

I concur with the P/T Recommendation. M. Serabian 01/03/22

I concur with the P/T Recommendation. C. Saeui 01/03/22

FOOD AND DRUG ADMINISTRATION
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Pharmacology/Toxicology Branch

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PRODUCT: CARVYKTI™ (ciltacabtagene autoleucel) suspension for intravenous infusion

APPLICANT: Janssen Biotech, Inc.

PROPOSED INDICATION: Treatment of adult patients with relapsed or refractory (r/r) multiple myeloma (MM), who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody.

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EXECUTIVE SUMMARY:

CARVYKTI™ (ciltacabtagene autoleucel; cilta-cel; JNJ-68284528; or LCAR-B38M CAR-T cells) is a cell suspension consisting of autologous T cells that are genetically modified *ex vivo* with a lentiviral vector (LV) encoding a chimeric antigen receptor (CAR) targeting the B cell maturation antigen (BCMA). The BCMA-targeting domain ((b) (4)) is comprised of two

single-domain antibodies, described as (b) (4)

In vitro pharmacology studies characterizing the mechanism of action of CARVYKTI™ demonstrated tumor cell cytotoxicity and cytokine release following exposure to BCMA-expressing MM cells. On-tumor/on-target specificity of the BCMA-targeting domain to human BCMA was also shown. Although binding between (b) (4) was detected in a (b) (4), the data suggest that the epitope primarily recognized by (b) (4) is found in BCMA. In addition, specific binding of (b) (4) or cilta-cel to healthy donor (HD)-derived myeloid cells that endogenously express native (b) (4) was not observed.

In vivo studies in mice and nonhuman primates (NHPs) did not reveal any adverse findings due to possible off-target binding to (b) (4). These data suggest a low risk of off-target adverse effects in humans. *In vivo* pharmacology studies showed significant dose-dependent anti-tumor activity and increased survival following administration of LCAR-B38M CAR-T cells in immune-deficient mice engrafted with human MM cells. Following tumor re-challenge, no increase in tumor growth was displayed.

In vitro data indicate that (b) (4) does not significantly bind to recombinant mouse or NHP BCMA expressed on (b) (4) cells. Therefore, animal studies evaluating the safety profile of CARVYKTI™ were limited due to lack of a pharmacologically relevant animal species. Traditional genotoxicity assays and carcinogenicity assessments were not conducted. The risk of insertional mutagenesis due to LV transduction, possibly leading to malignant transformation, was evaluated. The resulting data showed that the LV used to manufacture CARVYKTI™ does not preferentially integrate at or near specific genomic sites of concern for oncogenic transformation. In addition, an (b) (4) assay evaluation of CARVYKTI™ generated from six patients with MM and three HDs showed no signs of uncontrolled cellular proliferation. These data support the conclusion that any insertional events resulting from LV transduction methods used to generate CARVYKTI™ have minimal risk for oncogenic transformation.

No animal reproductive and developmental toxicity (DART) studies were conducted with CARVYKTI™, which is acceptable based on the product characteristics and safety profile. In addition, (b) (4) was not detected in human female or male reproductive organs. However, Section 8.1 of the proposed label describes the potential risks of CARVYKTI™ to the developing embryo or fetus if the transduced cells cross the placenta following administration in women of childbearing potential.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

There are no nonclinical deficiencies identified in this submission. There are no outstanding requests for additional nonclinical data for evaluation of CARVYKTI™. The nonclinical information provided in the BLA submission supports approval of the licensure application.

Formulation and Chemistry:

CARVYKTI™ is comprised of, 1) (b) (4) 2) BCMA targeting domain consisting of two different (b) (4) (single domain antibody, (b) (4) , 3) (b) (4) 4) human CD137 cytoplasmic domain, and 5) a human CD3 zeta cytoplasmic domain (CD3ζ). The expression of LCAR-B38M is driven and controlled by a (b) (4) promoter (Figure 1).

After LV transduction, T cells are expanded, washed, harvested, and cryopreserved in a freezing medium ((b) (4)) containing 5% DMSO. The target dose level of CARVYKTI™ for patients of ≤100 kg is 0.75 x 10⁸ CAR+ viable T cells/kg, with a specification range of 0.5-1.0 x 10⁸ CAR+ T cells/kg. CARVYKTI™ is formulated using an approximately 70-mL fill volume in a single (b) (4) freezing bag or a 30-mL fill volume in a single (b) (4) freezing bag. Refer to the CMC review memos for more details regarding the drug substance and drug product.

Figure 1: LCAR-B38M coding region



Source: Pharmacology Written Summary, Module 2.6.2, Section 1 of the BLA.

Abbreviations

ABC	Antibody binding capacity
BCMA	B cell maturation antigen
CML	Chronic myeloid leukemia
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
(b) (4)	(b) (4)
ECD	Extracellular domain
HD	Healthy donor
IV	Intravenous
IFNγ	Interferon-gamma
(b) (4)	(b) (4)
MM	Multiple myeloma
PBMCs	Peripheral blood mononuclear cells
(b) (4)	(b) (4)
UnT cells	Untransduced T cells

Related File(s)

IND #18080: Autologous Human T Cells Genetically Modified ex-vivo with Lentiviral Vector encoding Chimeric Antigen Receptor (CAR) for B Cell Maturation Antigen (BCMA) (JNJ-68284528); Immunotherapy for relapsed or refractory multiple myeloma, Janssen Research & Development LLC; ACTIVE

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INTRODUCTION

Multiple myeloma is a malignant plasma cell disorder that accounts for approximately 10% of all hematologic cancers and it is characterized by the production of monoclonal immunoglobulin proteins or protein fragments (M proteins) that have lost their function.^{1,2} The proliferation of MM cells leads to subsequent displacement of normal bone marrow hematopoietic precursors and overproduction of M proteins. The hallmark signs of MM include osteolytic lesions, anemia, susceptibility to infections, hypercalcemia, renal insufficiency or failure, and neurological complications.² Per the applicant, treatment options for MM, which have improved over time, vary depending on the aggressiveness of the disease, underlying prognostic factors, physical condition of the patient, and existing co-morbidities. Therapeutic options include agents such as proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and stem cell transplantation. Despite these treatments, the disease recurs and remains incurable.

¹ Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia*. 2009;23(1):3-9.

² Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med*. 2011;364(11):1046-1060.

BCMA, also known as CD269, is a member of the tumor necrosis factor protein receptor superfamily 17 (TNFRSF17) and is mainly expressed on the surface of mature B lymphocytes and MM cells. BCMA plays an important role in B cell maturation and subsequent differentiation into plasma cells.³ BCMA binds two ligands that induce B cell proliferation: a proliferation ligand (APRIL; CD256) and B cell activating factor (BAFF; CD257) that function to promote the survival and homeostasis of plasma cells.⁴ Serum levels of BCMA are elevated in patients with MM. Following stimulation with APRIL or BAFF, BCMA elicits a signaling cascade that is involved in the activation of MAP kinases and the induction of anti-apoptotic proteins, such as Bcl-2 and Bcl-XL.⁵

JNJ-68284528 (LCAR-B38M CAR-T) is an engineered autologous CAR-T cell immunotherapy directed against BCMA. Following binding to tumor cells expressing BCMA, this immunotherapy is activated, and subsequently proliferates and exerts cytotoxic effects against BCMA-expressing cells.

NONCLINICAL STUDIES

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies

The following pharmacology studies were conducted to support the rationale for the administration of cilta-cel in the proposed clinical population.

Note:

- Ciltacabtagene autoleucel (cilta-cel) is identified as ‘JNJ-68284528’ for studies sponsored by Janssen and as ‘LCAR-B38M CAR-T cells’ for studies conducted by Nanjing Legend Biotech (China). As described in Module 2.4, while the manufacturing process for the LV and the CAR-T cells has been modified during the product development program, the CAR expressed by the CAR-T cells is identical. When the LV was first developed by Legend Biotech, a (b) (4) -generation LV, LCAR-B38M (Legend LV), was used in the initial nonclinical studies. (b) (4) then developed and manufactured a (b) (4) generation (b) (4) ((b) (4) LV (b) (4)). The (b) (4) LV (b) (4), was subsequently introduced to reduce the potential for patient sensitivity to (b) (4). The (b) (4) LV (b) (4), was used to generate cilta-cel for several nonclinical studies and for initial cohorts in the Phase 1b clinical trial. These various products are identified in this reviewer’s summaries of the nonclinical studies provided in this review memo.

³ Tai YT, Anderson KC. Targeting B-cell maturation antigen in MM. Immunotherapy. 2015;7(11):1187-1199.

⁴ Rickert, R. C., Jellusova, J., & Miletic, A. V. (2011). Signaling by the tumor necrosis factor receptor superfamily in B-cell biology and disease. Immunological reviews, 244(1), 115–133.

⁵ Moreaux J, Legouffe E, Jourdan E, Quittet P, Rème T, Lugagne C, Moine P, Rossi JF, Klein B, Tarte K. BAFF and APRIL protect myeloma cells from apoptosis induced by interleukin 6 deprivation and dexamethasone. Blood. 2004;103:3148–57

In vitro Studies

Study Number	Study Title	Report Number
1	(b) (4)	LB-PA-NCSR004
2	(b) (4)	LB-PA-NCSR005
3	(b) (4)	LB-PA-NCSR006
4	In vitro Cytotoxicity Assay on (b) (4) Cells with LCAR-B38M CAR-T Prepared from Varied Donors	LB-PA-NCSR007
5	(b) (4)	LB-PA-NCSR008-S1
6	(b) (4)	LB-PA-NCSR008-S2
7	In vitro Study of LCAR-B38M CAR-T Cytotoxicity on Human Cell Lines	LB-PA-NCSR009
8	In vitro Study of LCAR-B38M CAR-T Cytokine Release in Co-culture with Human Cell Lines	LB-PA-NCSR010
9	Binding study of BCMA Extra-Cellular Domain to LCARB38M CAR	LB-PA-NCSR013
10	Normal Tissue Binding Profiling of BCMA Targeting Domain of LCAR-B38M	LB-PA-NCSR014
11	(b) (4)	LB-PA-NCSR015
12	Assessment of CAR T cell binding profile using a (b) (4)	RP493
13	Assessment of the binding profile of JNJ-68284528 using a (b) (4)	RP582
14	(b) (4)	TR2020T-001
15	BCMA-(b) (4) analysis	TR2019T-007
16	In Vitro Pharmacological Characterization of JNJ-68284528 CAR-T Cells	DD19000
17	(b) (4)	BD2019ST-003
18	(b) (4)	BD2019ST-004

In vivo Studies

In Vivo Studies in Tumor Xenograft Animal Models


Study Number	Study Title	Report Number
19	Dose escalating study of LCAR-B38 CAR-T on (b) (4) engrafted immune deficient mice	LB-PA-NCSR011
20	In vivo Efficacy Study of LCAR-B38M on (b) (4) Engrafted Immune Deficient Mouse	C7122BK100

Overview of Pharmacology Studies

In vitro Studies





Study #1

(b) (4)



Study #2

(b) (4)






Reviewer Comment:

- Studies #1 and #2 were not conducted with the final clinical product, as (b) (4) through (b) (4) had (b) (4) different (b) (4) (BCMA binding domain) combinations. However, these studies provided overall support for selection of an optimal construct, such as that in the investigational product (LCAR-B38M CAR-T) to target BCMA+ tumor cells.

Study #3

(b) (4)



Results:

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Study #4

Title: In vitro Cytotoxicity Assay on (b) (4) Cells with LCAR-B38M CAR-T Prepared from Varied Donors

Report No.: LB-PA-NCSR007

Study Performed by Nanjing Legend Biotech Co., Ltd, China

Objective: To assess the *in vitro* cytotoxicity on (b) (4) -expressing MM tumor cell line (b) (4), with LCAR-B38M CAR-T cells prepared from patients with MM.

Methods: The LCAR-B38M CAR-T cells were generated from eight (8) individuals with r/r MM. The transduced cells or untransduced T cells (UnT cells) were co-incubated with (b) (4) tumor cells at E/T ratios ranging from 1:1 to 20:1, for 20-24 hours, followed by assessment of cytotoxicity.

Results:

All preparations of LCAR-B38M CAR-T cells showed robust cytotoxicity on (b) (4) cells. Co-culturing of all eight LCAR-B38M CAR-T cell products with the (b) (4) cells at an E/T ratio of 20:1 resulted in only $2.5 \pm 8\%$ viable target cells remaining. Lower E/T ratios of 5:1 and 1:1 resulted in $19.4 \pm 2.0\%$ and $56.8 \pm 2.2\%$, respectively, viable target cells. UnT cells exhibited a viability of $100 \pm 1.7\%$.

Study #5

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

Study #6

(b) (4)



Study #7

Title: In vitro Study of LCAR-B38M CAR-T Cytotoxicity on Human Cell Lines

Report No.: LB-PA-NCSR009

Study Performed by Nanjing Legend Biotech Co., Ltd., China

LCAR-B38M CAR-T cell Lot Nos.: (b) (6) (derived from r/r MM Donor # (b) (6); manufactured at Legend Biotech) and (b) (6) (derived from a HD; manufactured at (b) (4)).

Objective: To study the selectivity and specificity of LCAR-B38M to understand possible off-target evaluation by cytotoxicity assessment on various human cell lines.

Methods:

Target cell lines

Cell lines expressing (b) (4) generated by Legend Biotech:

- (b) (4) (human MM cell line)
- (b) (4) (human (b) (4) cell line)
- (b) (4) (Human (b) (4) cancer cell line)
- (b) (4) (Human (b) (4) cancer cell line)
- (b) (4) (Human (b) (4) cancer cell line)

- (b) (4) (b) (4) cells expressing (b) (4))
- (b) (4) ((b) (4) cell line)

LCAR-B38M CAR-T cells or UnT cells were co-cultured with each target cell line at an E/T ratio of 20:1, 5:1, or 1:1 for 20-24 hours, followed by determination of (b) (4) expression.

Note:

- The supernatants were assayed for cytokine levels. Refer to Report No. LB-PA-NCSR010 (Study #8) for these results.

Results:

The MM cell line (b) (4) showed strong BCMA expression (88.3%), while BCMA expression levels on the other cell lines were below 1%. LCAR-B38M CAR-T cells from Lot (b) (6) were cytotoxic to the (b) (4) cells. Depending on the E/T cell ratio, the percentage of viable tumor cells ranged from $4.13 \pm 0.48\%$ to $68.98 \pm 2.24\%$ compared to the numbers of viable cells following co-incubation with UnT cells. Both Lot Nos. (b) (6) were comparably cytotoxic to the (b) (4) cells. At an E/T ratio of 20:1, the percentage of remaining viable tumor cells was $14.50 \pm 1.77\%$ and $13.91 \pm 1.97\%$ for Lot Nos. (b) (4), respectively. At E/T ratios of 5:1 / 1:1, the remaining viable cells were $35.53 \pm 3.24\%$ / $23.73 \pm 1.79\%$, and $93.15 \pm 3.06\%$ / $84.72 \pm 3.57\%$ for Lot Nos. (b) (6), respectively.

Study #8

Title: In vitro Study of LCAR-B38M CAR-T Cytokine Release in Co-culture with Human Cell Lines

Report No.: LB-PA-NCSR010

Study Performed by Nanjing Legend Biotech Co., Ltd., China

Test Articles(s) Lot Nos: (b) (6)

Objective: Measurement of cytokine levels for the supernatants collected in Report No. LB-PA-NCSR009 (Study #7).

Methods: Refer to Study #7 for a description of the various target cell lines and the co-culture method with the LCAR-B38M CAR-T cells or UnT cells. Levels of IFN- γ and TNF- α in the supernatants collected from the co-cultures were measured.

Results:

LCAR-B38M (both lots) CAR T cell supernatants generated from co-incubation with the human MM cell line (b) (4) contained the highest mean levels of IFN- γ (approximately 1500 pg/mL and 1900 pg/mL for Lot Nos. (b) (6), respectively) and TNF- α (approximately 1300 pg/mL and 1200 pg/mL, respectively), compared to the other cell lines (0-500 pg/mL of IFN- γ or TNF- α). The pattern of IFN- γ or TNF- α release in the supernatants in the co-culture assays reflected the cytotoxicity data reported in Study #7.

Study #9

Title: Binding study of BCMA Extra-Cellular Domain to LCARB38M CAR

Report No.: LB-PA-NCSR013

Study Performed by Nanjing Legend Biotech Co., Ltd., China

Objective: To measure the binding affinity of recombinant human BCMA ECD to the LCAR-B38M CAR-T cells.

Methods: (b) (4)

Results:

Recombinant human BCMA-ECD protein binding to LCAR-B38M CAR-T cells expressed on the (b) (4) cell line showed a mean affinity ($K_d \pm SE$) of (b) (4). No significant binding of BCMA-ECD protein to non-transduced (b) (4) cells was observed. The BCMA-ECD protein carries a (b) (4) at the C-terminus and has a calculated molecular weight of (b) (4); however, (b) (4). Therefore, assuming a molecular weight of (b) (4), the binding affinity of the BCMA-ECD protein on LCAR-B38M CAR-T cells was (b) (4).

Study #10

Title: Normal Tissue Binding Profiling of BCMA Targeting Domain of LCAR-B38M

Report No.: LB-PA-NCSR014

Study Performed by Nanjing Legend Biotech Co., Ltd., China

Objective: To study the off-target binding profile of the (b) (4) protein ((b) (4)) in normal human tissues.

Methods:

(b) (4) analysis was performed on an array of (b) (4) normal human tissues obtained from three healthy individuals. A purified (b) (4) primary antibody was used to detect BCMA expression on the cell membrane.

Results:

(b) (4) staining of stomach tissue ranged from weak to strong, while moderate (b) (4) staining was observed in hypophysis tissue, and weak staining was detected in bone marrow. No staining of other tissues including, cerebrum, cerebellum, ovary, thyroid gland, breast, thymus gland, lung, heart, esophagus, small intestine, colon, tongue, kidney, prostate, uterus, cervix, striated muscle, skin, nerve, eye, and larynx was identified.

Study #11

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Study #12

Title: Assessment Of CAR T Cell Binding Profile Using A (b) (4)

Report No.: RP493

Study Performed by (b) (4)

Objective: To screen anti-BCMA CAR T cells (also identified as 'Test CAR T cells' in this report) for off-target binding using (b) (4) analysis.

Methods: The study was divided into three phases:

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Results:

Initial screening showed binding of the Test CAR T cells and mock transduced T cells to (b) (4) known CAR-independent T cell interacting proteins: (b) (4). However, only the Test CAR T cells showed binding to over-expressed BCMA protein. The

primary screening identified (b) (4) primary hits with the Test CAR T cells, including the primary target BCMA protein (TNFRSF17). Confirmation screening showed over-expression of all (b) (4) hits in (b) (4) cells and all except for the BCMA protein (TNFRSF17) were also recognized by the mock transduced T cells.

Study #13

Title: Assessment of The Binding Profile Of JNJ-68284528 Using a (b) (4)

Report No.: RP582

Study Performed by (b) (4)

JNJ-68284528 Lot No.: Not specified

Notes:

- Cilta-cel was identified as 'JNJ-68284528' for nonclinical studies conducted or sponsored by Janssen.
- This study follows the same methods as for Study #12, except the test article tested was identified as JNJ-68284528 (cilta-cel).

Objective: To screen JNJ-68284528 for off-target binding using (b) (4) analysis.

Methods:

An initial screening was performed to determine the levels of background binding of JNJ-68284528, control UnT cells, and (b) (4). Primary screening for binding of these articles was against (b) (4). The confirmation screening was performed to confirm all primary hits and assess CAR specificity.

Results:

Initial screening showed binding of JNJ-68284528 and the UnT cells to the (b) (4) known CAR-independent T cell interacting proteins: (b) (4). Only JNJ-68284528 showed binding to over-expressed BCMA protein. The primary screening identified (b) (4) primary hits with different levels of (b) (4), including the primary target BCMA protein ((b) (4)). Additional screening confirmed all (b) (4) hits, with (b) (4) hits by both JNJ-68284528 and the UnT cells. The two hits by JNJ-68284528 only were BCMA (strong positive hit) and (b) (4); weak/medium hit). (b) (4) showed specific binding to BCMA, but not (b) (4).

Study #14

(b) (4)


Note:

- (b) (4)

Study #15

(b) (4)

(b) (4)



Study #16

Title: In Vitro Pharmacological Characterization of JNJ-68284528 CAR-T Cells

Report No.: DD19000

Study Performed by Oncology Translational Research; Janssen Biotech

JNJ-68284528 Lot No.: Not specified

Objectives:

- To demonstrate the ability of the expressed CAR to bind specifically to BCMA.
- To determine the levels of JNJ-68284528 CAR-T cell cytolytic activity (measured by target-cell killing).
- To demonstrate CAR-T activation (measured by cytokine release) when cocultured with various human cancer cell lines expressing a range of BCMA.
- To evaluate any differences in the activity of JNJ-68284528 generated from HDs versus patients with MM.

Methods:

JNJ-68284528 were generated from four (4) HDs and from three (3) patients with MM. The target cells consisted of a MM cell line (BCMA positive (b) (4) cells) and different BCMA negative cancer cell lines engineered to express (b) (4). The (b) (4) cells expressed human BCMA in

addition to (b) (4)

A (b) (4) assay was performed to study the antibody binding capacity of the BCMA-expressing tumor lines. Cytokine production was measured by an (b) (4) assay.

Results:

Concentration-dependent binding of BCMA-Fc protein to (b) (4) cells was observed, with a half-maximal binding concentration of (b) (4). Binding of BCMA-Fc to the parental (b) (4) cells was minimal. The MM cell line, (b) (4), had the highest BCMA expression, with the (b) (4) cells the next highest.


JNJ-68284528 manufactured from HD # (b) (6) ((b) (4) CAR+) resulted in cytotoxicity of (b) (4) cells and (b) (4) cells at dose-dependent E:T ratios. Co-culture of JNJ-68284528 with (b) (4) cells elicited release of IFN- γ , IL-2, and TNF- α , and lower IL-6 levels. Co-culture of these three cell lines with UnT cells did not lead to increased cytokine production.

JNJ-68284528 manufactured from HDs or patients with MM induced cytolytic activity and release of IFN- γ , IL-2, and TNF- α when co-cultured with (b) (4) cells, but not with (b) (4) cells, indicating activity was dependent on target-cell expression of BCMA. A significant difference was observed in the TNF- α levels between JNJ-68284528 CAR-T cells manufactured from HDs and patients with MM following co-culture with the (b) (4) target line. Higher TNF- α levels were released from the CAR T cells generated from patients with MM. No significant differences in other assessed parameters were detected.

Study #17


(b) (4)

(b) (4)

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Study #18

(b) (4)

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(b) (4)

Overview of In Vivo Studies

In Vivo Studies in Syngeneic Tumor Animal Models

Study #19

Report Number		LB-PA-NCSR011
Date Report Signed		21-Mar-2018
Title		Dose escalating study of LCAR-B38 CAR-T on (b) (4) engrafted immune deficient mice
GLP Status		No
Testing Facility		Legend Biotech - Nanjing Legend Biotech Co., Ltd.
Objective(s)		<p>Primary: to study the <i>in vivo</i> efficacy of escalating dose levels of LCARB38M CAR-T cells following administration in an (b) (4) MM murine model.</p> <p>Secondary: to compare the <i>in vivo</i> performance of LCAR-B38M CAR-T cells from a HD and from a patient with MM.</p>
Study Animals	Strain/Breed	(b) (4)
	Species	(b) (4)
	Age	6-7 weeks old
	Body Weight	20 ±2 grams
	#/sex/group	3/sex/group
	Total #	60 animals
Test Article(s)		<ul style="list-style-type: none"> LCAR-B38M CAR-T cells derived from r/r MM Donor # (b) (6); Lot No.: (b) (6); manufactured at Legend Biotech LCAR-B38M CAR-T cells derived from a HD; Lot No.: (b) (6); manufactured at (b) (4)
Control Article(s)		<ul style="list-style-type: none"> UnT cells from (b) (6) Hank's Balanced Salt Solution (HBSS; (b) (4))
Route of Administration		IV injection
Description of the Disease/Injury Model and Implant Procedure		<p>On Day -14 the mice were IV injected (tail vein) with approximately 4×10^6 (b) (4) cells/animal (in 0.4 ml).</p> <p>(b) (4) was performed on Day -1 to evaluate tumor engraftment, prior to randomized enrollment into groups.</p>

Study Groups and Dose Levels	See below Approximate dose levels: <u>Dose 1</u> : 1 x 10 ⁶ cells/kg <u>Dose 2</u> : 5 x 10 ⁶ cells/kg <u>Dose 3</u> : 2.5 x 10 ⁷ cells/kg
Dosing Regimen	IV injection on Day 0
Randomization	Yes; method not specified
Description of Masking	None
Scheduled Sacrifice Time Points	Day 55

Study Groups and Dose Levels

Group	Batch No.	Dose level/mouse, (CAR positive cells)	Sex
Group 1	LCAR- B38M (b) (6)	<u>Dose 1</u>	M
Group 2			F
Group 3		<u>Dose 2</u>	M
Group 4			F
Group 5		<u>Dose 3</u>	M
Group 6			F
Group 7	LCAR- B38M (b) (6)	<u>Dose 1</u>	M
Group 8			F
Group 9		<u>Dose 2</u>	M
Group 10			F
Group 11		<u>Dose 3</u>	M
Group 12			F
Group 13	unT from (b) (6)	<u>Dose 1</u>	M
Group 14			F
Group 15		<u>Dose 2</u>	M
Group 16			F
Group 17		<u>Dose 3</u>	M
Group 18			F
Group 19	HBSS	0	M
Group 20	HBSS	0	F

Key Evaluations and Assessments:

- Body weights were measured twice per week.
- Tumor growth was measured using (b) (4) every 14 days for the duration of the study.
- Blood was collected at Days 0, 6, 20, 35, and 48 and analyzed using (b) (4) for DNA presence.

- Statistical Analysis: Tumor volume (photon numbers from (b) (4)) and body weights were analyzed using Student's t-test; P< 0.05 was statistically significant.
- The *in vitro* cytotoxicity assay was conducted in a manner similar to the method for Study #7. LCAR-B38M CAR-T cells from Lot Nos. (b) (6) and (b) (6)) and UnT cells (from Lot No. (b) (6)) were incubated with (b) (4) cells (human MM cell line) at different E:T ratios (20:1 to 1:1) for 20-24 hours.

Key Results:

In vitro cytotoxicity of LCAR-B38M CAR-T cells

- LCAR-B38M CAR-T cells (Lot Nos. (b) (6) and (b) (6)) were cytotoxic to the (b) (4) cells at comparable E/T ratios.

In vivo dose escalating studies of LCAR-B38M CAR-T cells

- A dose-dependent positive trend in the survival rate was observed over time in mice administered with the LCAR-B38M CAR-T cell lots. By Day 41, there were no surviving mice in the UnT control groups.
- Mean body weights for mice administered the LCAR-B38M CAR-T cell lots remained stable over time compared to the mice administered the UnT cells.
- On Day 27 groups dosed with 2.5×10^7 cells/kg of (b) (6) CAR-T cells or (b) (6) CAR-T cells showed no detectable tumor cell imaging signal, while the mice dosed with UnT cells displayed strong tumor cell imaging signals.
- CAR gene copy number in blood samples collected from mice administered Dose 3 of Lot Nos. (b) (6) or (b) (6) increased starting on Day 20 and reached a maximum value at Day 35, followed by a decrease to baseline by Day 48 post-dose.

Reviewer Comment:

- Although according to the study design, tumor growth was measured every 14 days during the study, no data for these assessments were provided.

Study #20

Report Number		C7122BK100
Date Report Signed		April 5, 2017
Title		In vivo Efficacy Study of LCAR-B38M on (b) (4) Engrafted Immune Deficient Mouse
GLP Status		No
Testing Facility		(b) (4)
Objective(s)		To evaluate the <i>in vivo</i> anti-tumor efficacy of LCAR-B38M CAR-T cells following administration in an (b) (4) MM murine model.
Study Animals	Strain/Breed	(b) (4)
	Species	(b) (4)
	Age	6-7 weeks old
	Body Weight	20 ±2 grams

	#/sex/group	8 female/group
	Total #	16 animals
Test Article(s)		LCAR-B38M CAR-T cells derived from r/r MM Donor # (b) (6); Lot No. not specified); manufactured at Legend Biotech
Control Article(s)		UnT cells
Route of Administration		IV injection
Description of the Disease/Injury Model and Implant Procedure		<ul style="list-style-type: none"> On Day -14 animals were IV injected (tail vein) with approximately 3.5×10^6 (b) (4) cells (0.35 ml). <u>Re-challenge</u>: On Day 69, the mice were re-injected (tail vein) with approximately 0.75×10^6 (b) (4) cells/mouse (0.15 ml). Note: An explanation for the re-challenge with a lower amount of tumor cells was not provided.
Study Groups and Dose Levels		Group 1 – UnT cells – 4×10^6 cells/mouse (1.6×10^7 Cells/kg) Group 2 – LCAR-B38M CAR-T cells – Same dose level as Group 1
Dosing Regimen		IV injection on Day 0
Randomization		Yes; method not specified
Description of Masking		None
Scheduled Sacrifice Time Points		Day 98

Key Evaluations and Assessments:

- Cytotoxicity (*in vitro*) of the (b) (4) cells
- Body weights were measured weekly and animal survival was recorded.
- Tumor growth was measured using (b) (4) every 14 days for the duration of the study.

Reviewer Comment:

- The study report did not include a detailed methodology for the cytotoxicity assessment.

Key Results:

- The LCAR-B38M CAR-T cells were cytotoxic to the (b) (4) cells. At E/T ratios of 20:1 and 5:1, greater than 90% of the (b) (4) cells were killed, while at a 1:1 E:T ratio approximately 50% of the (b) (4) cells were killed compared to UnT cells.
- There were no significant differences in mean body weights between the groups.
- The median survival rate of Group 1 was 20 days, while the median survival rate of Group 2 was 45.5 days ($P < 0.01$).
- No increase in tumor growth was observed in the surviving animals following tumor re-challenge.

SAFETY PHARMACOLOGY STUDIES

No safety pharmacology studies with JNJ-68284528 were conducted.

PHARMACOKINETIC STUDIES (Biodistribution)

No biodistribution studies with JNJ-68284528 were conducted.

TOXICOLOGY STUDIES

Summary List of Toxicology Studies

The following toxicology studies were conducted to evaluate the safety of cilta-cel following administration in various animal species. The following pharmacology studies were conducted to support the rationale for the administration of ciltacabtagene autoleucel (JNJ-68284528) to treat the proposed clinical population.

Study Number	Study Title / Publication Citation	Report Number
21	In vivo Pilot Tolerability of LCAR-B38M in the (b) (4) Monkeys	GSCQBBUY2016071772

Study #21

Report Number		GSCQBBUY2016071772
Date Report Signed		April 1, 2018
Title		<i>In vivo</i> Pilot Tolerability of LCAR-B38M in (b) (4) Monkeys
GLP Status		No
Testing Facility		(b) (4)
Objective(s)		To assess the tolerability of LCAR-B38M CAR-T cells in NHPs Note: Although the product administered in this study was identified as 'LCAR-B38M CAR-T cells' in the study report, the administered CAR-T cells were derived from autologous NHP T cells.
Study Animals	Strain/Breed	(b) (4) monkeys
	Species	(b) (4)
	Age	Not provided
	Body Weight	3.6-3.8 kg
	#/sex/group	1 male/group
	Total #	2 NHPs Note: The rationale for: 1) testing in NHPs and 2) the inclusion of only two animals in the study was not provided in the study report. However, in Section 4.2 of Module 2, the applicant acknowledged the small number of animals, as well as the lack of a concurrent control group. The applicant also noted that cilta-cel is not cross-reactive to BCMA in NHPs, thus assessment of potential on-target/off-tumor toxicity of the human-derived product in NHPs would be of limited value.
Test Article		Autologous PMBC-derived CAR-T cells; Lot No. not provided
Control Article		None
Route of Administration		IV infusion
Study Groups and Dose Levels		Group 1 – Animal #120117 was infused with 5 x 10 ⁶ cells/kg Group 2 – Animal #120545 was infused with 40 x 10 ⁶ cells/kg
Dosing Regimen		The NHPs were infused with cyclophosphamide (22.3 mg/kg) on Day -3, followed by IV infusion of the CAR T cells on Day 0.

Scheduled Sacrifice Time Points	Day 30 Note: The study report did not specify whether any post-mortem analyses (gross pathology, organ weights, histopathology) were performed on the animals, thus the reason for sacrifice of the NHPs is unclear.
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Key Evaluations and Assessments:

- Clinical observations were performed daily, while body weights and temperature checks were recorded every 2 days, from Day -4 through Day 30.
- Hematology and serum chemistry parameters were evaluated every 3 days, from Day -15 through Day 30.⁸

Key Results:

- There were no test article-related adverse effects on survival, clinical signs, body weights or body temperatures.
- Animal #120117 had mild increases (2-3-fold above baseline values) in ALP, AST/ALT, TBI, CKI, LDH, and UA levels on Day 3. Transient increases in lipids (TGL, HDL and LDL) were observed on Days 3 and 19, with no further increase post-CAR-T cell infusion.
- Animal #120545 had no significant increases in any serum chemistry or hematology parameter for the duration of the study.
- In both NHPs, slight decreases (less than 2-fold below respective baseline values) in WBC, RBC, hemoglobin, and/or platelet levels were detected post CAR-T cell infusion (study days for assessment of these parameters were not specified). These changes resolved by the end of the study (Day 30).

Reviewer Comment:

- Although the study design was limited, no adverse findings related to off-target binding to (b) (4) were observed.

DART Studies:

Per the applicant, MM predominantly occurs in elderly patients and is rare in patients 40 years or younger. The results from Study #10 showed that (b) (4) (the BCMA binding domain) was not detected in human female or male reproductive organs. In addition, (b) (4) did not bind to recombinant mouse or NHP BCMA expressed on (b) (4) cells (Studies #6 and #18), demonstrating that rodents and NHPs are not pharmacology relevant species for testing cilta-cel. Therefore, traditional DART studies were not conducted. Section 8.1 of the proposed label describes the potential risks of cilta-cel to the developing fetus if the transduced cells cross the placenta.

⁸ Alkaline phosphatase (ALP); Aspartate transaminase/Alanine transaminase (AST/ALT); total bilirubin (TBI); creatine kinase isoenzyme (CKI); Lactate dehydrogenase (LDH); high density lipoprotein (HDL); low density lipoprotein (LDL); uric acid (UA); triglyceride (TGL); red blood cells (RBCs); white blood cells (WBCs); hemoglobin; platelets

Genotoxicity Studies:

22	Lentivirus Vector Integration Site Analysis (ISA) Testing of Pre-Infusion JNJ-68284528 Autologous Anti-BCMA Chimeric Antigen Receptor-T (CAR-T) Cells (Drug Product).	TOX14554
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Study #22

Title: Lentivirus Vector Integration Site Analysis (ISA) Testing of Pre-Infusion JNJ-68284528 Autologous Anti-BCMA Chimeric Antigen Receptor-T (CAR-T) Cells (Drug Product)

Report No: TOX14554; non -GLP

Study Performed by (b) (4)

JNJ-68284528 Lot Nos.: Not specified

JNJ-68284528 were derived from three HDs and seven patients with MM (Table 1). Samples of UnT cells served as the negative controls and a (b) (4) from the LV long terminal repeat (LTR) area served as the positive control.

Table 1. List of Janssen samples (JNJ-68284528).

Project	Sample	Celltype	Sample Type	Donor(s)	Vector Manufacturing Site	Lentiviral Vector Manufacturing Process**	ELN(s)*
JAN01GW	(b) (6)	CAR-T	Healthy Donor	(b) (6)	(b) (4)	(b) (4)	JNJ-68284528-n001-06552
JAN01GW		CAR-T	Healthy Donor				JNJ-68284528-n001-06552
JAN01GW		CAR-T	Multiple Myeloma Patient				JNJ-68284528-n001-06166
JAN01GW		CAR-T	Multiple Myeloma Patient				JNJ-68284528-n001-06166
JAN01GW		CAR-T	Multiple Myeloma Patient				JNJ-68284528-n001-06528
JAN01GW		CAR-T	Multiple Myeloma Patient				JNJ-68284528-n001-06592
JAN01GW		CAR-T	Multiple Myeloma Patient				JNJ-68284528-n001-04210
JAN01GW		CAR-T	Multiple Myeloma Patient				JNJ-68284528-n001-04210
JAN01GW		CAR-T	Multiple Myeloma Patient				JNJ-68284528-n001-06697
JAN01GW		T-cells	Blank - Not Transduced				NA
JAN01GW		T-cells	Blank - Not Transduced				NA
JAN01GW		CAR-T	Healthy Donor				JNJ-68284528-n001-05404

* ELN(s), Electronic Laboratory Notebook, reference to internal Janssen laboratory documentation

** the lentiviral vector construct is the same (b) (4) generated using a (b) (4) generation packaging system) produced by an (b) (4) process. CAR-T cell samples were manufactured by transducing donor-derived T cells with a lentiviral vector described as (b) (4). These CAR-T cells are representative of JNJ-68284528.

*** (b) (6) were derived from the same donor apheresis material, but with LV vector manufactured from two different manufacturing sites

Source: Page 10 of Study Report TOX14554, Module 4 of the BLA.

Objective: To determine the integration site of the (b) (4)-generation LV, (b) (4) used to transduce T cells obtained from both HDs and patients with MM.

Methods: (b) (4)

Results:

All (b) (4) transduced CAR-T cells samples showed a highly polyclonal semi-random integration profile with a strong similarity to previously published LV datasets. The integration patterns identified for (b) (4) were consistent with the patterns reported for other LVs. In-depth analysis performed on the (b) (4) transduced CAR-T cell IS datasets revealed standard LV integration patterns. There was no evidence of clonal dominance, no preferred integration near genes associated with severe adverse events, and no detectable clones with higher frequencies of vector IS near cancer-associated genes. Overall, the data suggest that there are no increased risks for JNJ-68284528 compared to other LV-transduced T cells.

Carcinogenicity/Tumorigenicity Studies:

No carcinogenicity/tumorigenicity studies with cilta-cel were conducted.

Other Safety/Toxicology Studies:

Study Number	Study Title / Publication Citation	Report Number
23	In Vitro Characterization of JNJ-68284528 for Cytokine Independent Growth	TOX14678

(b) (4)

Study #23

Title: In Vitro Characterization of JNJ-68284528 for Cytokine Independent Growth

Report No: TOX14678; non-GLP

Study Performed by Janssen Research & Development, LLC

JNJ-68284528 was derived from three HDs and six patients with MM (Table 2):

Table 2: JNJ-68284528 and Donor Matched UnT Drug Product Batches and Characteristics

Source ID	Donor	Patient ^a or HD	LV ^b Vector	Vector Site
(b) (6)	(6)	Patient	(b) (4)	(4)
		Healthy		
		Patient		
		Patient		
		Patient		
		Patient		
		Healthy		
		Healthy		
		Healthy		
		Patient		

^a Patient derived JNJ-68284528 are prepared from apheresis material from patients with MM, while HD derived JNJ-68284528 are prepared from apheresis material from HDs.

^b The lentiviral vector construct is the same (b) (4) generated using a (b) (4) generation packaging system) produced by an (b) (4) process.

Source ID is synonymous with a Batch ID. (b) (6) were derived from the same donor apheresis material, but with LV vector manufactured from two different sites. Donor matched unT samples were manufactured from the same batches of donor apheresis material and undergo a similar enrichment and expansion protocol as JNJ-68284528 but are not transduced with LV.

(b) (4); CAR = chimeric antigen receptor; (b) (4)
; HD = healthy donor; ID = identifier; LV = lentiviral vector; (b) (4)
; unT = un-transduced T cell

Source: Page 10, Section 2.1, Module 4 of the BLA.

Objectives:

- To characterize the potential for enhanced proliferation of JNJ-68284528 by evaluating whether cells proliferate in the absence of (b) (4) as compared to donor-matched UnT cells.
- To evaluate any differences in the proliferative ability of JNJ-68284528 generated from HDs vs. patients with MM.
- To evaluate any differences in the proliferative ability of JNJ-68284528 packaged using an (b) (4) process vs. a (b) (4) process.

Methods:

(b) (4)

(b) (4)

Results:

Proliferation of JNJ-68284528 in the absence of (b) (4) was not observed. In addition, there were no statistically significant differences in donor-to-donor variation between JNJ-68284528 and the donor-matched UnT cells ($P > 0.05$). Thus, LV integration into the T cell genome during transduction did not lead to enhanced growth of JNJ-68284528 as compared to donor matched UnT cell controls. Following activation of JNJ-68284528 and the UnT cells with (b) (4) and (b) (4) antibodies in the presence of (b) (4) the cells proliferated and remained viable over time. There was a statistically significant difference in the proliferation profile of JNJ-68284528 with and without (b) (4) supplementation ($P < 0.0001$).

Differences were observed in the proliferation profile (without (b) (4)) of JNJ-68284528 generated from HDs versus patients with MM ($P < 0.05$). The effect of the LV packaging process using (b) (4) on the proliferation of JNJ-68284528 without (b) (4) was minimal.

APPLICANT'S PROPOSED LABEL

- Subsections 8.1-8.3 of Section 8 ('Use in Specific Populations') should be revised to comply with 21 CFR 201.56(d)(1), 201.57(c)(9), and 201.57(c)(14), as applicable.¹⁴
- Section 13 ('Nonclinical Toxicology') should be revised, as applicable, to accurately reflect the available nonclinical data.

CONCLUSION OF NONCLINICAL STUDIES

Review of the nonclinical studies did not identify any safety concerns that could not be addressed in the product label. The nonclinical data support approval of the license application.

KEY WORDS/TERMS

CARVYKTI™, ciltacabtagene autoleucel, Cilta-cel, JNJ-68284528, LCAR-B38M CAR-T cells, Multiple Myeloma, BCMA, Chimeric Antigen Receptor, pharmacology, toxicology, lentivirus

¹⁴ *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format*, available at:
<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm450636.pdf>.