional scales (physical, role, emotional, cognitive, and social) and greater symptom severity on the symptom scales (fatigue, nausea/vomiting, pain).

[GPROQLQ01B.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\GPROQLQ01B.SAS] 23OCT2020, 15:08

Pain Symptom subscale:

An overall reduction in pain severity was seen beginning at day 7 (LS mean -1.9 [95% CI: -8.5 to -4.6]) and continued to improve through day 352 (LS mean -17.6 [95% CI: -32.6 to -2.6]).

Figure 22. Mean (+/- SE) of EORTC QLQ-C30 Pain Symptom Scale Over Time; All Treated Analysis Set (Study 68284528MMY2001)



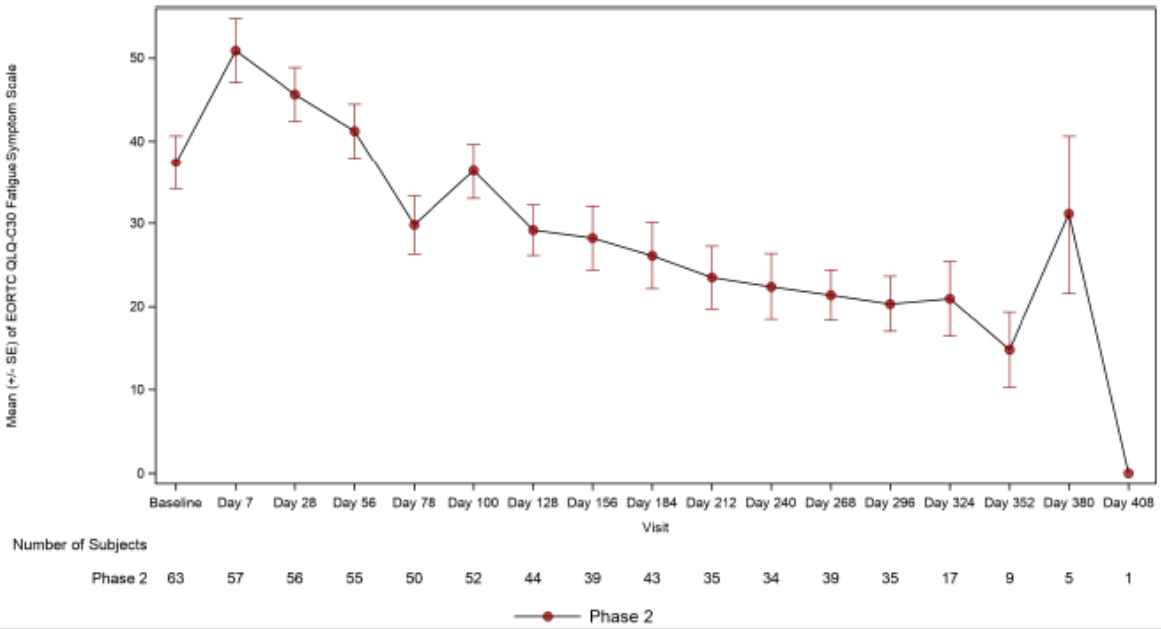
Note: All the scores are presented in the range of 0-100 after linear transformation from raw scores (in the range of 1-4). A higher score indicates better health on the global health and functional scales (physical, role, emotional, cognitive, and social) and greater symptom severity on the symptom scales (fatigue, nausea/vomiting, pain).

[GPROQLQ01G.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\GPROQLQ01G.SAS] 23OCT2020, 15:09

Fatigue Symptom subscale:

After an initial increase in fatigue at day 7 consistent with the onset of cilta-cel related adverse events (LS mean 10.3 [95% CI: 4.6 to 16.1]), an overall reduction in fatigue continued through day 352 (LS mean -15.7 [95% CI: -27.7, -3.7]).

Figure 23. Mean (+/- SE) of EORTC QLQ-C30 Fatigue Symptom Scale Over Time; All Treated Analysis Set (Study 68284528MMY2001)



Note: All the scores are presented in the range of 0-100 after linear transformation from raw scores (in the range of 1-4). A higher score indicates better health on the global health and functional scales (physical, role, emotional, cognitive, and social) and greater symptom severity on the symptom scales (fatigue, nausea/vomiting, pain).

[GPROQLQ01H.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\GPROQLQ01H.SAS] 23OCT2020, 15:09

EORTC QLQ-MY20

Table 25. Meaningful Change (Literature-Based) in EORTC QLQ-MY20 Items and Future Perspective Subscale; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 2									
	Day 7		Day 28		Day 56		Day 78		Day 100	
	N	Achieved Meaningful Change, n (%)	N	Achieved Meaningful Change, n (%)	N	Achieved Meaningful Change, n (%)	N	Achieved Meaningful Change, n (%)	N	Achieved Meaningful Change, n (%)
Analysis set: all treated	57		55		55		49		53	
Restless or agitated	57	41 (71.9%)	55	50 (90.9%)	55	45 (81.8%)	49	40 (81.6%)	53	43 (81.1%)
Thinking about illness	57	15 (26.3%)	55	21 (38.2%)	55	26 (47.3%)	49	25 (51.0%)	53	27 (50.9%)
Worried about dying	57	20 (35.1%)	55	19 (34.5%)	55	21 (38.2%)	49	20 (40.8%)	53	22 (41.5%)
Worried about health in the future	57	15 (26.3%)	55	23 (41.8%)	55	23 (41.8%)	49	26 (53.1%)	53	17 (32.1%)
Future perspective scale	57	28 (49.1%)	55	33 (60.0%)	55	33 (60.0%)	49	36 (73.5%)	53	35 (66.0%)

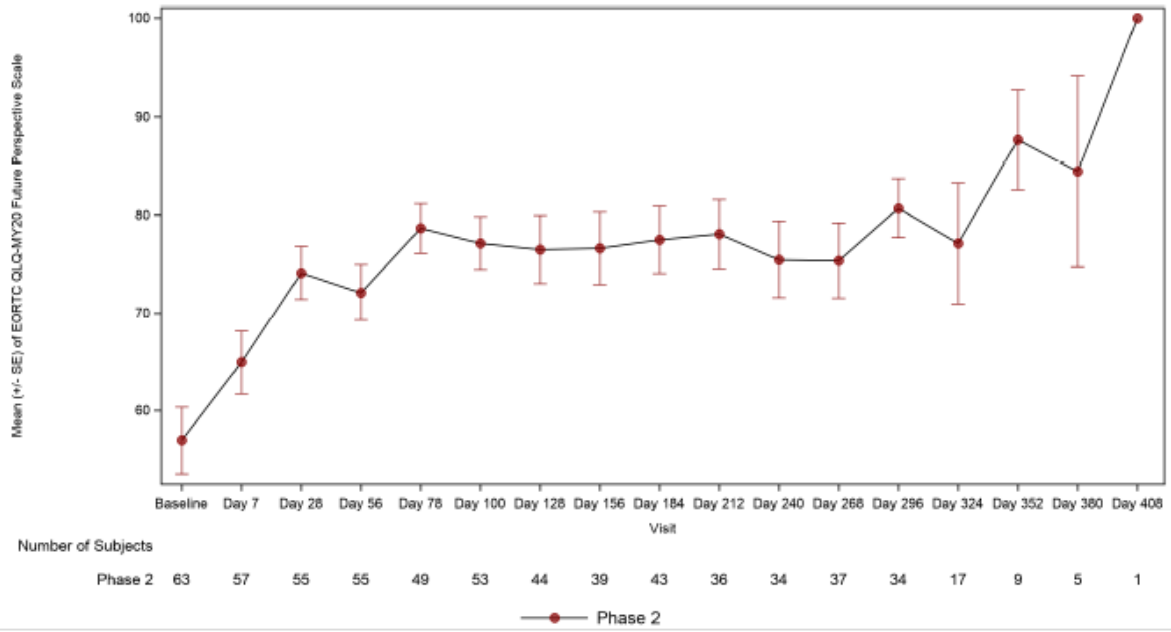
Key: MID = minimum importance difference.
Note: For literature-based MID, 10 points is used.
Note: Percentages are based on the number of subjects with non-missing prior to JNJ-68284528 infusion and post JNJ-68284528 infusion assessment.

[TPROQLQ07B.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TPROQLQ07B.SAS] 23OCT2020, 15:13

Future Perspective Subscale

Despite variability throughout the duration of study, subjects reported an improvement in their future perspective starting at Day 7 (LS mean 9.7 [95% CI: 5.2 to 14.1]) and continued to show positive improvement through Day 380 (LS mean 23.1 [95% CI: 7.4 to 38.7]).

Figure 24. Mean (+/- SE) of EORTC QLQ-MY20 Future Perspective Scale Over Time:; All Treated Analysis Set (Study 68284528MMY2001)



Note: All the scores are presented in the range of 0-100 after linear transformation from raw scores (in the range of 1-4). A higher score for restless or agitation indicates a worse health; whereas the higher score for the future perspectives, including worry about death and health in the future and thinking about illness, indicates better outcome.

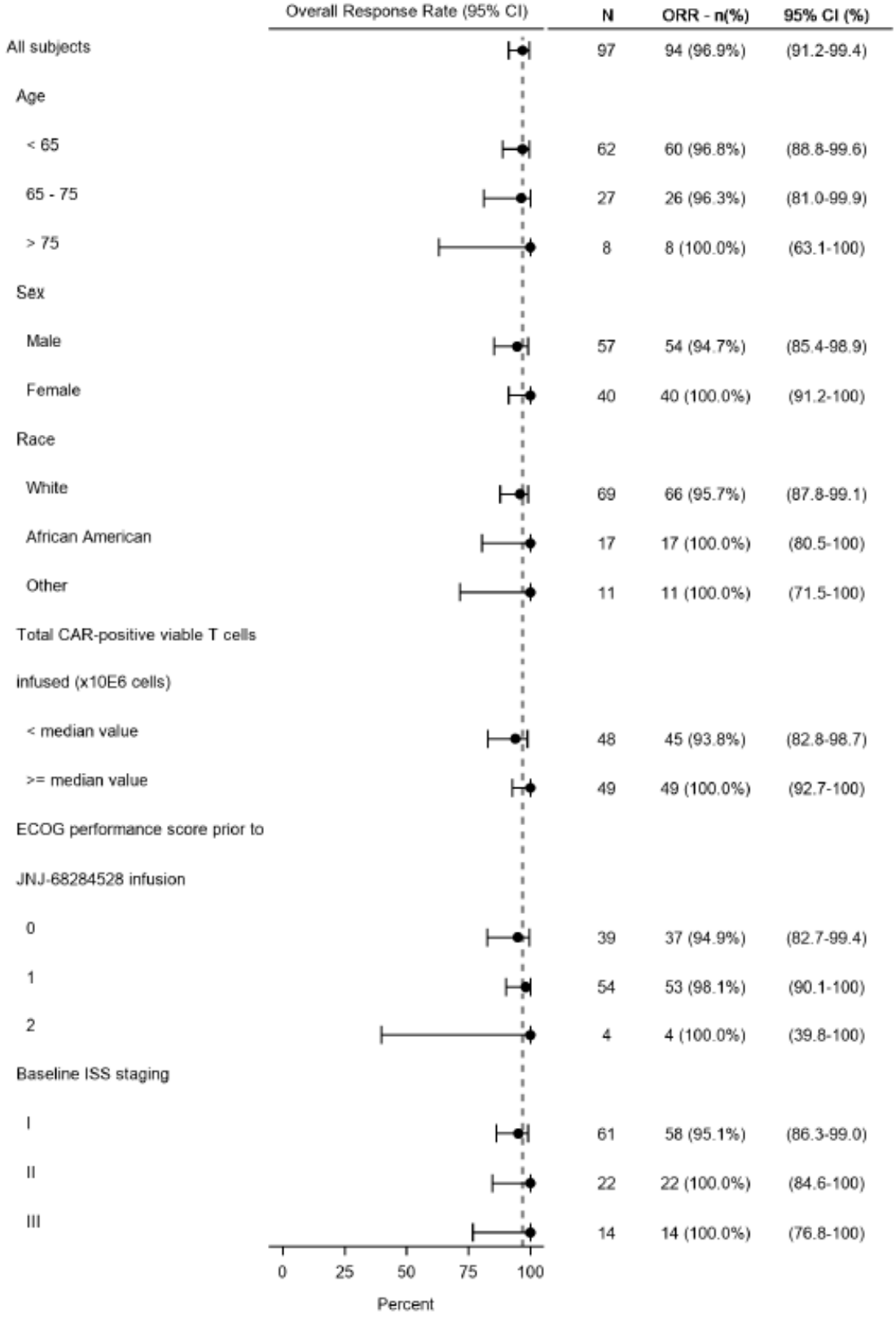
[GPROQLQ02A.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\GPROQLQ02A.SAS] 23OCT2020, 15:09

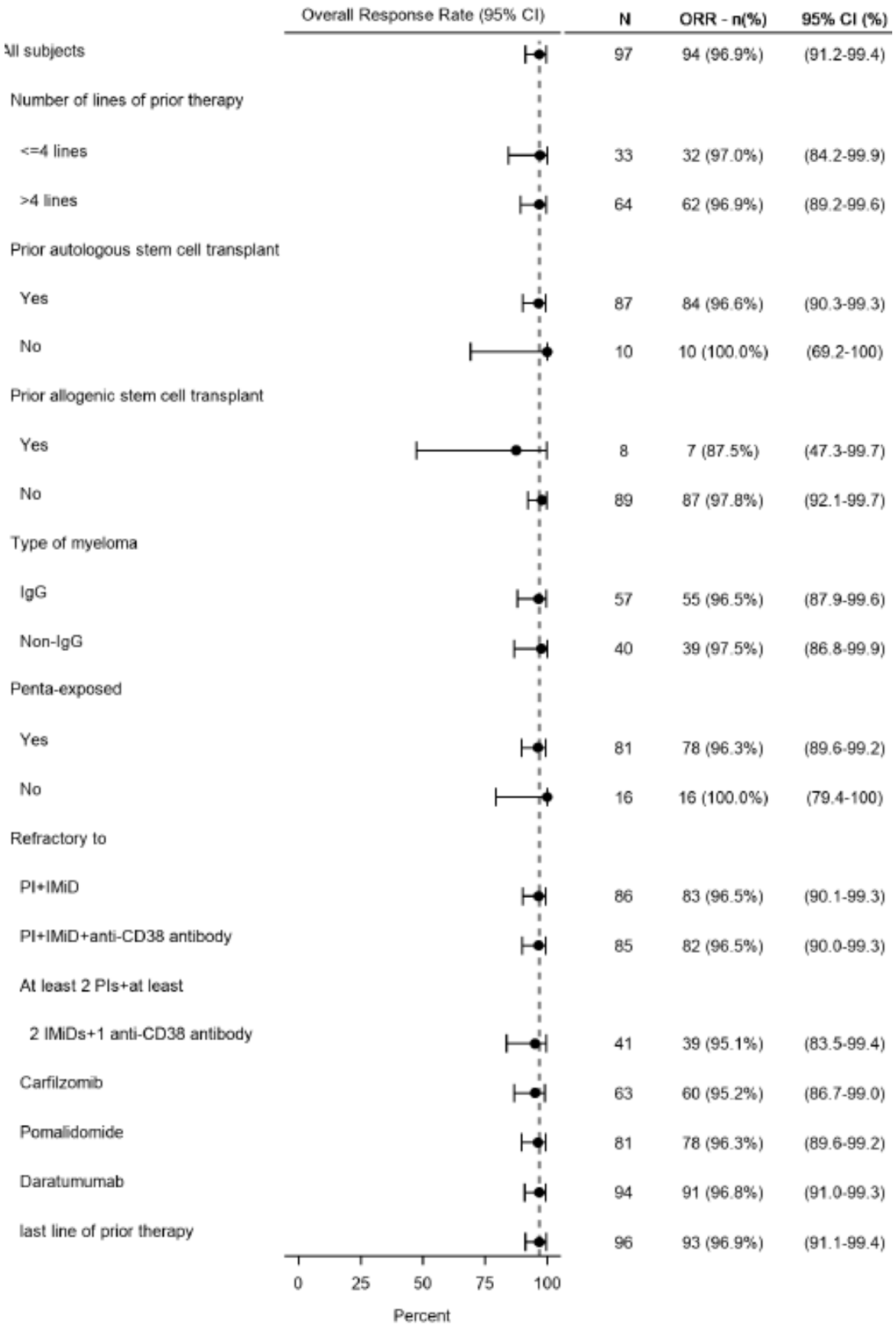
- **Ancillary analyses**

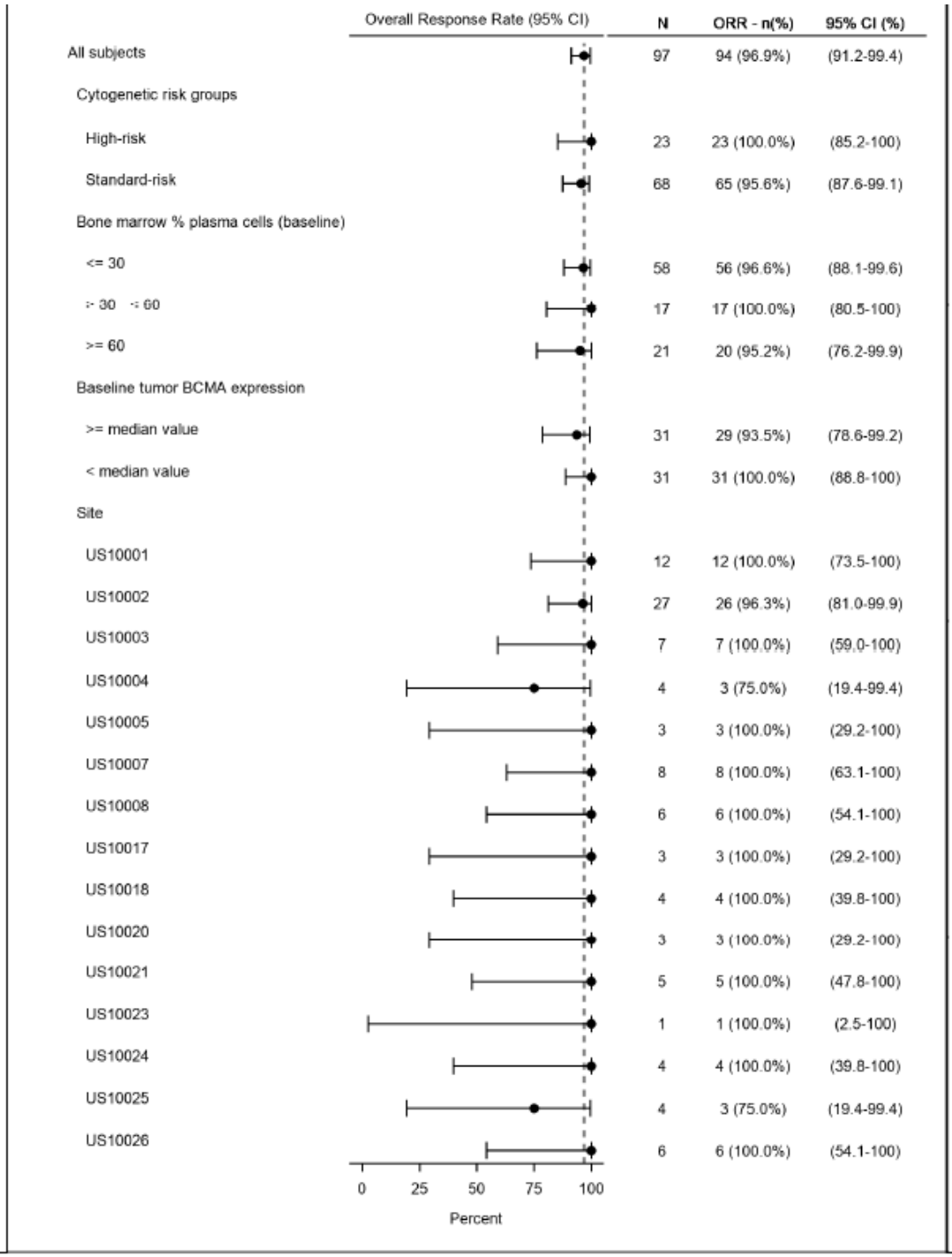
Subgroup Analysis of Overall Response Rate

The observed ORR was consistent across all subgroups examined when the assessment was based on the IRC data (Table 26). A consistent effect across subgroups was also observed when ORR was based on computerised algorithm assessment (data now shown).

Table 26. Forest Plot of Subgroup Analyses of Overall Response Rate Based on Independent Review Committee (IRC) Assessment; All Treated Analysis Set (Study 68284528MMY2001)




Overall Response Rate (95% CI)
N
ORR - n(%)
95% CI (%)
All subjects
97
94 (96.9%)
(91.2-99.4)
Number of lines of prior therapy
<=4 lines
33
32 (97.0%)
(84.2-99.9)
>4 lines
64
62 (96.9%)
(89.2-99.6)
Prior autologous stem cell transplant
Yes
87
84 (96.6%)
(90.3-99.3)
No
10
10 (100.0%)
(69.2-100)
Prior allogenic stem cell transplant
Yes
8
7 (87.5%)
(47.3-99.7)
No
89
87 (97.8%)
(92.1-99.7)
Type of myeloma
IgG
57
55 (96.5%)
(87.9-99.6)
Non-IgG
40
39 (97.5%)
(86.8-99.9)
Penta-exposed
Yes
81
78 (96.3%)
(89.6-99.2)
No
16
16 (100.0%)
(79.4-100)
Refractory to
PI+IMiD
86
83 (96.5%)
(90.1-99.3)
PI+IMiD+anti-CD38 antibody
85
82 (96.5%)
(90.0-99.3)
At least 2 PIs+at least
2 IMiDs+1 anti-CD38 antibody
41
39 (95.1%)
(83.5-99.4)
Carfilzomib
63
60 (95.2%)
(86.7-99.0)
Pomalidomide
81
78 (96.3%)
(89.6-99.2)
Daratumumab
94
91 (96.8%)
(91.0-99.3)
last line of prior therapy
96
93 (96.9%)
(91.1-99.4)
0
25
50
75
100
Percent



Key: BCMA = B-cell maturation agent; CI = confidence interval; IMiD = Immunomodulatory drug; PI = proteasome inhibitor.
Note: Exact 95% confidence intervals are provided.
Note: Race Other includes American Indian or Alaska native (1 subject), Asian (1 subject), Native Hawaiian or other Pacific islander (1 subject), and Not Reported (8 subjects).
[GEFRESP03A.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\GEFRESP03A.SAS] 26OCT2020, 09:58

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 27. Summary of efficacy for trial 68284528MMY2001 (CARTITUDE-1)

Title: A Phase 1b-2, Open-Label Study of JNJ- 68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Relapsed or Refractory Multiple Myeloma			
Study identifier	68284528MMY2001 (CARTITUDE-1, EudraCT Number: 2018-000121-32)		
Design	MMY2001 is a Phase 1b-2, open-label study in adult subjects with relapsed or refractory multiple myeloma study conducted at multiple sites in the United States. This is a single-arm trial without randomised control group.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		First subject consented in Phase 1b: 05 July 2018. Enrolment completed <not applicable> <not applicable>
Hypothesis	The hypothesis is that treatment with cilta-cel will demonstrate acceptable safety and will have significant anti-myeloma activity greater than 30% (ie, the lower limit of two-sided 95% confidence interval [CI] for ORR, as assessed by the IRC, is greater than 30%) at the targeted recommended Phase 2 dose (RP2D) dose level in subjects with advanced relapsed or refractory multiple		
Treatments groups	Single arm, open-label study		113 subjects enrolled (apheresed) 101 subjects received conditioning regimen 97 subjects received cilta-cel
Endpoints and definitions	Primary endpoint	ORR	Overall response rate (ORR) defined as the proportion of subjects who achieve a partial response (PR) or better as assessed by the Independent Review Committee (IRC) and based on International Myeloma Working Group (IMWG) criteria.
	Secondary endpoints	VGPR or Better Rate	Very good partial response (VGPR) or better rate was defined as the proportion of subjects who achieved a stringent complete response (sCR), complete response (CR), or VGPR as assessed
		DOR	Duration of response (DOR) will be calculated among responders (with a PR or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease (PD), as assessed by the IRC and based on IMWG Criteria
		MRD Negative Rate	Minimal residual disease (MRD) negativity rate is defined as the proportion of subjects who have negative MRD by bone marrow aspirate at any timepoint after initial dose of JNJ-68284528 and before disease progression or starting subsequent therapy or retreatment with JNJ-
		Time to Response	Time to first response (PR or better), best response, and CR or better; based on IRC assessment
		PFS	Progression-free survival (PFS) defined as the time from the date of the initial infusion of JNJ-68284528 to the date of first documented disease progression, as assessed by the IRC and based on IMWG criteria, or death due to any cause, whichever occurs first
		OS	Overall Survival (OS) measured from the date of the initial infusion of JNJ-68284528 to the date
Database lock	30 September 2020		

Results and Analysis			
Analysis description	**Primary Analysis (Based on IRC Assessment; 01 September 2020 Data Cut)**		
Analysis population and time point description (median study duration of follow-up = 12.4 months)	All Enrolled (intent-to-treat, ITT) = subjects who underwent apheresis All Treated (modified intent-to-treat, mITT) = subjects who received cilta-cel at the within the recommended dose range		
Descriptive statistics and estimate variability	All Enrolled (ITT)Analysis set		
	Number of subjects	113	
	ORR (% Responder)	83.2%	
	95% CI	(75.0% to 89.6%)	
	All Treated (mITT)Analysis set		
	Number of subjects	97	
	ORR (% Responder)	96.9%	
	95% CI	(91.2% to 99.4%)	
Analysis description	**External control arm based on real-world data from the MAMMOTH study**		
Average treatment effects on the treated (ATT) weighted analysis	ORR All Enrolled (intent-totreat, ITT)	Comparison groups	CARTITUDE-1 vs MAMMOTH
		% Responder	83% vs 34%
		Odds Ratio (% CI)	9.7 (4.9 – 19.2)
	ORR All Treated (modified intent-to-treat, mITT)	Comparison groups	CARTITUDE-1 vs
		% Responder	97% vs. 36%
		Odds Ratio (%CI)	50.4 (14.4 – 176.4)
Notes	As this is a single-arm trial the comparison with historical data is no confirmatory comparison. The comparison with an external control arm can only be interpreted in exploratory manner. Results may be biased in favour of the study treatment. For overall response rate, the weighted logistic regression model containing treatment group indicator only was adopted to estimate the treatment effect in terms of the odds ratio and its 95% CI using robust variance estimator.		
Analysis description	**Secondary Analyses (01 September 2020 Data Cut)**		
Descriptive statistics and estimate variability	VGPR or Better Rate	All Enrolled (ITT)	79.6% (95% CI: 71.0% to 86.6%) sCR: 57.5% (95%CI: 47.9%, to 66.8%)
		All Treated (mITT)	92.8% (95% CI: 85.7% to 97.0%) sCR: 67.0% (95%CI: 56.7% to 76.2%)
	DOR	Median Not Reached	
	MRD Negative Rate	MRD negativity at 10^{-5} threshold of sensitivity: 54.6% (N=53) with 34.0% (N=33) also achieving MRD-negative CR/sCR	

	Time to Response (median)	Time to first response: 0.95 months (range: 0.9 to 8.5) Time to best response: 2.56 months (range: 0.9 to 14.5) Time to CR or better: 1.87 months (range: 0.9 to 14.5)	
	PFS	Median PFS = not reached	
		12-month PFS rate All Enrolled (ITT)	70.7% (95% CI: 60.9% to 78.5%)
		12-month PFS rate All Treated (mITT)	76.6% (95% CI: 66.0% to 84.3%)
	OS	Median OS not reached	
		12-month OS rate All Enrolled (ITT)	81.3% (95% CI: 72.6% to 87.6%)
		12-month OS rate All Treated (mITT)	88.5% (95% CI: 80.2% to 93.5%)
Analysis description	**External control arm based on real-world data from the MAMMOTH study**		
Average treatment effects on the treated (ATT) weighted analysis	PFS All Enrolled (intent-totreat, ITT)	Comparison groups	CARTITUDE-1 vs MAMMOTH
		12 mo PFS (95% C.I.)	71% (62%-81%) vs 12% (6% - 21%)
		Hazard Ratio for PFS (95% C.I.)	0.15 (0.1 – 0.23)
	PFS All Treated (modified intent-to-treat, mITT)	Comparison groups	CARTITUDE-1 vs MAMMOTH
		12 mo PFS (95% C.I.)	78% (69% - 89%) vs 16% (10% - 28%)
		Hazard Ratio for PFS (95% C.I.)	0.13 (0.07 – 0.22)
	OS All Enrolled (intent-totreat, ITT)	Comparison groups	CARTITUDE-1 vs MAMMOTH
		12 mo OS (95% C.I.)	81% (74% - 89%) vs 42% (33% - 53%)
		Hazard Ratio for OS (95% C.I.)	0.24 (0.14 – 0.41)
	OS All Treated (modified intent-to-treat, mITT)	Comparison groups	CARTITUDE-1 vs MAMMOTH
		12 mo OS (95% C.I.)	90% (83% - 96%) vs 39% (29% - 52%)
		Hazard Ratio for OS (95% C.I.)	0.14 (0.07 – 0.27)
Notes	Weighted Cox proportional hazard (PH) model using ATT was applied to estimate the treatment effect in terms of the hazard ratio (HR) with 95% Waldtype CI using robust sandwich variance estimator.		

Results and Analysis	
Analysis description	**Primary Analysis (Based on IRC Assessment; 11 February 2021 Data Cut)**
Analysis population and time point description (median study duration of follow-up = 18 months)	All Enrolled (intent-to-treat, ITT) = subjects who underwent apheresis All Treated (modified intent-to-treat, mITT) = subjects who received cilta-cel at the within the recommended dose range
Descriptive statistics	All Enrolled (ITT)Analysis set

and estimate variability	Number of subjects	113	
	ORR (% Responder)	84.1%	
	95% CI	(76.0% to 90.3%)	
	All Treated (mITT)Analysis set		
	Number of subjects	97	
	ORR (% Responder)	97.9%	
	95% CI	(92.7% to 99.7%)	
Analysis description	**Secondary Analyses (11 February 2021 Data Cut)**		
Descriptive statistics and estimate variability	VGPR or Better Rate	All Enrolled (ITT)	81.4% (95% CI: 73.0% to 88.1%) sCR: 69.0% (95% CI: 59.6% to 77.4%)
		All Treated (mITT)	94.8% (95% CI: 88.4% to 98.3%) sCR: 80.4% (95% CI: 71.1% to 87.8%)
	DOR	Median DOR = 21.8 months (95% CI: 21.8, NE)	
	MRD Negative Rate	MRD negativity at 10^{-5} threshold of sensitivity: 57.7% (N=56) with 34.0% (N=33) also achieving MRD negative CR/sCR	
	Time to Response (median)	Time to first response: 0.95 months (range: 0.9 to 10.7) Time to best response: 2.60 months (range: 0.9 to 15.2) Time to CR or better: 2.63 months (range: 0.9 to 15.2)	
	PFS	Median PFS =24.31 months (ITT) (95% CI: 19.81, NE) 22.80 months (mITT) (95% CI: 22.80, NE)	
		12-month PFS rate All Enrolled (ITT)	70.5% (95% CI: 60.9% to 78.1%)
		12-month PFS rate All Treated (mITT)	76.3% (95% CI: 66.5% to 83.6%)
	OS	Median OS not reached	
		12-month OS rate All Enrolled (ITT)	81.5% (95% CI: 72.7% to 87.6%)
		12-month OS rate All Treated (mITT)	87.6% (95% CI: 79.2% to 92.8%)

2.6.5.3. Clinical studies in special populations

No separate analysis/data in special populations is presented. The subgroup analysis contains data on age groups. There´s no significant change in efficacy for the elderly in the analysed age groups (<65, 65-75, >75 yrs), although the number of patients in the >75 yrs is rather low (n=8).

2.6.5.4. Supportive study(ies)

Comparison of Cilta-cel to Real-World Data Conventional Treatment in Patients with RRMM

In the absence of a direct comparator in the single arm CARTITUDE-1 study, the purpose of this analysis is to contextualize the efficacy results reported by using real-world data in patients treated with currently available treatment options. The MAMMOTH study (Monoclonal Antibodies in Multiple Myeloma: Outcomes after Therapy Failure) is a multi-centre, retrospective chart review study to investigate the natural history and outcomes of patients with multiple myeloma refractory to CD38 monoclonal antibodies. A total of 275 patients were identified at 14 academic institutions in the US with diagnosis of active multiple myeloma who were refractory to CD38 monoclonal antibody administered alone or in combination. MAMMOTH study data were collected between January 2017 and June 2018 by myeloma investigators at the participating institutions. Eligible patients had received treatment with a CD38 monoclonal antibody for at least 4 weeks and had evidence of progressive disease as defined by International Myeloma WorkingGroup (IMWG) Response Criteria.

The comparison between MAMMOTH cohort and CARTITUDE-1 cohort were made for ORR, progression-free (PFS) and overall survival (OS) for both ITT and mITT populations.

Table 28. Clinical Outcome – Unadjusted Analysis and Multivariate Analysis for ITT and mITT Populations

	Intent-to-treat Population (CARTITUDE-1 N=113, MAMMOTH N=190)			Modified Intent-to-treat Population (CARTITUDE-1 N=97, MAMMOTH N=122)		
	ITT (apheresis), CARTITUDE-1	ITT, MAMMOTH	P-value	mITT (treated), CARTITUDE-1	mITT, MAMMOTH	P-value
Unweighted Univariate Analysis						
ORR	94(83%)	57 (30%)		94(97%)	46 (38%)	
Odds ratio for ORR (95% C.I.)	11.5 (6.4-20.7)		<0.001	51.8 (15.5-173.0)		<0.001
12 mo PFS (95% C.I.)	72% (63-80%)	7% (2%-11%)		75% (65%-85%)	7% (1%-13%)	
Hazard Ratio for PFS (95% C.I.)	0.13(0.09-0.19)		<0.001	0.10 (0.06-0.16)		<0.001
12 mo OS (95% C.I.)	81% (74%-89%)	37% (30%-44. %)		89% (82%-95%)	40% (30%-50%)	
Hazard Ratio for OS (95% C.I.)	0.21 (0.14-0.33)		<0.001	0.15 (0.09 -0.28)		<0.001
Unweighted Multivariate Analysis*						
Adjusted Odds ratio for ORR (95% C.I.)	11.3 (6.0-21.4)		<0.001	71.9 (18.9-273.7)		<0.001
Adjusted Hazard Ratio for PFS (95% C.I.)	0.13 (0.08-0.19)		<0.001	0.09 (0.05-0.14)		<0.001
Adjusted Hazard Ratio for OS (95% C.I.)	0.23 (0.14-0.36)		<0.001	0.15 (0.08-0.27)		<0.001

*: *covariates included were treatment, age, number of prior lines of therapy, time from diagnosis to treatment, race, sex, prior ASCT, presence of high-risk cytogenetics, ISS3, Penta-exposed, penta-refractory, triple class refractory.*

CI=confidence interval, ITT=intent to treat, mITT=modified intent to treat, ORR=overall response rate, OS=overall survival, PFS=progression-free survival

Table 29. inical Outcome –Propensity Score Based 1:1 Matching Analysis for ITT and mITT Populations

	Intent-to-treat Population 1:1 PS matched (CARTITUDE N=95, MAMMOTH N=95)			Modified Intent-to-treat Population 1:1 PS matched (CARTITUDE-1 N=69, MAMMOTH N=69)		
	ITT (apheresis), CARTITUDE	ITT, MAMMOTH	P-value	mITT (treated), CARTITUDE	mITT, MAMMOTH	P-value
Matched Analysis						
ORR	80 (84%)	27 (28%)		66(96%)	21 (30%)	
Odds ratio for ORR (95% C.I.)	13.4 (6.6-27.3)		<0.001	50.3 (14.2-178.3)		<0.001
12 mo PFS (95% C.I.)	73% (64% - 83%)	12% (6% - 21%)		79% (69% - 90%)	15% (7% - 28%)	
Hazard Ratio for PFS (95% C.I.)	0.11 (0.05 - 0.22)		<0.001	0.02 (0.01 - 0.14)		<0.001
12 mo OS (95% C.I.)	83% (76% - 91%)	39% (30% - 51%)		88% (81% - 96%)	35% (24% - 51%)	
Hazard Ratio for OS (95% C.I.)	0.2 (0.1 - 0.39)		<0.001	0.05 (0.01 - 0.22)		<0.001

CI=confidence interval, ITT=intent to treat, mITT=modified intent to treat, ORR=overall response rate, OS=overall survival, PS=propensity score

Figure 25. PFS and OS by Propensity Score Based 1:1 Matching Analysis

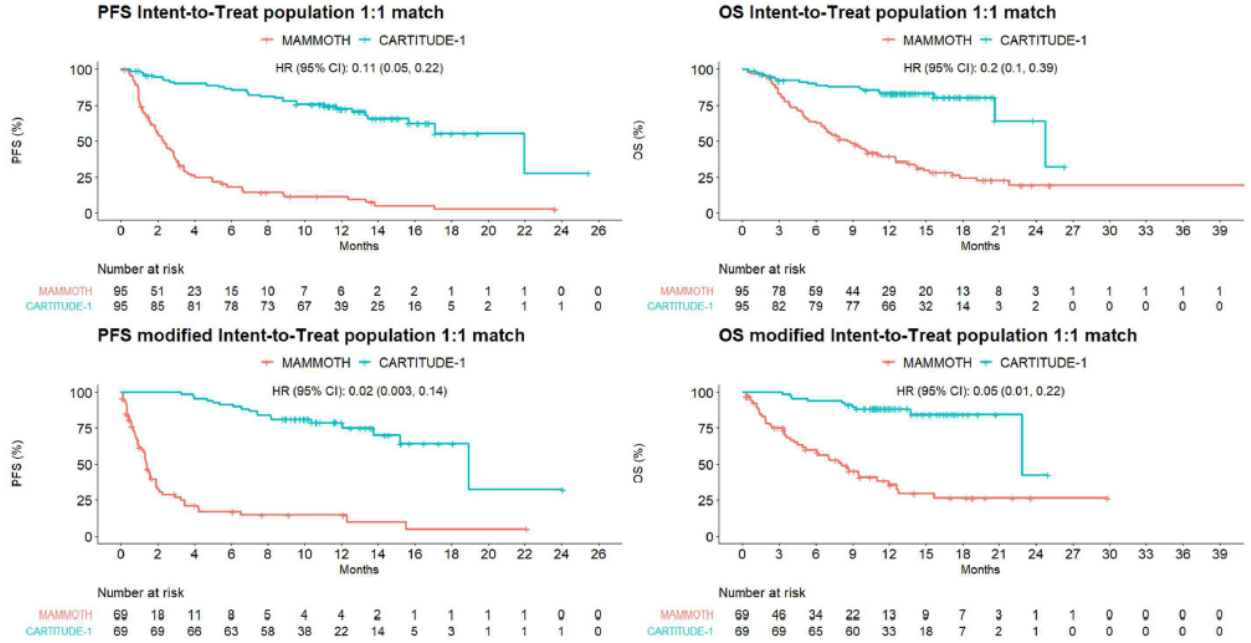


Table 30. Clinical Outcome –Propensity Score Based Weighted Analysis for ITT and mITT Populations

	Intent-to-treat Population "trimmed" to exclude patients with PS outside overlapping range (CARTITUDE N=107, MAMMOTH N=177)			Modified Intent-to-treat Population "trimmed" to exclude patients with PS outside overlapping range (CARTITUDE N=88, MAMMOTH N=117)		
	ITT (apheresis), CARTITUDE	ITT, MAMMOTH	P-value	mITT (treated), CARTITUDE	mITT, MAMMOTH	P-value
Weighted Analysis (sIPTW)						
ORR	93 (84%)	56 (32%)		93 (98%)	43 (37%)	
Odds ratio for ORR (95% C.I.)	11.3 (5.8 – 21.9)		<0.001	67.6 (19.1 – 239.7)		<0.001
12 mo PFS (95% C.I.)	71% (62%-80%)	9% (5%-16%)		78% (69%-88%)	11% (6%-21%)	
Hazard Ratio for PFS (95% C.I.)	0.14 (0.09 – 0.22)		<0.001	0.11 (0.06 – 0.19)		<0.001
12 mo OS (95% C.I.)	80% (73% - 88%)	39% (32% - 47%)		88% (82% - 95%)	39% (30% - 51%)	
Hazard Ratio for OS (95% C.I.)	0.23 (0.13 – 0.41)		<0.001	0.16 (0.07 – 0.32)		<0.001
Weighted Analysis (ATT)						
ORR	89 (83%)	36 (34%)		85 (97%)	33 (36%)	
Odds ratio for ORR (95% C.I.)	9.7 (4.9 – 19.2)		<0.001	50.4 (14.4 – 176.4)		<0.001
12 mo PFS (95% C.I.)	71% (62% - 81%)	12% (6% - 21%)		78% (69% - 89%)	16% (10% - 28%)	
Hazard Ratio for PFS (95% C.I.)	0.15 (0.1 – 0.23)		<0.001	0.13 (0.07 – 0.22)		<0.001
12 mo OS (95% C.I.)	81% (74% - 89%)	42% (33% - 53%)		90% (83% - 96%)	39% (29% - 52%)	
Hazard Ratio for OS (95% C.I.)	0.24 (0.14 – 0.41)		<0.001	0.14 (0.07 – 0.27)		<0.001

CI=confidence interval, ITT=intent to treat, mITT=modified intent to treat, ORR=overall response rate, OS=overall survival, PFS=progression-free survival, PS=propensity score

Figure 26. PFS and OS by Propensity Score Based Weighted Analysis Using sIPTW Weight

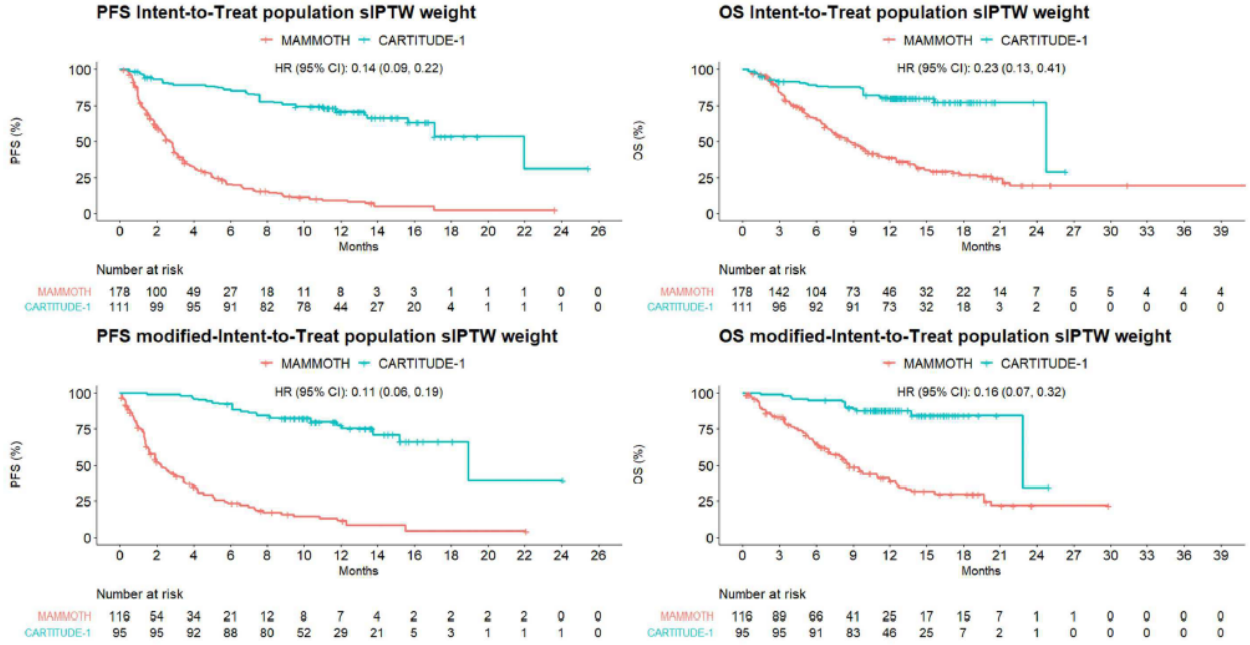
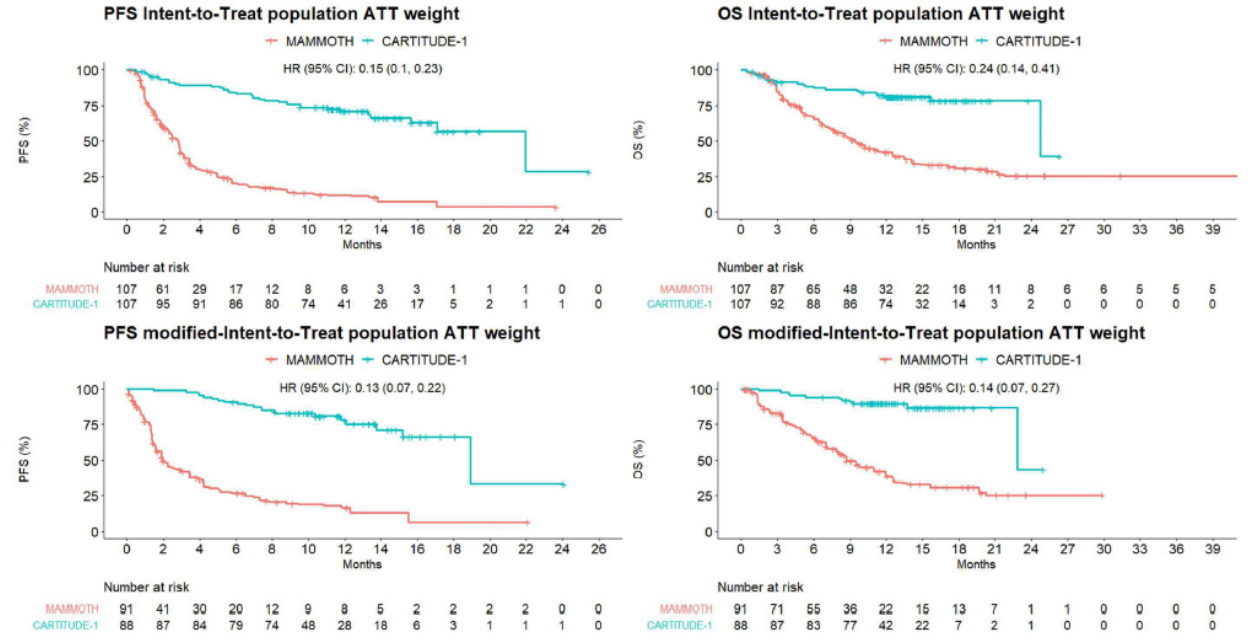


Figure 27. PFS and OS by Propensity Score Based Weighted Analysis Using ATT Weight



Clinical data on comparison of the two manufacturing processes:

Preliminary clinical data provided by the applicant to compare the efficacy of the two manufacturing processes were obtained in the ongoing 68284528MMY2003 study. Cohort A includes subjects with progressive disease after 1 to 3 prior lines of therapy for multiple myeloma including a proteasome inhibitor (PI) and immunomodulatory therapy (IMiD) either individually or in combination. In addition, all study subjects were required to be refractory to lenalidomide. Subjects who received prior therapy that is targeted to BCMA were excluded from this cohort.

A total of 30 subjects received cilta-cel in Cohort A; 20 subjects received cilta-cel manufactured with clinical lentiviral vector (LV) and 10 subjects received cilta-cel manufactured with commercially representative LV(commercial product). The current preliminary data are insufficient to exclude efficacy differences. However, it is considered, that the patients treated with the commercial product still have a positive benefit/risk.

Table 31. Overall Best Response Based on Computerised Algorithm Assessment at 6 Months Median Follow-up; Cohort A All Treated Analysis Set (Study 68284528MMY2003)

	Cohort A					
	Commercially representative LV		Clinical LV		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: all treated	10		20		30	
Best response						
Stringent complete response (sCR)	3 (30.0%)	(6.7%, 65.2%)	9 (45.0%)	(23.1%, 68.5%)	12 (40.0%)	(22.7%, 59.4%)
MRD-negative CR/sCR [a]	3 (30.0%)	(6.7%, 65.2%)	3 (15.0%)	(3.2%, 37.9%)	6 (20.0%)	(7.7%, 38.6%)
Complete response (CR)	2 (20.0%)	(2.5%, 55.6%)	6 (30.0%)	(11.9%, 54.3%)	8 (26.7%)	(12.3%, 45.9%)
Very good partial response (VGPR)	2 (20.0%)	(2.5%, 55.6%)	2 (10.0%)	(1.2%, 31.7%)	4 (13.3%)	(3.8%, 30.7%)
Partial response (PR)	2 (20.0%)	(2.5%, 55.6%)	2 (10.0%)	(1.2%, 31.7%)	4 (13.3%)	(3.8%, 30.7%)
Minimal response (MR)	0	(NE, NE)	0	(NE, NE)	0	(NE, NE)
Stable disease (SD)	1 (10.0%)	(0.3%, 44.5%)	1 (5.0%)	(0.1%, 24.9%)	2 (6.7%)	(0.8%, 22.1%)
Progressive disease (PD)	0	(NE, NE)	0	(NE, NE)	0	(NE, NE)
Not evaluable (NE)	0	(NE, NE)	0	(NE, NE)	0	(NE, NE)
Overall response (sCR + CR + VGPR + PR)	9 (90.0%)	(55.5%, 99.7%)	19 (95.0%)	(75.1%, 99.9%)	28 (93.3%)	(77.9%, 99.2%)
Clinical benefit (Overall response + MR)	9 (90.0%)	(55.5%, 99.7%)	19 (95.0%)	(75.1%, 99.9%)	28 (93.3%)	(77.9%, 99.2%)
VGPR or better (sCR + CR + VGPR)	7 (70.0%)	(34.8%, 93.3%)	17 (85.0%)	(62.1%, 96.8%)	24 (80.0%)	(61.4%, 92.3%)
CR or better (sCR + CR)	5 (50.0%)	(18.7%, 81.3%)	15 (75.0%)	(50.9%, 91.3%)	20 (66.7%)	(47.2%, 82.7%)

Key: CI = confidence interval.
[a]MRD-negative CR/sCR. Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death / progression / subsequent therapy (exclusive) are considered.
Note: Response was assessed by Computerised Algorithm based on International Myeloma Working Group (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.
Note: Results presented for Commercially representative LV is based on clinical cut-off reflecting a median follow-up of 6.14 months, results for the Clinical LV is based on clinical cut-off reflecting a median follow-up of 5.82 months.

For efficacy, no further relevant supportive studies are presented.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The MMY2001 pivotal study is the only study from which efficacy data are included for this MAA.

The current ESMO GL (March 2021) allows inclusion of MM patients into clinical trials at a second or subsequent relapse. Given the chosen indication of patients with no further therapeutic option, and in the light of the efficacy results, the single arm design is acceptable. Additionally, the spplicant provided an analysis comparing efficacy with real world data derived external control, with the terms agreed in EMA SAs, which is deemed to be supportive.

No formal dose finding took place in the Legend-2 study, however, the design of the CARTITUDE-1 study allowed for potential dose adjustments. The safety and efficacy data in the CARTITUDE-1 study represent strong arguments for the selected dose.

By the inclusion criteria relapsed or double (PI and IMID) refractory state was required for enrolment. Patients should have received at least three lines of treatment being the median number reported of 6 and these should have included a PI, an IMiD, and an anti-CD38 monoclonal antibody (mAb). Refractoriness to an anti-CD38 mAb has been indirectly defined as an inclusion criteria, by requiring previous exposure and evidence of progressive disease. Patients previously exposed to e.g. anti-BCMA mAb were excluded for the MMY2001 study. These patients are expected to be investigated throughout the development programme.

Eligibility for enrolment was determined prior to leukapheresis, and patients were considered enrolled at the time of leukapheresis. The inclusion and exclusion criteria are considered appropriate and in accordance with other clinical studies in RRMM.

Overall, the objectives and endpoints of the study are acceptable. The primary endpoint was ORR according to the IMWG criteria assessed by an IRC. This is an acceptable primary endpoint in an uncontrolled trial as it is a direct measure of the drug´s antitumour activity. Additionally, data on duration of response, TTP/PFS, and available data on OS were also reported, although the interpretation of these measures is difficult without a randomised reference. The same is valid for clinical benefit rate data.

The protocol allowed bridging therapy. This is acceptable. Subgroup analysis revealed that there is no obvious difference in the outcome of patients, who experienced tumour burden reduction following bridging therapy. Retreatment was allowed under certain conditions; however, as it is stated in the latter parts of the CSR, there was only one patient who was retreated, so the general efficacy/benefit aspects of retreatments cannot be evaluated at this stage.

A standard CY + FLU lymphodepletion chemotherapy regimen was administered. This is considered acceptable.

The first analysis was planned to be conducted approximately 6 months after the last subject received their initial dose of cilta-cel. An update of the analysis was planned to be provided at approximately 9–12 months after last subject receives their initial dose of cilta-cel and at the end of the study, which is defined as 2 years after the last subject has received their initial dose. The planned time point for the initial analyses is earlier than those proposed for other similar (CAR-T) products. This issue could impact results and the interpretation of the data, given that responses to CAR-T cells are rapid, and relapse has been described in more than 50% of patients in around 12 months.

Efficacy data and additional analyses

The baseline characteristics were relatively well balanced. However, in important prognostic factors, some discrepancies were observed: cytogenetic risk based grouping included 70.1% standard risk, 23.7% high-risk patients, and a certain tilt towards younger patients was observed. ISS staging also indicated that about 2/3 of patients had stage I disease. It is also noted that the patients were heavily treated before study enrolment.

The majority of patients (75.3%) received a bridging therapy between the time of apheresis and the first dose of the conditioning regimen. Among the 73 patients received any bridging therapy, 33 subjects (45.2%) had a transient decrease in tumour burden. Subgroup analysis did not reveal an influence of bridging therapy on efficacy outcomes.

The ORR (PR or better) as assessed by the IRC based on IMWG Criteria was:

- All Treated population (n=97): 96.9% (95% CI: 91.2% to 99.4%)

- All Enrolled population (n=113): 83.2% (95% CI: 75.0% to 89.6%). These values are statistically significant, and better than the null hypothesis.

At the 11 February 2021 data cut-off date treatment of these subjects with cilta-cel resulted in an overall response rate (ORR) of 97.9% with 95 of 97 subjects in the All Treated analysis set achieving a partial response (PR) or better as assessed by Independent Review Committee (IRC) (based on International Myeloma Working Group [IMWG] criteria). The ORR for the 113 subjects in the All Enrolled analysis set (includes 16 subjects who did not receive a cilta-cel infusion) was 84.1%, representing a slight improvement over time for both measurements.

Subgroup analyses were performed in the cilta-cel treated population. The observed ORR was consistent across all subgroups examined including evaluation by age, sex, race, total CAR-T positive cells infused, baseline ECOG performance score, baseline ISS staging, lines of prior therapy, disease type, refractory status, cytogenic risk groups, baseline bone marrow plasma cells, baseline BCMA expression, and study site.

The only difference would be stem cell transplant history. Stem cell transplant history in an autologous setting was not found to have an impact on ORR. However, patients treated with allogeneic stem cells had an apparently lower ORR (87.5% vs. 97.8%) when compared to patients without prior allogeneic stem cell transplant history. Yet the low number of patients (n= 8) does not allow any conclusions at this stage- so this aspect may be relevant for post-MA follow-up.

Very good partial response (VGPR) or better rate was defined as the proportion of subjects who achieved a sCR, CR, or VGPR according to IMWG response criteria.

The overall response of VGPR or better as assessed by the IRC was:

- All Treated population (n=97): 92.8% (95% CI: 85.7% to 97.0%)
- All Enrolled population (n=113): 79.6% (95% CI: 71.0% to 86.6%)

Duration of response (DOR) was not reached at first clinical cut-off. At the 11 February 2021 data cut-off date deep and durable responses were induced by cilta-cel as demonstrated by a very good partial response (VGPR) or better rate of 94.8% in the allttreated analysis set. Seventy-eight subjects (80.4%) achieved a sCR. At a median follow-up of 18.0 months, median duration of response (DOR) was 21.8 months (95% CI: 21.8 months, not estimable [NE]) at the time of the clinical cut-off. The probabilities of the responders remaining in response at 9 months and 12 months were 79.7% (95% CI: 70.0%, 86.5%) and 72.9% (95% CI: 62.6%, 80.9%), respectively. The median DOR for subjects achieving CR/sCR has not yet reached.

Fifty-three subjects achieved MRD negativity. At the 11 February 2021 data cut-off date, 56 subjects (91.8%) achieved MRD negativity in bone marrow at a sensitivity level of 10^{-5}. MRD results indicate that a high proportion of complete responders achieved deep responses to the therapy.

In the all-treated population, 74.2% of subjects' PFS data was censored at the clinical cut off, which resulted in a median PFS not reached for assessment based on IRC review. As of clinical cut off the 12-month PFS rates are as follows:

- All Treated population (n=97): 76.6% (95% CI: 66.0% to 84.3%)
- All Enrolled population (n=113): 70.7% (95% CI: 60.9% to 78.5%).

At the 11 February 2021 data cut-off date, at a median duration of follow-up of 18.0 months, median progression-free survival (PFS) was 22.8 months (95% CI: 22.8, NE) and the median PFS for subjects who achieved CR/sCR was not yet reached. At 12 months post cilta-cel infusion, 76.3% of subjects (95% CI: 66.5% to 83.6%) remained progression free.

At the time of clinical cut off, 14 subjects (14.4%) had died in the all treated population. Overall survival data are yet to be mature enough to provide a reliable estimate for median OS. However, the estimated OS rates at 12 months were:

- All Treated population (n=97): 88.5% (95% CI: 80.2% to 93.5%)
- All Enrolled population (n=113): 81.3% (95% CI: 72.6% to 87.6%).

At the 11 February 2021 data cut-off date, median overall survival (OS) has not been reached. The 12-month OS rate was 87.6% (95% CI: 79.2% to 92.8%). While data continue to mature, available data suggests that there may be a positive association between depth of response and favourable PFS and OS.

While data on PFS and OS are presented in the efficacy assessment, single arm trials in oncology are not suitable to ascertain a treatment effect on OS or PFS due to the lack of a comparator. Data on these endpoints are therefore not included in the PI.

To contextualize the efficacy results, namely time to event endpoints, the applicant has reported real-world data from the retrospective MAMMOTH study, a multi-centre, retrospective chart review study to investigate the natural history and outcomes of patients with MM refractory to CD38-mAb. Limitations of these type comparisons are noted and data is considered to be supportive.

Only one subject was retreated. This subject initially progressed 511 days after the first cilta-cel infusion. The retreated subject developed new and worsening lytic disease and was diagnosed with PD 32 days after retreatment. The value of retreatment with cilta-cel is uncertain in terms of benefit/risk. Only one patient has been retreated in study MMY2001.

Seventeen subjects (17.5%) had PD after cilta-cel infusion. Eleven of these subjects received subsequent anti-myeloma therapy after disease progression.

Health-related Quality of Life assessment revealed meaningful improvements for all analysed parameters.

Regarding the proposed commercial manufacturing process, comparability of commercial product with clinical trial lots could not be fully established at the quality level. Currently, only few clinical data are available for patients treated with lots from the commercial process, supporting the efficacy of these lots but not excluding slight differences. Thus, further clinical data on clinical safety and efficacy for clinical LV and commercially representative LV treated patients are requested as a post-authorisation measure (REC).

Additional efficacy data needed in the context of a conditional MA

Following the MO relating to the comprehensiveness of data and granting of a full marketing authorisation, the applicant submitted a request for a conditional marketing authorisation in the proposed indication. As main deficiencies for lack of comprehensiveness, limited patient numbers and duration of follow-up were listed. The package submitted by the applicant is considered to fulfil the requirements of a CMA.

The applicant will submit the final data after 24 month follow up of the main study for this application (study CARTITUDE-1; MMY2001)(due date December 2022) and data from a Phase 3 randomised study comparing JNJ-68284528, a CAR-T therapy directed against BCMA vs PVd or DPd in subjects with relapsed and lenalidomide-refractory multiple myeloma (study CARTITUDE-4; MMY3002) expected to release final results by December 2026. In principle, these studies are considered suitable as specific obligations to the MA.

2.6.7. Conclusions on the clinical efficacy

Cilta-cel showed clinically significant response rates in a heavily pre-treated RRMM population. Since the pivotal study had a single-arm design, the applicant provided a comparison with real world data that can be considered as supportive evidence. Besides the ORR data, sCR is also showing convincing results.

However, due to the missing randomised control group, uncertainties about the actual treatment effect exists. The proposed indication would also cover RRMM patients with at least three, but in total fewer prior lines of treatment than in the MMY2001 trial. A similar efficacy may be anticipated in these less pre-treated patients. Additionally, MRD results also indicate that the majority of complete responders achieved deep responses to the therapy.

The CAT considers the following measures necessary to address issues related to efficacy:

- In order to further characterise the long-term safety and efficacy of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall submit the results of the long-term follow-up study for participants previously treated with ciltacabtagene autoleucel. (68284528MMY4002). Due date: June 2043.

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

- In order to confirm the efficacy and safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy, the MAH should submit the final study results of the pivotal study CARTITUDE-1 (MMY2001). Due date: December 2022.

- In order to confirm the efficacy and safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy, the MAH should submit the results of the Phase 3 study CARTITUDE-4 (MMY3002). Due date: December 2026.

The CHMP endorses the CAT conclusion on clinical efficacy as described above.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The initial safety database for Marketing Authorisation Application comprised the following ongoing studies and follow-up periods:

1. The pivotal cohort of the Phase 1b/2 open-label multi-centre Study 68284528MM2001 (MMY2001; CARTUTUDE-1) with Data Cut Off (DCO) 01 September 2020, resulting in a total median duration of follow-up of 12.4 months for n= 97 patients (All Treated Population).

2. The supportive cohort (Japan cohort) of MMY2001 with DCO 01 September 2020, resulting in a median duration of FU of 2.4 months for n=9 patients.
3. The supportive phase 2 multi-cohort open-label study 68284568MMY2003 (MMY2003; CARTUTUDE-2) with DCO 23 July 2020, resulting in a median FU of 1.6 months for n=18 patients.

Both trials MMY2001 and MMY2003 are ongoing. The target dose, patients received in both trials was 0.75x106 CAR-positive T cells/kg BW as a single infusion five to seven days after administration of conditioning therapy.

Furthermore, during assessment a clinical safety update has been provided through more recent data cut off dates, which presents the following progress of the studies and subjects treated with cilta-cel:

- The pivotal main cohort of study MMY2001 (DCO 11 February 2021): Safety data are now available for n=97 subjects with a median safety FU of 18 months. No additional subjects have been enrolled/treated since last DCO.
- The supportive cohort of MMY2001 (Japanese Cohort) through DCO 11 February 2021: Safety data are now available for n=9 subjects with a median safety FU of 8 months. No additional subjects have been enrolled/treated since last DCO.
- The supportive study MMY2003 (DCO 15 April 2021): Additional 55 subjects have been treated since last DCO. Data are now available for n=73 subjects treated:
  a) For n=18 subjects with a median safety FU of 6 months,
  b) For n= 51 subjects with a median safety FU of more than 3 months.
- Study MMY3002: Safety data are provided for n=23 subjects through DCO 15 April 2021. The provided results on the safety parameters of cilta-cel in study MMY3002, such as CRS, neurotoxicity, cytopenia etc. can be regarded comparable to those reported for the trials MMY2001 and MMY2003. No additional safety concerns could be identified as of DCO 15 April 2021, no death cases were reported.

No major changes and clinical relevant additional safety signals, respectively, could be identified in the presented clinical safety update in subjects treated within the ongoing trials, late breaking information on neurotoxicity as of DCO April 2021 included.

2.6.8.2. Adverse events

MMY2001

All subjects who received cilta-cel had at least one adverse event and all subjects experienced one or more grade 3 or 4 treatment emerged adverse event (TEAE). The most common reported ≥ grade 3 or 4 TEAEs were cytopenias (neutropenia [95.9%], anaemia [81.4%], thrombocytopenia [79.4%], leukopenia [61.9%], and lymphopenia [52.6%]) and CRS (94.8%) along with hypoalbuminaemia (n=27; 27.8%), alanine transferase increase (n=24; 24.7%) and aspartate aminotransferase increase (n=28; 28.9%). They were observed more often during the first 4-8 weeks after infusion of cilta-cel in comparison to ≥ 8 weeks post-infusion.

There were no additional subjects enrolled in the trial MMY2001 (pivotal cohort and Japan cohort), and there are no changes reported for the subjects treated with regard to incidence and grading of adverse events in general and TEAEs, CRS, ICANS, neurotoxicity, MNTs, (movement and neurocognitive

TEAEs), cytopenia, infections or adverse drug reactions in particular since the 01 September 2020 cut-off date.

Deaths

As of the cut-off date for the clinical safety update, 21 subjects (21.6%) have died, which means an increase of 7 death cases (5 due to PD, 1 due acute myeloid leukemia on Day718 and 1 due to ascites on Day45) since 01 September 2020 initial cut-off. The provided narratives reveal no major concerns; the death case due to ascites is considered attributed to clinical complications. All deaths cases are reported for the pivotal cohort of MMY2001; no deaths were reported for the Japan cohort.

Second Primary Malignancy (SPM)

Three new cases have been reported in addition to the 7 subjects as of 01 September 2020. All SPM were considered not related to cilta-cel by investigator assessment.

CRS

Eighty-eight subjects (90.7%) received supportive treatment for CRS. The most commonly prescribed medications (>15% of subjects) used to treat CRS included: paracetamol (72.2%), tocilizumab (69.1%), cefepime (27.8%), sodium chloride solution (23.7%), dexamethasone (20.6%) and anakinra (18.6%). Six subjects (6.2%) required oxygen as a supportive measure to treat CRS.

There was one Grade 5 CRS. This patient received tocilizumab, anakinra, cyclophosphamide, etanercept and methylprednisolone. Supportive oxygen was also needed. First onset of CRS was on Day 11 and was never recovered. The patient also presented Grade 4 sepsis which was ongoing at the date of death.

Neurotoxicity

ICANS

Sixteen subjects (16.5%) had an ICANS event, which included symptoms of aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness, and confusional state. For 15 of these subjects ICANS occurred concurrent with CRS and for 1 subject ICANS occurred 4 days after recovery from CRS. Most of ICANS events were reported as grade 1 or 2. One subject experienced a grade 3/4 event. All 16 subjects recovered. The median time from cilta-cel infusion to ICANS onset was 8 days and the median duration was 4 days.

At the time of clinical cutoff, all 16 subjects who had experienced ICANS had recovered. All subjects who experienced ICANS also experienced CRS. Fifteen subjects experienced ICANS concurrent with CRS, and 1 subject experienced ICANS 4 days after the recovery of CRS.

Table 32. Summary of Immune Effector Cell-associated Neurotoxicity (ICANS) with Onset After Cilta-cel Infusion; All Treated Analysis Set

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Number of subjects with ICANS	3 (10.3%)[a]	13 (19.1%)	16 (16.5%)
Maximum toxicity grade			
Grade 1	2 (6.9%)	8 (11.8%)	10 (10.3%)
Grade 2	0	4 (5.9%)	4 (4.1%)
Grade 3	1 (3.4%)	0	1 (1.0%)
Grade 4	0	1 (1.5%)	1 (1.0%)
Grade 5	0	0	0
Time from initial infusion of JNJ-68284528 to first onset of ICANS			
N	3	13	16
Mean (SD)	6.3 (2.89)	7.5 (2.22)	7.3 (2.29)
Median	8.0	8.0	8.0
Range	(3; 8)	(4; 12)	(3; 12)
Duration of ICANS (days)			
N	3	13	16
Mean (SD)	3.7 (2.08)	5.2 (3.09)	4.9 (2.93)
Median	3.0	4.0	4.0
Range	(2; 6)	(1; 12)	(1; 12)
Number of subjects with treatment of ICANS	3 (10.3%)	13 (19.1%)	16 (16.5%)
IL-1 receptor antagonist anakinra	0	3 (4.4%)	3 (3.1%)
Anti-IL6 receptor tocilizumab	1 (3.4%)	3 (4.4%)	4 (4.1%)
Corticosteroid	1 (3.4%)	8 (11.8%)	9 (9.3%)
Levetiracetam	0	2 (2.9%)	2 (2.1%)
Dexamethasone	1 (3.4%)	8 (11.8%)	9 (9.3%)
Methylprednisolone sodium succinate	0	1 (1.5%)	1 (1.0%)
Pethidine	0	1 (1.5%)	1 (1.0%)
Outcome of ICANS			
N	3	13	16
Recovered or resolved	3 (100.0%)	13 (100.0%)	16 (100.0%)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Concurrent CRS			
Yes	3 (100.0%)	12 (92.3%)	15 (93.8%)
No	0	1 (7.7%)	1 (6.3%)
ICANS prior to CRS	0	0	0
ICANS following CRS	0	1 (7.7%)	1 (6.3%)

Key: CRS = Cytokine Release Syndrome, ICANS = Immune Effector Cell-Associated Neurotoxicity, TE = treatment-emergent.
[a] For 2 subjects in Phase 1b, the reported term is CAR-T cell Related Encephalopathy Syndrome (CRES). These events were reported prior to publication of the ASTCT consensus grading system and graded according to NCI-CTCAE version 5.0. For these 2 subjects, the maximum toxicity grade was Grade 1 and Grade 3, respectively according to NCI-CTCAE version 5.0
Note: ICANS evaluated according to the ASTCT consensus grading system (Lee et al 2019) or NCI-CTCAE version 5.0.
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of ICANS and concurrent CRS for which percentages are calculated with the number of subjects with ICANS in the all treated analysis set as denominator.
Note: Treatments for ICANS include treatments administered for ICANS and symptoms of ICANS.
Note: ICANS and CRS are considered to be concurrent if there is an overlap in the duration of these respective events.
[TSFAE26.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TSFAE26.SAS] 10NOV2020, 13:11
Source: Mod5.3.5.2/68284528MMY2001/Tab44

Other Neurotoxicity

Twelve subjects (12.4%) experienced Other Neurotoxicity not defined as ICANS assessed by the Investigator. Reported symptoms and severity of these events were varying (disturbances in consciousness, coordination and balance disturbances, movement disorders, mental impairment disorders, cranial nerve disorders, and peripheral neuropathies. The median time from cilta-cel infusion to first onset of other neurotoxicities was 26.5 days. Eight subjects (8.2%) experienced Grade 3 or 4 toxicities and 1 subject (1.0%) experienced a Grade 5 toxicity. At the time of clinical cut off, 6 of these 12 cases had resolved, 5 cases had not yet resolved, and 1 case was fatal.

Other Neurotoxicity Characterised by Movement and Neurocognitive Treatment-Emergent

Five of the above reported 12 subjects experienced a similar presentation of movement and neurocognitive TEAEs, reported to progress to an inability to work or care for oneself. These events had a median onset of 27.0 days from cilta-cel infusion. At the time of the clinical cut off 1 subject had

recovered, 1 subject had ongoing symptoms but was recovering, and 3 subjects died (neurotoxicity, septic shock, and lung abscess) and had ongoing neurotoxicity at the time of death. An analysis in these 5 patients was performed in order to identify underlying common (risk) factors. The movement and neurocognitive TEAEs in these 5 subjects appear to be potentially associated with a combination of 2 or more factors such as high tumour burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence.

TLS

Tumour lysis syndrome (TLS) was observed in one subject (1.0%), experiencing a Grade 3 increase in blood creatinine and Grade 4 TLS. These events were determined to be very likely related to cilta-cel, and both resolved.

Hypogammaglobulinaemia

The total number of subjects with hypogammaglobulinaemia was n=11(11.3%). Twenty-three subjects (23.7%) received IVIG as prophylaxis and 16 subjects (16.5%) were treated as response to the AE hypogammaglobulinaemia.

Infections

Infections occurred in 56 subjects (57.7%), with 19 subjects (20%) experiencing Grade 3 or 4 infections. Three subjects (3.1%) had Grade 5 infections (lung abscess, sepsis, and septic shock). Viral infections were reported for 22 subjects (22.7%), and bacterial infections were reported in 8 subjects (8.2%) with the most common infectious agent being Staphylococcal bacteraemia in 2 subjects (2.1%). Fungal infections and protozoal infections were reported in 1 subject (1.0%). Hepatitis B reactivation was not reported for any subject.

Other Adverse Events

Cytopenias

Cytopenias were reported for all 97 subjects (100.0%) in the All Treated population. Ninety-six subjects (99.0%) reported 1 or more Grade 3 or 4 cytopenic adverse events. No subjects experienced Grade 5 cytopenic adverse events. Among these events, 3 subjects (3.1%) experienced serious thrombocytopenia, and one subject (1.0%) experienced serious neutropenia. Overall, febrile neutropenia was observed in 10 subjects (10.3%) with 4 subjects (4.1%) experiencing serious febrile neutropenia.

There were 60 subjects with Grade 3 or 4 thrombocytopenia after Day 1 (cilta-cel infusion), 40 subjects (41.2% of the all treated population) had not recovered by Day 30. At Day 60, 25 subjects (25.8% of the all treated population) continued to experience Grade 3 or 4 thrombocytopenia.

There were 95 subjects with Grade 3 or 4 neutropenia after Day 1 (cilta-cel infusion), all but 29 subjects (29.9% of the all treated population) had recovered by Day 30. At Day 60, 10 subjects (10.3% of the all treated population) continued to experience Grade 3 or 4 neutropenia. There were 96 subjects with Grade 3 or 4 lymphopenia after Day 1 (cilta-cel infusion), all but 12 subjects (12.4% of the all treated population) had recovered by Day 30. At Day 60, 8 subjects (8.2% of the all treated population) continued to experience Grade 3 or 4 lymphopenia. There were some subjects who had initially recovered from cytopenias and developed Grade 3-4 cytopenias after Day 60: 6 (6.2%) subjects with thrombocytopenia, 12 (12.4%) reporting neutropenia and 30 (30.9%) presenting lymphopenia.

Hypersensitivity Reactions

Hypersensitivity reactions related to cilta-cel were reported in 4 subjects (4.1%). These reactions, all Grade 1, included flushing (3 subjects [3.1%]), chest discomfort (2 subjects [2.1%]), tremor (1 subject [1.0%]), tachycardia (1 subject [1.0%]), and wheezing (1 subject [1.0%]). All of these events resolved on the day of infusion.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious TEAEs were reported for 53 subjects (54.6%) with grade 3 or 4 TEAEs reported for 29 subjects (29%). The most common serious adverse event and reported in more than 5 patients was CRS (n=20; 20.6%) along with pneumonia (n= 5; 5.2%), sepsis (n=5; 5.2%) and ICANS (n=5; 5.2%). For forty-two subjects (43.3%) serious TEAEs related to cilta-cel have been observed. Grade 4 TEAEs were reported for 84 subjects (86.6%). At the time of clinical cut off, 14 subjects (14.4%) in the all treated population had died. All of these deaths occurred more than 30 days after cilta-cel infusion (range 45 to 694 days) and 2 were within 100 days of infusion. Six subjects (6.2%) experienced an adverse event with an outcome of death (Grade 5), all of which were deemed to be related to the study drug.

Table 33. Overall Summary of Treatment-emergent Adverse Events; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Any TEAE	29 (100.0%)	68 (100.0%)	97 (100.0%)
Study drug-related	29 (100.0%)	67 (98.5%)	96 (99.0%)
Any serious TEAE	11 (37.9%)	42 (61.8%)	53 (54.6%)
Study drug-related	10 (34.5%)	32 (47.1%)	42 (43.3%)
Maximum severity of any TEAE			
Grade 1	0	0	0
Grade 2	0	0	0
Grade 3	2 (6.9%)	5 (7.4%)	7 (7.2%)
Grade 4	26 (89.7%)	58 (85.3%)	84 (86.6%)
Grade 5	1 (3.4%)	5 (7.4%)	6 (6.2%)
TEAE with outcome death [a]	1 (3.4%)	5 (7.4%)	6 (6.2%)
Study drug-related	1 (3.4%)	5 (7.4%)	6 (6.2%)

Second primary malignancies

Second primary malignancies have been reported. Six subjects (6.2%) had haematologic malignancies [myelodysplastic syndrome in 5 subjects (5.2%) and acute myeloid leukemia in two subjects (2.1%), both of which resulted in death]. In one subject has been reported cutaneous/non-cutaneous invasive malignancies. One patient experienced acute myeloid leukemia and prostate cancer.

Table 34. Summary of Second Primary Malignancies During Study; All Treated Analysis Set

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Subjects with second primary malignancies	5 (17.2%)	2 (2.9%)	7 (7.2%)
Type			
Preferred term			
Hematologic malignancies	5 (17.2%)	1 (1.5%)	6 (6.2%)
Myelodysplastic syndrome	4 (13.8%)	1 (1.5%)	5 (5.2%)
Acute myeloid leukaemia	2 (6.9%)	0	2 (2.1%)
Cutaneous/non-invasive malignancies	0	1 (1.5%)	1 (1.0%)
Basal cell carcinoma	0	1 (1.5%)	1 (1.0%)
Non-cutaneous/invasive malignancies	1 (3.4%)	0	1 (1.0%)
Prostate cancer	1 (3.4%)	0	1 (1.0%)

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 23.0.
[TSFAE28.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TSFAE28.SAS] 23OCT2020, 13:22

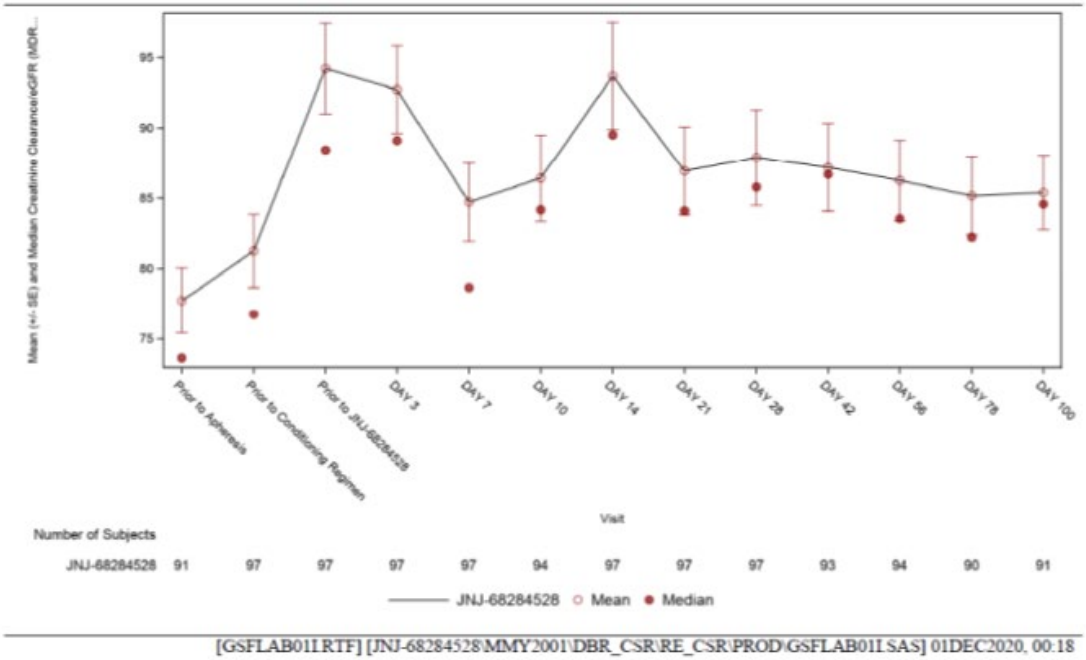
2.6.8.4. Laboratory findings

The most frequently laboratory findings all grades were electrolyte abnormalities [(hypocalcaemia n=31 (32.0%), hypophosphataemia n= 30 (30.9%), hyponatriaemia n=22 (22.7%)] and blood and lymphatic system abnormalities [anaemia grade 3 or 4 n= 92 (94.8%), neutropenia grade 3 or 4 n=96 (99.0%), thrombocygaemia grade 3 or 4 n=58 (59.8%) and lymphopenia n= 48 (49.5%).]

Creatinine Clearance

After an increase as a result of the conditioning regimen, baseline mean creatinine clearance was 94.23 mL/min/1.73m^2. Mean creatinine clearance reached a nadir of 84.72 mL/min at Day 7. After an increase in values through Day 14 with a mean value of 93.70 mL/min/1.73m^2 a second decline was observed by Day 100 toward recovery with a mean value 85.39 mL/min/1.73m^2 (range 18.8 to 216.8). Nearly the same trend was observed with the laboratory values for alanine aminotransferase and the infection parameters C-reactive protein and ferritin, while return to levels by Day 100 were more slowly.

Figure 28. mean (+/- SE) and Median Creatinine Clearance/eGFR (MDRD) (mL/min/1.73m^2) Over Time; All Treated Analysis Set (Study 68284528MMY2001)



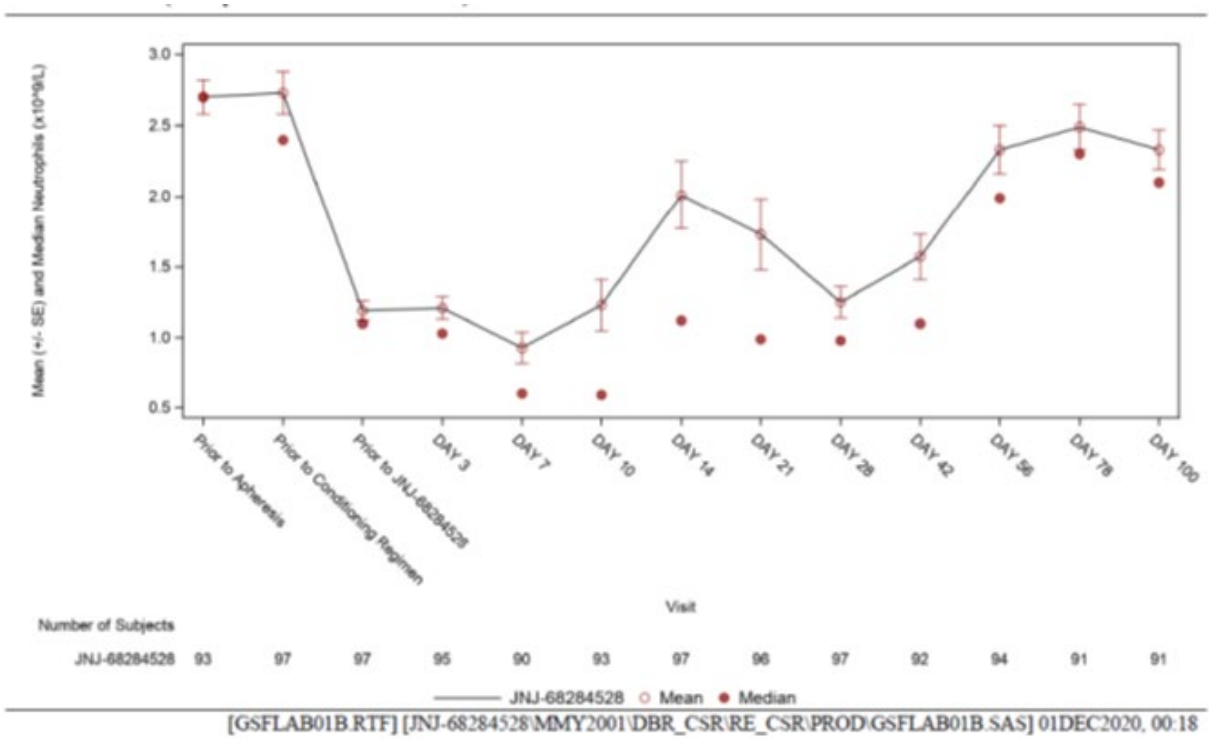
[GSFLAB01I.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\GSFLAB01I.SAS] 01DEC2020, 00:18

Haematology

Neutrophils

After a decline as a result of the conditioning regimen, baseline mean neutrophils values were 1.191 x10^9/L (range 0.11 to 3.60). Neutrophil counts reached an initial nadir of 0.932 x10^9/L at Day 7. After an increase in values through Day 14 with a mean value of 2.007 x10^9/L (range 0.00 to 13.17), a second decline was seen through Day 28 with a mean value 1.248 x10^9/L. By Day 100, values have returned to slightly above baseline levels.

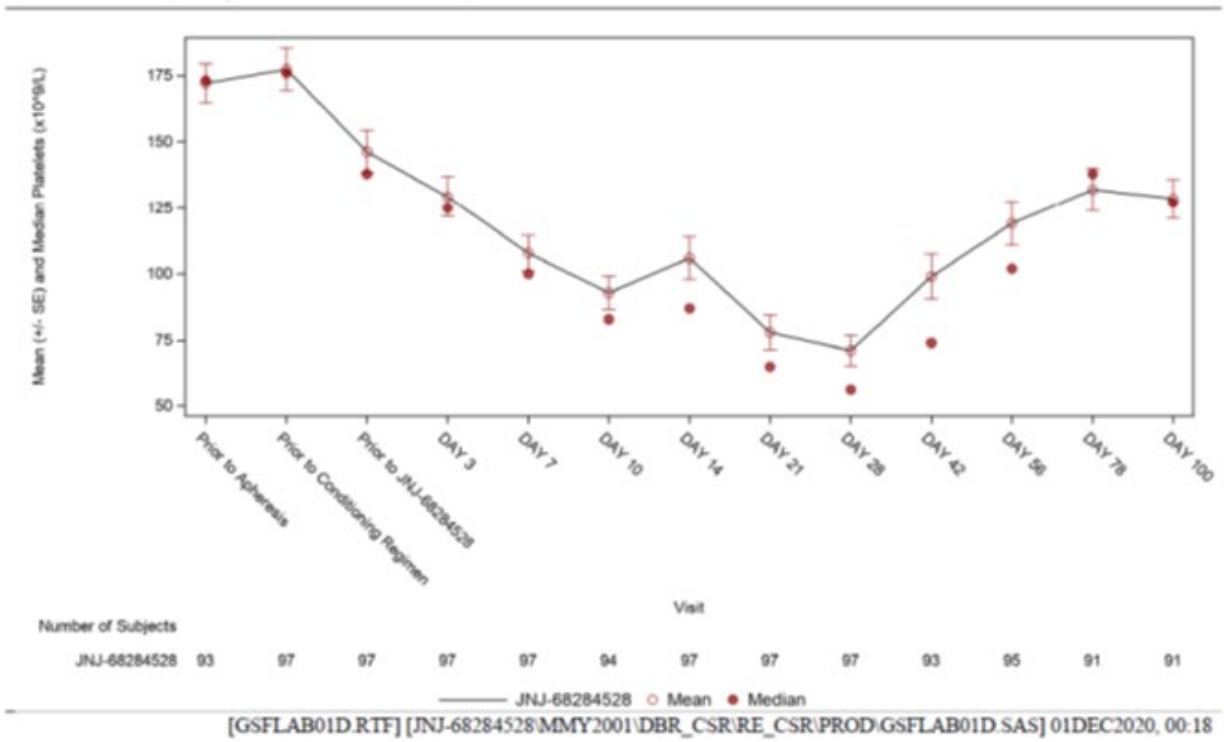
Figure 29. Mean (+/- SE) and Median Neutrophils (x10^9/L) Over Time; All Treated Analysis Set (Study 69284528MMY2001)



Platelets

After a decline in platelets as a result of the conditioning regimen, baseline mean platelet values were 146.4 x10^9/L. Platelet values declined until reaching a nadir of 71.2 x10^9/L at Day 28 then steadily increased toward recovery by Day 100.

Figure 30. Mean (+/- SE) and Median Platelets (x109/L) Over Time; All Treated Analysis Set (Study 60284528MMY2001)



Coagulation

In 19 subjects (19.6%), fibrinogen has been measured, and 9 of them (47.4%) were within normal limits. One subject (5.3%) experienced a grade 2 decrease, 5 subjects (26.3%) a grade 3 decrease and 4 subjects (21.1%) a grade 4 decrease. Grade 5-decreses have not been observed.

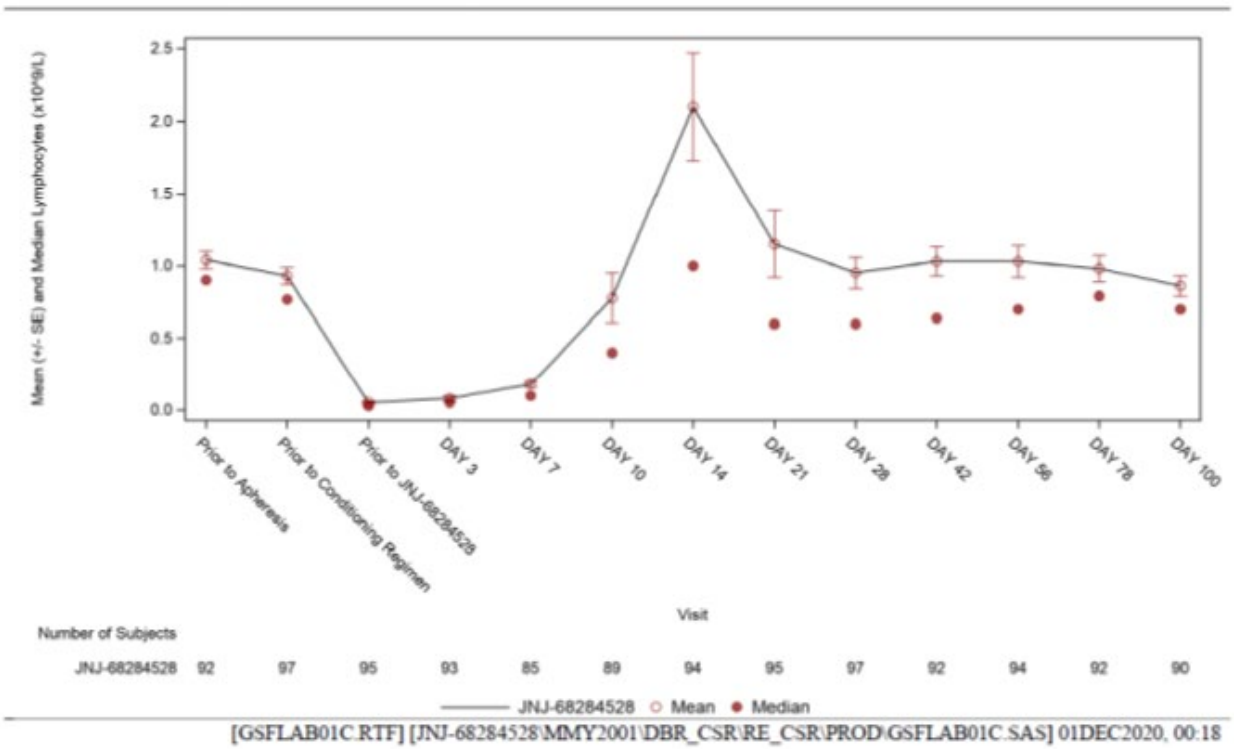
Activated partial thromboplastin time was assessed in 18 subjects (18.6%), and 11 of them (61.1%) were within normal limits. Six subjects (33.3%) experienced grade 1 prolonged activation time and 1 subject (5.6%) a grade 3 prolonged activation time. Grade 4 or 5 events have not been observed.

International Normalization Rate (INR) was assessed in 17 subjects (17.5%), and 11 of them (64.7%) were within normal limits. Four subjects (23.5%) experienced grade 1 increase and 2 subjects (11.8%) a grade 2 increase in INR.

Lymphocytes

After a decline in lymphocytes as a result of the lymphodepletion/conditioning regimen, baseline mean lymphocyte values were 0.077 $x10^9$/L. Lymphocyte values increased from baseline to a maximum mean value of 2.100 $x10^9$/L on Day 14 (range 0.0 to 25.92) followed by return to pre-conditioning values through Day 100.

Figure 31. Mean (+/- SE) and Median Lymphocytes (x109/L) Over Time; All Treated Analysis Set (Study 68284528MMY2001)



2.6.8.5. Safety in special populations (MMY2001)

Results on adverse events, considering frequency and grading, were evaluated among the subgroups of gender, age, race, total CAR-positive T cells infused, and bone marrow % plasma cells at baseline. There were no clinically meaningful differences in subgroup analyses observed. Rates of AEs, grade 3 and 4 AEs, and the occurrence of SAEs were similar. There is one exemption of patients (all within the phase 2 of MMY2001), who experienced the cluster of movement and neurocognitive TEAEs. Regarding sex, a slightly higher rate of SAEs was observed in male compared with female (59.6% vs. 47.5%, respectively), including SAEs of infections (26.3% vs. 15.0%), CRS (22.8% vs. 17.5%), ICANS (7% vs. 2.5%) and Parkinsonism (5.3% vs. 0).

2.6.8.6. Immunological events (MMY2001)

Among the 97 subjects in the all-treated population of the pivotal cohort of MMY2001 (29 subjects in Phase 1b and 68 subjects in Phase 2), 15 subjects (15.5%) were measured positive for anti-cilta-cel antibodies (9 subjects [31.0%] in Phase 1b and 6 subjects [8.8%] in Phase 2). For the ADA-positive subjects, titers of anti-cilta-cel antiodies started to be detectable around the Day 100 post-infusion. There were no major differences observed in the kinetic of expansion of cilta-cel between patients with positive ADA and patients with negative ADA. no clear evidence of association between ADA and cilta-cel persistence has been concluded.

2.6.8.7. Discontinuation due to adverse events (MMY2001)

There were a total of 30 discontinuations (26.5%), and the majority was attributed to PD. There was one adverse event of thrombocytopenia related to lymphodepletion and one case of cardiac arrest on day 14 post-apheresis, which both led to withdrawal of the respective patient.

MMY2003

Taking the all-treated population, which is larger (n=73), the overall summary of adverse events as of DCO 01February 2021 can be considered more or less in line with the reported adverse events as of prior safety cut-off for n=18 subjects.

Cytokines Release syndrome in study MMy2003 are reported in the table below.

Table 35 Summary of Treatment-emergent Cytokine Release Syndrome (CRS) Events; All Treated Analysis Set (Study 68284528MMY2003)

	Total
Analysis set: all treated	73
Number of subjects with CRS	57 (78.1%)
Maximum toxicity grade	
Grade 1	31 (42.5%)
Grade 2	23 (31.5%)
Grade 3	1 (1.4%)
Grade 4	2 (2.7%)
Grade 5	0
Time from initial infusion of JNJ-68284528 to first onset of CRS (days)	
N	57
Mean (SD)	7.4 (1.73)
Median	7.0
Range	(2; 11)
Duration of CRS [a] (days)	
N	56
Mean (SD)	4.2 (2.34)
Median	4.0
Range	(1; 11)
Interquartile range	(3.0; 5.0)
<=7 days	50 (89.3%)
Number of subjects with supportive measures to treat CRS [b]	55 (75.3%)
Anti-IL-6 receptor Tocilizumab	39 (53.4%)
IL-1 receptor antagonist Anakinra	5 (6.8%)
Corticosteroids	17 (23.3%)
IV fluids	9 (12.3%)
Vasopressor used	2 (2.7%)
Oxygen used	5 (6.8%)
Blow-by	0
Nasal cannula low flow (≤6L/min)	5 (6.8%)
Nasal cannula high flow (>6L/min)	1 (1.4%)
Face mask	0
Non-Rebreather mask	0
Venturi mask	0
Other	1 (1.4%)
Positive pressure	1 (1.4%)
Bilevel Positive Airway Pressure	1 (1.4%)
Analgesics/Anti-inflammatory	37 (50.7%)
Anti-infectives	31 (42.5%)
Antiepileptics	1 (1.4%)
Other	5 (6.8%)
Outcome of CRS	
N	57
Recovered or resolved	56 (98.2%)
Not recovered or not resolved	1 (1.8%)

Key: CRS = Cytokine Release Syndrome.
[a] Calculated for CRS with outcome recovered/resolved.
[b] Supportive measures to treat CRS and CRS symptoms are included.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of CRS for which percentages are calculated with the number of subjects with CRS in the all treated analysis set as denominator and duration of CRS for which percentages are calculated with the number of subjects with CRS duration calculated in the all treated analysis set as denominator.
Note: CRS evaluated according to the ASTCT consensus grading system (Lee et al 2019).

[TSFAE24.RTF] [JNJ-68284528\MMY2003\DBR_BLA_4MSU_2021\RE_BLA_4MSU_2021\PROD\TSFAE24.SAS] 01JUL2021, 12:28

Four subjects experienced treatment-emergent HLH, including 2 subjects for whom HLH was identified by the investigator as a serious symptom of CRS. HLH was the only serious symptom of CRS reported for more than 1 subject.

All-grade CAR-T cell neurotoxicity was reported for 15 subjects (20.5%) in the clinical safety update. All-grade ICANS was reported for 8 subjects (11.0%). Seven of 8 subjects had concurrent CRS at the time of ICANS onset, and ICANS had resolved for 7 of 8 subjects at the time of clinical cutoff.

Other Neurotoxicity not defined as ICANS was reported for 8 subjects (11.0%). At the time of the latest clinical cutoff for this Safety Update, 1 subject (1.4%) had movement and neurocognitive TEAEs characterised by bradykinesia, bradyphrenia, cognitive disorder, gait disturbance, and motor dysfunction in addition to serious encephalopathy.

Sixty-five of the 73 subjects (89.0%) included in the clinical safety update experienced 1 or more Grade 3 or 4 cytopenia adverse events and 30 subjects experienced serious treatment-emergent cytopenias. Treatment-emergent infections were reported for 23 subjects (31.5%) and serious infections were reported for 8 subjects (11.0%).

Five subjects had died as of the clinical cutoff for the clinical safety update: Three subjects experienced Grade 5 TEAEs (COVID-19 pneumonia, subarachnoid haemorrhage in the setting of angio-invasive aspergillosis, and C. difficile colitis. The subjects who died due to subarachnoid haemorrhage and C. difficile colitis both experienced HLH within 16 days of receiving cilta-cel infusion. A fourth subject experienced Grade 5 acute respiratory failure with onset on Day 161 in the setting of COVID-19 infection. A fifth subject died due to disease progression. HLH All-grade CRS was reported for 57 subjects (78.1%) in the updated analysis with Grade 3 and Grade 4 CRS reported for 1 subject (1.4%) and 2 subjects (2.7%), respectively.

There were no cases of TLS or second primary malignancy.

Summary of adverse reaction in the total safety data set

Table 36: Adverse reactions in Multiple Myeloma Patients Treated with JNJ-68284528 in MMY2001 and MMY2003 (Cohorts A, B, C, D)(N=179)

System organ class	Frequency	Adverse Reaction	Incidence (%)	
			All grades	grade ≥ 3
Infections and infestations	Very common	Bacterial infection*#	10	4
		Upper respiratory tract infection*	32	2
	Common	Sepsis[1]#	8	6
		Pneumonia*#	7	7
		Viral infection*	6	2
		Cytomegalovirus infection*	2	2
Blood and lymphatic system disorders	Very common	Neutropenia*	91	90
		Thrombocytopenia	73	52
		Anaemia	72	58
		Leukopenia	54	53
		Lymphopenia*	45	43
		Febrile neutropenia	12	11
		Coagulopathy*	15	2
		Hypofibrinogenaemia*	12	2
Immune system disorders	Very common	Cytokine release syndrome#	88	4
	Common	Haemophagocytic lymphohistiocytosis#	3	2

Table 36: Adverse reactions in Multiple Myeloma Patients Treated with JNJ-68284528 in MMY2001 and MMY2003 (Cohorts A, B, C, D)(N=179)

System organ class	Frequency	Adverse Reaction	Incidence (%)	
			All grades	grade ≥ 3
		Hypogammaglobulinaemia*	9	1
Metabolism and nutrition disorders	Very common	Hypocalcaemia	27	5
		Hypophosphataemia	26	8
		Decreased appetite	22	2
		Hypokalaemia	20	3
		Hypoalbuminaemia	19	1
		Hyponatraemia	17	3
		Hypomagnesaemia	16	0
Psychiatric disorders	Common	Delirium[2]	4	1
		Personality changes[3]	4	1
		Insomnia	9	0
Nervous system disorders	Very common	Encephalopathy[4]	22	4
		Immune effector cell-associated neurotoxicity syndrome	13	2
		Motor dysfunction[5]	15	4
		Dizziness*	17	1
		Headache	25	0
	Common	Aphasia[6]	7	1
		Paresis[7]	6	1
		Ataxia[8]	6	1
		Neuropathy peripheral[9]	9	2
		Tremor*	7	0
		Neurotoxicity#	2	1
Cardiac disorders	Very common	Tachycardia*	23	1
	Common	Cardiac arrhythmias[10]	6	2
Vascular disorders	Very common	Hypotension*	41	8
		Hypertension	15	4
	Common	Haemorrhage*#	7	2
Respiratory, thoracic and mediastinal disorders	Very common	Hypoxia*	12	5
		Dyspnoea[11#]	18	3
		Cough*	25	0
Gastrointestinal disorders	Very common	Diarrhoea	28	2
		Nausea	26	1
		Vomiting	18	0
		Constipation	17	0
		Abdominal pain*	10	0
Hepatobiliary disorders	Common	Hyperbilirubinaemia	6	2
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain*	43	3
Renal and urinary disorders	Common	Renal failure*	7	4
General disorders and administration site conditions	Very common	Pyrexia	88	6
		Fatigue*	40	6
		Chills	23	0
		Oedema*	22	2
		Pain*	12	1
Investigations	Very common	Transaminase elevation*	37	16

Table 36: Adverse reactions in Multiple Myeloma Patients Treated with JNJ-68284528 in MMY2001 and MMY2003 (Cohorts A, B, C, D)(N=179)

System organ class	Frequency	Adverse Reaction	Incidence (%)	
			All grades	grade ≥ 3
		Gamma-glutamyltransferase increased	13	7
		Serum ferritin increased	12	3
		Blood lactate dehydrogenase increased	11	0
		Blood alkaline phosphatase increased	10	3
	Common	C-reactive protein increased	8	2

Adverse reactions are reported using MedDRA version 23.0
[#] Contains fatal outcome(s).
[*] Based on grouped term.
[1] Sepsis includes bacteraemia, septic shock.
[2] Delirium includes agitation, delirium, hallucination, irritability, and restlessness.
[3] Personality changes includes apathy, flat affect, and reduced facial expression.
[4] Encephalopathy includes amnesia, bradyphrenia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, noninfective encephalitis, psychomotor retardation and sleep disorder.
[5] Motor dysfunction includes bradykinesia, cogwheel rigidity, dysgraphia, micrographia, muscle rigidity, myoclonus, parkinsonism, posture abnormal, and stereotypy.
[6] Aphasia includes dysarthria, slow speech, and speech disorder.
[7] Paresis includes cranial nerve paralysis.
[8] Ataxia includes balance disorder, and gait disturbance.
[9] Neuropathy peripheral includes peripheral motor/sensory neuropathy.
[10] Cardiac arrhythmias includes supraventricular/ventricular tachycardia.
[11] Dyspnoea includes respiratory failure.

2.6.8.8. Post marketing experience

n/a

2.6.9. Discussion on clinical safety

The overall assessment of the safety profile of cilta-cel is based on n= 97 subjects (pivotal cohort) plus n=9 subjects (supportive cohort), having been treated in the clinical trial MMY2001, a phase 1b/2 study, and on n=73 subjects treated in the supportive trial MMY2003, a phase 2 study. The median safety follow up for the 97 subjects in the pivotal cohort of the trial MMY2001 is 18 months. For the patients in the supportive Japanese cohort of MMY2001, the median safety FU is 8 months. The median safety follow-up for n=73 subjects treated in the supportive trial MMY2003 is the following: a median safety FU of 6 months for n=18 subjects and a median safety FU of more than 3 months for n= 51 subjects.

No specific critical issues have been identified in the safety profile of cilta-cel, which is reported to be in line with the one of the products in the same class. Most common adverse events documented were neutropenia (95.9%), anaemia (81.4%), thrombocytopenia (79.4%), leukopenia (61.9%) and lymphopenia (52.6%). Serious TEAEs (grade 3 or 4) have been reported for 53 subjects (54.6%). CRS and CAR T cell neurotoxicity (ICANS included) occurred in 94.8 % in the pivotal cohort of MMY2001 and in the supportive cohort of MMY2001 and in the supportive trial MMY2003. For the characterised safety adverse events (CRS, neurotoxicity, cytopenia, infection, etc), routine risk minimisation measures and risk management is widely described in section 4.4 of the SmPC. No consistent trends in the profile of adverse events could be identified by age, gender and the other subgroup analysis. For subjects older than 65 years compared with younger subjects, adverse events have been reported with

a slightly higher frequency. These were fatigue, oedema, confusional state and hypertension. These differences, however, currently do not allow for recommendations on dose adjustment for patients older than 65 years.

The majority of TEAEs recovered without sequelae, and most of the subjects (n=88; 90.7%) received supportive treatment for CRS, with 70 subjects (72.2%) receiving paracetamol and 67 subjects (69.1%) receiving tocilizumab, 21 subjects (21.6%) receiving corticosteroids, and 18 subjects (18.6%) receiving anakinra.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Additional safety data needed in the context of a conditional MA

With respect to (long-term) safety data on Carvykti further data are needed and will be provided according to SOBs, the long term follow up studies and the registry studies.

2.6.10. Conclusions on the clinical safety

The safety profile of cilta-cel can be regarded consistent with the current knowledge on CAR T cell therapy and related toxicities. Cilta-cel related adverse advents of CRS and neurotoxicity were common in both clinical trials MMY2001 and MMY2003, and most of them were graded mild to moderate. The AEs were generally manageable in the administered dose ranges of cilta-cel by following the management recommendations according to the guidance provided in the SmPC.

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

- In order to further characterise the long-term safety and efficacy of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall submit the results of the long-term follow-up study for participants previously treated with ciltacabtagene autoleucel. Due date: June 2043
- In order to further characterise the long-term safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of an observational post-authorisation safety study based on a registry. Due date: December 2042
- In order to further characterise the long-term safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of an observational post-authorisation safety study based on patient's data primarily from the EU region. Due date: December 2042

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

- In order to confirm the efficacy and safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have

demonstrated disease progression on the last therapy, the MAH should submit the final study results of the pivotal study CARTITUDE-1 (MMY2001). Due date: December 2022

- In order to confirm the efficacy and safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy, the MAH should submit the results of the Phase 3 study CARTITUDE-4 (MMY3002). Due date: December 2026

The CHMP endorses the CAT conclusion on clinical safety as described above.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important Identified Risks	Cytokine release syndrome (including HLH)
	Neurologic toxicities (including ICANS and other neurotoxicities)
	Prolonged cytopenia (excluding anaemia)
	Serious infections
	Hypogammaglobulinaemia
Important Potential Risks	Second primary malignancy
	Decrease in cell viability due to inappropriate handling or preparation of the product
	Tumour lysis syndrome
	Aggravation of Graft versus Host Disease
	Generation of replication competent lentivirus
Missing Information	Long-term safety
	Impact on pregnancy and lactation
	Use in patients with pre-existing autoimmune disease
	Use in patients with pre-existing neurodegenerative disorders
	Use in patients with active CNS involvement by malignancy
	Use in patients with chronic controlled HIV and HBV/HCV infection

2.7.2. Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Planned	Primary: To collect long-term follow-up data on delayed adverse events after administration of ciltacabtagene autoleucel, and to characterize and understand the long-term safety profile of ciltacabtagene autoleucel. Secondary: To collect additional long-term data on RCL, ciltacabtagene autoleucel persistence, efficacy, and OS. This study will include subjects who received ciltacabtagene autoleucel in company sponsored clinical trials. Consented subjects will be enrolled in this study once the individual study is completed and will be followed up for 15 years after their last dose of ciltacabtagene autoleucel.	Neurologic toxicities (including ICANS and other neurotoxicities) Prolonged cytopenia (excluding anaemia) Serious infections Hypogammaglobulinaemia Second primary malignancy Aggravation of GvHD Generation of RCL Long-term safety Impact on pregnancy and lactation Use in patients with chronic controlled HIV and HBV/HCV infection	Protocol submission FPI Interim report Final report	Jun 2021 Jun 2022 CSRs every 3 years from study start (ie, Q4 2025 and every 3 years thereafter) and routine PBRER and DSUR reporting Jun 2043
68284528MMY4004: An Observational Post-authorisation Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Planned	Primary: To evaluate the short- and long-term safety and risk of subsequent malignancy of ciltacabtagene autoleucel in adult patients with multiple myeloma. Secondary: To evaluate the effectiveness of ciltacabtagene autoleucel in adult patients with multiple myeloma. This study will include data from patients receiving ciltacabtagene autoleucel in the commercial setting, using data from patients consecutively enrolled in a registry as applicable. Other data sources may also include analysis from tumour samples or adverse events spontaneously reported to the MAH, where available.	CRS (including HLH) Neurologic toxicities (including ICANS and other neurotoxicities) Prolonged cytopenia (excluding anaemia) Serious infections Hypogammaglobulinaemia Second primary malignancy TLS Aggravation of GvHD Generation of RCL (to be addressed in the company-owned registry Study 68284528MMY4009) Long-term safety Impact on pregnancy and lactation Use in patients with pre-existing autoimmune disease Use in patients with pre-existing neurodegenerative disorders Use in patients with active CNS involvement by malignancy Use in patients with chronic controlled HIV and HBV/HCV infection	Draft Protocol Final Protocol FPI Interim report Final report	Feb 2022 Apr 2022 Jun 2022 Mar 2023 and annually thereafter and routine PBRER and DSUR reporting Dec 2042

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
68284528MMY4009: A Post-authorisation Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene autoleucel Planned	Primary: to evaluate the short- and long-term safety and risk of subsequent malignancy of ciltacabtagene autoleucel in adult patients with multiple myeloma. Secondary: To evaluate the effectiveness of ciltacabtagene autoleucel in adult patients with multiple myeloma.	CRS (including HLH) Neurologic toxicities (including ICANS and other neurotoxicities) Prolonged cytopenia (excluding anaemia) Hypogammaglobulinaemia Serious infections TLS Aggravation of GvHD Generation of RCL Second primary malignancy Long-term safety Impact on pregnancy and lactation Use in patients with pre-existing autoimmune disease Use in patients with pre-existing neurodegenerative disorders Use in patients with active CNS involvement by malignancy Use in patients with chronic controlled HIV and HBV/HCV infection	Draft Protocol	Feb 2022
			Final Protocol	Apr 2022
			FPI	Dec 2022
			Interim report	Mar 2023 and annually thereafter and routine PBRER and DSUR reporting
			Final report	Dec 2042
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				
Category 3 - Required additional pharmacovigilance activities				
Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Programme and the Product Handling Training Planned	Survey to measure the effectiveness of the HCP Educational Programme and the Product Handling Training: Guide for Health Care Professionals, an additional risk minimisation measure to advise and increase awareness of the risks of CRS (including HLH) and neurologic toxicity (including ICANS and other neurotoxicities) and how to minimize these. To measure information on awareness of the HCP of the existence of the Patient Alert Card, as well as the intention and time of providing it to the patients.	CRS (including HLH) Neurologic toxicity (including ICANS and other neurotoxicities) Decrease in cell viability due to inappropriate handling or preparation of the product	Protocol submission	3 months after EC decision
			Initiation of survey (wave 1)	within 18 months of availability of the approved educational materials in selected countries: Oct 2023
			Initiation of survey (wave 2)	within 3 years of availability of the approved educational materials in selected countries: May 2025

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	Product Handling Training, an additional risk minimisation measure intended to increase awareness of the potential risk of decrease in cell viability due to inappropriate handling or preparation of the product.		Reports	24 months and 3.5 years after approval of educational materials. Updates will also be reported in the PBRER and PSUR.

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
CRS (including HLH)	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 6.6 • PL Section 2 • PL Section 3 • PL section 4 • Requirement to have tocilizumab (or suitable alternative measures if not available and listed in the EMA shortage catalogue) and emergency equipment available prior to infusion and during the recovery period is included in SmPC Sections 4.2, 4.4, and 6.6. • Recommendation for monitoring patients daily for signs and symptoms of CRS for 14 days after dosing and periodically for an addition 2 weeks are included in SmPC Section 4.4. • Recommendation for patients to remain within the proximity of a qualified clinical facility for at least 4 weeks following infusion is provided in SmPC Section 4.4 and in PL Section 3. • Recommendation to counsel patients to seek immediate medical attention if signs and symptoms of CRS occur, and recommendation to evaluate the patient for hospitalisation and institute treatment at the first sign of CRS is provided in SmPC Section 4.4. • Recommendation to delay ciltacabtagene autoleucel infusion for patients with unresolved serious adverse reactions from preceding lymphodepleting or bridging chemotherapies (including cardiac toxicity and pulmonary toxicity), rapid disease progression, or clinically significant active infection is provided in SmPC Section 4.4. • Recommendations for the treatment of ongoing infections (which may increase the risk of a fatal CRS event) and	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4004: An Observational Post-authorisation Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorisation Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Programme and the Product Handling Training Final report: 3.5 years after approval of educational materials

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	recommendation to delay ciltacabtagene autoleucel infusion until any infections are resolved, are provided in SmPC Section 4.4. • Recommendation for potential early use of tocilizumab in patients with high tumour burden or early or persistent fever is provided in SmPC Section 4.4. • Recommendations for evaluation, treatment, and management of CRS are provided in SmPC Section 4.4. • Recommendations for treating high grade CRS that remains severe following use of tocilizumab and corticosteroids are provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors (particularly GM-CSF) during CRS is provided in SmPC Section 4.4. • Recommendation to evaluate for HLH in patients with severe or unresponsive CRS is provided in SmPC Section 4.4. • Recommendation for reducing baseline burden of disease with bridging therapy prior to infusion in patients with high tumour burden in SmPC Section 4.4. • Information regarding the incidence of CRS and the specific signs and symptoms seen in clinical trials is provided in SmPC Section 4.8. • Patients should inform their doctor or nurse immediately if CRS symptoms occur, as described in PL Section 2, and should seek medical help as described in PL Section 4. • Use restricted to physicians experienced in the treatment of haematological cancers **Additional risk minimisation measures:** • Controlled Distribution Programme and Availability of Tocilizumab • HCP Educational Programme • Patient Educational Programme	
Neurologic toxicities (including ICANS and other neurotoxicities)	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to consider reducing baseline disease burden with bridging therapy prior to infusion in patients with high tumour burden is included in SmPC Section 4.4. • Recommendation for monitoring patients daily for signs and symptoms of neurologic events for 14 days after dosing and periodically for an addition 2 weeks are included in SmPC Section 4.4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Topic of Interest Questionnaire (TOIQ) on cases of movement and neurocognitive toxicity **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorisation Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorisation Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Recommendations on monitoring patients for signs and symptoms of ICANS for 4 weeks after infusion and thereafter for other neurotoxicity are included in SmPC Section 4.4. • Recommendation to continue to monitor patients for signs and symptoms of neurologic toxicity after recovery from CRS and/or ICANS is provided in SmPC Section 4.4. • Recommendations on treating patients with symptoms of neurotoxicity, including intensive care supportive therapy (including steroids) for severe of life-threatening cases, are included in SmPC Section 4.4. • SmPC Sections 4.4 and 4.8 provide information on a subset of patients with a cluster of movement and neurocognitive adverse reactions that progressed in some to an inability to work or care for oneself. These events were associated with 2 or more factors at baseline such as higher tumour burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. • Instructions for treatment of neurotoxicities with early and aggressive supportive care (including steroids) in patients presenting with higher grade CRS or any grade ICANS is included in SmPC Section 4.4. • Recommendation to refrain from driving and engaging in hazardous occupations or activities in the 8 weeks following infusion is provided in SmPC Section 4.7. • Information regarding the incidence of neurologic toxicities (including ICANS and other neurotoxicities) and the specific symptoms seen in clinical trials is provided in SmPC Section 4.8. • Patients should inform their doctor or nurse immediately if symptoms of ICANS or other neurotoxicities occur, as described in PL Section 2, and should seek medical help for ICANS as described in PL Section 4. • Use restricted to physicians experienced in the treatment of haematological cancers **Additional risk minimisation measures:** • Controlled Distribution Programme and Availability of Tocilizumab • HCP Educational Programme • Patient Educational Programme	Final report: Q4 2042 Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Programme and the Product Handling Training Final report: 3.5 years after approval of educational materials
Prolonged cytopenia (excluding anaemia)	**Routine risk minimisation measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to monitor blood counts prior to and after ciltacabtagene autoleucel infusion is provided in SmPC Section 4.4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Recommendation to consider supportive care with transfusions for treatment of thrombocytopenia is provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors (particularly GM-CSF) during CRS is provided in SmPC Section 4.4. • Information regarding the incidence of prolonged cytopenia (excluding anaemia) is provided in SmPC Section 4.8. • Patients should inform their doctor right away if they have any symptoms of prolonged cytopenia, as described in PL Sections 2 and 4. • Use restricted to physicians experienced in the treatment of haematological cancers **Additional risk minimisation measures:** • None	68284528MMY4004: An Observational Post-authorisation Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorisation Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Serious infections	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to delay lymphodepletion therapy if a patient has clinically significant active infection is provided in Section 4.2. • Recommendation that infection prophylaxis should follow local guidelines, and that infections are known to complicate the course and management of concurrent CRS, are provided in SmPC Section 4.4. • Recommendation to delay ciltacabtagene autoleucel infusion until any clinically significant active infection is resolved is provided in SmPC Section 4.4. • Recommendation on monitoring patients for signs and symptoms of infection is provided in SmPC Section 4.4. • Recommendations for the management and treatment of febrile neutropenia are included in SmPC Section 4.4. • Recommendation to screen for HBV, HCV, and HIV prior to collection of cells for manufacturing is included in SmPC Section 4.4. • Recommendation to monitor immunoglobulin levels after treatment and treat according to standard guidelines, including administration of immunoglobulin replacement, antibiotic prophylaxis and monitoring for infection is included in SmPC Section 4.4. • Information regarding the incidence of serious infections is provided in SmPC Section 4.8.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorisation Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorisation Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Patients should tell their doctor right away if they have any signs or symptoms of infection, as described in PL Sections 2 and 4. • Use restricted to physicians experienced in the treatment of haematological cancers **Additional risk minimisation measures:** • None	
Hypogamma-globulinaemia	**Routine risk minimisation measures:** • SmPC Section 4.4 • SmPC Section 4.6 • SmPC Section 4.8 • Recommendation that immunoglobulin levels should be monitored after treatment and treated according to standard guidelines, including administration of immunoglobulin replacement, antibiotic prophylaxis and monitoring for infection, is described in SmPC Section 4.4. • Recommendation that assessment of immunoglobulin levels in newborns of mothers treated with ciltacabtagene autoleucel should be considered is provided in SmPC Section 4.6. • Information regarding the incidence of hypogammaglobulinaemia infections is provided in SmPC Section 4.8. • Use restricted to physicians experienced in the treatment of haematological cancers **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Second primary malignancy	**Routine risk minimization measures:** • SmPC Section 4.4 • Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. • Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4. • Use restricted to physicians experienced in the treatment of haematological cancers **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Topic of Interest Questionnaire (TOIQ) on cases of second primary malignancy **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Decrease in cell viability due to inappropriate handling or preparation of the product	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 6.3 • SmPC Section 6.4	**Additional pharmacovigilance activities:** Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Programme and the Product Handling Training

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• SmPC Section 6.6 • Instructions for preparation of ciltacabtagene autoleucel, including thawing, are provided in SmPC Section 4.2. • Shelf life and special precautions for storage of ciltacabtagene autoleucel are provided in SmPC Sections 6.3 and 6.4. • Special precautions for disposal and other handling are provided in SmPC Section 6.6. **Additional risk minimisation measures:** Product Handling Training	Final report: 3.5 years after approval of educational materials be determined based on results from the initial report
TLS	**Routine risk minimisation measures:** • Use restricted to physicians experienced in the treatment of haematological cancer **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Aggravation of GvHD	**Routine risk minimisation measures:** • SmPC Section 4.4 • PL Section 2 • Instruction that ciltacabtagene autoleucel infusion should be delayed if a patient has active GvHD is provided in SmPC Section 4.4. • Instruction for patients to tell their doctor prior to infusion of ciltacabtagene autoleucel if they have signs or symptoms of GvHD in provided in PL Section 2. • Use restricted to physicians experienced in the treatment of haematological cancer **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Generation of RCL	**Routine risk minimisation measures:** • Use restricted to physicians experienced in the treatment of haematological cancer **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Long-term safety	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Impact on pregnancy and lactation	**Routine risk minimisation measures:** • SmPC Section 4.6 • PL Section 2 • Recommendations that pregnancy status for females of childbearing age should be verified prior to starting treatment is provide in SmPC Section 4.6. • Recommendation on the need for effective contraception in patients who receive the lymphodepleting chemotherapy according to the corresponding prescribing information is provided in SmPC Section 4.6. • Recommendation to advise pregnant or breastfeeding women that there may be risks to the fetus or the breast-fed infant is provided in SmPC Section 4.6. • Recommendation that for any pregnant woman who receives ciltacabtagene autoleucel, assessment of immunoglobulin levels in newborns of mothers should be considered is provided in SmPC Section 4.6. • Patients should notify their doctor immediately if they are pregnant or think they may be pregnant following treatment with ciltacabtagene autoleucel, as described in PL Section 2. • Use restricted to physicians experienced in the treatment of haematological cancers	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: • None	
Use in patients with pre-existing autoimmune disease	**Routine risk minimisation measures:** • Use restricted to physicians experienced in the treatment of haematological cancers **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Use in patients with pre-existing neurodegenerative disorders	**Routine risk minimisation measures:** • SmPC Section 4.4 • PL Section 2 • A warning indicating that patients with significant CNS disease are likely to be more vulnerable to the consequences of adverse reactions observed with ciltacabtagene autoleucel and may require special attention is provided in SmPC Section 4.4. • Patients should tell their doctor before treatment with ciltacabtagene autoleucel if they have current or past nervous system disorders, as described in PL Section 2. • Use restricted to physicians experienced in the treatment of haematological cancers **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Use in patients with active CNS involvement by malignancy	**Routine risk minimisation measures:** • Use restricted to physicians experienced in the treatment of haematological cancers **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Use in patients with chronic controlled HIV and HBV/HCV infection	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 4.4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Instructions for screening of HBV, HCV, and HIV are included in SmPC Sections 4.2 and 4.4. • Use restricted to physicians experienced in the treatment of haematological cancers **Additional risk minimisation measures:** • None	68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042

2.7.4. Conclusion

The CAT considers that the risk management plan version 1.6 is acceptable.

The CHMP endorses the CAT conclusion on the RMP as described above.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP and CAT 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 CAT/CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28th February 2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that ciltacabtagene autoleucel has not been previously authorised in a medicinal product in the European Union.

The CAT/CHMP, based on the available data, consider ciltacabtagene autoleucel to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The applicant will submit the results of a user consultation with target patient groups on the package leaflet that 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 prior to placing the product on the market.

2.10.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group. The applicant specifically requested that in countries where there is a requirement to have more than one official EU language expressed in the product labelling, the text is provided in English only for the infusion bag label and outer cassette label. The package leaflet will however be provided in all EU official languages, as applicable. The applicant also confirmed that the Lot Information Sheet will be provided in the local language. The Group accepted the request due to the orphan status of the medicinal product and low prevalence of the disease, the fact that the medicinal product will not be delivered directly to the patient for self-administration, and the space constraints encountered on the immediate and outer labels. As part of the outcome the applicant was made aware that in Maltese the outer carton, labelling and package leaflet could also be distributed in English, in order to facilitate the logistics.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Carvykti (ciltacabtagene autoleucel) 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 has a PASS imposed either at the time of authorisation or afterwards; [REG Art 9(4)(cb), Art 10a(1)(a), DIR Art 21a(b), Art 22a(1)(a)];
- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Carvykti is indicated 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.

3.1.2. Available therapies and unmet medical need

Despite multiple therapeutic options, multiple myeloma remains incurable. All patients eventually relapse and become refractory to existing treatments.

The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, response and tolerance to the previous treatment, the number of prior treatment lines, the remaining available 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).

Treatment of RRMM patients who received two or more prior lines of therapy is becoming challenging (Dimoupoulos, 2015). For patients who have been exposed or are refractory to both bortezomib and lenalidomide, and have not received a mAb, Dara-Kd or Isa-Kd are suitable options.

The combinations of elotuzumab or isatuximab with pomalidomide and dexamethasone (EloPd and IsaPd, respectively) are suitable options for patients who have failed to $\geq$2 lines of previous therapies, including lenalidomide and a PI. The combination of daratumumab with pomalidomide and dexamethasone (DaraPd) is also a suitable option for patients who have failed $\geq$2 lines of previous therapies, including lenalidomide and a PI.

For triple-class refractory patients, selinexor-dexamethasone (Sd) or belantamab-mafodotin monotherapy may be suitable options.

The reported overall response rate (ORR) for approved therapies for the population of heavily pre-treated and refractory patients with multiple myeloma, is approximately 30% (not including CARt cell treatment).

With each successive relapse, symptoms return, quality of life worsens, and the chance and duration of response typically decreases. There is therefore 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.

3.1.3. Main clinical studies

Study MMY2001 is a Phase 1b-2, single arm, open-label, multicentre study investigating the safety and efficacy of cilta-cel in adult subjects with RRMM who had measurable disease at screening; had received at least 3 prior lines of therapy or are double refractory to a PI and an IMiD; received a PI, an IMiD, and anti-CD38 antibody; and had documented disease progression during, or within 12 months of their most recent anti-myeloma therapy. The study was conducted within the United States.

Subjects who satisfied all study inclusion and exclusion criteria during the Screening Phase were considered eligible for the study. Study intervention then comprised 3 steps: apheresis for collection of peripheral blood mononuclear cells, conditioning with cyclophosphamide and fludarabine, and infusion of cilta-cel. Subjects were considered enrolled at the time of apheresis and were assessed before each of these steps to ensure that he or she remained eligible to continue intervention.

Eligible subjects underwent apheresis for collection of peripheral blood mononuclear cells (PBMC) on the day of study enrolment. Subjects could receive bridging therapy if clinically indicated to maintain disease stability while cilta-cel manufacturing was underway. After notification by the sponsor that manufacture and quality testing of cilta-cel had been completed, eligible subjects received a conditioning regimen of intravenous (IV) cyclophosphamide 300 mg/m2 and fludarabine 30 mg/m2 in

3 daily doses. Five to 7 days after the start of the conditioning regimen, cilta-cel was administered as a single infusion with a total targeted dose of 0.75 x 106 CAR-positive viable T cells/kg (range: 0.5-1.0 x 106 CAR-positive viable T cells/kg).

The primary efficacy endpoint was ORR defined as the proportion of subjects who achieve a partial response (PR) or better as assessed by the Independent Review Committee (IRC) and based on International Myeloma Working Group (IMWG) criteria. Secondary efficacy endpoints were very good partial response (VGPR) or better rate (defined as the proportion of subjects who achieved a stringent complete response (sCR), complete response (CR), or VGPR as assessed by the IRC and based on IMWG response criteria), DOR, MRD negativity rate, time to response, PFS and OS.

The reported data in the current assessment report came from the data cutoff date of 1 September/2020, which corresponds to a time point 6 months after the last subject received his or her initial dose of cilta-cel. At the time of clinical cut off the median duration of follow-up for all subjects was 12.42 months.

An updated efficacy analysis has been also provided as of the clinical cut-off of 11 February/2021, the median duration of follow-up was 18.0 months (range: 1.5 months [subject died] to 30.5 months). The study will be completed 2 years after the last subject has received his or her initial dose of cilta-cel.

The cut-off defining success was set at ORR >50% and contextualisation of the data was provided in terms of an adjusted, indirect treatment comparison to an external control arm, based on a global, non-interventional, retrospective study (MAMMOTH study).

3.2. Favourable effects

In a median duration of follow-up of 18 months as per the second data cut off provided during the assessment, the primary endpoint was met with an ORR of 84.1% (95% CI: 76.0% to 90.3%) for the ITT population with 95 of 113 (ITT) subjects achieving a partial response (PR) or better as assessed by Independent Review Committee (IRC; based on International Myeloma Working Group [IMWG] criteria) and 97.9% (95% CI: 92.7% to 99.7%) for the mITT population.

Clinically meaningful activity was also observed for key secondary efficacy endpoints:

- VPGR or better rate was 81.4% (95% CI: 73.0% to 88.1%) for the ITT and 94.8% (95% CI: 88.4% to 98.3%) for the mITT population, whereas sCR was 69.0% (95% CI: 59.6% to 77.4%) for the ITT and sCR: 80.4% (95% CI: 71.1% to 87.8%) for the mITT population.
- Responses were durable with median duration of response (DoR) was 21.8 months (95% CI: 21.8 months, not estimable [NE]).
- Responses were rapid; the median time to first response was 0.95 months and a median time to best response was 2.56 months.
- MRD negativity at 10^{-5} threshold of sensitivity: 57.7% (N=56) with 34.0% (N=33) also achieving MRD negative CR/sCR.

3.3. Uncertainties and limitations about favourable effects

Data were collected in a small, single arm trial. This poses well know limitations with regards to interpretation of data, in particular with regards to assessment of time to event endpoints.

Clinical experience with cilta-cel is limited in terms of study size (97 subjects in the Phase 1b/2 Study MMY2001) and duration of follow-up (median 12.42 months; range: 1.5 months [subject died] to 24.9 months). In the context of the conditional marketing authorisation, additional information will be collected from the imposed studies as specific obligations.

Of note mainly young patients with a good performance (ECOG PS 0-1) were recruited in the study, which raises concern with regards to the external validity of data generated and extrapolation to the overall population of patients with relapse and refractory MM in clinical practice.

The evaluation of MRD negativity is impacted by the fact that not all subjects had evaluable samples.

Regarding the proposed commercial manufacturing process, comparability of commercial product with clinical trial lots could not be fully established at the quality level. Currently, only few clinical data are available for patients treated with lots from the commercial process, supporting the efficacy of these lots but not excluding slight differences. Additional data on such regards will be provided post authorisation through a post authorisation (REC) submission.

3.4. Unfavourable effects

Unfavourable effects of Carvykti correspond to the safety profile in the class of products; adequate risk minimisations and risk management have been included in the SmPC and the RMP in line with the expect safety profile of the product.

At least one TEAE any grade has been reported for the majority of subjects in MMY2001 and MMY2003. CRS was common, but most cases were documented as grade 1 or 2. Grade 3-4 CRS was reported in only 4 (4.1%) subjects.

Serious adverse events were reported for 53 subjects (54.6%) with Grade 3 or 4 serious adverse events reported in 29 subjects (29.9%). Six patients died due to treatment-related adverse events.

Cases of neurotoxicity, ICANS and other neurotoxicity summarised, occurred in 20.6% of the subjects. Aside from ICANS, a specific cluster of symptoms of neurotoxicity was observed in 5/12 subjects. patients. Symptoms included changes in movement (micrographia, tremors, etc.), cognitive functions (memory loss, disturbance in attention, etc.) and personality (reduced facial expression, flat affect, etc.), resulting in their inability to work. The data on those adverse events are not yet sufficient to draw solid conclusion, and the identified MNT will be further pursued as postauthorisation measures in the imposed safety and efficacy studies for the Conditional Marketing Authorisation. The number of deaths has increased by additional 7 patients since last DCO 20 September 2020, most of them due to PD.

Sixteen (16.5%) subjects experienced ICANS. Of these, there was 1 Grade 3 and 1 Grade 4 adverse event. The median time to onset of ICANS was of 8 days (range: 3, 12) with a median duration of 4 days (range: 1; 12). At the time of the DCO all events had resolved. In all cases ICANS was concurrent with CRS (15 patients) or occurred after CRS (1 patient; 4 days after CRS). All patients received treatment for ICANS, such as corticosteroids, anakinra and tocilizumab

Pancytopenia ≥grade 3 or 4 was observed in nearly all patients and considered related to the treatment. The exact mechanism that leads to pancytopenia remains elusive, but may be related to conditioning as well as cilta-cel.

Infections were reported by 56 (57.7%) subjects. For 19 (19.6%) subjects, these were of Grade 3-4 severity and Grade 5 infections were reported by 3 (3.1%) subjects, as discussed above. Viral infections were more commonly reported than bacterial infections (22.7% vs. 8.2%) although the latest seemed more severe.

All cases of second primary malignancy events have been assessed as not related to cilta-cel by the investigators.

According to the PD data, the overall incidence of antibodies to cilta-cel was 15.5%. Based on the current data, there was no clear evidence to suggest an association between ADA and cilta-cel kinetics of initial expansion and persistence, efficacy, or safety.

3.5. Uncertainties and limitations about unfavourable effects

The clinical safety data has been increased as described by both number of patients treated and follow-up periods, and may be considered sufficient for granting conditional marketing authorisation provided the current outstanding issues are addressed in a satisfactory manner. However, the fact remains that the cilta-cel safety profile is mainly based only on Study MMY2001, a single arm trial in heavily treated population and patients going through apheresis and conditioning regimen, even bridging therapy for a high percentage of subjects (75.3%).

3.6. Effects Table

Table 37. Effects Table for Carvykti, indication: RRMM. Data cut-off: 11 February 2021.

Effect	Short Description	Unit	Treatment	Cntrl	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR	Overall response rate (ORR) defined as the proportion of subjects who achieve a partial response (PR) or better as assessed by the Independent Review Committee (IRC) and based on International Myeloma Working Group (IMWG) criteria.	%	**ITT: 84.1** (n=113) (95% CI: 76.0, 90.3) **mITT**: **97.9** (n=97) (95% CI: 92.7, 99.7)	N/A	Single arm trial subject to selection bias	

Effect	Short Description	Unit	Treatment	Cntrl	Uncertainties / Strength of evidence	References
VGPR or Better Rate	Very good partial response (VGPR) or better rate was defined as the proportion of subjects who achieved a stringent complete response (sCR), complete response (CR), or VGPR as assessed by the IRC and based on IMWG response criteria.	%	**ITT: 81.4** (95% CI: 73.0 to 88.1) **ITT sCR: 69.0** (95%CI: 59.6, to 77.4) **mITT: 94.8** (95% CI: 887 to 98.3) **mITT sCR: 80.4** (95%CI: 71.1 to 87.8)	N/A	Supportive evidence	
MRD Negative Rate	Minimal residual disease (MRD) negativity rate is defined as the proportion of subjects who have negative MRD by bone marrow aspirate at any timepoint after initial dose of JNJ-68284528 and before disease progression or starting subsequent therapy or retreatment with JNJ-68284528.	%	**ITT: 49.6** (n=56) (95%CI: 40.0 to 59.1) **mITT: (57.7) (n=56)** (95%CI: 47.3 to 67.7)	N/A	Supportive evidence	

Effect	Short Description	Unit	Treatment	Cntrl	Uncertainties / Strength of evidence	References
Unfavourable Effects						
Deaths	Deaths after 30 days post cilta-cel infusion	%	14 (n=14 subjects)	N/A	Six deaths due to CAR-T related AEs [CRS/HLH (n=1), neurotoxicity (n=1), respiratory failure (n=1), lung abscess and ongoing neurotoxicity (n=1), sepsis (n=1), septic shock with ongoing neurotoxicity n=1)]	
CRS	≥ Grade 3	%	5.2	N/A	Strong evidence of relationship to the treatment	
CAR-T Cell Neurotoxicity	≥ Grade 3	%	10.3	N/A	Strong evidence of relationship to the treatment	
Cytopenias	≥ Grade 3	%	22.7	N/A	Strong evidence of relationship to the treatment	
TLS	≥ Grade 3	%	1	N/A	Very likely relationship to the treatment	
Hypogammaglobulinaemia	≥ Grade 3	%	2.1		Strong evidence of relationship to the treatment	

Abbreviations: ITT: Intention-to-Treat, mITT: modified ITT
Notes: ITT population is the enrolled population. mITT population is the treated population.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite multiple and increasing available therapeutic options, MM remains incurable and all patients finally relapse. With each relapse, the chance and duration of response typically decreases, and the disease becomes refractory to the existing treatments. It is acknowledged that there is a significant unmet need for new therapeutic options that can achieve a better control of the disease; provide deeper, more sustained responses; and yield better long-term outcomes including maintenance of QoL.

In this scenario, treatment with single infusion cilta-cel among the heavily pre-treated population of subjects in study MMY2001 showed efficacy with 84.1% of ORR in the ITT population (which includes 16 subjects who did not receive cilta-cel).

The reported ORR across multiple clinically relevant subgroups, including age, was consistent with that in the overall study population. Responses were durable, with a median DoR of 21.8 months; median follow up time for DoR of 18 months. Time to response was rapid and the depth of response in the ITT population was also notable for this highly refractory patient population.

However, even if an outstanding rate of durable responses with cilta-cel has been achieved in a heavily pre-treated RR MM population a number of uncertainties remain. This mainly relate to a limited sample size in the context of an uncontrolled pivotal trial hampering assessment of clinically relevant (long-term) outcomes and interpretation of subgroups. In addition, follow-up is not long, including for assessment of safety, and for a better understanding/estimation of reported results.

Characterisation of cilta-cel safety profile based mainly on the results of Study MMY2001 is challenging: the single arm trial design, a heavily treated population and patients going through apheresis and conditioning regimen, even bridging therapy for a high percentage of subjects (75.3%), hamper any data interpretation. Therefore, it is not feasible to differentiate post-infusion toxicity of cilta-cel from adverse events related to previous therapies or the conditioning regimen.

Another point to consider, as previously noted, is that overall, the safety population was comprised by relatively young patients with a good performance status, which raises concerns of the external validity of this data and the extrapolation to the overall population of patients with relapse and refractory MM in clinical practice, were no such strict restrictions can always be done.

Overall, the currently reported safety profile of cilta-cel, provided updated safety information included, is generally consistent with the current understanding of the mechanism of action of CAR T therapies. CRS was common but most cases were low grade and seemed to have been managed effectively with supportive therapy. CAR-T cell neurotoxicity, including ICANS and other neurotoxicity, was reported in 20.6% of subjects. However, a longer follow-up is still being needed to support the safety findings.

Development of second primary malignancies (SPM) is also a major concern with CAR-T treatment. Up to now, none of them reported in the clinical trials has been assessed related to cilta-cel.

In this regard, a 15-year follow-up of patients that have been included in the clinical trial in a long-term follow-up study (68284528-MMY4002) and the conduct and submission of the results of an observational post-authorisation safety study (68284528MMY4004) together with the conduct and submission of the results of a post-authorisation safety study to evaluate the long-term safety of patients treated with ciltacabtagene autoleucel (68284528MMY4009) have been proposed.

Comments received from HCP and patients are appreciated and consider that the primary and secondary objectives for the long-term FU studies MMY4002 and MMY4004, in essence, are considered

acceptable. Specific recommendations expressed inter alia were inclusion of 'physical and neurological examination' in the follow-up measurements among ECOG performance status and validated quality of life measurements in order to assess long-term effect of neurotoxicity/ICANS/CRS, when earlier occurred. Further requirements expressed, are assessment of the effect of cilta-cel on comorbid conditions such as extramedular metastases/plasmocytoma as additional objective and inclusion of haematologic disorders and infection any grade (and not only grade 3 and 4) in the list of 'new incidence of adverse events'. Those additional requirements are addressed in the LOI, as continuous and comprehensive assessment of long-term consequences of prior CRS, neurotoxicity and ICANS on patients having been treated with cilta-cel is of clinical importance. However, the proposed clinical trial protocols, and reporting of SAEs, will have to be further evaluated in the context of the applicant's response.

3.7.2. Balance of benefits and risks

Cilta-cel treatment leads to relevant response rates, which appear similar to a recently approved product and are much higher than the response rates reported with other current standard of care or in the literature. ORR, sCR or MDR negativity responses seem to be compelling and are considered clinically meaningful. Responses seem to be durable, however, uncertainty remains regarding the true magnitude and the duration of these effects, related to the uncontrolled trial, the limited patient numbers and the limited follow-up.

Based on the pivotal cohort of MMY2001, the safety profile of cilta-cel overall appears to be acceptable in view of the therapeutic context, the observed benefits, and the fact that any remaining uncertainties are being addressed in the long-term follow-up studies. Even if in clinical practice the toxicity could be slightly higher, this is not expected to change the main conclusions. Although the majority of the adverse effects are likely to occur during the first months of treatment, delayed immunological responses and secondary expansion cannot be ruled out without sufficient safety data. For the long-term safety, studies are proposed to further characterise the incidence and severity of selected adverse drug reactions.

3.7.3. Additional considerations on the benefit-risk balance

This application is based on a single arm trial which has been accepted for the purpose of MAA in scientific advice. Nevertheless, the evidence for efficacy generated in a single arm trial is less robust and subject to different types of bias, most notably selection bias. It is accepted that randomised trials are difficult to conduct in late line therapeutic setting as is the case here. Based on the observed data it is expected that this estimate for efficacy is reasonably precise for the studied population, but quite possibly biased. Even though ORR is accepted as an endpoint for regulatory purposes the ultimate patient benefit as reflected in OS cannot be reliably determined in a single arm trial. While some of the reported endpoints (ORR, sCR, MRD) suggest a significant efficacy of the therapy, the duration of efficacy cannot be fully estimated, as the efficacy follow-up is short and further data are required to estimate this aspect. As regards safety, several issues were identified that are still under further scrutiny. Although the subgroup analyses are reassuring, there is the observation that patients with good prognostic characteristics constitute the majority of the study population. From an efficacy perspective the main uncertainties therefore lie in the area of external validity with a small and a selected trial population. MoA is well understood and there are no doubts on causality of effects. There is a good understanding of the natural history of the disease. Historical data have been provided to put the trial data into context. While the results need to be interpreted with caution due to several limitations, the comparison of effects with real world data provides some further perspectives and adds additional context to interpret the findings. In summary the data provided for MA are not regarded as

comprehensive with respect to the duration of efficacy, and the exposure and length of follow-up for safety.

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was proposed by the CAT/CHMP during the assessment, after having consulted the applicant, and the applicant submitted a formal request during the assessment.

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. In addition, the product is designated as an orphan medicinal product.

Furthermore, the CAT considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed above.
- It is likely that the applicant will be able to provide comprehensive data by post-approval specific obligations as follow:
  As main deficiencies for lack of comprehensiveness, limited patient numbers and duration of follow-up were listed and the two ongoing studies (CARTITUDE-1 (MMY2001) and CARTITUDE-4 (MMY3002)) will indeed provide further longer-term efficacy and safety data and will also consolidate efficacy outcome. Furthermore, in the ongoing phase 3 trials considering the enlargement of the number of subjects treated with Carvykti in a clinical study setting and the comparative nature of the study should provide more solid time-to-event outcomes in the proposed indication.
  The following 2 ongoing studies are agreed to provide the necessary information in a reasonable time frame. The wording of the SOBs is as described below:
    - In order to confirm the efficacy and safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy, the MAH should submit the final study results of the pivotal study CARTITUDE-1 (MMY2001). Expected date for submission is 31 December 2022
    - In order to confirm the efficacy and safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy, the MAH should submit the results of the Phase 3 study CARTITUDE-4 (MMY3002). Expected date for submission is 31 December 2026
- Unmet medical needs will be addressed as follow: it is agreed that although there are authorised treatments of MM in the EU, all patients with this disease will eventually relapse after initial response and require further therapy. In patients who have received at least 3 prior therapies, and are refractory to at least one iMID, one PI, and one anti-CD38 antibody, there are available treatment options with a different mechanism of action, e.g. belantamab mafodotin or selinexor. These options, however, offer limited clinical benefit and the unmet medical need can be agreed. In the setting where patients are not triple refractory, the greater availability and efficacy of SOC treatment options with a different mechanism of action introduces higher uncertainty as to the true magnitude of cilta-cel effect. Nevertheless, the response rates achieved with cilta-cel in such less refractory patients seem compelling and major therapeutic advantage of cilta-cel can be considered demonstrated by providing a treatment alternative acting through a different mechanism of action and a distinct safety

profile. In this context, it is noted that the observed response rate and duration of response with cilta-cel is also expected to address the unmet medical need in the targeted patient population to a similar extent than idecabtagene vicleucel (Abecma) i.e. the first genetically modified autologous immunotherapy consisting of human T cells transduced with lentiviral vector (LVV) encoding a CAR that recognises BCMA, which is conditionally authorized in the EU for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an iMID, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. As benefit-risk balance on basis of the current data is regarded positive, an additional therapy option for RR multiple myeloma patients with three or more previous systemic therapies is considered beneficial.

The CHMP endorses the CAT conclusion on conditional marketing authorisation as described above.

3.8. Conclusions

The overall B/R of Carvykti is positive, subject to the specific obligations and conditions imposed for the approved Conditional Marketing Authorisation in order to obtain further clinical data to generate a comprehensive clinical data set and inform the long-term efficacy and safety profile of the product.

The CHMP endorses the CAT conclusion on Benefit Risk balance as described above

4. Recommendations

Similarity with authorised orphan medicinal products

The CAT by consensus decision is of the opinion that Carvykti is not similar to Darzalex, Farydak, Imnovid, Kyprolis, Ninlaro, Blenrep and Abecma within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

The CHMP endorses the CAT conclusion on similarity as described above.

Outcome

Based on the CAT review of data on quality, safety and efficacy, the CAT considers by consensus decision that the benefit- risk balance of Carvykti is favourable in the following indication(s):

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

The CAT therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Based on the draft CHMP opinion adopted by the CAT and the review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit- risk balance of Carvykti in 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 is favourable and 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**

Controlled distribution programme and availability of tocilizumab

To minimise the risks of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity) associated with the treatment of Carvykti the MAH will ensure that centres that dispense Carvykti are qualified in accordance with the agreed controlled distribution programme by:

- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Carvykti infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the MAH will ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.

Carvykti will only be supplied to centres that are qualified and only if the Healthcare professional (HCP) involved in the treatment of a patient has completed the HCP educational programme.

Educational programme: Prior to the launch of Carvykti in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

HCP educational programme

The MAH shall ensure that in each Member State where Carvykti is marketed, all HCPs who are expected to prescribe, dispense, and administer Carvykti shall be provided with guidance:

- to increase awareness of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity) and its appropriate monitoring, prevention, and management, including the importance of on-site availability of tocilizumab before treating a patient.
- to facilitate patient counseling relevant information.
- on reporting these serious adverse reactions associated with Carvykti.
- before treating a patient, to ensure that tocilizumab for each patient is available on site; in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site

Medicinal product handling training

The MAH shall ensure that all HCPs and other personnel involved in the transport, storage, thawing, preparation, or handling of Carvykti shall be provided training:
- to increase awareness of the important potential risk of decrease in cell viability due to inappropriate handling or preparation of the medicinal product.
- to provide guidance on precautions to take before handling or administering Carvykti (i.e., how to check the medicinal product prior to administration, how to thaw, and how to administer).

Patient educational programme

To inform and explain to patients:
- the risks of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity) associated with Carvykti and increase awareness of symptoms requiring immediate medical attention.
- the need to carry the patient alert card at all times and share it with any HCP providing care (including emergency) so the HCP can contact the CAR-T treating HCP.

The CHMP does endorses the CAT conclusion on the additional risk minimisation measures.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term efficacy and safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of the long-term follow-up study for participants previously treated with ciltacabtagene autoleucel.	June 2043
In order to further characterise the long-term efficacy and safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of an observational post-authorisation safety study to evaluate the safety of multiple myeloma patients treated with ciltacabtagene autoleucel.	December 2042
In order to further characterise the long-term efficacy and safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of a post-authorisation	December 2042

safety study to evaluate the long-term safety of patients treated with ciltacabtagene autoleucel.	

The CHMP endorses the CAT conclusion on the obligation to conduct post-authorisation measures as described above.

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 Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy, the MAH should submit the final study results of the pivotal study CARTITUDE-1 (MMY2001).	December 2022
In order to confirm the efficacy and safety of Carvykti in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy, the MAH should submit the results of the Phase 3 study CARTITUDE-4 (MMY3002) comparing the efficacy and safety of Carvykti vs. PVd or DPd in subjects with relapsed and lenalidomide-refractory multiple myeloma.	December 2026

The CHMP endorses the CAT conclusion on the specific obligation to complete post-authorisation measures for the conditional marketing authorisation as described above.

New Active Substance Status

Based on the review of available data on the active substance, the CAT considers that ciltacabtagne autoleucel is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

The CHMP endorses the CAT conclusion on the new active substance status claim.