swissmedic

Date: 22 November 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

CARVYKTI

International non-proprietary name: ciltacabtagene autoleucel

Pharmaceutical form: dispersion for infusion

Dosage strength(s): The finished product is packaged in one infusion bag containing a dispersion for infusion of 3.2 x 10^6 to 1 x 10^8 CAR-positive viable T cells suspended in a cryopreservative solution.

Route(s) of administration: for intravenous use only

Marketing authorisation holder: Janssen-Cilag AG

Marketing authorisation no.: 67956

Decision and decision date: approved on 08.08.2022

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for ciltacabtagene autoleucel in the above-mentioned medicinal product.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 14 May 2020.

2.2 Indication and dosage

2.2.1 Requested indication

CARVYKTI is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody.

2.2.2 Approved indication

CARVYKTI is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, with at least a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

2.2.3 Requested dosage

Summary of the requested standard dosage:
A single dose of CARVYKTI is 0.5-1.0 x 10^6 CAR-positive viable T cells per kg body weight up to a maximum of 1 x 10^8 CAR-positive viable T cells suspended in either a 30 mL or 70 mL patient specific infusion bag.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	16 June2021
Formal control completed	21 June 2021
List of Questions (LoQ)	27 September 2021
Response to LoQ	23 March 2022
Preliminary decision	18 May 2022
Response to preliminary decision	18 July 2022
Final decision	8 August 2022
Decision	approval

3 Medical context

Adopted from Dimopoulos et al. 2021 “Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up”
Multiple myeloma is a rare disease. Worldwide, an estimated 160,000 incident cases of multiple myeloma were diagnosed in 2018, with a crude incidence rate of 2.1 cases per 100,000 persons and a world population age-standardised incidence rate of 1.7 cases per 100,000 persons (Bray 2018). There was a 126% increase in the global incidence of multiple myeloma between 1990 and 2016 (Cowan 2018). Variation in the incidence of multiple myeloma is marked across countries; countries with older populations and greater access to diagnoses have more cases (Cowan 2018).
Multiple myeloma is a plasma cell neoplasm that accounts for 1%-1.8% of all cancers and is the second most common haematological malignancy with an estimated incidence in Europe of 4.5-6.0/100,000/y. 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. One third of patients are >75 years at diagnosis (Dimopoulos 2021).
Multiple myeloma is one of the most common haematological malignancies in Switzerland (Cantoni 2014).
Myeloma incidence is strongly related to age, with the elderly experiencing the highest incidence rates. The median age at diagnosis is approximately 70 years; 37% of patients are younger than 65 years, 26% are between the ages of 65 and 74 years, and 37% are 75 years of age or older (Palumbo 2011).
Multiple myeloma is more common in men than women. Globally, the age-standardised incidence rate of multiple myeloma was estimated to be 2.1 per 100,000 in men and 1.4 per 100,000 in women in 2018 (Bray 2018).
Risk factors for developing multiple myeloma include the following:

- age
- sex (men are slightly more likely to develop multiple myeloma than women)
- race (multiple myeloma is more than twice as common among blacks compared with whites)
- exposure to radiation
- family history
- workplace exposures (some studies have suggested that workers in certain petroleum-related industries may be at a higher risk)
- obesity
- other plasma cell diseases (people with monoclonal gammopathy of undetermined significance (MGUS) or solitary plasmacytoma are at higher risk)
  (American Cancer Society 2018; Normandin 2019).

Multiple myeloma is a cytogenetically heterogeneous clonal plasma cell proliferative disorder and is almost always preceded by an asymptomatic premalignant stage termed MGUS. MGUS is present in roughly 3% to 4% of the population over the age of 50 years. The rate of progression of MGUS to multiple myeloma is 0·5–1% per year, but the precise risk is affected by the concentration of the monoclonal protein, type of monoclonal protein, serum free light chain ratio, bone marrow plasmacytosis, proportion of phenotypically clonal plasma cells, and presence of immunoparesis (Rajkumar 2014).
Anticipated adverse events in this population as multiple myeloma progresses include infections, cytopenia, renal failure, osteolytic bone disease, hypercalcaemia, and hyperviscosity (Blimark 2015). Pancytopenia in multiple myeloma may be attributed to several reasons. Most often it is due to the plasma cell proliferation replacing normal haematopoietic cells. Other causes include fas-ligand-mediated apoptosis or cytokine-mediated bone marrow failure or even renal failure-induced erythropoietin deficiency. A study reported pancytopenia in 9% of multiple myeloma patients; however, they also reported 71% of patients having haemoglobin of <8.5g/dL and thrombocytopenia of <100 x 109/L in 16.4% of cases (Sridevi 2015). A review summarised that renal insufficiency (serum creatinine >1.3 mg/dL) is found in almost 50% of patients with multiple myeloma at presentation, and severe renal insufficiency is observed in 15% to 20% of cases (Korbet 2006). Since myeloma patients are mostly elderly and have less muscle mass, the actual prevalence of renal insufficiency may be underestimated on the basis of serum creatinine (Eleutherakis-Papaiakovou 2007). Multiple myeloma is the disease with the highest incidence of bone involvement among the malignant diseases. A study from Denmark

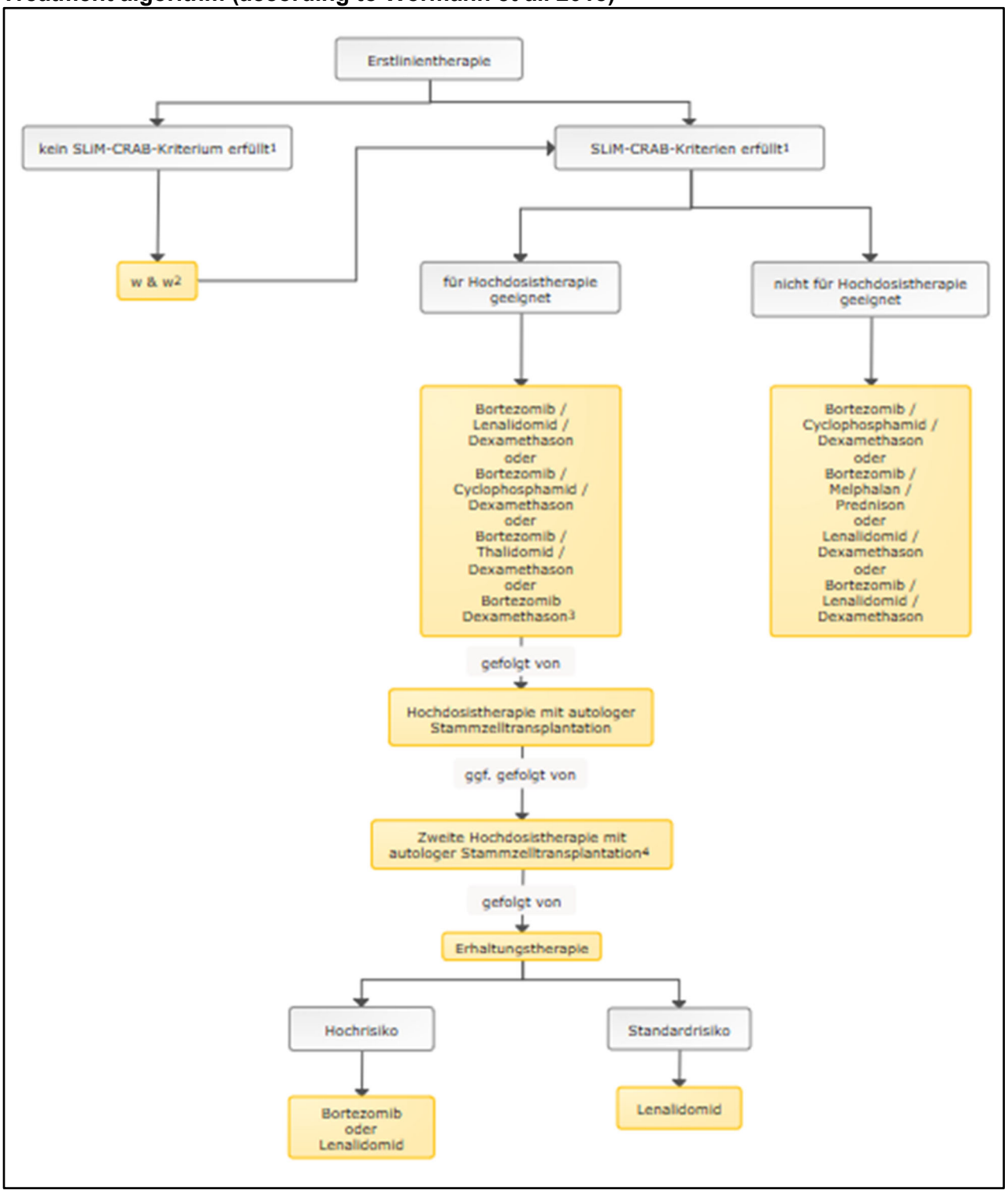
showed that multiple myeloma patients had a 2-fold increase in the risk of fractures compared to controls (Thorsteinsdottir 2020). Hyperviscosity syndrome is a rare complication of multiple myeloma that occurs most frequently in immunoglobulin G myeloma, with a reported incidence of 4.2% (Kistler 2017).

The aggressiveness of multiple myeloma depends upon several variables that impact disease biology. Genetic abnormalities seen in the myeloma cells are one of the strongest predictors of tumour aggressiveness. The Revised International Staging System ([R-ISS] (Udupa 2020)) divides myeloma into 3 stages incorporating cytogenetic abnormalities and lactate dehydrogenase in addition to the parameters in R-ISS. For patients with R-ISS stage I, the median OS was not reached and the median PFS was 66 months, compared with OS and median PFS of 83 months and 42 months, respectively, for patients with R-ISS stage II and OS, and median PFS of 43 and 29 months, respectively, for patients with R-ISS stage III (Palumbo 2015).

Patients with multiple myeloma tend to be elderly and therefore subject to age-related comorbidities. For instance, the elderly population may be at an increased risk of chronic diseases including ischaemic cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), diabetes, cancer, degenerative central nervous system diseases, and depression (Kaweme 2021).

Worldwide, there were 106,105 deaths (1.1% of total cancer deaths) from multiple myeloma reported in 2018. The age-standardised mortality rate of multiple myeloma in Europe was estimated to be 2.2 per 100,000 in 2012 (Ferlay 2013). The age-standardised mortality rate worldwide was estimated at 1.0 per 100,000 (Ferlay 2015).

Treatment algorithm (according to Wörmann et al. 2018)



[1] symptomatic
[2] w&w - watch and wait
[3] The efficacy of bortezomib/dDexamethasone is lower than that of the triple combinations
[4] in patients with risk factors

Treatment options

Treatment options for multiple myeloma have substantially improved over time and vary depending on the aggressiveness of the disease, underlying prognostic factors, physical condition of the patient, and existing co-morbidities (Moreau 2017). The introduction of PIs (e.g. bortezomib, carfilzomib, and ixazomib), histone deacetylase inhibitors (e.g. panobinostat, vorinostat), immunomodulatory agents

(e.g. thalidomide, lenalidomide, and pomalidomide), and monoclonal antibodies (mAB, e.g. daratumumab, isatuximab, and elotuzumab) has opened up numerous therapeutic avenues for patients with multiple myeloma. Despite these therapeutic achievements, the disease recurs and remains incurable, thus warranting the need for novel therapeutic approaches (Pinto 2020).
One of the most significant improvements in the response criteria is the introduction of minimal residual disease (MRD) both in the bone marrow (using either next-generation sequencing or next-generation flow cytometry) and outside the bone marrow (using positron emission tomography-computed tomography [PET-CT]; imaging MRD) (Kumar et al. 2016).
MRD negativity in the bone marrow in patients who have achieved conventional complete response (CR) consistently correlates with prolonged progression-free survival (PFS) and overall survival (OS) in both newly diagnosed multiple myeloma and relapsed/refractory multiple myeloma (RRMM) patients. MRD negativity using deep sequencing is a major prognostic factor in multiple myeloma (Munshi et al. 2017, Perrot et al. 2018).
A recent study revealed that patients who are refractory to 2 PIs, 2 ImiDs, and a CD38 mAb have a median OS of 5.6 months only (Gandhi et al 2019).
For patients who have been exposed or are refractory to both bortezomib and lenalidomide and who have not received a mAb, daratumumab/ carfilzimib/ dexamethasone or isatuximab/ carfilzimib/ dexamethasone are suitable options. The combinations of elotuzumab or isatuximab with pomalidomide and dexamethasone are suitable options for patients who have failed ≥2 lines of previous therapies, including lenalidomide and a PI, based on the results of 2 studies. The first was a Phase II study in which patients were randomly assigned to receive either elotuzumab/ pomalidomide/ dexamethasone (n = 60) or pomalidomide/ dexamethasone (n = 57). After a follow-up period of 9 months, the median PFS was 10.3 months in the elotuzumab/ pomalidomide/ dexamethasone group and 4.7 in the pomalidomide/ dexamethasone group (HR = 0.54; P = 0.008) (Dimopoulos et al. 2018). The second was a Phase III study in which patients were randomised to receive either isatuximab/ pomalidomide/ dexamethasone (n = 154) or Pd (n = 153). At a median follow-up of 11.6 months, median PFS was 11.5 months in the isatuximab/ pomalidomide/ dexamethasone group versus 6.5 months in the pomalidomide/ dexamethasone group (HR = 0.596; P = 0.001) (Attal et al. 2019). Elotuzumab/ pomalidomide/ dexamethasone and isatuximab/ pomalidomide/ dexamethasone were approved by Swissmedic in this setting.
For triple-class refractory patients, selinexor-dexamethasone or belantamab mafodotin monotherapy may be suitable options (Dimopoulos et al. 2021). Selinexor-dexamethasone and belantamab mafodotin are not approved in Switzerland.
On 26 March 2021 the Food and Drug Administration approved idecabtagene vicleucel (Abecma, Bristol Myers Squibb) for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. This is the first FDA-approved cell-based gene therapy for multiple myeloma. More recently, the Committee for Medicinal Products for Human Use (CHMP) of the European Union adopted a positive opinion regarding approval of a BMCA directed CAR-T cell therapy (Abecma) for treatment of relapsed and refractory multiple myeloma. The final decision of the European Commission is outstanding (European Medicines Agency 2021).

Drugs approved for treatment of multiple myeloma in Switzerland:
- Daratumumab
- Bortezomib
- Mephalan
- Plerixafor
- Carfilzomib
- Panobinostat
- Ixazomib citrate
- Doxorubicin
- Zolendronat
- Elotuzumab
- Lenalidomide
- Pomalidomide

4 Quality aspects

CARVYKTI is a customised, patient-specific gene therapy. The process begins with the collection of autologous T cells from the patient's peripheral blood cells by apheresis and ends with the infusion of the modified reprogrammed T cells.
The selected autologous T cells are expanded and genetically engineered using an integrating, replication-incompetent lentiviral vector carrying the transgene that encodes for the chimeric antigen receptor (CAR) targeting B-cell maturation antigen (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. CAR expression directs the transduced T cells toward the BCMA-expressing tumour cells. Upon binding to the target cells, the CAR promotes T cell activation, expansion, and elimination of these malignant cells.
CARVYKTI is classified as an *ex vivo* gene therapy product.

4.1 Drug substance

CARVYKTI (ciltacabtagene autoleucel) is comprised of *ex vivo* genetically engineered autologous T cells directed against B-cell maturation antigen (BCMA). BCMA is primarily expressed on the surface of malignant multiple myeloma B-lineage cells, but also on non-degenerate late-stage B cells and plasma cells.

BCMA is a potential target for treatment of B-cell malignancies. The BCMA CAR is a second-generation chimeric antigen receptor composed of an extracellular antigen binding domain and an intracellular activation and signalling domain.

Lentiviral vector LCAR2SIN_KAN
The lentiviral vector LCAR2SIN_KAN carrying the transgene for anti-BCMA-CAR is used for *ex vivo* gene transfer into the target cells. The vector is based on human immunodeficiency virus 1 (HIV1) containing necessary regulatory sequences and the anti-BCMA-CAR transgene. The vector is replication-incompetent, containing self-inactivating sequences, and pseudo-typed with vesicular stomatitis virus (VSV) envelope glycoprotein.

The vector is produced in the HEK-293F production cell line. HEK-293F cells are expanded and transiently transfected with a mix of transfer and helper plasmids carrying the transgene and the sequences necessary for the production and assembly of the viral vector. A 2-tiered cell bank system was established and qualified according to ICH Q5. The supernatant of the cell cultures containing the vector is collected, sterile filtered, and subjected to several purification and concentration steps. The buffer is exchanged by diafiltration and the final formulation is then filled into sterile primary containers.
Sufficient information on the vector manufacturing process and the control strategy was provided. The process was validated and the presented data of several batches demonstrated that the manufacturing process is capable of producing vector batches that consistently meet predefined acceptance criteria.
The ability of the LCAR2SIN_KAN vector to infect and stably integrate the transgene into the genome of the target cells was confirmed. Successful production and the activation of the functional anti-BCMA CAR in the patient's cells upon transgene integration was shown.
The vector release specification contains a panel of tests to confirm identity, purity, biological activity, and to determine the potency. In addition to other safety attributes, the absence of replication-competent viruses is confirmed.
A shelf-life for the LCAR2SIN_KAN vector under long-term storage conditions of -70 ± 10°C was proposed and accepted.

CARVYKTI (ciltacabtagene autoleucel, cilta-cel)

Ciltacabtagene autoleucel is a customised, autologous chimeric antigen receptor T cell (CAR-T) therapy composed of a suspension of expanded T cells derived from the patient's peripheral blood. T cells are genetically modified *ex vivo* to express a CAR transgene directed against BCMA.

Peripheral blood cells are collected in a process called leukapheresis. One manufacturing run initiated from a single patient's leukapheresis corresponds to 1 batch of the personalised medicinal product.

Leukapheresis is performed in qualified centres and the collected cells are cryopreserved and transported under validated conditions to the product manufacturing facility for further processing.

An apheresis centre qualification programme is in place to ensure proper oversight of the apheresis process and to initiate and maintain both chain of custody (COC) and chain of identity (COI).

The patient's T cells are selected from the incoming leukapheresis material and undergo activation with suitable reagents followed by transduction using a replication-incompetent lentiviral LCAR2SIN_KAN vector.

The cells are then expanded in selective medium. The transduced and expanded cells are washed and concentrated prior to formulation into the final product.

Overall, the manufacturing process including process parameters and controls was described in sufficient detail. Performance parameters for cilta-cel manufacturing are classified as critical process parameters (CPP) or non-critical process parameters (nCPP) and are evaluated as controllable within proven acceptable ranges (PARs).

In-process controls (IPCs), CPPs and nCPPs, and processing times are listed for each unit operation for the manufacturing process. Compositions of cell culture media and solutions were provided.

Manufacturing process development including process changes was adequately described and supporting data from comparability studies between batches manufactured by the proposed commercial process, clinical batches, and development batches were provided.

Process performance qualification (PPQ) was performed using material from healthy donors. PPQ runs fulfilled predefined validation acceptance criteria for process parameters, process controls, and the predefined release specifications.

Transport of the leukapheresis material and transport of the cryopreserved intermediate in qualified shippers were validated.

Extended characterisation of the PPQ batches demonstrated that the product cellular composition was within expected ranges based on clinical batches, with expected variability that can be attributed to the high variability of the patients' starting material.

The biological and physical properties and the subcellular composition and biological activity of the drug substance were extensively characterised using state-of-the-art analytical methods. Product-related and process-related impurities were addressed and, wherever applicable, their elimination to acceptable levels was demonstrated.

4.2 Drug product

CARVYKTI is a single-dose cell suspension for infusion containing the anti-BCMA CAR-expressing viable T cells in a dispersion for infusion. The recommended dose is 0.5 - 1.0 x 10^6 CAR-positive viable T cells per kg body weight, up to a maximum of 1 x 10^8 CAR-positive viable T cells, suspended in either a 30 mL or a 70 mL patient-specific infusion bag.

The drug product is delivered cryopreserved in infusion bags from the manufacturing site and is infused back into the patient at the qualified centre after thawing.

The cryopreservation medium (CryoStor CS10) containing dimethyl sulfoxide in a final concentration of 5% (v/v) is the only excipient used for formulation of the drug product.

The primary container used for storage of CARVYKTI is an ethylene vinyl acetate (EVA) cryopreservation bag. Two sizes of the same type of container can be used depending on the calculated volume needed for the required dose. The suitability of the primary container was demonstrated. Each cryopreservation bag is stored in an individual aluminium cryocassette.

The manufacturing process of the finished product consists of formulation of the expanded cells with the cryopreservation medium, followed by filling into the primary containers, inspection, and labelling. Subsequently, the drug product is cryopreserved and stored in the vapour phase of liquid nitrogen.

The manufacturing process was validated as a continuous process. The transport of the cryopreserved finished product to the health care centres takes place in the vapour phase of liquid nitrogen using qualified shippers. The transport was appropriately validated.

The release specification covers all relevant tests to confirm identity, purity, potency, and safety. Analytical methods were adequately described. Non-compendial procedures have been validated according to ICH guidelines and compendial methods were verified for corresponding matrices.

CARVYKTI is a cell-based therapy and not amenable to terminal sterilisation or terminal viral inactivation. Thus, adventitious agent safety relies on the proper control and qualification of all materials used in the process. Microbial contamination control within the manufacturing process is ensured by using aseptic techniques and closed system manipulations whenever possible. A mycoplasma release test on harvest day is performed. Raw materials used are procured sterile or are sterile filtered prior to use in manufacture. Aseptic processing was adequately validated. Confirmation of sterility is done at the level of the final product. Sufficient information on the viral safety of the reagents and for the lentiviral vector was provided.

The drug product is stored at temperatures not higher than ≤-120 °C in the vapour phase of liquid nitrogen in the original container. Adequate stability data have been presented to establish the shelf-life.

The drug product is thawed at 37 °C prior to administration. Hold-time stability of the product for 2.5 hours, when exposed to ambient light conditions and room temperature, has been adequately demonstrated. It is recommended that CARVYKTI should be infused within 2.5 hour after thawing. Compatibility with different commercial infusion sets made from different polymeric construction materials, dual-spike, and single-spike infusion sets, was demonstrated.

4.3 Quality conclusions

Satisfactory and consistent quality of the active substance and finished product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Ciltacabtagene autoleucel is an autologous BCMA-targeting Chimeric Antigen Receptor T-cell (CAR-T) immunotherapy developed for the treatment of multiple myeloma. Autologous peripheral blood T-cells are genetically modified using a lentiviral (LV) vector controlled by a human elongation factor 1 alpha promoter. The coding sequence of the LV vector is composed of (i) the cytoplasmic signalling domains CD3 zeta with the co-stimulatory domain CD137, (ii) a CD8 alpha hinge with transmembrane domain, (iii) a human CD8 alpha signal peptide linker, and (iv) 2 BMCA-targeting nanobodies (V_HH1 and V_HH2; 2 llama-derived single-domain of heavy chain-only Ab). Despite the complete absence of the VL and constant domain, nanobodies have comparable binding capacity, specificity, and stability as compared to conventional antibodies. The target dose is 0.75 x 10^6 CAR+ viable T cells/kg patient weight. In nonclinical studies, ciltacabtagene autoleucel is identified as either JNJ-68284528 or LCAR-B38M CAR-T for studies conducted/sponsored by Janssen or by Legend, respectively.

LAB003-His, a construct comprising the identical BCMA-binding domain of the CAR expressed by ciltacabtagene autoleucel demonstrated high specificity to human BCMA but no binding to mouse or non-human primate BCMA. A binding affinity in the pico- to nanomolar range was observed for LAB003-His against human BCMA. Cell viability, proliferation, and cytotoxicity against BCMA-positive cells was demonstrated with LV transduced BCMA-targeting CAR-T cells from healthy and multiple myeloma (MM) patients in *in vitro* and *in vivo* studies.

In cytotoxicity and cytokine release assays, the BCMA-positive cell lines RPMI8226 cells and Raji cells were co-cultured with BCMA-targeting CAR-T cells and showed a BCMA-dependent cytotoxicity and cytokine release. BCMA-targeting CAR-T cells against RPMI8226 cells demonstrated an increased response as compared to Raji cells.

In vivo proof-of-concept studies using a MM xenograft model in immunodeficient NCG mice demonstrated that following a single-dose of ciltacabtagene autoleucel injection, tumour growth was significantly inhibited and survival increased. A dose-effect relationship of these effects as well as increased persistence and expansion was demonstrated in a CAR-T dose-escalation study. Moreover, no tumour regrowth was noted following re-challenge of cured mice. Comparability studies have assessed the cytotoxicity potential of the different generations of LV used in the studies and data suggest comparable activation and cytotoxic potential. Moreover, *in vivo* studies including second, second/third, and third generation LV showed comparable anti-tumour activity.

An off-target study carried out with ciltacabtagene autoleucel, donor matched un-transduced T cells, and LAB003-His investigated their potential binding interaction to HEK293 expressing human proteins. Ciltacabtagene autoleucel demonstrated binding to BCMA and claudin-9. Despite the high degree of extracellular domain homology of the members of the claudin family to claudin-9, no binding interaction with any family member was determined. Further investigations showed a partial overlap of the extracellular domain of claudin-9 with the BMCA binding epitope. Claudin-9 overexpressing cells from cell lines showed binding to LAB003-His and JNJ-68284528 but no binding interaction was detected with primary immune cells. Whereas claudin-3, claudin-4, and claudin-6 partially overlap the alignment sequence of claudin-9 with the BCMA binding epitope, none of these claudins interacts with BCMA.

Due to the inherent nature of the autologous CAR-T cells and the absence of interaction of their extracellular component (LAB003-His) with investigated animal model BCMA-positive cells, neither secondary pharmacodynamics nor safety pharmacology studies were provided. Taking into account that the observed on-target/off-tumour effects are predominantly restricted to the target B-cell population, this is considered acceptable.

5.2 Pharmacokinetics

Conventional ADME studies are not applicable to CAR-T cell therapy products. Moreover, no pharmacologically relevant model has been available for this product. The pharmacokinetics data provided are restricted to *in vivo* absorption and persistence for ciltacabtagene autoleucel. Taking into account the aforementioned limitations, this is considered acceptable. As part of the pharmacodynamics dose-escalation study in NCG mice, dose-dependent persistence and absorption of ciltacabtagene autoleucel was quantified by quantitative polymerase chain reaction (qPCR) of the CAR gene copy number in whole blood samples. CAR-positive cells showed an increased CAR gene copy number at Day 35 followed by a decrease to baseline level at Day 48. In the course of this study, no statistically significant increase could be observed with un-transduced T cells. Taking advantage of known biodistribution patterns of similar products, the potential for biodistribution of ciltacabtagene autoleucel was evaluated. Literature evaluation indicates that CAR-T cells primarily distribute to the lung, liver, spleen, and potentially to other organs when infiltrated by tumour cells.

5.3 Toxicology

A non-GLP toxicology study performed in cynomolgus monkeys was provided to assess the single-dose toxicity of autologous CAR-T cells. Due to the absence of binding between LAB003-His and rhesus monkey BCMA expressing on HEK293T cells or recombinant cynomolgus monkey BCMA proteins, potential on-target toxicities cannot adequately be evaluated. Hence, this model cannot be considered a relevant model and findings from it are of limited value.
Cynomolgus monkey ciltacabtagene autoleucel was generated from cynomolgous peripheral blood samples following a similar-to-human CAR-T cell manufacturing process. There was no IL-2 independent growth of transduced T cells as compared to donor matched un-transduced primary cells. Statistical mean differences in proliferation of transduced cells between healthy donors and MM patients was noted. This was considered not relevant, primarily due to similar differences observed in un-transduced cells between healthy donors and MM patients.

A single dose was injected into 2 cynomolgus monkeys (5×10^6 or 40×10^6 cells/kg) preconditioned with cyclophosphamide. Serum chemistry, complete blood count, body weight, and temperature were monitored prior to post dosing. Note that neither the percentage of CAR-positive cells, T cell viability, nor the T cell purity was determined. In addition, the persistence and absorption of cynomolgus monkey ciltacabtagene autoleucel was not assessed. At study completion, both animals survived and a decrease in white blood cell, red blood cell, and haemoglobin counts was observed in both animals following IV infusion of autologous ciltacabtagene autoleucel. Considering that no cyclophosphamide and/or vehicle control group was included in the study, the potential impact of cyclophosphamide on these measured effects could not be assessed.

Given the lack of relevant non-clinical animal model and the single-dose regimen of ciltacabtagene autoleucel, no repeat dose toxicity study was performed.

Although no conventional genotoxicity or carcinogenicity studies have been performed, integration studies to investigate the comparability to known vector integration profiles, common integration sites, integration diversity, and proto-oncogene proximity integration analysis were carried out. Post-infusion ciltacabtagene autoleucel was generated from 7 MM and 3 healthy donors. Integration site analysis showed a high degree of polyclonality with neither signs of clonal dominance nor clustering at oncogenic hotspots. A typical integration profile of LV vectors showing limited presence of clones close to cancer-associated genes was observed.

No local tolerance, reproductive, developmental, or germline transmission studies have been conducted. In view of the therapeutic indication, clinical history with similar CAR-T products, and the expression of BCMA in tissues, this is considered acceptable.

5.4 Nonclinical conclusions

Final risk assessment

The submitted nonclinical data support the proposed mechanism of action of ciltacabtagene autoleucel. Note that none of the studies provided were GLP compliant. Study findings demonstrated LV vector-mediated transfection of BCMA-targeting CAR expression, specific activation upon binding to BCMA antigen, and functional cytotoxicity against BCMA-positive cells. An *in vivo* proof-of-concept was carried out in a multiple myeloma xenograft model in NCG mice with LV-mediated BCMA-targeting CAR expression, exhibiting tumour inhibition and enhanced survival. Pharmacokinetic findings were restricted to the investigation of the persistence of the CAR-T cells within the pharmacodynamics dose-escalation study of a multiple myeloma model in NCG mice. The provided *in vivo* safety data were generated from a study in cynomolgus monkeys and are of limited value as this model is considered not relevant for investigation of potential safety risks of ciltacabtagene autoleucel in humans. Off-target toxicity was evaluated in various *in vitro* studies showing BCMA expression predominantly restricted to B lineage cells. Claudin-9 was identified as a potential off-target, and its binding interaction with BCMA-targeting CAR-T cells was observed with engineered cell line overexpressing CLND9 but not in primary cells. Obvious claudin-9 off-target effects of ciltacabtagene autoleucel were not reported in clinical study reviews. Based on the aforementioned off-target findings, the potential claudin-9 off-target-related consequences for treated patients are expected to be low. Analysis of LV vector integration profiles into T cell genome was carried out and the results demonstrated a high degree of polyclonality and lentivirus-like integration patterns, suggesting a low risk of insertional oncogenicity. Based on the aforementioned supporting non-clinical findings and the poor prognosis associated with the therapeutic indication, it can be concluded that an unacceptable risk for ciltacabtagene autoleucel is not expected. From a non-clinical point of view, ciltacabtagene autoleucel can be approved.

6 Clinical aspects

6.1 Clinical pharmacology

The clinical pharmacology assessment of ciltacabtagene autoleucel was conducted in adult subjects (men and women) ≥18 years of age, with a documented diagnosis of multiple myeloma according to International Myeloma Working Group diagnostic criteria. The first subject in the Phase 1b portion of the study was dosed on 27 August 2018. The first subject in the Phase 2 portion of the study was dosed on 2 July 2019 and the last subject was dosed on 24 February 2020.
Preliminary evidence supporting the utility of ciltacabtagene autoleucel CAR-T cell immunotherapy was provided in the first-in-human Legend-2 study: a Phase 1, single-arm, open-label, multicentre study to determine the safety and efficacy of ciltacabtagene autoleucel CAR-T cells.
Study 68284528MMY2001 (CARTITUDE-1) is a pivotal Phase 1b-2, open-label, multicentre study to evaluate the safety and efficacy of JNJ-68284528. The co-primary objectives of Study 68284528MMY2001 were:

1. to characterise the safety of JNJ-68284528 and establish the dose (RP2D) (Phase 1b), and
2. to evaluate the efficacy of JNJ-68284528 (Phase 2).

Additionally, data from patients with heavily pre-treated, relapsed, and refractory multiple myeloma with additional supportive safety data from a cohort of subjects from Japan (n = 9) and subjects in the Phase 2 Study 68284528MMY2003 (CARTITUDE-2) were evaluated.
The pharmacokinetic and/or pharmacodynamic properties of ciltacabtagene autoleucel were studied in 97 subjects with relapsed and refractory multiple myeloma in the Phase 1b/2 study conducted at multiple sites in the US. Biomarker analyses included: soluble BCMA (soluble BCMA), cytogenetics, and cytokine profiling. Minimal residual disease (MRD) negativity was evaluated as a potential surrogate for progression-free survival (PFS) and overall survival (OS). The potential presence of replication-competent lentivirus (RCL) was also evaluated. The key efficacy endpoint included in the E-R analysis was overall response rate (ORR). Other efficacy endpoints (duration of response [DOR], PFS, and OS) were also explored. All PK parameters were calculated using conventional non-compartmental methods using actual times of sampling. Population PK analysis used a nonlinear mixed-effects approach to generate the PK parameters.
The targeted dose (equivalent to the recommended Phase 2 dose [RP2D]) is a single infusion of ciltacabtagene autoleucel 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). The median dose of ciltacabtagene autoleucel administered in Study 68284528MMY2001 (CARTITUDE-1) was 0.709 x 10^6 cells/kg (range: 0.51-0.95 x 10^6 cells/kg). The median dose administered was similar in Phase 1b (0.722 x 10^6 cells/kg [range: 0.52-0.89 x 10^6 cells/kg) and Phase 2 (0.707 x 10^6 cells/kg [range: 0.51-0.95 x 10^6 cells/kg]). The median duration of the ciltacabtagene autoleucel infusion was 19.0 minutes (range: 5-71 minutes); 20.0 minutes (range: 14-38 minutes) in Phase 1b and 17.0 minutes (range: 5-71 minutes) in Phase 2.
According to pivotal Study 68284528MMY2001 (CARTITUDE-1):
Ciltacabtagene autoleucel pharmacokinetics were characterised by CAR transgene levels in peripheral blood and bone marrow. The pharmacokinetic parameters (see table below) were determined for ciltacabtagene autoleucel based on serial pharmacokinetic measurements obtained in both transgene levels (by a validated quantitative polymerase chain reaction, Taqman method) and CAR+ T cells (by validated flow cytometry methods).
The ciltacabtagene autoleucel transgene exposure parameters maximum observed analyte concentration (C_{max}) and 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-below quantification limit) analyte concentration ($AUC_{0\text{-}last}$) showed higher mean values in Phase 2 than in Phase 1b, but with high inter-individual variability (%CV: 49.8%-123.6%) and different sample sizes (29 in Phase 1b and 68 in Phase 2). Detectable ciltacabtagene autoleucel transgene exposures in bone marrow indicate a distribution of ciltacabtagene autoleucel from systemic circulation to bone marrow.
Classical pharmacological concepts such as ADME and other pharmacokinetic and pharmacodynamic aspects are hardly applicable to adoptive cell therapies including CAR-T cells. Pharmacokinetic

parameters are used to describe cellular kinetics in terms of expansion (“absorption”, “distribution”) and persistence (“elimination”): whereas the maximum expansion and the time when the maximum expansion is reached are described by C_{max} and t_{max}, AUC, $t_{1/2}$ and t_{last} provide information about the persistence of CAR-T cells.
After a single infusion of the median dose of 0.709 x 10^6 CAR-positive viable T cells/kg (range: 0.51-0.95 x 10^6 cells/kg), mean ciltacabtagene autoleucel transgene levels in blood samples were below the quantification limit (<50 CAR-T copies per µg genomic DNA) until Day 7 or 10. The median t_{max} of ciltacabtagene autoleucel transgene levels in blood was 13 days.

Table 3 (Summary of clinical pharmacology studies): Summary of pharmacokinetic results of ciltacabtagene autoleucel transgene levels in blood after a single infusion

Parameter (Unit)	Mean (SD) Median (Range) for t_{max}, t_{last}, and t_{bql}		
	Phase 1b n=29[a]	Phase 2 n=68[b]	Phase 1b + 2 n=97[c]
C_{max} (copies/µg genomic DNA)	38965 (19408)	52568 (29311)	48501 (27362)
t_{max} (day)	11.06 (8.75 – 25.68)	12.83 (8.71 – 54.59)	12.71 (8.71 – 54.59)
C_{last} (copies/µg genomic DNA)	1191 (2628)	4195 (10003)	3297 (8588)
t_{last} (day)	95.91 (26.15 – 438.02)	99.72 (20.04 – 240.04)	99.69 (20.04 – 438.02)
t_{bql} (day)	67.03 (27.04 – 274.96)	98.08 (27.89 – 231.95)	79.74 (27.04 – 274.96)
$AUC_{0\text{-}28d}$ (copies*day/µg genomic DNA)	347250 (200513)	571649 (425174)	504561 (385428)
$AUC_{0\text{-}6m}$ (copies*day/µg genomic DNA)	553271 (444586)	1256186 (1552207)	1036998 (1348041)
$AUC_{0\text{-}last}$ (copies*day/µg genomic DNA)	578710 (463849)	1165580 (1344425)	990124 (1182015)
$t_{1/2}$ (day)	16.4 (17.9)	25.4 (31.7)	22.3 (27.9)

$AUC_{0\text{-}28d}$=area under the analyte concentration-time curve from time 0 to 28 days; $AUC_{0\text{-}6m}$=area under the analyte concentration-time curve from time 0 to 6 months; $AUC_{0\text{-}last}$=area under the analyte concentration-time curve from time 0 to time of last measurable (non-BQL) concentration; BQL=below quantification limit; C_{last}=last observed measurable (non-BQL) analyte concentration; C_{max}=maximum observed analyte concentration; $t_{1/2}$=apparent terminal elimination half-life; t_{bql}=time of first BQL concentration after reaching C_{max}; t_{last}=time of last measurable (non-BQL) analyte concentration; t_{max}=time to reach maximum observed analyte concentration.
[a] n=20 for t_{bql}, n=14 for $t_{1/2}$.
[b] n=64 for $AUC_{0\text{-}6m}$, n=37 for t_{bql}, n=27 for $t_{1/2}$.
[c] n=93 for $AUC_{0\text{-}6m}$, n=57 for t_{bql}, n=41 for $t_{1/2}$.

In the bone marrow, ciltacabtagene autoleucel acts by direct interaction with BCMA+ cells present in multiple myeloma patients. Therefore, the concentration of CAR-T cells and their persistence were evaluated in bone marrow samples. After a single infusion of the median dose of 0.709 x 10^6 CAR-positive viable T cells/kg (range: 0.51-0.95 x 10^6 cells/kg), bone marrow samples were collected for transgene level evaluation on Days 28, 56, and 184. The highest mean level of ciltacabtagene autoleucel transgene levels in bone marrow samples was reached on Day 28 of 9315 copies/µg genomic DNA (%CV: 156.5%). Thereafter, levels of ciltacabtagene autoleucel transgene in bone marrow decreased over time with mean concentrations on Day 56 of 3995 copies/µg genomic DNA (%CV: 202.3%). By Day 184, mean concentrations had decreased further to below the quantification limit.
Similar to blood transgene levels, bone marrow transgene levels also declined over time and exhibited high inter-individual variability.
The overall incidence of antibodies to ciltacabtagene autoleucel (ADA) was 15.5%. Based on the current data, the kinetic of initial expansion of ciltacabtagene autoleucel was similar between patients with positive ADA compared with patients with negative ADA. There was no clear evidence to draw a conclusion on the association between ADA and ciltacabtagene autoleucel persistence.

At study start in Phase 1b, CD3+CAR+ cell levels were analysed using 2 different flow cytometry methods from Navigate BioPharma Services, Inc. and Bio Analytical Research Corporation (BARC). The Navigate flow cytometry assay was analytically validated prior to starting the Phase 1b part of the study. The BARC flow cytometry assay was only exploratory during Phase 1b and was analytically validated prior to initiating the Phase 2 part of the study. As a result, cellular PK data are summarised for Phase 1b and Phase 2 separately using Navigate and BARC flow cytometry PK assays, respectively,

and data from the 2 different assays cannot be numerically compared. However, an analysis performed by the MAA concluded that either method is appropriate for quantitation of CAR-T cells in subjects treated with ciltacabtagene autoleucel.
After a single infusion of ciltacabtagene autoleucel (median of 0.722 x10^6 cells/kg (range: 0.52 x 10^6 to 0.89 x10^6 cells/kg), mean CD3+CAR+ cells in blood samples were generally observed from Day 7 or Day 10 onwards for Phase 1b. Median t_{max} and $t_{1/2}$ values of CD3+CAR+ cells in blood were 12.9 days and 21.1 days, respectively, in Phase 2, which were comparable to the values for CAR transgene. Consistent with what was observed for the CAR transgene blood levels, inter-individual variability was high for both C_{max} (96.1%) and AUC values (ranging from 79.2%-99.5%) of CD3+CAR+ cells in blood.

Table 20 (Study Report 68284528MMY2001): Summary of pharmacokinetic results of CD3+CAR+ cells in blood after a single infusion in Phase 1b (Study 68284528MMY2001-Navigate)

Pharmacokinetics of JNJ-68284528 transgene (mean [SD], t_{max}, t_{last} and t_{bql}: median [range])	**Phase 1b**
n	29[a]
C_{max}, cells/µL	483 (464)
t_{max}, day	12.85 (7.67 – 19.95)
C_{last}, cells/µL	16.3 (14.2)
t_{last}, day	84.08 (12.89 – 350.96)
t_{bql}, day	88.49 (19.85 – 252.92)
$AUC_{0\text{-}28d}$, cells*day/µL	3932 (3540)
$AUC_{0\text{-}6m}$, cells*day/µL	7608 (6978)
$AUC_{0\text{-}last}$, cells*day/µL	7624 (7588)
$t_{1/2}$, day	21.1 (18.7)

AUC=area under the curve
[a] n=28 for $AUC_{6\ months}$, n=24 for t_{bql}, and n=11 for $t_{1/2}$.

In general, mean CD3+CAR+ cells in blood samples were also observed from Day 7 or Day 10 onwards for Phase 2 following single ciltacabtagene autoleucel administration (median of 0.707 x 10^6 cells/kg [range: 0.51 x 10^6 to 0.95 x 10^6 cells/kg]). Median t_{max} and $t_{1/2}$ values of CD3+CAR+ cells in blood were 13.6 and 25.1 days, respectively, in Phase 2. High inter-individual variability was also observed in both C_{max} (143.7%) and AUC values (ranging from 104.6%-220.5%) of CD3+CAR+ cells in blood. Median t_{max} and $t_{1/2}$ values for the CD3+CAR+ cells were comparable to the values for ciltacabtagene autoleucel transgene.

Table 21 (Study Report 68284528MMY2001): Summary of pharmacokinetic results of CD3+CAR+ cells in blood after a single infusion in Phase 2 (Study 68284528MMY2001-BARC)

Pharmacokinetics of JNJ-68284528 transgene (mean [SD], t_{max}, t_{last} and t_{bql}: median [range])	**Phase 2**
n	68[a]
C_{max}, cells/µL	1455 (2091)
t_{max}, day	13.60 (8.71 - 22.01)
C_{last}, cells/µL	175 (479)
t_{last}, day	98.95 (20.04 - 240.04)
t_{bql}, day	97.96 (27.89 - 231.95)
$AUC_{0\text{-}28d}$, cells/µL	15609 (24498)
$AUC_{0\text{-}6m}$, cells/µL	39740 (87626)
$AUC_{0\text{-}last}$, cells/µL	34822 (73712)
$t_{1/2}$, day	25.1 (19.5)

AUC=area under the curve
[a] n=61 for $AUC_{6\ months}$, n=36 for t_{bql} and n=27 for $t_{1/2}$.

Taken together, the PK data from Study 68284528MMY2001 were characterised using data corresponding to ≥ 3 months of follow-up after the last subject was infused with ciltacabtagene autoleucel. The key PK endpoints included area under the curve of the transgene level from time of dose to 28 days post-infusion ($AUC_{0\text{-}28days}$), maximum transgene level (C_{max}), and time of maximum observed transgene level (T_{max}). Following ciltacabtagene autoleucel infusion, the CAR+ T cells proliferated and underwent rapid multi-log expansion, followed by a rapid decline with initial peak expansion at a median T_{max} of ~13 days. After the cell expansion, the persistence phase of the ciltacabtagene autoleucel transgene levels was observed for all subjects. The median time of last measurable (non-below quantification limit) observed ciltacabtagene autoleucel transgene level included all 97 subjects and was comparable in Phase 1b (95.9 days; range: 26.2-438.0 days) and Phase 2 (99.7 days; range: 20.0-240.0 days). Among the 57 out of 97 subjects whose ciltacabtagene autoleucel transgene levels returned to the pre-dose baseline level of below the quantification limit at the time of the data cut-off, the median time to return to below the quantification limit was shorter in Phase 1b than Phase 2, but ranges were overlapping. Overall, the median time to return to below the quantification limit was 79.7 days (range: 27.0-275.0 days) post-infusion.
The baseline of the JNJ-68284528 subsets and dynamic changes/persistence and activation of CAR-positive viable T cells may be associated with the depth and durability of response. An evaluation of these cell populations may be performed by flow cytometry or cytometry by time of flight or both and correlated with response.
No studies in patients with renal and hepatic impairment were conducted. No paediatric patients were enrolled in in the study.
Population PK analysis confirmed that ciltacabtagene autoleucel CAR transgene C_{max} and $AUC_{0\text{-}28d}$ in subjects with mild hepatic dysfunction (defined as total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase > ULN, or ULN < total bilirubin ≤ 1.5 x ULN) (Patel 2004; National Cancer Institute 2020)) were similar to subjects with normal hepatic function.
Population PK analysis confirmed that ciltacabtagene autoleucel CAR transgene C_{max} and $AUC_{0\text{-}28d}$ in subjects with mild renal dysfunction (defined as 60 mL/min ≤ creatinine clearance [CRCL] < 90 mL/min) were similar to subjects with normal renal function (CRCL ≥ 90 mL/min).
As part of Study 68284528MMY2001, several pre-specified covariates were evaluated for their potential impact on cellular expansion parameters, including C_{max} and $AUC_{0\text{-}28days}$. No statistically significant associations were observed for covariates such as age, race, ethnicity, sex, bodyweight, and ADA status.
Ciltacabtagene autoleucel is a cellular product that is not cleared by the usual mechanisms that apply to small molecules or antibodies. Therefore, no pharmacokinetic drug-drug interactions are expected for adoptive cell therapies. No dedicated drug-drug interaction studies have been performed.

6.2 Dose finding and dose recommendation

In Study 68284528MMY2001 (Cartitude-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. A Safety Evaluation Team was established to ensure safety monitoring and sponsor oversight during the Phase 1b part of the study. The Safety Evaluation Team reviewed all available treatment-emergent data (e.g. pharmacokinetics, pharmacodynamics, safety, efficacy) at pre-defined enrolment milestones to evaluate the need for dose level escalation or de-escalation. For the first 24 subjects enrolled, Safety Evaluation Team evaluation was required after every 6 subjects had received treatment at a given ciltacabtagene autoleucel 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 Safety Evaluation Team review of data from at least 24 subjects. Since 96.9% of subjects were responders, a conclusion on the exposure-response relationship between CAR transgene PK exposure and ORR could not be drawn. Exposure-response relationships between systemic ciltacabtagene autoleucel CAR transgene levels and disease progression, as measured by DOR, PFS, and OS, could not be readily evaluated due to

the limited number of subjects and events (median PFS, DOR, and OS had not been reached) in the current dataset.
In summary, the reviewer comes to the conclusion that a real dose-finding process had not taken place. Numbers are too small to reach firm conclusions. Numerical trends in the studies Legend-2 and 68284528MMY2001 support the proposed ciltacabtagene autoleucel target dose of 0.75 × 10^6 CAR+ T cells and dose range of 0.5–1.0 x 10^6 CAR-positive viable T cells per kg bodyweight, but formal statistical testing between different dose cohorts has not been done. Additionally, dosing up to a maximum of 1 x 10^8 CAR-positive viable T-cells per kg bodyweight is proposed within the application submitted. No rationale for using 1 x 10^8 CAR-positive viable T-cells per kg bodyweight has been submitted.

6.3 Efficacy

Study 68284528MMY2001 (CARTITUDE-1)
The primary endpoint was overall response rate (ORR), defined as the proportion of subjects who achieve a partial response (PR) or better according to the IMWG response criteria, as assessed by IRC. This was to be measured in the modified intent-to-treat (mITT) population, which consists of all patients treated at the targeted RP2D dose level. The mITT population is the same as the all-treated population, since all subjects treated received the RP2D. The ORR and its 2-sided 95% Clopper-Pearson exact confidence interval (CI) were to be presented, and the p-value from a 1-sided exact binomial test for the null hypothesis of ORR ≤ 30% was to be provided.
This trial was conducted in China and USA.
Secondary endpoints
The major secondary endpoints were very good partial response (VGPR) or better, duration of response (DOR), minimum residual disease (MRD) negativity rate, time to response (TTR), progression free survival (PFS), and overall survival (OS).
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 transplantations (ASCT).
Eight subjects (8.2%) received allogenic transplantations.
The subjects' HRQoL (disease-related symptoms, functioning, and general well-being) was captured using patient-reported outcome (PRO) measures.
The pivotal trial represents a highly refractory population of patients with multiple myeloma, studied to date, who have very limited treatment options. Ninety-nine percent of subjects were refractory to their last line of treatment (87.6% were triple-refractory and 42.3% penta-refractory; 96.9% refractory to daratumumab, 83.5% refractory to pomalidomide, and 64.9% refractory to carfilzomib).
The primary endpoint ORR was 96.9% (91.2% - 99.4%; p < 0.0001). Median DOR was not reached with a median follow-up of 12.4 months at the time of clinical cut-off. The probabilities of the responders remaining in response at 9 months and 12 months were 80.2% and 68.2%, respectively.
Sixty-five subjects (67.0%) achieved complete response (CR) or better. Ninety subjects (92.8%) achieved VGPR or better. CBR was 96.9%. Of 57 subjects with evaluable samples, 93.0% achieved MRD negativity in bone marrow at a sensitivity level of 10-5. The median time to first response (PR or better) and to best response was 0.95 and 2.56 months, respectively. Results of patient-reported outcome measures suggest improved HRQoL after treatment with ciltacabtagene autoleucel. The probabilities of the responders remaining in response at 9 months and 12 months were 80.2% and 68.2%, respectively. Sixty-five subjects (67.0%) achieved complete response (CR) or better. Ninety subjects (92.8%) achieved VGPR or better.

The observed ORR was consistent across all subgroups examined when the assessment was based on the IRC data including evaluation by age, sex, race, total CAR-T positive cells infused, baseline ECOG performance score, baseline ISS staging, lines of prior therapy, stem cell transplant history, disease type, refractory status, cytogenic risk groups, baseline bone marrow plasma cells, baseline BCMA expression, and study site.
Notably, 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.
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%)
Seventeen subjects (17.5%) had progression of disease. The most common reason for disease progression was the development of/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%]).
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%)
Taken together:
One hundred and thirteen patients were enrolled (35 Phase Ib, 78 Phase II).
One hundred and one patients (30 Phase Ib, 71 Phase II) received a conditioning regimen.
Reasons for discontinuation: 2 withdrew consent, 2 due to disease progression, and 8 died.
Ninety-seven patients were treated with JNJ-68284528.
Two of them refused future study treatment, 1 withdrew due to an adverse event, and 1 died.
At the clinical cut-off, the median duration of follow-up for the all-treated analysis Safety Evaluation Team was 12.4 months.
Median time since initial diagnosis to enrolment was 5.94 years (range:1.6 to 18.2 years).
Median number of lines of prior therapy was 6 (range: 3 to 18).
Median age was 61 years (range: 43 to 78 years) -> Data regarding younger adults (20-40 years) missing.
All subjects had received prior treatment with a PI, IMiD, and anti-CD38 antibody therapy.
Ninety-nine percent of subjects were refractory to the last line of therapy prior to study entry, 87.6% were triple-refractory (refractory to an anti-CD38, a PI, and a IMiD), and 42.3% penta-refractory (refractory to an anti-CD38, at least 2 PIs, and at least 2 IMiDs), respectively.
A total of 89.7% of subjects had one or more prior autologous stem cell transplant(s) and 8.2% had a prior allogeneic transplant.
Ninety-four subjects achieved response of PR or better based on IRC assessment.
ORR (defined as the proportion of subjects who achieve a PR or better according to the IMWG response criteria) was 96.9% with 95% exact CI (91.2%, 99.4%).
Median duration of response (DOR) was not reached with 95% CI (15.9, NE) months.
Sixty-five subjects (67.0%) achieved CR.
Ninety subjects (92.8%) achieved very good partial response (VGPR) or better.
CBR was 96.9%. Of 57 subjects with evaluable samples 93.0% achieved MRD negativity in bone marrow at a sensitivity level of 10-5.
The median time to first response (PR or better) and to best response was 0.95 and 2.56 months.
With a median duration of follow-up of 12.42 months, median progression-free survival (PFS) was not reached.
The 12-month PFS rate (95% CI) was 76.6% (66.0%, 84.3%).
Results of patient-reported outcome measures suggest improved HRQoL after treatment with ciltacabtagene autoleucel.

Median duration of follow-up for the 97 subjects who received ciltacabtagene autoleucel infusion was 12.42 months (range: 1.5 months [subject died] to 24.9 months) at the time of clinical cut-off.
At the time of clinical cut-off, 1 subject (1.1%) received re-treatment with ciltacabtagene autoleucel infusion.

Study Legend-2
Legend-2 is a Phase 1, single-arm, open-label, multi-centre study to determine the safety and efficacy of LCAR-B38M CAR-T cells used to treat subjects with relapsed or refractory multiple myeloma. The ongoing first-in-human clinical study has provided initial proof-of-concept that LCAR-B38M CAR-T cells may be a highly effective modality for treating relapsed or refractory multiple myeloma and has a manageable safety profile consistent with its known mechanism of action. Enrolled subjects underwent leukapheresis to obtain PBMC. T cells were purified from PBMC, and CD3-positive T cells were transduced with second generation LCAR-B38M lentiviral vector to express anti-BCMA CAR. Lymphodepletion using 3 doses of cyclophosphamide on Days -5, -4, and -3 was followed by infusion of the engineered LCAR-B38M CAR-T cells. At the study sites in Xi'an (Site 1) and Shanghai (Site 2 and Site 3), the dose was split into 3 infusions administered over 7 days. In general, the number of CAR-T cells administered increased with each infusion. At the Nanjing site (Site 4), the dose was given as a single administration on Day 1.
As of the 26 November 2019 update, the median follow-up for all patients (n = 74) was 30.42 months (range: 0.4-42.8). The overall response rate (ORR) (complete response [CR] + very good partial response [VGPR]+PR) by sponsor assessment was 87.8% (95% CI: 78.2, 94.3). Complete response was achieved by 54 (73%) subjects (95% CI: 61.4, 82.6), and 50 (67.6%) subjects (95% CI: 55.7, 78) with CR were negative for minimal residual disease (MRD) as assessed by bone marrow 8-coloured flow cytometry assay. The overall median time to first response of PR or better was 1.02 months (range: 0.4-3.5). As of the clinical cut-off, 36 (55.4%) subjects who achieved PR or better subsequently progressed based on the sponsor's assessment. The Kaplan-Meier estimate of median duration of response was 22.34 months (95% CI: 13.04, 29.14). Forty-seven (63.5%) subjects had died or progressed, and the Kaplan-Meier estimate of median progression-free survival was 18.04 months (95% CI 10.61, 25.56). There were no major differences in safety or efficacy between the 8 subjects who received lymphodepletion chemotherapy with cyclophosphamide and fludarabine compared with the remaining 66 subjects who received lymphodepletion chemotherapy with cyclophosphamide monotherapy. Administration of the LCAR-B38M CAR-T cells as split doses did not appear to have a different safety or efficacy profile compared with administration as a single dose.

Study 68284528MMY2002 (CARTIFAN-1)
CARTIFAN-1 is a Phase 2, open-label, confirmatory, multi-centre study to evaluate the efficacy and safety of LCAR-B38M CAR-T cells in adult Chinese subjects with relapsed or refractory multiple myeloma. Enrolled subjects underwent apheresis to acquire peripheral blood mononuclear cells (PBMCs), and LCAR-B38M CAR-T cells were prepared using the subject's T-cells selected from the apheresis product. Upon sponsor's approval, study subjects may receive bridging therapy with an adequate washout period between apheresis and the start of lymphodepletion chemotherapy. After LCAR-B38M CAR-T cell production and product release, subjects received a 3-day conditioning regimen of cyclophosphamide and fludarabine, followed by LCAR-B38M CAR-T cell infusion 5 to 7 days after the start of conditioning. Subjects were monitored closely for safety and disease assessments during the post-infusion period (Day 1 to Day 100). Assessments during the post-treatment period (Day 101 to study completion) were performed every 28 days.
The study was started with an initial target 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). The final target dose was confirmed as 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) at the second SET meeting after reviewing the safety data of the first 12 subjects, as well as data from the ongoing 68284528MMMY2001 study. The study report submitted summarised the results from the interim analysis. As of the clinical cut-off date (23 June 2020), a total of 57 subjects (data from 2 subjects, who had completed apheresis and were still in the process between apheresis and conditioning, were not

transferred into the database by the study cut-off) were enrolled and a total of 39 subjects received LCAR B38M CAR-T cells.
The primary endpoint was overall response rate (ORR), defined as the proportion of subjects who achieved a partial response (PR) or better according to the IMWG response criteria. Analysis of very good partial response (VGPR) or better response rate, duration of response (DOR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) was conducted at the same cut-off as the ORR. The distribution (median and Kaplan-Meier curves) of DOR was to be provided using Kaplan-Meier estimates for subjects who achieved response during the study. Similar analysis was performed for OS, PFS, and TTR for the mITT analysis set.
At the data cut-off date of 23 June 2020, a total of 57 subjects were enrolled in the study and underwent apheresis. The primary analysis population for all efficacy summaries was the modified intent-to-treat (mITT) population, which included 29 subjects who received a LCAR-B38M CAR-T cell infusion at the final target dose. The all treated population includes 30 subjects who received a LCAR-B38M CAR-T cell infusion. The median time from apheresis to LCAR-B38M CAR-T cell infusion was 43.0 days (range: 35 to 79 days), the median total number of CAR-positive viable T cells infused was 40.65 x 10^6 (range: 22.54 to 58.46 x 106 cells), and the median dose formulated and administered was 0.664 x 10^6 cells/kg (range: 0.42 to 0.79 x 10^6 cells/kg) and 0.664 x 10^6 cells/kg (range: 0.42 to 0.84 x 10^6 cells/kg), respectively. All subjects received the protocol target dose except for one subject who was given 0.42 x 10^6 CAR-positive viable T cells/kg, which was below the target dose range (0.5 x 10^6 -1.0 x 10^6 CAR-positive viable T cells/kg). In the all-treated analysis set of the interim analysis, the median duration of follow-up was 6.24 months at clinical cut-off for the interim analysis data set. A total of 3 subjects (10.0%) died after LCAR-B38M CAR-T cell infusion. The deep and durable response induced by LCAR-B38M CAR-T cells was demonstrated by a VGPR or better rate of 79.3% and a complete response (CR) or better rate of 48%, and the 12-month DOR rate is 92.3% (95% CI: 56.6%, 98.9%). A total of 27 subjects achieved a response of PR or better based on computerised algorithm assessment; the ORR was 93.1% (95% CI: 77.2%, 99.2%). Two non-responders are non-evaluable for a response since they died before the first post-baseline efficacy assessment was performed. Fourteen subjects (48.3%) achieved CR or better, and 23 subjects (79.3%) achieved VGPR or better. At the time of clinical cut-off, no subject showed signs of disease progression. The median time to first response and to best response was 0.95 and 1.84 months, respectively. Minimal residual disease (MRD) negativity rate at the 10-5 testing threshold: 15 subjects had an MRD assessment after receiving LCAR-B38M CAR-T cells. Among the 15 subjects with evaluable MRD samples, the MRD negativity rate was 100% (95% CI: 78.2%, 100%). For the entire mITT analysis set, the MRD negativity rate was 51.7% (95% CI: 32.5%, 70.6%), and 44.8% of subjects achieved MRD-negative CR/sCR. PFS: median PFS was not yet evaluable due to the short follow-up time (median: 6.2 months); the 12-month PFS rate was 85.9% (95% CI: 59.7%, 95.6%). OS: median OS was not evaluable, also due to the short follow-up time (median: 6.2 months); the 12-month OS rate was 86.5% (95% CI: 61.4%, 95.7%).
ORR across multiple clinically relevant subgroups was consistent with the overall study population. Data from this interim analysis demonstrates that the LCAR-B38M CAR-T cells resulted in consistent improvements in clinical measures in the treatment of patients with relapsed and refractory multiple myeloma.

Study 68284528MMY2003 (Cartitude-2)
Study 68284528MMY2003 is an ongoing Phase 2, multi-cohort, open-label, multi-centre study to determine whether treatment with ciltacabtagene autoleucel (alone or with other treatment regimens) results in minimal residual disease (MRD) negativity in adult subjects with multiple myeloma. At the time of the clinical cut-off, the median duration of follow-up for the 18 subjects in Study 68284528MMY2003 was 1.58 months (range: 0.1 to 5.2 months). Subjects are ongoing in follow-up and will have more than 100 days post-dose by the time the applicant responds to the List of Questions. Interim safety data for 18 subjects who received a ciltacabtagene autoleucel infusion in Study 68284528MMY2003 as of the 23 July 2020 clinical cut-off date are provided in the Summary of Clinical Safety.

6.4 Safety

Subject study disposition as of the clinical cut-off Date (1 September 2020); Study 68284528MMY2001

All 97 subjects (100.0%) who received ciltacabtagene autoleucel infusion experienced 1 or more treatment-emergent adverse events. Serious adverse events were reported for 53 subjects (54.6%), 42 subjects (43.3%) experienced serious treatment-emergent adverse events (TEAEs) related to ciltacabtagene autoleucel. Grade 4 TEAEs were reported for 84 subjects (86.6%). Six subjects (6.2%) experienced an adverse event with an outcome of death (Grade 5), all of which were deemed to be related to ciltacabtagene autoleucel. These events included CRS complicated by secondary HLH (1 subject), neurotoxicity (1 subject), respiratory failure (1 subject), and infection (3 subjects).
The most frequently reported TEAEs of any grade (≥ 20% subjects, Study 68284528MMY2001) included:
neutropenia (95.9%),
CRS (94.8%),
anaemia (81.4%),
thrombocytopenia (79.4%),
leukopenia 61.9%,
lymphopenia (52.6%),
fatigue (37.1%),
cough (35.1%),
hypocalcaemia (32.0%),
hypophosphataemia (30.9%),
diarrhoea (29.9%),
decreased appetite (28.9%),
aspartate aminotransferase increased (28.9%),
hypoalbuminaemia (27.8%),
nausea (27.8%),
alanine aminotransferase increased (24.7%),
hyponatraemia (22.7%),
constipation (21.6%),
chills (20.6%),
pyrexia (20.6%),
hypokalemia (20.6%).

Cytopenias

Cytopenias were the most common TEAE in Study 68284528MMY2001 experienced by subjects treated with ciltacabtagene autoleucel. Grade 3 or 4 lymphopenia, neutropenia, and thrombocytopenia were experienced by 96 subjects (99.0%), 95 subjects (97.9%), and 60 subjects (61.9%), respectively in the first 100 days after ciltacabtagene autoleucel infusion. The majority of initial cytopenic events recovered to Grade 2 or below within the 60 days of ciltacabtagene autoleucel infusion. After Day 60 following ciltacabtagene autoleucel infusion, 8 (8.2%), 10 (10.3%), and 25 (25.8%) of subjects had Grade 3 or higher lymphopenia, neutropenia, and thrombocytopenia, respectively.
In the Legend-2 study, Grade 3 and 4 cytopenias included leukopenia (25.7%), thrombocytopenia (18.9%), anaemia (14.9%), and neutropenia (2.7%).

Cytokine release syndrome
Cytokine release syndrome (all grades) was common, reported in 92 subjects (94.8%). All events recovered, with the exception of 1 (1.1%) fatal event in a subject with CRS complicated by HLH. Cytokine release syndrome is an anticipated event based on the mechanism of CAR-T activity. While 5.1% of CRS cases were severe, the majority of cases were low grade and symptoms were effectively managed with available treatments including tocilizumab and corticosteroids.

Neurotoxicity
Overall, CAR-T cell neurotoxicity was reported in 20.6% of subjects and categorised as immune effector cell-associated neurotoxicity syndrome (ICANS) as well as other neurotoxicity determined by the

investigator to be related to CAR-T therapy and occurring after recovery from CRS and/or ICANS. ICANS is a known/expected event associated with CAR-T therapy. ICANS (all grades) was reported for 16 (16.5%) subjects and was also generally mild. Two subjects (2.1%) had maximum Grade 3 or 4 events. Concurrent CRS was noted for 15 out of 16 subjects and no case of ICANS occurred prior to CRS. All subjects were treated for ICANS with agents including corticosteroids, anakinra, and tocilizumab, and all subjects recovered from their events. Twelve subjects (12.4%) experienced other events of CAR-T cell neurotoxicity not defined as ICANS as assessed by the Investigator, either due to symptoms or time of onset by the Safety Evaluation Team (i.e. occurring after the period of recovery from CRS and/or ICANS). Eight subjects (8.2%) experienced Grade 3 or 4 toxicities and 1 subject (1.0%) experienced a Grade 5 toxicity. Five of these 12 subjects (5.2% of the all-treated population) experienced a similar presentation of movement and neurocognitive TEAEs. These included a cluster of movement (e.g. micrographia, tremors, etc.), cognitive (e.g. memory loss, attention deficits, etc.), and personality changes (e.g. reduced facial expression, flat affect, etc.). TEAEs were observed in some subjects to progress to an inability to work or care for oneself. This cluster of movement and neurocognitive TEAEs appears to potentially be 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.

Infections

Infections were reported for more than half of subjects (56 subjects [57.7%]) with nearly 20% (19 subjects [19.6%]) experiencing Grade 3 or 4 infections. Three subjects (3.1%) experienced Grade 5 infections including lung abscess, sepsis, and septic shock. While multiple myeloma patients have an increased risk of infections due to underlying disease causing hypogammaglobulinaemia (11.3% of subjects experienced hypogammaglobulinaemia) and immunosuppression (Terpos 2015), the occurrence of infection should be noted and monitored. Administration of ciltacabtagene autoleucel may increase the risk due to cytopenias or hypogammaglobulinaemia.

Hypogammaglobulinaemia was reported for 11 subjects (11.3%), including 2 subjects (2.1%) with Grade 3 or 4 hypogammaglobulinaemia. A total of 37 subjects (38.1%) received intravenous immunoglobulin (IVIG) therapy either as prophylaxis (23 subjects [23.7%]) or for treatment of TEAEs (16 subjects [16.5%]).

Although tumour lysis syndrome is uncommon in subjects with multiple myeloma, tumour lysis syndrome (Grade 4) with elevated blood creatinine (Grade 3) was reported for 1 subject (1.0%). Tumour lysis syndrome onset occurred on Day 3 and had a duration of 6 days. Elevated blood creatinine onset on Day 11 with a duration of 7 days. Additionally, 1 subject in the Phase 1 study Legend-2 experienced fatal TLS.

Hypersensitivity reactions related to ciltacabtagene autoleucel were reported in 4 subjects (4.1%). All were Grade 1 severity and 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

Replication-competent lentivirus was not detected up to 12 months after ciltacabtagene autoleucel infusion.

Rates of adverse events were evaluated among various subgroups including sex, age, race, total CAR-positive viable T-cells infused, and bone marrow % plasma cells at baseline. Across all subgroups, rates of AEs, Grade 3 and 4 AEs, and SAEs were similar with no clinically meaningful differences.

Safety findings for 97 subjects enrolled into the main cohort of Study 68284528MMY2001 demonstrate that ciltacabtagene autoleucel has a manageable safety profile generally consistent with the current understanding of CAR-T therapy. Safety data for 27 subjects from 2 additional sources (i.e. Japan cohort of Study 68284528MMY2001 and Study 68284528MMY2003) were consistent with this assessment.

A total of 14 subjects (14.4%) died after ciltacabtagene autoleucel infusion (range: 45 to 694 days from ciltacabtagene autoleucel infusion) during follow-up of Study 68284528MMY2001. Nine subjects died due to an adverse event (with 6 (6.2%) related to ciltacabtagene autoleucel) and 5 due to progressive disease.

In Study 68284528MMY2001, 4 subjects (4.1%) received infusions of ciltacabtagene autoleucel product that did not meet all pre-specified release criteria. For 2 of these subjects, the single product bag manufactured contained a lower than specified dose, requiring 2 product infusion bags to supply the required dose. Both subjects received ciltacabtagene autoleucel within the target range of 0.5 to 1.0 x 10^6 CAR-T cells/kg. For 2 other subjects, the batches of ciltacabtagene autoleucel product infused were out of specification for either CD3+ positive cells or natural killer (NK) cells. The first subject's batch contained 88% CD3+ cells (release specification ≥ 90% CD3+ cells) and 10% NK cells (release specification < 5% NK CD3-CD16+CD56). The second subject's batch contained 75% CD3+ cells (release specification ≥ 80% CD3+ cells). The safety profile observed for subjects who received out-of-specification ciltacabtagene autoleucel was consistent with that observed for subjects who received within-specification ciltacabtagene autoleucel product.
In Study 68284528MMY2001, prophylactic antivirals were prescribed for 96 subjects (99.0%), most commonly acyclovir, which was prescribed for 88 subjects (90.7%). Prophylactic anti-bacterials were prescribed for 70 subjects (72.2%), most commonly levofloxacin, which was prescribed for 43 subjects (44.3%), and sulfamethoxazole/trimethoprim, which was prescribed for 40 subjects (41.2%). Prophylactic antifungals were prescribed for 66 subjects (68.0%) most commonly fluconazole, which was prescribed for 54 subjects (55.7%). Prophylactic IVIG was prescribed for 23 (23.7%) subjects.

6.5 Final clinical benefit-risk assessment

The overall benefit-risk ratio of ciltacabtagene autoleucel for the treatment of adult patients with multiple myeloma who have received at least 3 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, is positive. Convincing efficacy results – ORR was reached with additional support from secondary endpoints – are based on a small, open-label, single-arm study and must be interpreted with caution. Safety issues seem to be manageable in a hospitalisation setting.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for CARVYKTI was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

CARVYKTI

Composition

Active substances

Ciltacabtagene autoleucel is an immunotherapy with genetically modified autologous T-cells transduced with a lentiviral vector (LVV) encoding a chimeric antigen receptor (CAR) and directed against the B-cell maturation antigen (BCMA).

Excipients

Cryostor CS5 which contains dimethyl sulfoxide.

Pharmaceutical form and active substance quantity per unit

Dispersion for infusion
The finished product is packaged in one infusion bag containing a dispersion for infusion of 3.2×10^6 to 1×10^8 CAR-positive viable T-cells suspended in a cryopreservative solution.

Indications/Uses

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

Dosage/Administration

For autologous use only. For intravenous use only.
CARVYKTI must be administered in a qualified treatment centre with direct access to appropriate intensive care units. CARVYKTI therapy must be initiated under the direction and supervision of a healthcare professional experienced in the treatment of haematological malignancies and trained for the administration and management of patients treated with CARVYKTI, including the treatment of cytokine release syndrome (CRS) and neurotoxicity.
A single dose of CARVYKTI is $0.5\text{-}1.0\times10^6$ CAR-positive viable T-cells per kg body weight up to a maximum of 1×10^8 CAR-positive viable T-cells suspended in a patient-specific infusion bag.
In addition to T-cells, CARVYKTI may contain natural killer cells.

Usual dosage

Adults (≥18 years)

The information on pretreatment and premedication should be taken into account (see *Administration schedule*).
CARVYKTI is provided as a single-dose for infusion containing a suspension of chimeric antigen receptor (CAR)-positive viable T-cells.
The dose is 0.5-1.0×10^6 CAR-positive viable T-cells per kg of body weight, with a maximum dose of 1×10^8 CAR-positive viable T-cells per single infusion.

Patients with hepatic disorders

No studies have been conducted on the use of CARVYKTI in patients with hepatic impairment.

Patients with renal disorders

No studies have been conducted on the use of CARVYKTI in patients with renal impairment.

Elderly patients

No dose adjustment is required in patients ≥65 years of age.

Children and adolescents (17 years of age and younger)

The safety and efficacy of CARVYKTI in children aged below 18 years of age have not been established.
No data are available.

ADMINISTRATION SCHEDULE

Preparing Patient for CARVYKTI Infusion

Confirm availability of CARVYKTI prior to starting the lymphodepleting regimen.

Lymphodepleting regimen

Administer a lymphodepleting regimen of cyclophosphamide 300 mg/m^2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days. Administer CARVYKTI infusion 5 to 7 days after the start of the lymphodepleting regimen. If resolution of toxicities due to the lymphodepleting regimen to Grade 1 or lower takes more than 14 days, resulting in delays to CARVYKTI dosing, re-administration of the lymphodepleting regimen should be considered after a minimum of 21 days following the first dose of the first -lymphodepleting regimen. For dose modifications, see corresponding manufactures prescribing information of fludarabine and cyclophosphamide, respectively.
Lymphodepleting regimen must be delayed if a patient has serious adverse reactions from preceding bridging therapies (including clinically significant active infection, cardiac toxicity, and pulmonary toxicity).

Clinical assessment prior to CARVYKTI infusion

CARVYKTI infusion should be delayed if a patient has any of the following conditions:

- clinically significant active infection.
- Persistent serious adverse events (especially pulmonary or cardiac adverse reactions or hypotension), including those after previous chemotherapy.
- Grade ≥3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning except for Grade 3 nausea, vomiting, diarrhoea, or constipation. CARVYKTI infusion should be delayed until resolution of these events to Grade ≤1.
- Development of clinically significant worsening of multiple myeloma leading to medically significant organ dysfunction or clinical deterioration following chemotherapy for lymphodepletion.
- Active graft versus host disease.

Premedication

Administer the following pre-infusion medications to all patients (30 to 60 mins) prior to CARVYKTI infusion:

- Antipyretics (oral or intravenous paracetamol/acetaminophen 650 to 1000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Avoid use of prophylactic systemic corticosteroids as it may interfere with the activity of CARVYKTI.

Preparation of CARVYKTI for infusion

This medicinal product contains genetically modified human blood cells. Healthcare professionals working with CARVYKTI must take appropriate precautions (wearing gloves and protective goggles) to avoid potential transmission of infectious diseases.

Preparation of CARVYKTI for infusion

Do not thaw the product until it is ready to be used. Coordinate the timing of CARVYKTI thaw and infusion. Confirm the infusion time in advance and adjust the start time for thaw so that CARVYKTI is available for infusion when the patient is ready.

- Confirm patient identity: Prior to CARVYKTI preparation, match the patient's identity with the patient identifiers on the CARVYKTI cassette. Do not remove the CARVYKTI product bag from the cassette if the information on the patient-specific label does not match the intended patient.
- Once patient identification is confirmed, remove the CARVYKTI product bag from the cassette.
- Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. Do not administer if the bag is compromised and follow the local guidelines (or contact the company).
- Place the infusion bag inside a sealable plastic bag (preferably sterile) prior to thawing.

- Thaw CARVYKTI at 37°C±2°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Total time from start of thaw until completion of thawing should be no more than 15 minutes.
- Remove the infusion bag from the sealable plastic bag and wipe dry. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not pre-filter into a different container, wash, spin down, and/or resuspend CARVYKTI in new media prior to infusion.
- Once thawed, the CARVYKTI infusion must be administered and completed within 2.5 hours at room/ambient temperature (20°C to 25°C).
- Do not re-freeze or refrigerate thawed product.

Administration

- Administer CARVYKTI at a certified healthcare facility.
- Prior to infusion and during the recovery period, ensure 2 doses of tocilizumab in case of a cytokine release syndrome and emergency equipment are available for use. The treatment centre must have access to an additional dose within 8 hours after administration of the last dose of tocilizumab.
- Confirm the patient's identity with the patient identifiers on the infusion bag. Do not infuse CARVYKTI if the information on the patient-specific label does not match the intended patient.
- Once thawed, administer the entire contents of the CARVYKTI bag by intravenous infusion within 2.5 hours using infusion sets fitted with an in-line filter.
- Do NOT use a leukodepleting filter.
- Gently mix the contents of the bag during CARVYKTI infusion to disperse cell clumps.
- After the entire content of the product bag is infused, flush the administration line inclusive of the in-line filter, with sodium chloride 9 mg/mL (0.9%) solution (normal saline) to ensure all product is delivered.

For special precautions for disposal, see *Instructions for handling.*

Monitoring after infusion

Monitor patients daily for 14 days after the CARVYKTI infusion at a certified healthcare facility and then periodically, at the decision of the doctor, for an additional two weeks after CARVYKTI infusion for signs and symptoms of cytokine release syndrome (CRS), neurologic events and other toxicities (see *Warnings and Precautions*).

Instruct patients to remain within proximity (maximum of 2 hours away) of a certified healthcare facility for at least 4 weeks following infusion.

Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify CRS based on clinical presentation (see *Warnings and Precautions*)
If CRS is suspected, manage according to the recommendations in Table 1. Administer supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) as appropriate. Consider laboratory testing to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function. Other monoclonal antibodies targeting cytokines (for example, anti-IL1 and/or anti-TNFα) or therapy directed at reduction and elimination of CAR-T-cells may be considered for patients who develop high grade CRS and hemophagocytic lymphohistiocytosis (HLH) that remains severe or life-threatening following prior administration of tocilizumab and corticosteroids.

Table 1: Guidelines for management of Cytokine Release Syndrome with Tocilizumab and Corticosteroids

Grade	Presenting Symptoms	Tocilizumab[a]	Corticosteroids[b]
Grade 1	Temperature ≥38°C[c]	May be considered	N/A
Grade 2	Temperature ≥38°C[c] with either: Hypotension responsive to fluids and not requiring vasopressors. Or, oxygen requirement of low-flow nasal canula[d] or blow-by	Administer tocilizumab[b] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per guidance below if no improvement within 24 hours of starting tocilizumab.
Grade 3	Temperature ≥38°C[c] with either: Hypotension requiring one vasopressor with or without vasopressin. Or, oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement, administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4	Temperature ≥38°C[c] with either: Hypotension requiring multiple vasopressors (excluding vasopressin). Or, oxygen requirement of positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen.	As above or administer methylprednisolone 1000 mg intravenously per day for 3 days per physician discretion. If no improvement or if condition worsens, consider alternate immunosuppressants.[b]

		Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	

[a] Refer to tocilizumab prescribing information for details

[b] Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.

[c] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (eg, tocilizumab or steroids).

[d] Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

Neurologic Toxicities

Neurological toxicities, which may be serious or life-threatening, have occurred after treatment with CARVYKTI, including concurrently with CRS, after resolution of CRS and without CRS (see section «Adverse Effects – Description of selected adverse reactions – Neurological toxicities»).
General management for neurologic toxicity e.g., Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) with or without concurrent CRS is summarized in Table 2.
At the first sign of neurologic toxicity, including ICANS, other causes of neurological symptoms should be excluded. Patients should be monitored for signs or symptoms of neurological toxicities for at least 4 weeks after infusion and treated immediately. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities (see «Warnings and Precautions»).
If concomitant CRS is suspected during neurological toxicity, it should be treated according to the recommendations in Table 1 and the more aggressive intervention should be used for the two events listed in Tables 1 and 2.
Patients should be instructed to seek immediate medical attention if signs or symptoms of neurological toxicity occur at any time.

Table 2: Guidelines for management of ICANS

ICANS Grade[a]	**Presenting Symptoms[b]**	**Concurrent CRS**	**No Concurrent CRS**
Grade 1	ICE score 7-9[c] or depressed level of consciousness[d]: awakens spontaneously.	Management of CRS per Table 1.	Consider dexamethasone.
Grade 2	ICE score-3-6[c] or depressed level of consciousness[d]: awakens to voice.	Administer tocilizumab per Table 1 for management of CRS. If no improvement after starting tocilizumab, administer 10 mg IV dexamethasone[e] every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until resolution to ≤Grade 1 then taper.	Administer 10 mg IV dexamethasone[e] every 6 hours. Continue dexamethasone use until resolution to ≤ Grade 1, then taper.
Grade 3	ICE score-0-2[c]	Administer tocilizumab per Table 1 for management of CRS.	Administer dexamethasone[e] 10 mg

	or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures[d], either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention, or raised intracranial pressure (ICP): focal/local edema on neuroimaging[d].	In addition, administer dexamethasone[e] 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until resolution to ≤ Grade 1, then taper.	intravenously every 6 hours. Continue dexamethasone use until resolution to ≤ Grade 1, then taper.
Grade 4	ICE score-0[c] or depressed level of consciousness[d] either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[d], either: • life-threatening prolonged seizure (>5 min), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[d]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP / cerebral edema[d], with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, • decerebrate or decorticate posturing, • cranial nerve VI palsy, • papilledema, • Cushing's triad.	Administer tocilizumab per Table 1 for management of CRS. As above or consider administration of IV methylprednisolone 1000 mg per day with first dose of tocilizumab and continue IV methylprednisolone 1000 mg per day for 2 or more days.	As above or consider administration of IV methylprednisolone 1000 mg per day for 3 days; if improves, then manage as above.
		In case of raised ICP/cerebral edema, refer to institutional guidelines for management.	

[a] **Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any grade ICANS.**

[b] Management is determined by the most severe event, not attributable to any other cause

[c] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., “show me 2 fingers” or “close your eyes and stick out your tongue” = 1 point); **Writing** (ability to write a standard sentence = 1 point; and **Attention** (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

[d] Attributable to no other cause.

[e] All references to dexamethasone administration are dexamethasone or equivalent

Mode of administration

For intravenous use only.

Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section «Composition».
Contraindications to lymphodepleting chemotherapy must be considered.

Warnings and precautions

General

Patients with active or prior history of significant central nervous system (CNS) disease or inadequate renal, hepatic, pulmonary, or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Cytokine Release Syndrome (CSR)

Cytokine release syndrome, including fatal or life-threatening reactions, can occur after CARVYKTI infusion.
95% of patients experienced CRS after CARVYKTI infusion with majority of these being Grade 1 or Grade 2 (90%) (see «Undesirable effects»). The median time from CARVYKTI infusion (Day 1) to onset of CRS was 7 days (range of 1 to 12 days). Approximately 90% of patients experienced onset of CRS after Day 3 of receiving the CARVYKTI infusion.
In almost all cases, duration of CRS ranged from 1 to 14 days (median duration 4 days), with 88% of patients having a CRS duration of ≤ 7 days.
Clinical signs and symptoms of CRS may include but are not limited to fever (with or without rigors), chills, hypotension, hypoxia, and elevated liver enzymes. Risk factors for severe CRS include high pre-infusion tumour burden, active infection and early onset of fever or persistent fever after 24 hours of symptomatic treatment. Infections may also occur concurrently with CRS and may increase the risk of a fatal event. Potentially life-threatening complications of CRS may include cardiac dysfunction, neurologic toxicity, and HLH. CRS has been reported to be associated with findings of haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) and the physiology of the syndromes may overlap. Patients should be closely monitored for signs or symptoms of these events, including fever and treatment should be according to institutional standards.
Appropriate prophylactic and therapeutic treatment for infections should be provided, and complete resolution of any active infections should be ensured prior to CARVYKTI infusion.
Ensure that at least two doses of tocilizumab are available prior to infusion of CARVYKTI. Monitor patients for signs and symptoms of CRS daily for 14 days after the CARVYKTI infusion at a certified healthcare facility and then periodically for an additional two weeks after CARVYKTI infusion.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids as indicated in Table 1 (see «Dosage/Administration»).
Evaluation for HLH should be considered in patients with severe or unresponsive CRS. For patients with high pre-infusion tumour burden, early onset of fever, or persistent fever after 24 hours, early tocilizumab should be considered. The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), should be avoided during CRS. Consider reducing baseline burden of disease with bridging therapy prior to infusion with CARVYKTI in patients with high tumour burden.

Neurologic toxicities

Neurologic toxicities occur frequently following treatment with CARVYKTI and can be fatal or life-threatening (see «Undesirable effects»). The onset of neurologic toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS.
Adverse reactions of neurologic toxicity (≥5%) were ICANS, aphasia, and confusional state. Five percent of patients experienced a cluster of movement and neurocognitive adverse reactions which occurred after recovery from CRS and/or ICANS; that in some patients progressed to an inability to work or care for oneself (see «Undesirable effects»).
Consider reducing baseline burden of disease with bridging therapy prior to infusion with CARVYKTI in patients with high tumor burden which may mitigate the risk of developing neurologic toxicity (see «Undesirable effects»). Monitor patients for signs or symptoms of ICANS for four weeks after infusion. At the first sign of ICANS, immediately evaluate patient for hospitalization and institute treatment with supportive care as indicated in Table 2 (see «Dosage/Administration»). Early detection and aggressive treatment of CRS or ICANS may be important to prevent neurologic toxicity from occurring or worsening. Counsel patients to seek immediate medical attention should signs and symptoms of neurologic toxicities occur after recovery from CRS and/or ICANS.

Prolonged Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and CARVYKTI infusion and should be managed according to local guidelines. In Study MMY2001, nearly all patients had one or more Grade 3 or 4 cytopenic adverse reactions. Most patients had a median time from infusion to first onset of Grade 3 or 4 cytopenia of less than two weeks with the majority of patients recovering to ≤Grade 2 by Day 30 (see «Undesirable effects»).
Monitor blood counts after CARVYKTI infusion. For thrombocytopenia consider supportive care with transfusions. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after CARVYKTI or until CRS has resolved.

Serious Infections and febrile neutropenia

Serious infections, including life-threatening or fatal infections, occurred in patients after CARVYKTI infusion (see «Undesirable effects»).
Monitor patients for signs and symptoms of infection, employ surveillance testing prior to and during treatment with CARVYKTI and treat patients appropriately. Administer prophylactic antimicrobials according to local guidelines. Infections are known to complicate the course and management of concurrent CRS. Patients with clinically significant active infection should not start CARVYKTI treatment until the infection is controlled.
In the event of febrile neutropenia, infection should be evaluated and managed appropriately with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.

Viral reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia.
There is currently no experience with manufacturing CARVYKTI for patients testing positive for HIV, active HBV, or active HCV. Screening for HBV, HCV, HIV and other infectious agents must be performed in accordance with local clinical guidelines before collection of cells for manufacturing.

Hypogammaglobulinemia

Hypogammaglobulinemia may occur in patients receiving CARVYKTI.
Monitor immunoglobulin levels after treatment, and treat according to standard guidelines, including administration of immunoglobulin replacement, antibiotic prophylaxis and monitoring for infection.

Live vaccines

The safety of immunization with live viral vaccines during or following CARVYKTI treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy during CARVYKTI treatment, and until immune recovery following treatment with CARVYKTI.

Secondary Malignancies

Patients treated with CARVYKTI may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact (the company) to obtain instructions on patient samples to collect for testing.

Hypersensitivity

Allergic reactions may occur with infusion of CARVYKTI. Serious hypersensitivity reactions, including anaphylaxis, may also be due to the dimethyl sulfoxide (DMSO), or residual kanamycin in CARVYKTI.

Blood, organ, tissue and cell donation

Patients treated with CARVYKTI should not donate blood, organs, tissues and cells for transplantation.

Interactions

No interaction studies have been performed with CARVYKTI.
HIV and the lentivirus used to make CARVYKTI have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests (NATs) may yield false-positive results in patients who have received CARVYKTI.

Pregnancy, lactation

Pregnancy

There are no available data on the use of CARVYKTI in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with CARVYKTI. It is not known whether CARVYKTI has the potential to be transferred to the foetus and cause foetal toxicity. Therefore, CARVYKTI is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised there may be risks to the foetus.
Pregnancy after CARVYKTI therapy should be discussed with the treating physician.
Pregnant women who have received CARVYKTI may have hypogammaglobulinemia. Assessment of immunoglobulin levels in new-borns of mothers treated with CARVYKTI should be considered.

Females and males of reproductive potential

Pregnancy testing

Pregnancy status for females of child-bearing age should be verified prior to starting treatment with CARVYKTI.

Contraception

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with CARVYKTI.
In clinical trials, female patients of childbearing potential were advised to practice a highly effective method of contraception, and male patients with partners of childbearing potential or whose partners were pregnant, were instructed to use a barrier method of contraception until one year after the patient has received CARVYKTI infusion.
See the prescribing information for lymphodepleting chemotherapy for information on the need for contraception in patients who receive the lymphodepleting chemotherapy.

Breast-feeding

There is no information regarding the presence of CARVYKTI in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CARVYKTI and any potential adverse effects on the breastfed infant from CARVYKTI or from the underlying maternal condition.

Fertility

There are no data on the effect of CARVYKTI on fertility. Effects of CARVYKTI on male and female fertility have not been evaluated in animal studies.

Effects on ability to drive and use machines

Due to the potential for neurologic events, patients receiving CARVYKTI are at risk for altered or decreased consciousness or coordination in the 8 weeks following CARVYKTI infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery during this initial period and in the event of new onset of any neurological symptoms.

Undesirable effects

Summary of the safety profile

The safety data described in this section reflect the exposure to CARVYKTI in two open label clinical trials in which 124 adult patients with multiple myeloma received CARVYKTI infusion (see «Clinical Efficacy»): Study MMY2001 (N=106), which included patients from the main Phase 1b/2 cohort (United States; n=97; with a median duration of follow-up of 12.4 months)) and an additional cohort (Japan; n=9), and Study MMY2003 (n=18).
The most common CARVYKTI adverse reactions (≥20%) were neutropenia, CRS, pyrexia, anemia, thrombocytopenia, leukopenia, lymphopenia, hypotension, transaminase elevation, musculoskeletal pain, fatigue, upper respiratory tract infection, cough, hypocalcemia, diarrhea, hypophosphatemia, chills, nausea, decreased appetite, tachycardia, headache, edema, hypoalbuminemia, hyponatremia, encephalopathy, hypokalaemia, dyspnoea, vomiting and constipation.
Serious adverse reactions occurred in 44% of patients; serious adverse reactions reported in ≥5% of patients were CRS (19%), sepsis (6%), encephalopathy (6%), and pneumonia (6%).
The most common (≥10%) Grade ≥3 non-haematological adverse reactions were transaminase elevation (19%), pneumonia (10%) and hypotension (10%).
The most frequent (≥25%) Grade ≥3 haematological abnormalities were neutropenia (94%), leukopenia (60%), anaemia (64%) and thrombocytopenia (56%) and lymphopenia (47%).

Below are the adverse reactions that occurred in patients receiving CARVYKTI summarised .

Within each MedDRA system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1‘000 to <1/100); rare (≥1/10‘000 to <1/1‘000); very rare (<1/10‘000); not known (cannot be estimated from the available data).

Tabelle 3: Adverse reactions in patients with multiple myeloma treated with CARVYKTI (N = 124)

System organ class	Frequency	Adverse reaction	Incidence (%)	
			Any Grade	Grade ≥ 3
Infections and infestations	Very common	Upper respiratory tract infection[1]	35	2
		Pneumonia[2]	10	10
		Sepsis[3#]	10	6
	Common	Bacterial infection[4#]	7	3
		Viral infection[5]	7	2
		Cytomegalovirus infection[6]	2	2
Blood and lymphatic system disorders	Very common	Neutropenia	94	94
		Anemia	77	64
		Thrombocytopenia	77	56
		Leukopenia	60	60
		Lymphopenia	49	47
		Coagulopathy[7]	18	2
		Febrile neutropenia	12	11
		Hypofibrinogenemia[8]	10	1
Immune system disorders	Very common	Cytokine release syndrome[#]	91	5
		Hypogammaglobulinaemia	10	2
	Common	Haemophagocytic lymphohistiocytosis[#]	1	1
Metabolism and nutrition disorders	Very common	Hypocalcaemia	30	4
		Hypophosphataemia	28	7
		Decreased appetite	25	2
		Hypoalbuminaemia	23	1
		Hyponatraemia	23	5
		Hypokalaemia	22	2
		Hypomagnesaemia	13	0
Psychiatric disorders	Very common	Insomnia	12	0
	Common	Delirium[9]	5	1
		Personality changes[10]	3	1
Nervous system disorders	Very common	Headache	24	0
		Encephalopathy[11]	23	5

		Dizziness[12]	19	1
		Motor dysfunction[13]	19	6
		Immune effector cell-associated neurotoxicity syndrome	15	2
		Neuropathy peripheral[14]	10	2
	Common	Aphasia[15]	8	0
		Ataxia[16]	7	0
		Tremor[17]	6	0
		Paresis[18]	6	2
		Neurotoxicity[#]	2	2
Cardiac disorders	Very common	Tachycardia[19]	25	1
	Common	Cardiac arrhythmias[20]	8	3
Vascular disorders	Very common	Hypotension[21]	46	10
		Hypertension	16	6
	Common	Hemorrhage[22]	8	2
Respiratory, thoracic and mediastinal disorders	Very common	Cough[23]	33	0
		Dyspnoea[24#]	21	4
		Hypoxia[25]	12	4
Gastrointestinal disorders	Very common	Diarrhoea	29	1
		Nausea	27	1
		Constipation	20	0
		Vomiting	20	0
	Common	Abdominal pain[26]	9	0
Hepatobiliary disorders	Common	Hyperbilirubinemia	6	2
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[27]	42	2
Renal and urinary disorders	Common	Renal failure[28]	8	5
General disorders and administration site conditions	Very common	Pyrexia	91	6
		Fatigue[29]	40	6
		Chills	28	0
		Edema[30]	24	2
		Pain[31]	13	1
Investigations	Very common	Transaminase elevation[32]	44	19
		Gamma-glutamyltransferase increased	15	8
		Blood alkaline phosphatase increased	12	3
		Blood lactate dehydrogenase increased	11	0
		Serum ferritin increased	10	2

	Common	C-reactive protein increased	7	3

Adverse events are reported using MedDRA version 23.0

[#] Contains fatal event/s.

[1] Upper respiratory tract infection includes Bronchitis, Nasal congestion, Paranasal sinus discomfort, Rhinitis, Rhinorrhoea, Rhinovirus infection, Sinus congestion, Sinusitis, Upper respiratory tract congestion, Upper respiratory tract infection, and Viral upper respiratory tract infection.

[2] Pneumonia includes Atypical pneumonia, COVID-19 pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, and Pneumonia aspiration.

[3] Sepsis includes Bacteraemia, Bacterial sepsis, Pseudomonal bacteraemia, Sepsis, Septic shock, and Staphylococcal bacteraemia.

[4] Bacterial infection includes Abscess limb, Clostridium difficile colitis, Clostridium difficile infection, Folliculitis, Klebsiella infection, Lung abscess, Osteomyelitis, Perirectal abscess, Skin infection, Staphylococcal infection, and Tooth infection.

[5] Viral infection includes Adenovirus test positive, COVID-19, Coronavirus infection, Influenza, and Parainfluenzae virus infection.

[6] Cytomegalovirus infection includes Cytomegalovirus syndrome, and Cytomegalovirus viraemia.

[7] Coagulopathy includes Activated partial thromboplastin time prolonged, Coagulopathy, Disseminated intravascular coagulation, Fibrin D dimer increased, International normalised ratio increased, Prothrombin level increased, and Prothrombin time prolonged.

[8] Hypofibrinogenemia includes Blood fibrinogen decreased, and Hypofibrinogenaemia.

[9] Delirium includes Agitation, Delirium, Hallucination, Irritability, and Restlessness.

[10] Personality changes includes Flat affect, Personality change, and Reduced facial expression.

[11] Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Lethargy, Memory impairment, Mental impairment, Mental status changes, Noninfective encephalitis, Psychomotor retardation, Sleep disorder, and Somnolence.

[12] Dizziness includes Dizziness, Presyncope, and Syncope.

[13] Motor dysfunction includes Bradykinesia, Cogwheel rigidity, Dysgraphia, Eyelid ptosis, Micrographia, Motor dysfunction, Muscle spasms, Muscle tightness, Muscular weakness, Myoclonus, Parkinsonism, Posture abnormal, and Stereotypy.

[14] Neuropathy peripheral includes Hypoaesthesia, Neuralgia, Paraesthesia, Paraesthesia ear, Peripheral motor neuropathy, Peripheral sensory neuropathy, and Sensory loss.

[15] Aphasia includes Aphasia, Dysarthria, Slow speech, and Speech disorder.

[16] Ataxia includes Ataxia, Balance disorder, and Gait disturbance.

[17] Tremor includes Resting tremor, and Tremor.

[18] Paresis includes Cranial nerve paralysis, Facial paralysis, Hemiparesis, and Peroneal nerve palsy.

[19] Tachycardia includes Sinus tachycardia, and Tachycardia.

[20] Cardiac arrhythmias includes Atrial fibrillation, Atrial flutter, Supraventricular tachycardia, Ventricular extrasystoles, and Ventricular tachycardia.

[21] Hypotension includes Hypotension, and Orthostatic hypotension.

[22] Haemorrhage includes Conjunctival haemorrhage, Epistaxis, Haemoptysis, Post procedural haemorrhage, Pulmonary haemorrhage, and Retinal haemorrhage.

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

[24] Dyspnoea includes Acute respiratory failure, Dyspnoea, Dyspnoea exertional, Respiratory failure, and Wheezing.

[25] Hypoxia includes Hypoxia, and Oxygen consumption decreased.

[26] Abdominal pain includes Abdominal pain, Abdominal pain upper, and Dyspepsia.

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

[28] Renal failure includes Acute kidney injury, Blood creatinine increased, and Chronic kidney disease.

[29] Fatigue includes Asthenia, Exercise tolerance decreased, Fatigue, and Malaise.

[30] Edema includes Face oedema, Fluid overload, Fluid retention, Generalised oedema, Joint swelling, Localised oedema, Oedema peripheral, Periorbital oedema, Peripheral swelling, Pulmonary congestion, Pulmonary oedema, and Scrotal oedema.

[31] Pain includes Catheter site pain, Ear pain, Eye pain, Non-cardiac chest pain, Pain, Pain in jaw, Proctalgia, and Toothache.

[32] Transaminase elevation includes Alanine aminotransferase increased, and Aspartate aminotransferase increased.

Description of selected adverse reactions

Cytokine release syndrome

In Study MMY2001 (N=97), CRS was reported in 95% of patients (n=92); 90% (n=87) CRS events were Grade 1 or Grade 2,4% (n=4) Grade 3 or 4, and 1% (n=1) was Grade 5. Ninety-nine percent of patients (n=91) recovered from CRS.

The duration of CRS was ≤14 days for all but one patient who had a duration of CRS of 97 days complicated by secondary HLH with a subsequent fatal outcome. The most frequent (≥10%) signs or symptoms associated with CRS included pyrexia (95%), hypotension (41%), Aspartate aminotransferase (AST) increased (21%), chills (14%), Alanine aminotransferase (ALT) increased (13%) and sinus tachycardia (10%). See «Warnings and Precautions» for monitoring and management guidance.

Neurologic toxicities

In Study MMY2001 (N=97), neurologic toxicity occurred in 21% of patients with 8% being Grade 3 or Grade 4 and 1% Grade 5.
ICANS occurred in 16% of patients (n=16), with 2% (n=2) experiencing Grade 3 or higher ICANS. Symptoms included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state. The median time from CARVYKTI infusion to first onset of ICANS was 8.0 days (range: 3 to 12 days) and the median duration was 4 days (range 1 to 12 days).
Adverse reactions of neurologic toxicity after recovery from CRS and/or ICANS occurred in 12% of patients (n=12). These events had a median onset of 26.5 days from CARVYKTI infusion (range, 11 to 108 days) with a median time to recovery of 74.5 days (range, 2 to 160 days). A variety of symptoms with varying severity were observed, including disturbances in consciousness, coordination and balance disturbances, movement disorders, mental impairment disorders, cranial nerve disorders, and peripheral neuropathies. Eight of these 12 patients had also previously experienced ICANS.
Five percent of patients (n=5; all male) experienced a cluster of movement and neurocognitive adverse reactions including movement (e.g., micrographia, tremors), cognitive (e.g., memory loss, disturbance in attention), and personality change (e.g., reduced facial expression, flat affect), often with subtle onset (e.g., micrographia, flat affect), that in some patients progressed to an inability to work or care for oneself. The median time to first symptom onset was 27 days (range 14 to 108 days). These patients all presented a combination of two or more factors such as high tumor burden (bone marrow plasma cell ≥80% or serum M-spike ≥ 5 g/dL or serum free light chain ≥ 5000 mg/L), prior Grade 2 or higher CRS, prior ICANS, and high CAR-T-cell expansion and persistence. Treatment with levodopa/carbidopa (n=2), was not effective in improving symptomatology in these patients.
One of these five patients experienced a fatal outcome attributed to neurotoxicity, and two patients had ongoing neurotoxicity at the time of death; the deaths were due to infection.
Of the remaining seven patients who reported adverse reactions of neurologic toxicity after recovery from CRS and/or ICANS, two patients had fatal outcomes with ongoing neurotoxicity at the time of death; the deaths were due to respiratory failure and sepsis respectively.

Prolonged Cytopenia

In Study MMY2001 (N=97), Grade 3 or higher cytopenias at Day 1 after dosing, not resolved to Grade 2 or lower by Day 30 following CARVYKTI infusion, included thrombocytopenia (41%), neutropenia (30%), and lymphopenia (12%). After Day 60 following CARVYKTI, 31%, 12%, and 6% of patients had an occurrence of Grade 3 or higher lymphopenia, neutropenia and thrombocytopenia respectively, after initial recovery of their Grade 3 or Grade 4 cytopenia.

Table 4 lists the incidences of Grade 3 or Grade 4 cytopenias occurring after dosing not resolved to Grade 2 or lower by Day 30 and Day 60 respectively.

	Grade 3/4 (%) after Day 1 Dosing	**Initial Grade 3/4 (%), not Recovereda to ≤ Grade 2 by Day 30**	**Initial Grade 3/4 (%), not Recovereda to ≤ Grade 2 by Day 60**	**Occurrence of Grade 3/4 (%) > Day 60 (after Initial Recoverya of Grade 3/4)**
Thrombocytopenia	60 (62%)	40 (41%)	25 (26%)	6 (6%)
Neutropenia	95 (98%)	29 (30%)	10 (10%)	12 (12%)
Lymphopenia	96 (99%)	12 (12%)	8 (8%)	30 (31%)

[a] The laboratory result with the worst toxicity grade will be used for a calendar day. Recovery definition: must have 2 consecutive Grade ≤2 results on different days if recovery period ≤10 days.

Notes: Lab results assessed after Day 1 until Day 100 are included in the analysis.

Thrombocytopenia: Grade 3/4 – Platelets count <50000 cells/μL.

Neutropenia: Grade 3/4 - Neutrophil count <1000 cells/μL.

Lymphopenia: Grade 3/4 - Lymphocytes count <0.5 x 109 cells/L.

Percentages are based on the number of treated subjects.

Serious Infections

Infections occurred in 56 patients (58%) in Study MMY2001 (N=97); 19 (20%) experienced Grade 3 or Grade 4 infections, and fatal infections occurred in 3 patients (3%); lung abscess, sepsis, and septic shock. The most frequently reported (≥5%) Grade 3 or higher infections were pneumonia and sepsis. Febrile neutropenia was observed in 10% of patients with 4% experiencing serious febrile neutropenia. See «Warnings and Precautions» for monitoring and management guidance.

Hypogammaglobulinemia

In Study MMY2001 (N=97) hypogammaglobulinemia occurred in 11% of patients with 2% of patients experiencing Grade 3 or Grade 4 hypogammaglobulinemia. See «Warnings and Precautions» for monitoring and management guidance.

Overdose

There are no data regarding the signs or sequelae of overdose with CARVYKTI.

Properties/Effects

ATC code

Not yet assigned.

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.
In vitro co-culture experiments demonstrated that ciltacabtagene autoleucel-mediated cytotoxicity and cytokine release (interferon-gamma, [IFN-γ], tumor necrosis factor alpha [TNF-α], interleukin [IL]-2) were BCMA-dependent.

Pharmacodynamics

After a single infusion of CARVYKTI, expansion of CAR-positive T-cells coincided with decreases of serum soluble BCMA, serum M-protein, and/or free light chains. Across all patients, levels of IL-6, IL-10, IFN-γ 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 2-3 months post-infusion.

Immunogenicity

The immunogenicity of CARVYKTI has been evaluated using a validated assay for the detection of binding antibodies against CARVYKTI pre-dose and at multiple timepoints post-infusion. In Study MMY2001, 19 of 97 patients (19.6%) were positive for anti-CAR antibodies.
There was no clear evidence to suggest that the observed anti-CAR antibodies impact CARVYKTI kinetics of initial expansion and persistence, efficacy, or safety.

Clinical efficacy

MMY2001 was an open label trial evaluating CARVYKTI for the treatment of patients with relapsed or refractory multiple myeloma who previously received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on or after the last regimen.
In total, 113 patients underwent leukapheresis; CARVYKTI was manufactured for all patients.
The median time from the day after receipt of leukapheresis material at manufacturing facility to release of product for infusion was 29 days (range 23 to 64 days) and the median time from initial leukapheresis to CARVYKTI infusion was 47 days (range 41 days to 167 days).

Following leukapheresis and prior to administration of CARVYKTI, 73 of the 97 patients (75%) received bridging therapy. The most commonly used agents as bridging therapies (≥20% of patients) included dexamethasone: 62 patients (64%), bortezomib: 26 patients (27%), cyclophosphamide: 22 patients (23%), and pomalidomide: 21 patients (22%).

CARVYKTI was administered as a single IV infusion 5 to 7 days after the start of a lymphodepleting chemotherapy (cyclophosphamide 300 mg/m^2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days). Ninety-seven patients received CARVYKTI at a median dose of 0.71×10^6 CAR-positive viable T-cells/kg (range: 0.51 to 0.95×10^6 cells/kg). All patients were hospitalized for CARVYKTI infusion and for a minimum of 10 days afterward. Sixteen patients were not treated with CARVYKTI (n=12 after leukapheresis and n=4 after lymphodepleting therapy), due to either withdrawal by patient (n=5), progressive disease (n=2) or death (n=9).

Of the 97 patients treated, 59% were male, 71% were Caucasian and 18% were African-American. The median patient age was 61 years (range: 43 to 78 years). Patients had received a median of 6 (range: 3 to 18) prior lines of therapy and 90% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-nine percent of patients were refractory to their last line of prior therapy and 88% were refractory to a proteasome inhibitor (PI), immunomodulatory agent, and anti-CD38 antibody.

Patients with known active, or prior history of significant central nervous system (CNS) disease including CNS multiple myeloma, allogenic stem cell transplant within 6 months before apheresis or ongoing treatment with immunosuppressants, creatinine clearance < 40mL/min, absolute lymphocyte concentration < 300/µL, hepatic transaminases > 3 times the upper limit of normal, cardiac ejection fraction < 45%, or with active serious infection were excluded from the trial.

Efficacy results were based on overall response rate as determined by the Independent Review Committee assessment using IMWG criteria (see Table 5).

Table 5: Efficacy results for Study MMY2001

	All Treated (N=97)
Overall Response Rate (sCR[a] + VGPR + PR), n (%) 95% CI (%)	95 (97,9) (92,7; 99,7)
Stringent complete response (sCR[a]) n (%)	78 (80,4)
Very good partial response (VGPR) n (%)	14 (14,4)
Partial response (PR) n (%)	3 (3,1)

Duration of Response (DOR)	
Number of responders	95
DOR (Months): Median (95% CI)	21,8 (21,8; NE)
Number of responders with sCR[a]	78
DOR if best response is sCR[a] (Months): Median (95% CI)	NE (21,8; NE)
Number of responders with VGPR or better	92
DOR if best response is VGPR or better (Months): Median (95% CI)	21,8 (21,8; NE)
Time to Response (months)	
Number of responders	95
Median	0,95
Range	(0,9; 10,7)
Time to sCR[a] (months)	
Number of responders with sCR[a]	78
Median	2,63
Range	(0,9; 15,2)

Notes: Based on a median duration of follow up of 18 months

[a] All complete responses were stringent CRs

NE = not estimable

Table 6: Summary of MRD negativity rate

	All Treated (N=97)
MRD negativity rate, n (%)	56 (57.7)
95% CI (%)	(47.3, 67.7)
MRD negative patients with sCRn (%)[a]	42 (43.3)
95% CI (%)	(33.3. 53.7)
	Evaluable patients (N=61)
MRD negativity rate, n (%)	56 (91.8)
95% CI (%)	(81.9, 97.3)

MRD= Minimal Residual Disease

Notes:Based on a median duration of follow up of 18 months

[a] Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death / progression / subsequent therapy (exclusive) are considered. All complete responses were stringent CRs.

With a median duration of follow-up of 18 months, median Progression Free Survival (PFS) was 22.8 months (95% CI: 22.8, not estimable). ed. The 12-month PFS rate (95% CI) was 76.3% (66.5%, 83.6%).

For patients who achieved sCR (all complete responses were stringent CRs), median PFS was not reached (95% CI: 22.8%, not estimable) with an estimated 12-month PFS rate of 88.5% (95% CI: 79.0%, 93.8%).

Median overall survival (OS) was not reached (95% CI: 23.59%, not estimable). The OS rate at 12 months was 87.6% (95% CI: 79.2%, 92.8%).

Health-related quality of life (HRQoL) was evaluated by the EORTC QLQ-C30 and completed at baseline (n=63) and during the post-infusion phase. The adjusted mean (95% CI) change from baseline in the EORTC QLQ-C30 Pain subscale was -1.9 (-8.5, -4.6) at day 7, -9.9 (-16.5, -3.3) at day 28, -6.3 (-12.9, -0.4) at day 56, -9.4 (-16.3, -2.5) at day 78, and -10.5 (-17.3, -3.8) at day 100, indicating overall reduction in pain following CARVYKTI infusion. Clinically meaningful improvements at Day 100 were seen in 72.2% of patients for the pain subscale, 53.8% for the fatigue subscale, 57.7% for the physical functioning subscale, and 53.7% for the global health status subscale.

Pharmacokinetics

CARVYKTI pharmacokinetics (PK) was assessed in 97 patients with multiple myeloma receiving a single CARVYKTI infusion at the median dose of 0.71×10^6 CAR positive viable T-cells/kg (range: 0.51×10^6 to 0.95×10^6 cells/kg).
Following a single infusion, CARVYKTI exhibited an initial expansion phase followed by a rapid decline and then a slower decline. However, high interindividual variability was observed.

Table 7: Pharmacokinetic Parameters of CARVYKTI in patients with multiple myeloma

Parameter	**Summary Statistics**	**Patetients (N=97)**
C_{max} (copies/µg genomic DNA)	Mean (SD), n	48’692 (27’174), 97
t_{max} (day)	Median (range), n	12,71 (8,73 - 329,77), 97
$AUC_{0\text{-}28d}$ (copies*day/µg genomic DNA)	Mean (SD), n	504’496 (385’380), 97
$AUC_{0\text{-}last}$ (copies*day/µg genomic DNA)	Mean (SD), n	1’098’030 (1'387’010), 97
$AUC_{0\text{-}6m}$ (copies*day/µg genomic DNA)	Mean (SD), n	1’033’373 (1’355’394), 96
$t_{1/2}$ (day)	Mean (SD), n	23,5 (24,2), 42
t_{last} (day)	Median (range), n	125,90 (20,04 – 702,12), 97

After the cell expansion, the persistence phase of the CARVYKTI levels was observed for all patients. At the time of analysis (n=65), the median time for CAR transgene levels in peripheral blood to return to the pre-dose baseline level was approximately 100 days (range: 28-365 days) post-infusion. Detectable CARVYKTI exposures in bone marrow indicate a distribution of CARVYKTI from systemic circulation to bone marrow. Similar to blood transgene levels, bone marrow transgene levels declined over time and exhibited high interindividual variability.
Some patients required tocilizumab, corticosteroids and anakinra for management of CRS. CARVYKTI continues to expand and persist following tocilizumab administration. Patients treated with

tocilizumab (n=68) had 81% and 72% higher CARVYKTI C_{max} and AUC_{0-28d}, respectively, as compared to patients (n=29) who did not receive tocilizumab. Patients who received corticosteroids (n=28) had 75% and 112% higher C_{max} and AUC_{0-28d}, respectively, compared with patients who did not receive corticosteroids (n=69). In addition, patients who received anakinra (n=20) had 41% and 72% higher C_{max} and AUC_{0-28d}, respectively, compared with patients who did not receive anakinra (n=77).

Absorption

NA

Distribution

NA

Metabolism

NA

Elimination

NA

Kinetics in specific patient groups

The pharmacokinetics of CARVYKTI (C_{max} and AUC_{0-28d}) were not impacted by age (range 43-78 years), including patients <65 years of age [n=62; 63.9%], 65-75 years (n=27; 27.8%) and >75 years of age (n=8; 8.2%).
Similarly, the pharmacokinetics of CARVYKTI (C_{max} and AUC_{0-28d}) were not impacted by gender, body weight, and race.

Hepatic impairment

Hepatic impairment studies of CARVYKTI were not conducted. CARVYKTI C_{max} and AUC_{0-28d} were similar in patients with mild hepatic dysfunction [(total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase >ULN) or (ULN < total bilirubin ≤ 1.5 times ULN)] and patients with normal hepatic function.

Renal impairment

Renal impairment studies of CARVYKTI were not conducted. CARVYKTI C_{max} and AUC_{0-28d} were similar in patients with mild renal dysfunction (60 mL/min ≤ creatinine clearance [CRCL] < 90 mL/min) and in patients with normal renal function (CRCL ≥ 90 mL/min).

Preclinical data

Nonclinical safety assessment of CARVYKTI confirmed the on-target specificity of CARVYKTI to BCMA.

Carcinogenicity

No genotoxicity or carcinogenicity studies have been performed.
The risk for insertional mutagenesis occurring during the manufacturing of ciltacabtagene autoleucel following transduction of autologous human T-cells with an integrating lentiviral vector (LV) was assessed by evaluating the integration pattern of the vector in pre-infusion CARVYKTI. This genomic insertional site analysis was performed on CARVYKTI products from 7 patients and 3 healthy volunteers. There was no evidence for preferential integration near genes of concern.
The potential for enhanced proliferation of CARVYKTI was assessed in an *in vitro* cytokine independent growth assay. Integration of LV into primary T-cell genome during transduction did not lead to cytokine independent uncontrolled growth in the absence of IL-2 (the cytokine that regulates T-cell growth and promotes T-cell survival) of CARVYKTI.

Reproductive toxicity

No reproductive and developmental toxicity animal studies have been conducted with CARVYKTI.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store ≤ -120°C, e.g., in a container for cryogenic storage in the vapour phase of liquid nitrogen.
Store in the original packaging containing the cassette protecting the infusion bag.
Once thawed, the product should be administered immediately, and the infusion should be completed within 2.5 hours at room/ambient temperature (20°C to 25°C). Thawed product should not be shaken, refrozen or refrigerated.
Keep out of reach of children.

Instructions for handling

Do not irradiate as this could lead to inactivation of the product.
CARVYKTI should be transported within the facility in closed, break-proof, leak-proof containers.
CARVYKTI contains human blood cells that are genetically modified with replication incompetent lentiviral vector. Follow universal precautions and local guidelines for handling and disposal of unused medicinal product or all material that has been in contact with CARVYKTI (solid and liquid waste) to avoid potential transmission of infectious diseases.

Authorisation number

67956 (Swissmedic)

Packs

Ethylene vinyl acetate (EVA) infusion bag with sealed addition tube and two available spike ports containing either 30 mL or 70 mL of cell dispersion [A].
Each infusion bag is individually packed in an aluminium cryo cassette.

Component Type	Mandatory content and placement instructions
Cassette	Do not irradiate. Do NOT use leukocyte depleting filter. Intravenous use For autologous use only. Properly identify intended recipient and product. <u>Storage conditions:</u> Store and transport frozen ≤ -120°C in vapour phase of liquid nitrogen. Do not thaw the product until use. Do not shake. Do not refreeze. Do not refrigerate.
Infusion Bag	For intravenous use only For autologous use only Verify Patient ID

Marketing authorisation holder

Janssen-Cilag AG, Zug

Date of revision of the text

August 2022

Revision history

Application ID	Milestone	Created on	Change	Initials