

Summary Report of Benefit-Risk Assessment

FUCASO suspension for infusion

NEW DRUG APPLICATION

Active Ingredient(s)	Equecabtagene autoleucel
Product Registrant	IASO BIO SGP PTE. LTD.
Product Registration Number	CGPR260618Y0001
Application Route	Full evaluation
Date of Approval	18 June 2026

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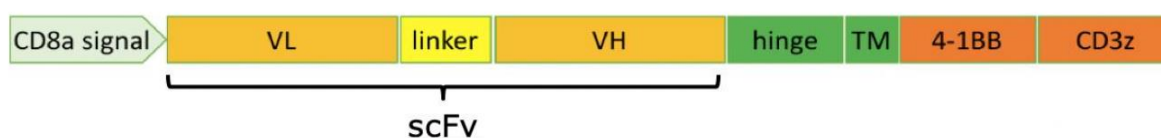
A INTRODUCTION

FUCASO (equecabtagene autoleucel) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM), who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), and have demonstrated disease progression on the last therapy.

FUCASO is manufactured from a patient's own T cells, which are collected from peripheral blood by leukapheresis and genetically modified *ex vivo* using a replication-incompetent lentiviral vector to express a chimeric antigen receptor (CAR). The CAR comprises a fully human BCMA-targeting single-chain variable fragment (scFv), a hinge and transmembrane domain, and intracellular 4-1BB costimulatory and CD3ζ signalling domains (Figure 1). The modified cells are expanded in cell culture, formulated, and cryopreserved before storage and transport to the treatment centre.

Following thawing at the point of care and intravenous infusion, the CAR T cells recognise and bind to BCMA, a protein highly expressed on malignant plasma cells in multiple myeloma. This activates the CAR T cells, leading to their proliferation and the targeted destruction of BCMA-expressing tumour cells.

Figure 1. Schematic Representation of the FUCASO (equecabtagene autoleucel) Chimeric Antigen Receptor (CAR)



Abbreviations: 4-1BB = 4-1BB co-stimulatory domain; CD3z = CD3 zeta signalling domain; CD8a = cluster of differentiation 8 alpha; scFv = single-chain variable fragment; TM = transmembrane domain; VH = variable heavy chain; VL = variable light chain.

Source: Company's submission.

B ASSESSMENT OF PRODUCT QUALITY

Overview

FUCASO is supplied as a frozen suspension for infusion in a single ethylene-vinyl acetate (EVA) cryobag containing viable autologous anti-BCMA CAR-positive T cells. Each patient-specific bag contains a variable number of viable CAR-positive T cells to deliver the target dose of 1.0×10^6 CAR-positive viable T cells/kg body weight. The cells are suspended in a cryopreservation medium comprising multiple electrolytes injection, human serum albumin, compound amino acid injection, vitamin C injection, glucose injection, and dimethyl sulfoxide.

The LV0037 lentiviral vector, equecabtagene autoleucel active substance and finished product are all manufactured at the same site at Nanjing IASO Medical Technology Co., Ltd. (Nanjing, China). The manufacturer is compliant with Good Manufacturing Practice.

Critical Starting Material

The critical starting material, LV0037 lentiviral vector, is a third-generation, replication-incompetent, self-inactivating (SIN) lentiviral vector produced by transient transfection of HEK293T cells using a four-plasmid system (comprising one transfer, one envelope and two packaging plasmids).

Adequate controls have been presented for the starting materials, intermediates, reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the lentiviral vector are considered appropriate. Process validation was conducted on production-scale batches.

The characterisation of the LV0037 lentiviral vector and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled in the manufacturing process and specifications.

The LV0037 specifications are considered acceptable, and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q2 guideline.

The submitted stability data supported the shelf life of 36 months at $-80 \pm 10^{\circ}\text{C}$. The container closure system for the finished lentiviral vector is 1.8 mL polypropylene cryovials.

Active substance

The active substance comprises viable autologous CD3-positive T cells genetically modified to express the anti-BCMA CAR following transduction with the LV0037 lentiviral vector.

Adequate controls have been presented for the starting materials, intermediates and reagents. Manufacture of active substance commences upon receipt of fresh autologous leukapheresis material and includes isolation and cryopreservation of peripheral blood mononuclear cells, followed by thawing, T-cell activation, lentiviral transduction, cellular expansion, bead removal and harvest. Manufacture of the active substance and finished medicinal product is a continuous process and the subsequent steps are described under the finished product. The in-process control tests and acceptance criteria applied during the manufacturing of the active substance are considered appropriate.

Given the autologous nature of the product, chain-of-identity and chain-of-custody systems have been implemented throughout collection, manufacture, storage, transport and clinical administration to ensure product traceability and correct patient assignment.

The characterisation of the active substance and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled in the manufacturing process and specifications.

The manufacture of FUCASO is a continuous process, the respective information on specifications, analytical methods and stability are presented in the finished product section below.

Finished product

The manufacturing process starts after cell harvest and comprises washing, formulation, aseptic filling, cryopreservation and storage. Adequate in-process controls are in place. Process validation of the commercial-scale patient batches demonstrated consistent manufacturing performance. Aseptic processing is validated by media-fill qualification studies.

Microbiological safety is ensured through aseptic manufacture, qualified raw materials, environmental monitoring, and in-process and release testing for sterility, mycoplasma and endotoxin. The overall microbiological control strategy is considered adequate.

The specifications are considered acceptable, and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline.

The submitted stability data supported the approved shelf life of 6 months when stored below –130°C in the vapour phase of liquid nitrogen. Following thawing, infusion should commence within 20 minutes, and the total time from thaw completion to the end of infusion should not exceed 40 minutes. The container closure system is a 50 mL EVA cryopreservation infusion bag.

Quality conclusion

Overall, satisfactory quality documentation has been provided for the LV0037 lentiviral vector, equecabtagene autoleucel active substance and finished product. Based on the totality of the submitted data, the quality of FUCASO is considered acceptable with no outstanding Chemistry, Manufacturing and Controls issues precluding approval.

C ASSESSMENT OF NON-CLINICAL STUDIES

Overview

The non-clinical development programme for FUCASO (equecabtagene autoleucel; CT103A) comprised *in vitro* and *in vivo* studies evaluating pharmacology, pharmacokinetics, toxicology, genotoxicity/insertional mutagenesis risk, including vector integration site analyses, tumourigenicity, local tolerance, and off-target binding and tissue cross-reactivity. Throughout the non-clinical programme, the product was referred to by its development code, CT103A. The pivotal *in vivo* pharmacology, biodistribution and general toxicology studies used the intravenous route, consistent with the intended clinical route. Additional studies, including tumourigenicity and local tolerance assessments, were conducted as appropriate. Although the non-clinical studies used an earlier development-process material, the quality assessment confirmed adequate comparability across manufacturing process changes to support relevance to the proposed commercial product.

Pharmacology

Primary pharmacodynamic studies were conducted to characterise the anti-tumour activity of CT103A against BCMA-expressing tumour cells. CT103A recognises BCMA expressed on malignant plasma cells, resulting in antigen-dependent T-cell activation, proliferation and tumour cell destruction. Published literature indicated that BCMA expression is largely restricted to mature B cells, plasma cells and multiple myeloma cells, with higher expression on malignant plasma cells than on normal B-lineage cells, thereby supporting BCMA as an appropriate therapeutic target.

The anti-BCMA scFv exhibited high affinity and specificity for BCMA on recombinant BCMA protein and BCMA-expressing tumour cells. The final CT103A product demonstrated specific and consistent binding to human BCMA across three manufacturing batches.

In vitro, CT103A exhibited potent, dose-dependent cytolytic activity against BCMA-expressing cells while sparing BCMA-negative cells. Antigen-dependent T-cell activation, proliferation and cytokine secretion, including interferon- γ (IFN- γ), interleukin-2 (IL-2), and tumour necrosis factor- α (TNF- α), confirmed specific functional activation following BCMA engagement. Functional activation/degranulation was not inhibited by soluble BCMA (sBCMA), supporting target engagement in the presence of soluble antigen.

In vivo proof-of-concept studies were conducted in immunodeficient mice bearing subcutaneous human multiple myeloma xenografts, as CT103A does not recognise endogenous rodent or non-human primate BCMA and no pharmacologically relevant animal model is available. Although interpretation was limited by xenogeneic graft-versus-host disease (xGvHD), an inherent feature of this model, CT103A produced complete tumour clearance by Day 19 following a single intravenous administration. Durable tumour-free responses were maintained through Day 105 in the lower-dose level (2×10^6 CAR-positive cells/animal, equivalent to 1×10^8 CAR-positive cells/kg), whereas earlier development of xGvHD was observed in the higher-dose level. Comparable anti-tumour activity was observed across CT103A products derived from different donors, supporting consistent pharmacological activity.

Dedicated safety pharmacology and pharmacodynamic drug interaction studies were not conducted, which was considered acceptable given the mechanism of action and the absence of organ-specific toxicity in the non-clinical safety studies.

Pharmacokinetics

Conventional pharmacokinetic concepts such as absorption, distribution, metabolism and excretion (ADME) are not directly applicable to CAR T-cell therapies. Instead, the non-clinical pharmacokinetic evaluation focused on biodistribution and persistence, assessed by quantitative polymerase chain reaction (qPCR) measurement of CAR transgene copy numbers in blood and tissues following a single intravenous administration in immunodeficient mice bearing subcutaneous human multiple myeloma xenografts.

CT103A distributed to all examined tissues, with the highest levels detected in lymphoid organs, lungs and liver, and minimal distribution to the brain. CAR T-cell accumulation was highest at the tumour site, where transgene copy numbers were substantially higher than in non-target tissues, consistent with antigen-driven expansion. CT103A persisted in lymphoid tissues throughout the observation period, whereas levels in blood and other major organs declined over time. Distribution to non-target tissues was not associated with product-related adverse histopathological findings.

Direct extrapolation of these findings to humans is limited by the xenograft model and its associated xenogeneic environment. However, the observed biodistribution profile is consistent with published experience for other CAR T-cell therapies, in which CAR T cells preferentially localise to lymphoid tissues and sites of tumour involvement. Overall, the biodistribution findings were consistent with the expected behaviour of autologous CAR T-cell therapies.

Toxicology

The safety of CT103A was evaluated in three Good Laboratory Practice (GLP)-compliant toxicity studies, with specified analytical components conducted outside of GLP. These studies were conducted in immunodeficient mice bearing subcutaneous human multiple myeloma xenografts. Single-dose and repeat-dose studies evaluated CT103A at dose levels above the proposed clinical dose (1×10^6 CAR-positive cells/kg). The No Observed Adverse Effect Levels (NOAELs) were 5×10^8 and 1×10^8 CAR-positive cells/kg in the single-dose and 13-week repeat-dose studies, respectively, while the 26-week repeat-dose study identified a Highest Non-Severe Toxic Dose (HNSTD) of 2×10^8 CAR-positive cells/kg. Deaths observed in the animal studies were attributed mainly to tumour burden, infection, immunocompromised status, xGvHD or background or model-related factors, with no clear direct CT103A-related severe toxicity identified.

Genotoxicity and insertional mutagenesis

No traditional genotoxicity studies were conducted. CT103A is manufactured using a replication-incompetent, SIN, third-generation lentiviral vector designed to minimise the risk of replication-competent lentivirus (RCL) and insertional mutagenesis. Integration site analysis by next-generation sequencing of FUCASO CAR T cells manufactured from 3 healthy donors and 41 patients demonstrated broad genomic distribution with no evidence of clonal dominance. Low-frequency integrations were observed near a small number of cancer-associated genes, consistent with the known integration profile of lentiviral vectors and without evidence of clonal expansion. The risk of insertional mutagenesis was considered low and will continue to be monitored through pharmacovigilance and long-term follow-up as specified in the Risk Management Plan.

Tumourigenicity

The tumourigenic potential of CT103A was evaluated in one *in vitro* and two *in vivo* studies. CT103A showed no evidence of tumourigenic potential in the soft agar colony formation assay or following subcutaneous administration in BALB/c nude mice. In non-obese diabetic severe combined immunodeficient (NOD-SCID) mice, repeat-dose intravenous administration showed no evidence of oncogenicity, with no treatment-related neoplastic findings or abnormal tissue retention. Overall, the available non-clinical data did not identify evidence of tumourigenic or oncogenic potential.

Reproductive and developmental toxicity

No dedicated reproductive or developmental toxicity studies were conducted, which was considered acceptable given the product characteristics, intended patient population and the established non-clinical assessment approach for CAR T-cell therapies. General toxicology studies identified no adverse effects on reproductive organs, and the risk of germline transmission was considered negligible, consistent with the European Medicines Agency guideline (EMA/273974/2005). Appropriate recommendations regarding contraception and pregnancy are included in the package insert, and the potential effects on fertility will continue to be evaluated through long-term clinical follow-up as part of the Risk Management Plan.

Local tolerance

CT103A demonstrated good local tolerability following intravenous and intramuscular administration in New Zealand White rabbits, with no evidence of local irritation on macroscopic or histopathological examination. CT103A also did not induce haemolysis or erythrocyte agglutination *in vitro* at clinically relevant concentrations.

Off-target binding and tissue cross-reactivity

Target specificity was evaluated using a membrane proteome array, functional validation assays and tissue cross-reactivity studies. Two proteins exhibited weak non-specific binding in screening assays; however, neither activated CT103A nor induced CD107a release, indicating no functional activation against these proteins in the assays conducted.

Non-clinical conclusion

The non-clinical programme supported the proposed mechanism of action of CT103A and demonstrated potent and selective anti-tumour activity against BCMA-expressing cells, with biodistribution and safety findings consistent with the expected behaviour of autologous CAR T-cell therapies. No functional off-target activation was identified in the available assays. No evidence suggestive of tumourigenic or oncogenic potential was identified in the available non-

clinical studies, and no unexpected non-clinical toxicities were identified, recognising the limitations of the xenograft models in predicting human CAR T-cell toxicities. Integration site analyses supported a low risk of insertional mutagenesis. The Genetic Modification Advisory Committee's environmental risk assessment concluded that biosafety and environmental risks had been adequately addressed. Overall, the non-clinical data package is considered adequate to support the proposed clinical use of FUCASO.

D ASSESSMENT OF CLINICAL EFFICACY

Clinical pharmacology

Overview

The clinical pharmacology of FUCASO was evaluated in two clinical studies in adults with RRMM, who had received at least three prior lines of therapy, including a PI and an IMiD. The Phase 1 dose-finding study (Study XL-LCYJ-0003; N = 23) characterised pharmacology across four dose levels ranging from 0.5 to 6.0×10^6 CAR-positive cells/kg and informed selection of the recommended Phase 2 dose (RP2D). The pivotal Phase 1/2 study (Study XL-LCYJ-0007, FUMANBA-1; N = 109) evaluated a single intravenous infusion of FUCASO at the RP2D of 1.0×10^6 ($\pm 30\%$) CAR-positive cells/kg. The clinical pharmacology programme evaluated pharmacokinetics, pharmacodynamics, immunogenicity, RCL, and lentiviral insertion site analysis.

Study XL-LCYJ-0007 (FUMANBA-1, Pivotal study)

Pharmacokinetics

As an autologous human cell-based product, CT103A does not undergo conventional ADME. Instead, CAR T-cell pharmacokinetics are characterised by *in vivo* expansion and persistence, described by parameters including maximum expansion (C_{max}), time to maximum expansion (T_{max}) and overall cellular exposure (AUC). CAR T-cell kinetics were evaluated using two complementary methods in serial peripheral blood samples: validated flow cytometry to quantify circulating BCMA CAR T cells, and validated droplet digital polymerase chain reaction (ddPCR) to quantify the vector copy number (VCN) of the CAR transgene as a measure of CAR T-cell persistence. Pharmacokinetic parameters were estimated using standard non-compartmental methods.

The median administration time was 11 minutes (range: 3–25 minutes). The median actual infusion dose was 0.920×10^6 CAR-positive cells/kg (range: 0.65 – 1.19×10^6), and 108 of 109 patients (99.1%) received FUCASO within the protocol-specified dose range of 0.7 – 1.3×10^6 CAR-positive cells/kg.

Flow cytometry and VCN analyses demonstrated concordant expansion and persistence profiles. Following infusion, FUCASO underwent rapid *in vivo* expansion, reaching peak peripheral blood CAR T-cell levels at a median of 10 days (range: 10–59 days), while peak VCN was reached at a median of 12 days (range: 0–23 days). No meaningful differences in expansion kinetics were observed between Phase 1 and Phase 2 patients. CAR T cells remained detectable in approximately one-third of patients at Month 24, demonstrating prolonged persistence. Considerable inter-patient variability was observed, consistent with the individualised nature of autologous CAR T-cell therapies. Summary pharmacokinetic parameters derived from VCN measurements are presented in Table 1.

Evaluation of pre-specified intrinsic and extrinsic factors identified no notable effects of age (39–70 years), sex, extramedullary disease, mild hepatic impairment, or moderate renal impairment on CAR T-cell pharmacokinetics. Formal hepatic or renal impairment studies had

not been conducted. Patients who received tocilizumab or systemic corticosteroids for the management of cytokine release syndrome (CRS) or neurotoxicity had higher CAR T-cell exposure. Higher CAR T-cell exposure was associated with improved treatment responses, including higher rates of partial response (PR) or very good partial response (VGPR), and with a higher incidence of CRS.

Table 1. Summary of Pharmacokinetic Parameters Following a Single Infusion of FUCASO

Parameter (Unit)	Statistic	Phase 1 (N = 17)	Phase 2 (N = 92)	Total (N = 109)
C_{max} (copies/ µg DNA)	Mean (SD)	87,843 (54,594)	86,229 (49,134)	86,481 (49,760)
T_{max} (days)	Median (Range)	11.9 (10–21)	11.7 (0–23)	11.8 (0–23)
AUC_{0–28d} (copies*day /µg DNA)	Mean (SD)	924,132 (931,839)	1,025,851 (735,184)	1,009,538 (765,969)

Abbreviations: AUC_{0–28d} = area under the concentration–time curve of the transgene level from time of dose to 28 days post-infusion; C_{max} = maximum observed transgene concentration; N = number of patients; SD = standard deviation; T_{max} = time to maximum observed transgene concentration; VCN = vector copy number.

As patients aged over 70 years were not enrolled in the clinical studies, clinical pharmacology data in this population are limited. No pharmacokinetic data are available in the paediatric population.

Pharmacodynamics

The pharmacodynamic effects of FUCASO were evaluated by measuring sBCMA as a marker of target engagement and tumour burden, together with inflammatory markers associated with immune activation including interleukin-6 (IL-6), C-reactive protein (CRP), and ferritin.

The median baseline sBCMA concentration was 217.059 ng/mL and declined to below the lower limit of quantification (LLOQ; 3.200 ng/mL) in 91.3% of patients by Month 3, consistent with target engagement and anti-myeloma activity. Suppression of sBCMA below the LLOQ was more frequent in treatment responders. Baseline sBCMA concentrations were also higher in patients who developed CRS than in those who did not. Although sBCMA concentrations gradually increased after Month 15, they remained substantially below baseline at Month 24, consistent with sustained pharmacodynamic activity.

Inflammatory markers (IL-6, CRP and ferritin) increased rapidly following FUCASO infusion, peaking within 7–10 days before returning towards baseline within 1–2 months, consistent with the expected inflammatory response accompanying CAR T-cell expansion.

Immunogenicity

Immunogenicity was evaluated by assessing the development of anti-CAR antibodies, including neutralising antibodies. In Study XL-LCYJ-0007, post-infusion anti-CAR antibodies were detected in 25.2% (27/107) of evaluable patients, of which only one patient developed neutralising antibodies. Two patients who died before the first post-infusion sample collection were not evaluable. Based on the available data, there was no evidence that anti-CAR antibody development adversely affected CAR T-cell expansion, persistence, efficacy, or safety.

Replication-competent lentivirus (RCL)

RCL was assessed using qPCR. No RCL was detected in Study XL-LCYJ-0007.

Lentiviral insertion site analysis

Lentiviral vector insertion site analysis was performed using next-generation sequencing to evaluate potential insertional oncogenic risk. No clinically significant clonal expansion was detected in Study XL-LCYJ-0007.

Study XL-LCYJ-0003 (Dose-finding study)

In the Phase 1 Study XL-LCYJ-0003 (N = 23), FUCASO demonstrated rapid *in vivo* expansion, with median $T_{\max}$ values of approximately 12–16 days, and CAR T cells persisted in some patients for up to 2 years. The sBCMA levels declined rapidly after infusion and remained suppressed in patients with durable responses, while increasing at disease progression. Anti-CAR antibodies were detected in one patient (4.3%) in the 3.0×10^6 CAR-T dose level. RCL testing and insertion site analysis were not performed in this study.

Clinical pharmacology conclusion

The clinical pharmacology of FUCASO was adequately characterised in Study XL-LCYJ-0007 (N = 109), supported by findings from Study XL-LCYJ-0003 (N = 23). FUCASO demonstrated rapid *in vivo* expansion, prolonged persistence, and sustained pharmacodynamic activity, consistent with its mechanism of action as a BCMA-directed CAR T-cell therapy. No notable effects of the evaluated intrinsic or extrinsic factors on pharmacokinetics were identified. Immunogenicity was low and did not appear to affect efficacy or safety, and no RCL or clinically significant clonal expansion was detected. Overall, the available clinical pharmacology data support the selection of the RP2D of 1.0×10^6 CAR-positive cells/kg and support the proposed clinical use of FUCASO.

Dose finding and dose recommendation

Overview

Dose selection for FUCASO was primarily informed by Study XL-LCYJ-0003, a Phase 1, single-centre, open-label, investigator-initiated dose-finding study, and subsequently evaluated in Study XL-LCYJ-0007. An overview of the Study XL-LCYJ-0003 is presented in Table 2.

Table 2. Overview of Study XL-LCYJ-0003

Study Population	Primary Objective	Number of Patients Planned / Enrolled / Treated	Duration of Follow-up	Study Status
Adult patients with plasma cell malignancies per IMWG diagnostic criteria, including relapsed/refractory multiple myeloma	Evaluate tolerability and safety of FUCASO; determine RP2D	Planned 21 to 27 Enrolled 29 Treated 23: • 0.5×10^6 (N = 5) • 1.0×10^6 (N = 9) • 3.0×10^6 (N = 6) • 6.0×10^6 (N = 3)	Primary: up to 2 years post-infusion Long-term: up to 15 years post-infusion	Completed 2-year primary follow-up (last patient visit 15 Sep 2021)

Abbreviations: IMWG = International Myeloma Working Group; N = number of patients; RP2D = recommended phase 2 dose.

Study XL-LCYJ-0003 (Dose-finding study)

The starting dose of 1.0×10^6 CAR T cells/kg was based on published clinical experience with anti-BCMA CAR T-cell products and was consistent with United States Food and Drug Administration guidance allowing prior clinical experience to inform starting dose selection. Using a 3+3 design, cohorts of 3 patients were enrolled at each planned dose level, with expansion to 6 patients if dose-limiting toxicity was observed. Escalation proceeded through planned dose levels of 3.0 and 6.0×10^6 CAR T cells/kg, at which point a Grade 4 CRS dose-limiting toxicity led the Safety Monitoring Committee to halt further dose escalation.

The 1.0×10^6 CAR T cells/kg dose level demonstrated an acceptable safety profile, satisfactory *in vivo* expansion, and favourable preliminary efficacy, and was therefore selected for the dose-expansion stage, during which six additional patients received this dose and five patients received a lower dose of 0.5×10^6 CAR T cells/kg. A total of 23 patients received FUCASO across four dose levels. Patients had a median age of 54.0 years (range: 39–68) and had received a median of four prior lines of anti-myeloma therapy (range: 3–6). All patients had previously received a PI and an IMiD.

Among all treated patients, investigator-assessed ORR within 3 months was 100% (95% CI: 85.2%–100.0%). The 0.5×10^6 CAR T cells/kg dose level showed less durable responses compared with the 1.0×10^6 CAR T cells/kg dose level (median DOR: 3.9 months vs >12 months), while higher doses did not appear to provide additional efficacy and were associated with greater toxicity.

Dose selection conclusion

Based on the totality of safety, pharmacokinetic, and efficacy data, 1.0×10^6 CAR T cells/kg was identified as the RP2D, which was subsequently confirmed in the dose-expansion Phase 1 of Study XL-LCYJ-0007.

Efficacy

Overview

The efficacy of FUCASO was primarily supported by one pivotal Phase 1/2, single-arm, open-label, multicentre study (XL-LCYJ-0007, FUMANBA-1; N = 109). Given the non-randomised design, efficacy interpretation was based primarily on magnitude and durability of response rather than direct comparative effectiveness. An overview of the Study XL-LCYJ-0007 is presented in Table 3.

Table 3. Overview of Study XL-LCYJ-0007 (FUMANBA-1)

Study Population	Primary Objective	Number of Patients Planned / Enrolled / Treated	Duration of Follow-up	Study Status
Adult patients with relapsed or refractory multiple myeloma per IMWG diagnostic criteria	Phase 1: Evaluate safety of FUCASO at RP2D Phase 2: Evaluate efficacy of FUCASO at RP2D	Phase 1: Planned 6 to 20 Enrolled 20 Treated 17 Phase 2: Planned 120 to 125 (including Phase 1) Enrolled 101 Treated 92	Primary: up to 2 years post-infusion Long-term: up to 15 years post-infusion	Completed 2-year primary follow-up (last patient visit 13 May 2025)

Abbreviations: IMWG = International Myeloma Working Group; RP2D = recommended phase 2 dose.

Study XL-LCYJ-0007 (FUMANBA-1, Pivotal study)

Study XL-LCYJ-0007 was conducted across 14 centres in China in accordance with Good Clinical Practice. Phase 1 evaluated safety, pharmacokinetics, pharmacodynamics and immunogenicity and established the RP2D of 1.0×10^6 CAR T cells/kg. Phase 2 evaluated efficacy and further characterised safety at the RP2D. An independent Data Monitoring Committee was established to periodically review accumulating efficacy and safety data.

Eligible patients were adults aged 18 to 70 years with RRMM per International Myeloma Working Group (IMWG) diagnostic criteria, who had received at least 3 prior lines of therapy including a PI and an IMiD, with documented disease progression within 12 months of the most recent line of therapy (this criterion did not apply where the last line was a CAR T-cell therapy). Patients were required to have positive BCMA expression on bone marrow plasma cells, measurable disease at screening, and Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Key exclusions included recent autologous haematopoietic stem cell transplant (HSCT) within 12 weeks, prior allogeneic HSCT, GvHD, requirement for long-term immunosuppression, central nervous system involvement, and plasma cell leukaemia.

Treatment

Following leukapheresis and during product manufacture, bridging therapy was permitted for patients with high tumour burden. Following manufacture of FUCASO, lymphodepletion with cyclophosphamide 500 mg/m²/day and fludarabine 30 mg/m²/day was administered for 3 consecutive days (days -7 to -2), followed by a single infusion of FUCASO at 1.0×10^6 CAR T cells/kg. Patients were hospitalised and observed for at least 2 weeks post-infusion.

Endpoints

The primary endpoint was ORR at 3 months, as assessed by an Independent Review Committee (IRC), defined as the proportion of patients achieving a PR or better according to IMWG response criteria. Given the advanced disease stage, heavily pre-treated population, and the heterogeneous treatment landscape with no single universally accepted standard of care in this setting, a single-arm study design with ORR as the primary endpoint was considered acceptable. IRC assessment was considered appropriate as it provided an objective measure of anti-tumour activity while minimising potential assessment bias.

The full analysis set (FAS) comprised all patients who received an infusion of FUCASO and was considered an appropriate primary analysis population for an autologous CAR T-cell product. Missing IRC-assessed ORR data were treated as non-response, representing a conservative analytical approach that minimises risk of overestimating treatment effect. The primary endpoint was considered met if the lower limit of the 95% confidence interval (CI) for the Phase 2 IRC-assessed 3-month ORR exceeded 35%. This prespecified control rate was selected based on the efficacy observed with approved treatments for heavily treated RRMM patients in China at the time of study initiation, where ORRs ranged from 19% to 29%.

Secondary endpoints included investigator and IRC-assessed ORR, investigator and IRC-assessed DOR, investigator and IRC-assessed progression free survival (PFS), overall survival (OS) and minimal residual disease (MRD) negativity rate and duration. MRD negativity has been associated with long-term outcomes in RRMM. In contrast, the interpretation of time-to-event endpoints of PFS and OS is limited by the absence of a control arm.

Patient population and baseline characteristics

The study population comprised 109 patients who received FUCASO infusion (Phase 1, N = 17; Phase 2, N = 92), of whom 54 received bridging therapy. The median time from

leukapheresis to lymphodepletion, leukapheresis to infusion, and lymphodepletion to infusion was 32 days (range: 19–73), 36 days (range: 22–77), and 5 days (range: 4–11), respectively.

Baseline demographic and disease characteristics of the treated population are summarised in Table 4 and were generally similar between Phase 1 and Phase 2. The overall treated population (N = 109) had a median age of 58 years (range: 39–70), with 78.0% of patients having an ECOG performance status of 1. Patients older than 70 years were not enrolled. Therefore, direct efficacy evidence in elderly patients above 70 years remains limited. Patients had received a median of four prior lines of therapy (range: 3–23). All had prior exposure to PIs, IMiDs, and glucocorticoids, and 89.0% were double refractory (refractory to a PI and an IMiD). Prior exposure to anti-CD38 monoclonal antibodies was reported in 23.9% of patients, reflecting regional treatment practices at the time of study initiation, with lower anti-CD38 exposure than that observed in international RRMM populations. Prior autologous HSCT was reported in 29.4% of patients.

Table 4. Baseline Demographic and Disease Characteristics of Treated Population

Parameter	Phase 1 (N = 17)	Phase 2 (N = 92)	Total (N = 109)
Age (years)			
Median (Min, Max)	58 (46, 69)	58 (39, 70)	58 (39, 70)
Sex			
Male, n (%)	13 (76.5)	45 (48.9)	58 (53.2)
Female, n (%)	4 (23.5)	47 (51.1)	51 (46.8)
ECOG Performance Status			
0, n (%)	5 (29.4)	19 (20.7)	24 (22.0)
1, n (%)	12 (70.6)	73 (79.3)	85 (78.0)
BCMA-Positive Plasma Cells at Screening			
<50%, n (%)	10 (58.8)	22 (23.9)	32 (29.4)
≥50%, n (%)	7 (41.2)	68 (73.9)	75 (68.8)
Not evaluable, n (%)	0	2 (2.2)	2 (1.8)
High-Risk Cytogenetics			
Yes, n (%)	3 (17.6)	33 (35.9)	36 (33.0)
No, n (%)	12 (70.6)	46 (50.0)	58 (53.2)
Not evaluable, n (%)	2 (11.8)	13 (14.1)	15 (13.8)
Extramedullary Disease (IRC)			
Yes, n (%)	5 (29.4)	9 (9.8)	14 (12.8)
No, n (%)	12 (70.6)	83 (90.2)	95 (87.2)
Prior Lines of Therapy			
Median (Min, Max)	5 (3, 23)	4 (3, 14)	4 (3, 23)
3–5 lines, n (%)	11 (64.7)	61 (66.3)	72 (66.1)
>5 lines, n (%)	6 (35.3)	31 (33.7)	37 (33.9)
Prior Treatment			
Proteasome inhibitors (PI), n (%)	17 (100)	92 (100)	109 (100)
Immunomodulatory agents (IMiD), n (%)	17 (100)	92 (100)	109 (100)
Anti-CD38 monoclonal antibodies, n (%)	2 (11.8)	24 (26.1)	26 (23.9)
Chemotherapy†, n (%)	16 (94.1)	86 (93.5)	102 (93.6)
Glucocorticoids, n (%)	17 (100)	92 (100)	109 (100)
Autologous HSCT, n (%)	3 (17.6)	29 (31.5)	32 (29.4)
CAR T-cell therapy, n (%)	6 (35.3)	6 (6.5)	12 (11.0)
Other, n (%)	3 (17.6)	7 (7.6)	10 (9.2)
Prior Drug Class Exposure			
Double-exposed, n (%)	17 (100)	92 (100)	109 (100)
Triple-exposed, n (%)	2 (11.8)	24 (26.1)	26 (23.9)
Disease Refractoriness*			
Double-refractory, n (%)	14 (82.4)	83 (90.2)	97 (89.0)
Triple-refractory, n (%)	2 (11.8)	17 (18.5)	19 (17.4)
Penta-refractory, n (%)	1 (5.9)	5 (5.4)	6 (5.5)

Abbreviations: BCMA = B-cell maturation antigen; CAR T-cell = chimeric antigen receptor T-cell; ECOG = Eastern Cooperative Oncology Group; HSCT = haematopoietic stem cell transplantation; IRC = independent review committee; N = number of patients.

Percentages are based on the number of patients in each analysis set unless otherwise specified.

†Chemotherapy excludes proteasome inhibitors and immunomodulatory agents.

#Double-refractory: refractory to a PI and an IMiD; Triple-refractory: refractory to a PI, an IMiD, and an anti-CD38; Penta-refractory: refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38.

Results

The primary efficacy analysis was conducted in the Phase 2 FAS (N = 92), while pooled Phase 1 and Phase 2 data were used for supportive analyses. At the time of final analysis, all infused patients had completed or prematurely discontinued the 2-year primary follow-up period. The median follow-up durations were 36.32 months (range: 0.36–52.96) for Phase 2 patients and 39.66 months (range: 0.36–58.45) for Phase 1/2 patients.

Primary endpoint: 3-Month ORR per IRC

In the Phase 2 FAS (N = 92), the primary endpoint was met as the IRC-assessed 3-month ORR was 88.0% (95% CI: 79.6–93.9). The rates of ≥VGPR and stringent complete response/complete response (sCR/CR) were 75.0% and 42.4%, respectively. Subgroup analyses demonstrated broadly consistent ORRs across a range of patient characteristics, including age, sex, cytogenetic risk, revised International Staging System (R-ISS) stage, BCMA expression, bone marrow plasma cell burden, prior lines of therapy, anti-CD38 exposure, prior HSCT, and use of bridging therapy. Notably lower response rates were observed in patients with extramedullary disease (35.7% per IRC) and those with prior BCMA-directed CAR T-cell therapy (50.0% per IRC). Given the exploratory and descriptive nature of these analyses, results should be interpreted with caution.

Secondary endpoints

The efficacy results in the Phase 2 FAS were supported by secondary efficacy endpoints. The investigator-assessed 3-month ORR was 91.3% (95% CI: 83.6–96.2), with ≥VGPR and sCR/CR rates of 80.4% and 43.5%, respectively, broadly consistent with the IRC assessment. The median DOR per IRC was 36.01 months (95% CI: 23.03–46.49). The median PFS per IRC was 30.19 months (95% CI: 21.16–44.48). The median OS had not been reached (95% CI: 42.15–NC), with 88.0% and 76.9% of patients alive at 12 and 24 months, respectively. The MRD negativity rate among evaluable patients was 95.6% (95% CI: 89.0–98.8) and was 100% among those achieving sCR/CR. The median duration of MRD negativity per IRC was 36.53 months (95% CI: 23.23–NC), extending to 37.09 months (95% CI: 27.43–NC) among patients achieving sCR/CR.

The supportive pooled Phase 1/2 analyses were consistent with the Phase 2 findings. A summary of key efficacy results in the Phase 2 and pooled Phase 1/2 FAS is presented in Table 5.

Table 5. Summary of Key IRC-Assessed Efficacy Results (Study XL-LCYJ-0007, Phase 2 FAS and pooled Phase 1/2 FAS)

Endpoint	Phase 2 [†] (N = 92)	Phase 1/2 [†] (N = 109)
Primary Endpoint		
ORR at 3 months	88.0% (79.6–93.9)	85.3% (77.0–91.6)
≥VGPR at 3 months	75.0% (64.9–83.4)	69.7% (59.8–78.4)
sCR/CR at 3 months	42.4% (32.1–53.1)	37.6% (28.2–47.8)
Duration of Response (DOR)		
Median DOR, months	36.01 (23.03–46.49)	34.99 (23.03–46.49)

Progression-Free Survival (PFS)		
Median PFS, months	30.19 (21.16–44.48)	30.19 (23.52–42.15)
Overall Survival (OS)		
Median OS, months	NC (42.15–NC)	53.72 (42.55–NC)
Minimal Residual Disease[#] (MRD)		
MRD negativity (evaluable patients)	95.6% (89.0–98.8)	95.3% (89.4–98.5)
MRD negativity (sCR/CR)	100% (95.2–100)	100% (95.7–100)
Median duration of MRD negativity, months	36.53 (23.23–NC)	36.53 (27.43–47.70)
Median duration of MRD negativity (sCR/CR), months	37.09 (27.43–NC)	41.20 (29.50–48.95)

Abbreviations: CR = complete response; sCR = stringent complete response; FAS = full analysis set; IRC = independent review committee; N = number of patients; NC = not calculable. For median OS, NC indicates that the median was not reached at the time of analysis; ORR = overall response rate; VGPR = very good partial response.

[†]Final analysis (data cut-off date: 13 May 2025), with median follow-up durations of 36.32 months for Phase 2 and 39.66 months for Phase 1/2. Data are presented as percentages or medians, as appropriate. Values in parentheses represent the 95% confidence interval (CI), except Phase 1/2 FAS 3-month ORR, $\geq$ VGPR and sCR/CR represent the 95.8% CI. [#]MRD was monitored with EuroFlow flow cytometry (sensitivity 10^{-5}).

Efficacy conclusion

The efficacy of FUCASO was demonstrated in the pivotal Study XL-LCYJ-0007 (FUMANBA-1), in which the primary endpoint was met. The IRC-assessed 3-month ORR was 88% (95% CI: 79.6–93.9), with the lower bound of the 95% CI exceeding the pre-specified historical control rate of 35%. Among evaluable patients, the MRD negativity rate was 95.6%, and all evaluable patients who achieved sCR/CR were MRD-negative at the assessed timepoint, as determined by EuroFlow flow cytometry (sensitivity 10^{-5}). The median DOR was 36.0 months. In the context of the limited treatment options available for heavily pre-treated RRMM patients, the magnitude, depth and durability of the observed responses support a clinically meaningful benefit of FUCASO in the proposed indication. Continued follow-up and post-approval evidence generation will further characterise the long-term durability of benefit.

E ASSESSMENT OF CLINICAL SAFETY

Overview

The safety population comprised 132 treated patients from the pivotal Phase 1/2 Study XL-LCYJ-0007 (N = 109), and the Phase 1 dose-finding Study XL-LCYJ-0003 (N = 23). The primary safety evaluation was based on patients treated at the RP2D in the pivotal study, in which all patients had completed at least 2 years of follow-up, with long-term follow-up continuing for up to 15 years. Supportive safety data were provided by Study XL-LCYJ-0003, which evaluated four dose levels (0.5, 1.0, 3.0, and 6.0×10^6 CAR T cells/kg) and included approximately 4 years of follow-up. An overview of the safety profile is presented in Table 6.

In Study XL-LCYJ-0007, all patients experienced at least one adverse event (AE), with treatment-related adverse events (TRAE) occurring in 99.1% (108/109) of patients. Serious adverse events (SAEs) occurred in 76.1% (83/109) of patients, although discontinuations due to AEs were uncommon (0.9%; 1/109). Sixteen deaths occurred, of which six (5.5%) were considered treatment-related, comprising five infection-related deaths and one death due to intracranial haemorrhage.

The most common TRAEs in Study XL-LCYJ-0007 were pyrexia (94.5%) and CRS (93.6%), followed by haematological toxicities including decreased neutrophil count and decreased white blood cell count (both 89.0%), decreased platelet count (79.8%), decreased lymphocyte count (75.2%), and anaemia (67.9%). Hypogammaglobulinaemia occurred in 63.3% of

patients. Other common TRAEs included blood lactate dehydrogenase increased (54.1%), aspartate aminotransferase increased (45.0%), hypoglobulinaemia and hypokalaemia (both 42.2%), pneumonia (40.4%), alanine aminotransferase increased and hypoalbuminaemia (both 33.0%), hypocalcaemia (29.4%), gamma-glutamyltransferase increased and blood fibrinogen decreased (both 28.4%), vomiting (27.5%), diarrhoea (25.7%), blood alkaline phosphatase increased (24.8%), and fibrin D-dimer increased (20.2%).

Study XL-LCYJ-0003 demonstrated a generally similar safety profile to that observed in the pivotal study, with all patients experiencing at least one AE and one TRAE, 65.2% experiencing SAEs, and no treatment-related deaths reported.

Table 6. Overview of Safety Profile

Adverse Events (AEs)	XL-LCYJ-0007 (N = 109)	XL-LCYJ-0003 (N = 23)
Any AE	109 (100%)	23 (100%)
Treatment-related Adverse Event (TRAE)	108 (99.1%)	23 (100%)
Serious Adverse Event (SAE)	83 (76.1%)	15 (65.2%)
Treatment-related SAE	55 (50.5%)	2 (8.7%)
Deaths	16 (14.7%)	4 (17.4%)
Treatment-related Deaths	6 (5.5%)	0 (0%)
Discontinuations due to AE	1 (0.9%)	1 (4.3%)
Treatment-related Discontinuations	1 (0.9%)	0 (0%)

Abbreviations: N = number of patients.

Study XL-LCYJ-0007 (FUMANBA-1, Pivotal study)

Cytokine release syndrome (CRS)

CRS, a common and expected AE associated with CAR T-cell therapies, occurred in 93.6% (102/109) of patients. The median time to onset was 6 days (range: 1–13 days), consistent with the expected onset following CAR T-cell therapy, and the median duration was 5 days (range: 2–30 days). Most events were Grade 1 or 2 and were managed with supportive care, including tocilizumab and corticosteroids when clinically indicated. One patient (0.9%) experienced Grade ≥3 CRS, associated with concurrent Grade 4 tumour lysis syndrome and fatal intracranial haemorrhage.

Neurotoxicity

Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 1.8% (2/109) of patients, and no Grade ≥3 neurotoxicity events were reported.

Prolonged cytopenias

Grade ≥3 cytopenias persisting for more than 30 days occurred in all patients. The most common prolonged Grade ≥3 cytopenias were decreased lymphocyte count (100%), decreased white blood cell count (96.3%), decreased neutrophil count (89.9%), haemoglobin decreased (68.8%), and platelet count decreased (59.6%). Prolonged cytopenias are an expected complication following lymphodepleting chemotherapy and CAR T-cell therapy and may contribute to an increased risk of infection and bleeding, requiring ongoing haematological monitoring and supportive care where clinically indicated.

Hypogammaglobulinaemia

Hypogammaglobulinaemia occurred in 63.3% (69/109) of patients, while 78.9% (86/109) had laboratory IgG concentrations below 500 mg/dL. This is an expected pharmacological

consequence of BCMA-directed CAR T-cell therapy, as BCMA is expressed on mature B lymphocytes and plasma cells. Depletion of these cells results in reduced immunoglobulin production, necessitating monitoring of immunoglobulin concentrations and, where clinically indicated, immunoglobulin replacement therapy.

Serious infections

Grade ≥ 3 infections occurred in 74.3% (81/109) of patients. Pneumonia was the most frequently reported Grade ≥ 3 infection, occurring in 56.9% (62/109) of patients. Patients with RRMM are predisposed to infection because of impaired immune function associated with the underlying disease. Treatment with FUCASO may further increase this risk through prolonged cytopenias and hypogammaglobulinaemia.

Other safety concerns

Tumour lysis syndrome, a known but uncommon AE associated with CAR T-cell therapy, occurred in 4.6% (5/109) of patients, including Grade ≥ 3 TLS in 3.7% (4/109) of patients. One Grade 4 case occurred in the setting of CRS and was associated with a fatal intracranial haemorrhage, while the other Grade 4 case resolved following treatment. Grade 2 haemophagocytic lymphohistiocytosis/macrophage activation syndrome occurred in 0.9% (1/109) of patients. No cases of uncontrolled CAR T-cell expansion, progressive multifocal leukoencephalopathy, secondary malignancies, or RCL were identified during clinical follow-up.

No notable differences in the safety profile were observed across the evaluated subgroups. Overall, the safety profile was consistent with the known toxicities of BCMA-directed CAR T-cell therapies and was generally manageable with routine monitoring, established supportive care measures and appropriate clinical intervention.

Study XL-LCYJ-0003 (Dose-finding study)

Study XL-LCYJ-0003 demonstrated a safety profile generally consistent with the pivotal study. CRS occurred in 95.7% (22/23) of patients, with a median time to onset of 3.5 days (range: 1–16 days), and Grade ≥ 3 CRS was reported in five patients (21.7%), likely reflecting the evaluation of higher dose levels (up to 6.0×10^6 CAR T cells/kg) in this dose-finding study. Treatment-related neurological AEs occurred in 21.7% (5/23) of patients, with no Grade ≥ 3 neurotoxicity reported. Grade ≥ 3 treatment-emergent serious infections and prolonged Grade ≥ 3 cytopenias occurred in 43.5% (10/23) and 78.2% (18/23) of patients, respectively. Hypogammaglobulinaemia was observed across all dose levels, with Grade ≥ 3 events occurring only at the highest dose level (6.0×10^6 CAR T cells/kg).

Safety conclusion

The safety profile of FUCASO was consistent with that expected for BCMA-directed CAR T-cell therapies. The key safety concerns included CRS, neurotoxicity, serious infections, prolonged cytopenias, and hypogammaglobulinaemia. These risks are addressed through the approved package insert and the local Risk Management Plan (see below), which include recommendations for routine monitoring, early recognition, and appropriate clinical management. Given the relatively limited size of the safety database and the duration of follow-up, continued long-term surveillance is warranted to further characterise uncommon and delayed AEs, including secondary malignancies. Overall, the available safety data support the proposed clinical use of FUCASO in the indicated patient population.

Risk Management Plan summary

The product registrant is required to:

- implement the approved Risk Management Plan for FUCASO, including educational materials comprising Healthcare Professional Educational Material, Clinical Safety Management Manual, Patient Medication Guide, and Patient Alert Card, to be distributed to all prescribing physicians before FUCASO is supplied.
- submit periodic benefit-risk evaluation reports for FUCASO in accordance with the timelines and intervals specified in Regulation 50 of the Health Products (Cell, Tissue and Gene Therapy Products) Regulations.

F ASSESSMENT OF BENEFIT-RISK PROFILE

Patients with RRMM who have received at least three prior lines of therapy have limited treatment options and poor clinical outcomes, representing an area of high unmet medical need. At the time of this assessment, no BCMA-directed CAR T-cell therapy had been approved locally for this indication.

In Study XL-LCYJ-0007 (FUMANBA-1), the primary efficacy endpoint was met. The IRC-assessed 3-month ORR was 88% (95% CI: 79.6–93.9), with the lower bound of the 95% CI exceeding the pre-specified historical control rate of 35%. Among evaluable patients, the MRD negativity rate was 95.6%, and all evaluable patients who achieved sCR/CR were MRD-negative at the assessed timepoint, as determined by EuroFlow flow cytometry (sensitivity 10^{-5}). The median DOR was 36.0 months. In the context of the limited treatment options available for heavily treated RRMM patients, the magnitude, depth and durability of the observed responses support a clinically meaningful benefit of FUCASO in the proposed indication. Continued follow-up and post-approval evidence generation will further characterise the long-term durability of benefit.

The safety profile of FUCASO was consistent with the expected safety profile of BCMA-directed CAR T-cell therapies. The key safety concerns included CRS, neurotoxicity, serious infections, prolonged cytopenias, and hypogammaglobulinaemia. These risks were considered manageable with appropriate monitoring and clinical management at experienced treatment centres, and are adequately addressed through relevant warnings, precautions, and recommendations in the Singapore package insert, together with the risk minimisation measures specified in the local Risk Management Plan.

Given the limited size of the safety database and the duration of follow-up, continued pharmacovigilance and long-term follow-up are warranted to further characterise uncommon, delayed, and long-term AEs, including secondary malignancies.

Overall, the benefits of FUCASO outweigh the risks for treatment of adult patients with RRMM, who have received at least three prior lines of therapy, including a PI and an IMiD, and have demonstrated disease progression on the last therapy.

G CONCLUSION

Based on the review of the quality, non-clinical, and clinical data, the benefit–risk balance of FUCASO for the treatment of adult patients with RRMM, who have received at least three prior lines of therapy, including a PI and an IMiD, and have demonstrated disease progression on the last therapy, was deemed favourable. Approval of the Cell, Tissue and Gene Therapy Product registration was granted on 18 June 2026.

APPROVED PACKAGE INSERT

FUCASO suspension for infusion

For autologous use only. For intravenous use only

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS, PROLONGED CYTOPENIA and SECONDARY HEMATOLOGICAL MALIGNANCIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with FUCASO. Do not administer FUCASO to patients with active infections or inflammatory diseases, or active graft-versus-host disease (GVHD). Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids [See Warnings and Precautions (5.5)].
- Neurologic toxicities, which may be fatal or life-threatening, occurred following treatment with FUCASO, and may occur concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic toxicities after treatment with FUCASO. Provide supportive care and/or corticosteroids as needed [See Warnings and Precautions (5.6)].
- Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), which may be fatal or life-threatening, occurred following treatment with FUCASO. HLH/MAS can occur with CRS or neurologic toxicities [see Warnings and Precautions (5.5)].
- Prolonged cytopenias have occurred following treatment with FUCASO [(see Warnings and Precautions (5.9)].
- T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies [See Warnings and Precautions (5.13)].

1. DESCRIPTION AND COMPOSITION

FUCASO (Equecabtagene Autoleucel) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy. FUCASO is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and genetically modified ex vivo by transduction with a replication incompetent lentiviral vector to express a chimeric antigen receptor (CAR) comprising an anti-BCMA targeting domain. The anti-BCMA CAR-T cells are expanded in cell culture, washed, formulated into a suspension and cryopreserved. FUCASO is thawed and then infused back into the patient, where the anti-BCMA CAR-T cells can recognize and eliminate BCMA-expressing target cells.

FUCASO is supplied in a patient-specific infusion bag containing approximately 20 mL of frozen suspension of genetically modified autologous anti-BCMA CAR-T cells with a range of $0.7\text{--}1.3 \times 10^6$ CAR-positive viable T cells per kg of body weight. The target dose is 1.0×10^6 anti-BCMA CAR-T cells/kg of patient body weight. The infusion bag is individually packed

in a metal cassette and placed in a qualified vapor-phase liquid nitrogen (LN₂) cryo-shipper container for storage and transport.

FUCASO is a white or yellowish frozen solid and turns into a slightly yellow suspension after thawing.

FUCASO contains the following excipients.

Table 1. Excipients in FUCASO

Excipients	Concentration of excipients in stock solution
Multiple Electrolytes Injection	32.5% (V/V)
Human Serum Albumin Injection (20%)	23.0% (V/V)
Glucose Injection (10%)	35.0% (V/V)
Compound Amino Acid Solution for Injection (18AA-II) (8.5%)	1.0% (V/V)
Vitamin C Injection (1g/5ml)	1.0% (V/V)
Dimethyl Sulfoxide (DMSO)	7.5% (V/V)

See Section 15. for full list of ingredients.

2. INDICATION

FUCASO is a BCMA-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least three prior lines of therapy, (including a proteasome inhibitor and an immunomodulatory agent), and have demonstrated disease progression on the last therapy.

3. DOSAGE AND ADMINISTRATION

FUCASO is for autologous use only. It is intended for single intravenous (IV) infusion only.

The treatment must be carried out in a certified healthcare facility by qualified healthcare professional with experience in the treatment of hematologic malignancies and trained for administration and management of patients treated with FUCASO.

3.1. Dosage Regimen

Treatment consists of a single dose for infusion containing a suspension of CAR-positive viable T cells in one infusion bag. The range is $0.7\text{--}1.3 \times 10^6$ CAR-positive viable T cells per kg of body weight. The target dose is 1.0×10^6 anti-BCMA CAR-T cells/kg of patient body weight.

3.2. Administration

Preparing Patient for FUCASO Infusion

Confirm availability of FUCASO prior to starting the lymphodepleting regimen.

- Pre-treatment (lymphodepleting regimen)

The lymphodepletion pretreatment should be completed within 2 to 7 days before the infusion of FUCASO. The recommended regimen is cyclophosphamide (500mg/m²) and fludarabine (30mg/m²) administered intravenously for three consecutive days. For dose modifications of cyclophosphamide and fludarabine, see corresponding package inserts of cyclophosphamide and fludarabine.

- Pre-medication

To reduce the risk of infusion reaction, it is recommended that promethazine 25mg or diphenhydramine 20mg be injected intramuscularly 15 to 30 minutes before administration. In case of fever (fever not caused by infection), treat with paracetamol or other non-steroidal anti-inflammatory drugs.

Since corticosteroids may affect the activity of FUCASO, systematic use of corticosteroids (except physiological replacement therapy) should be avoided 72 hours before infusion.

Preparation of FUCASO for Infusion

Coordinate the timing of FUCASO thaw and infusion. Confirm the infusion time in advance and adjust the start time of FUCASO thaw such that it will be available for infusion when patient is ready.

- Confirm patient identity: Prior to FUCASO preparation, match the patient identity with the patient identifiers on the frozen storage cassette.
- Do not remove the FUCASO infusion 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 FUCASO infusion bag from the cassette and check that the patient information on the cassette label matches the infusion bag label. If the patient's identity information does not match, do not administer this product.
- Inspect the infusion bag for any breaches of container integrity such as breaks or cracks before thawing. If the infusion bag is compromised, follow the local guidelines (or contact Nanjing IASO Medical Technology Co., Ltd at Tel: +86 400 966 5315).
- Thaw FUCASO at approximately 37°C using a water bath until there is no visible ice in the infusion bag. Gently mix the contents of the infusion bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the infusion bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, centrifuge, and/or re-suspend FUCASO before infusion.
- FUCASO should be infused as soon as possible at room temperature. Infusion should begin within 20 minutes of the end of thawing. The time from the end of thawing to the end of infusion should not exceed 40 minutes.

Administration

- For autologous use only.
- For intravenous (IV) use only.
- Do NOT irradiate.

- Ensure that corticosteroids, at least two doses of tocilizumab and emergency equipment are available prior to infusion and during recovery period.
- Use 20G or larger needles for infusion.
- Do NOT use any infusion filters (such as leukodepleting filters).
- Central venous access may be used for the infusion of FUCASO, if appropriate.
- Infusion should be carried out by qualified medical personnel in accordance with the prescribed procedures.
- Confirm the patient's identity matches the patient identifiers on the FUCASO infusion bag.
- Prime the tubing with 0.9% sodium chloride solution for infusion prior to infusion. Infuse the entire contents of the FUCASO infusion bag within 10 minutes at a rate of 60-96 drops/minute by gravity, throughout the entire administration process.
- After the entire content of the infusion bag is infused, rinse the tubing with 0.9% sodium chloride solution for infusion at the same infusion rate to ensure that all remaining cells in the tubing are infused into the patient's body.
- FUCASO is prepared from autologous T cells. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Clinical Assessment Prior to Infusion

- FUCASO treatment should be delayed in some patient groups at risk [see Warnings and Precautions (5.1)].

Monitoring Post Infusion

- FUCASO must be administered at a certified healthcare facility.
- Patient's vital signs, including body temperature, respiration, heart rate, blood pressure, and blood oxygen saturation must be monitored from 15 minutes before infusion to 1 hour after infusion. If the patient's vital signs are unstable after infusion, they need to be closely monitored until all indicators are stabilized and in a normal state.
- It is recommended that patients should be monitored in the certified healthcare facility for at least 14 days after infusion of FUCASO for signs and symptoms of CRS and neurologic toxicities.
- Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion, and to seek timely medical attention and corresponding treatment in case of possible serious or life-threatening adverse reactions.

4. CONTRAINDICATIONS

FUCASO is contraindicated in patients with known hypersensitivity to any component of the product formulation, including dimethyl sulfoxide (DMSO). Contraindications of the lymphodepleting chemotherapy must be considered.

5. WARNINGS AND PRECAUTIONS

5.1. General Warnings and Precautions

Due to the risks associated with FUCASO treatment, infusion should be withheld until resolution of any of the following conditions:

- Serious adverse reactions caused by previous chemotherapy have not recovered (especially pulmonary adverse reactions, cardiac adverse reactions or hypotension).
- Uncontrolled active infection.
- Graft versus host disease (GVHD).
- The axillary body temperature within 48 hours before the infusion of FUCASO is greater than 38 °C.

Patients treated with FUCASO should not donate blood, organs, tissues, sperms, oocytes and other cells for transplantation.

FUCASO is for **AUTOLOGOUS USE ONLY** and should **NOT** be given to other patients in any case. Before infusion of FUCASO, the patient's identity must match the patient identifiers on the packaging cassette and frozen FUCASO infusion bag. If it does not match, FUCASO should **NOT** be infused.

5.2. Concomitant Diseases

Patients with active central nervous system (CNS) disease or inadequate renal, hepatic, pulmonary or cardiac function may be more vulnerable to the consequences of the adverse reactions described below after FUCASO infusion and require special attention.

5.3. Solitary Plasmacytoma

There is no experience of use FUCASO in patients with Solitary Plasmacytoma. Therefore, risk/benefit of FUCASO has not been established in this population.

5.4. Multiple Myeloma with Plasma Cell Leukemia

There is no experience of use of FUCASO in multiple myeloma patients with plasma cell leukemia. The risk/benefit of FUCASO has not been established in this population.

5.5. Cytokine release syndrome (CRS)

CRS, including fatal or life-threatening reactions, occur following treatment with FUCASO (see Section 6. ADVERSE REACTIONS). Before infusion of FUCASO, ensure that corticosteroids (such as methylprednisolone and dexamethasone), at least two doses of tocilizumab and emergency equipment are available.

Signs and symptoms of CRS include fever at the onset and may include, hypotension, hypoxia, dyspnea, tachypnea, tachycardia, fatigue, headache, rigors, myalgia, arthralgia, nausea, vomiting, diarrhea, diaphoresis, rash, and anorexia. Organ dysfunction, including cardiac insufficiency, renal insufficiency, and liver injury with accompanying elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT) or elevated total bilirubin may also be observed. In addition, disseminated intravascular coagulation (DIC) with low fibrinogen levels, capillary leak syndrome (CLS), macrophage activation

syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) may occur in the setting of CRS. Patients should be closely monitored for signs or symptoms of these events including fever. Patients are required to be hospitalized for at least 14 days after receiving FUCASO and closely monitored for signs or symptoms of these events including fever.

Monitoring and management of CRS associated with FUCASO.

Ensure that two doses per patient of tocilizumab are available for administration prior to FUCASO infusion. The certified healthcare facility must have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Patients should be instructed to remain within proximity of the certified healthcare facility for at least 4 weeks following FUCASO infusion and continue to monitor for symptoms and signs of CRS. If the patients develop signs or symptoms of CRS, they should be instructed to seek medical attention and treatment immediately.

If the patient develops fever, hypoxia, hypotension, and other adverse reactions that may be related to CRS, the cause should be promptly evaluated and treatment and/or supportive care should be given. In case of risk of infection, refer to Section 5.7. Serious Infections. HLH/MAS is a potentially life-threatening condition, and patients should be closely monitored for evidence of HLH/MAS. Treatment of HLH/MAS should be administered per institutional guidelines.

If CRS is suspected, manage according to the recommendations in **Table 2**. Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

If Immune effector cell-associated neurotoxic syndrome (ICANS) is suspected, manage according to the CRS and ICANS grading and intervention measures in **Table 2** and **Table 3**.

Table 2. CRS Grading and Management Guidance

CRS Grading ^{*,a}	Corticosteroids ^{d,e}	Anti-IL-6 Therapy ^h	Additional Supportive treatment
Grade 1 Fever ($\geq 38^{\circ}\text{C}$)	For early-onset CRS (<72 hours after infusion), consider IV dexamethasone ^f 10mg, every 24 hours	For prolonged CRS (>3 days) in patients or those with significant symptoms, comorbidities and/or are elderly, consider 1 dose of IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg)	• Sepsis screen and empiric broad-spectrum antibiotics, consider G-CSFⁱ if neutropenic • Maintenance IV fluid for hydration • Symptomatic management of organ toxicities
Grade 2 Fever ($\geq 38^{\circ}\text{C}$) with:	For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy,	IV tocilizumab 8mg/kg over 1 hour (not to exceed 800mg/dose).	• IV fluid bolus as needed

CRS Grading^{*,a}	Corticosteroids^{d,e}	Anti-IL-6 Therapy^h	Additional Supportive treatment
Hypotension not requiring vasopressors, and/or. Hypoxia requiring low-flow nasal cannula^b or blow-by, or, Grade 2 organ toxicity^c	consider IV dexamethasone^f 10 mg every 12–24 hours	Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total	- For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring. Telemetry, ECG, troponin, and BNP if persistent tachycardia - Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy - Symptomatic management of organ toxicities
Grade 3 Fever ($\geq 38^{\circ}\text{C}$) with: Hypotension requiring a vasopressor with or without vasopressin and/or, Hypoxia requiring high-flow cannula^b, face mask, non-rebreather mask, or Venturi mask, or, Grade 3 organ toxicity or Grade 4 transaminitis	IV dexamethasone^f 10mg every 6 hours. If refractory, manage as grade 4	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	- Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring - Oxygen supplementation - IV fluid bolus and vasopressors as needed - Symptomatic management of organ toxicities
Grade 4 Fever ($\geq 38^{\circ}\text{C}$) with: Hypotension requiring multiple vasopressors (excluding vasopressin) and/or, Hypoxia requiring positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway	IV dexamethasone^f 10mg every 6 hours If refractory, consider 3 doses of IV methylprednisolone 1 g/day If refractory, consider dosing every 12 hours Other lines of therapy	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	- ICU care and hemodynamic monitoring Mechanical ventilation as needed - IV fluid bolus and vasopressors as needed - Symptomatic management of organ toxicities

CRS Grading ^{*,a}	Corticosteroids ^{d,e}	Anti-IL-6 Therapy ^h	Additional Supportive treatment
pressure [BiPAP], intubation, mechanical ventilation), or, Grade 4 organ toxicity (excluding transaminitis)	may be considered ^g		

CRS= Cytokine Release Syndrome; G-CSF= Granulocyte Colony-Stimulating Factor; IL-6= Interleukin-6;

IV= Intravenous; ICU= Intensive Care Unit

*Grading according to the ASTCT standard (2019), modified to include organ toxicity and follow the NCCN guidelines (2022. v1) management recommendations. Please refer to the latest or local applicable guidelines.

- Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anti-cytokine therapy (e.g., tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause.
- Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.
- Organ toxicity grading based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.
- After each dose, assess need for subsequent dosing.
- For patients receiving corticosteroid therapy for CRS, antifungal prophylaxis is strongly recommended.
- Alternative steroids at an equivalent dose may be considered. For example, methylprednisolone intravenous 1,000 mg/day can be administered for 3 days, followed by a rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.
- Other agents such as anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG, antithymocyte globulin (ATG), or extracorporeal cytokine adsorption with continuous renal replacement therapy (CRRT) might considered. Reported experience with these agents is limited.
- If there is no improvement after treatment with corticosteroids and IL-6 level are high, tocilizumab treatment can be considered. After each dose, assess need for subsequent dosing.
- GM-CSF is not recommended in the setting of CAR-T cell therapy.

The incidence of Grade 3-4 CRS in the clinical experience of FUCASO is low. The treatment principles refer to the recommended contents of the guidelines, and the dosage of corticosteroid can be adjusted according to the clinical practice.

5.6. Neurotoxicity

Neurologic toxicities, such as somnolence and immune effector cell-associated neurotoxicity syndrome (ICANS), have occurred following treatment with FUCASO.

Neurological events can be concurrent with CRS, following resolution of CRS or in the absence of CRS. Monitor patients for signs and symptoms of neurologic toxicities (ICANS and other neurologic toxicities) for 14 days following treatment with FUCASO. Continue monitoring for signs and symptoms of neurological events in a nearby qualified healthcare facility for at least 4 weeks after FUCASO infusion.

In case of neurological events, patients should be diagnostically worked up and managed depending on the underlying pathophysiology and in accordance with local standard of care. Provide intensive care and supportive treatment for severe or life-threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any grade of neurologic toxicities. If ICANS is suspected, manage according to the recommendations in **Table 3**.

Table 3. ICANS Grading and Management Guidance

ICANS Grading ^{*,a}	No Concurrent CRS ^f	Additional Therapy if Concurrent CRS
Grade 1 ICE^b score 7-9 Or depressed level of consciousness^c: Awakens spontaneously	Supportive care	IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg/dose)
Grade 2 ICE score 3-6 Or depressed level of consciousness: Awakens to voice	Supportive care 1 dose of IV dexamethasone 10 mg and reassess. Can repeat every 6–12 hours if no improvement^g	Anti-IL-6 therapy as per Grade 1ⁱ Consider transferring patient to ICU if neurotoxicity associated with grade ≥ 2 CRS
Grade 3^d ICE score 0-2 Or depressed level of consciousness: Awakens only to tactile stimulus Or seizure: Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention Or elevated ICP/cerebral edema: Focal/local edema on neuroimaging^e	ICU care is recommended IV dexamethasone 10 mg every 6 hours or IV methylprednisolone, 1 mg/kg every 12 hours Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥ 3 neurotoxicity	Anti-IL-6 therapy as per Grade 1 ⁱ
Grade 4^d ICE score 0 (Patient is unconscious and unable to perform ICE) Or depressed level of consciousness: • Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse • Stupor or coma Or seizure: • Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between Or motor findings: • Deep focal motor weakness such as hemiparesis or paraparesis Or elevated ICP/cerebral edema:	ICU care, consider mechanical ventilation for airway protection High-dose steroids^h Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent grade ≥ 3 neurotoxicity Treat convulsive status epilepticus per institutional guidelines	Anti-IL-6 therapy as per Grade 1 ⁱ

ICANS Grading ^{*,a}	No Concurrent CRS ^f	Additional Therapy if Concurrent CRS
• Diffuse cerebral edema on neuroimaging; • Decerebrate or decorticate posturing; or • Cranial nerve VI palsy; or • Papilledema; or • Cushing's triad		

ICANS=Immune Effector Cell-Associated Neurotoxicity Syndrome; CRS= Cytokine Release Syndrome; ICE Immune Effector Cell Encephalopathy; IV= Intravenous; IL-6= Interleukin-6; ICU= Intensive Care Unit; CT Computed Tomography; MRI Magnetic Resonance Imaging; ECG=Electrocardiogram; ICP= Intracranial Pressure.

^{*}Grading is based on the ASTCT standard (2019). The ICANS grades are determined by the highest level of events listed in the evaluation indicators that cannot be explained by other reasons (ICE score, consciousness level, epilepsy, abnormal motor ability, increased Intracranial pressure/brain edema).

- Although not used for ICANS grading, other signs or symptoms that may occur and may be related to immune effect cell therapy, such as headache, tremor, myoclonus, inability to maintain fixed posture and hallucination still require attention and treatment.
- In the ICE score, if one of the following tasks can be completed correctly, a score of 1 point (out of a total of 10 points) will be given: 1) Ability to tell the current year, month, city, and hospital (a total of 4 points); 2) Ability to name 3 objects, for example, a clock, pen, and button (3 points in total); 3) Ability to follow simple commands, for example, extending 2 fingers or closing eyes and sticking out tongue (1 point in total); 4) Ability to write a standard sentence, for example, "The national language of Singapore is Malay" (1 point in total); 5) Count backwards from 100 by 10 (1 point in total).
- Other reasons (e.g. use of sedatives) for decrease in consciousness level should be ruled out.
- Patients should undergo assessment for papilledema or other signs of elevated intracranial pressure. If intracranial pressure is excluded, a diagnostic lumbar puncture may be considered for patients with Grade 3–4 neurotoxicity.
- Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to the CTCAE v5.0 standard.
- The use of dexamethasone to prevent CRS may increase the risk of Grade 4 ICANS and persistent neurotoxicity.
- For patients receiving corticosteroid treatment for CRS and/or neurotoxicity, preventive antifungal therapy is strongly recommended.
- For example, methylprednisolone IV may be used for 3 days at a dose of 1g/day (which can be considered twice a day), and then quickly decreased to 250mg q12 for 2 days, 125mg q12 for 2 days, and 60mg q12 for 2 days.
- Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.

5.7. Serious Infections

Serious infections, including fatal or life-threatening infections, have occurred following treatment with FUCASO (See Section 6. ADVERSE REACTIONS). FUCASO should not be administered to patients with clinically significant active infections.

Patients should be monitored for signs and symptoms of infections before and after infusion of FUCASO and treated appropriately. Prophylactic antimicrobials should be administered according to local guidelines. Note: Infections with a CTCAE v5.0 grading of ≥ 3 are defined as serious infections.

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.

5.8. Virus Reactivation

Hepatitis B virus (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 FUCASO for patients testing positive for HIV, active HBV, or active HCV. Prior to collection of the patient's cells for FUCASO manufacturing, patient should be screened for CMV, HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) or any other infectious agents if clinically indicated in accordance with clinical guidelines.

Patients with previous HBV infection and positive hepatitis B core antibody (HBcAb) should be monitored. Consider antiviral therapy to prevent viral reactivation per local institutional guidelines/ clinical practice.

5.9. Prolonged Cytopenias

Patient may exhibit prolonged cytopenias for several weeks following lymphodepletion pretreatment and FUCASO infusion (see Section 6. ADVERSE REACTIONS). Monitor blood counts, before and after FUCASO infusion. Prolonged neutropenia has been associated with increased risk of infection. Manage cytopenia with hematopoietic therapy and/or blood transfusion according to local institutional guidelines. Myeloid growth factors, particularly GM-CSF, have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after FUCASO or until CRS has resolved.

5.10. Hypogammaglobulinemia

Hypogammaglobulinemia may occur in patients receiving treatment with FUCASO (see Section 6. ADVERSE REACTIONS). After FUCASO infusion, monitor the level of immunoglobulin to prevent possible infection, and if necessary, manage per local institutional guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

5.11. Attenuated Live Vaccines

The safety of immunization with live viral vaccines during or following FUCASO 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 FUCASO treatment, and until immune recovery following treatment with FUCASO.

5.12. Hypersensitivity Reactions

Hypersensitivity reactions have occurred after FUCASO infusions. Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) in FUCASO. All patients should receive prophylactic antihistamines before FUCASO infusion (see Section 3.2. Administration). If allergic reactions occur, FUCASO infusion should be stopped immediately and patients should be managed appropriately according to the severity of the hypersensitivity reaction.

5.13. Secondary Malignancies

No secondary tumors have been found in patients receiving treatment with FUCASO. Patients treated with FUCASO may develop secondary malignancies. T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies. Mature T cell

malignancies, including CAR positive tumors, may present as soon as weeks following infusion, and may include fatal outcomes.

Patients must be monitored life-long for secondary malignancies. In the event that a secondary malignancy of T-cell origin occurs, contact Nanjing IASO Medical Technology Co., Ltd. at email PV@iasobio.com to obtain instructions on patient samples to collect for testing.

5.14. Tumor Lysis Syndrome (TLS)

TLS, which may be severe, has occasionally been observed in clinical trials after FUCASO administration. To minimise risk of TLS, patients with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis, prior to FUCASO infusion. Signs and symptoms of TLS should be monitored, and events managed according to standard guidelines.

5.15. Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving FUCASO are at risk for altered or decreased consciousness or coordination in the 8 weeks following FUCASO 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.

6. ADVERSE REACTIONS

This section describes the adverse reactions observed in clinical studies and their approximate incidence rates that are suspected to be related to FUCASO. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1. Safety Data Summary

The safety summary of FUCASO is based on the data the exposure of 109 subjects included in the phase I/II relapsed/refractory multiple myeloma clinical trial (FUMANBA-1), including 17 subjects in phase I trial and 92 subjects in phase II trial. The median follow-up time for safety data was 39.66 months.

In the clinical trial, the incidence of all levels of adverse drug reactions of the subjects after receiving the treatment of FUCASO was 99.1%. The incidence of grade 3 and above adverse drug reactions was 94.5%.

6.2. Clinical Trial Experience

A total of 109 Chinese patients with relapsed/refractory multiple myeloma, aged 18 to 70 years, who had undergone ≥ 3 lines treatment (including chemotherapy based on proteasome inhibitors and immunomodulators) received FUCASO infusion in FUMANBA-1 study.

The incidence classification of adverse reactions recommended by the Council for International Organizations of Medical Sciences (CIOMS) are as follows: very common ($\geq 10\%$), common ($1\% \sim 10\%$, including 1%), occasional ($0.1\% \sim 1\%$, including 0.1%), rare ($0.01\% \sim 0.1\%$, including 0.01%), very rare ($<0.01\%$). Based on this classification, the adverse reactions occurring with FUCASO in FUMANBA-1 study have been summarized and provided below:

Very common adverse drug reaction (incidence $\geq 10\%$) includes: pyrexia, cytokine release syndrome, neutrophil count decreased, white blood cell count decreased, platelet count decreased, lymphocyte count decreased, anaemia, hypogammaglobulinaemia, blood lactate dehydrogenase increased, aspartate aminotransferase increased, hypoglobulinaemia, hypokalaemia, pneumonia, alanine aminotransferase increased, hypoalbuminaemia, hypocalcaemia, gamma-glutamyltransferase increased, blood fibrinogen decreased, vomiting, diarrhoea, blood alkaline phosphatase increased, fibrin D dimer increased, cough, upper respiratory tract infection, hyponatraemia, hypoxia, alpha hydroxybutyrate dehydrogenase increased, N-terminal prohormone brain natriuretic peptide increased, hypotension, sinus tachycardia, procalcitonin increased, herpes zoster, nausea, lymphocyte count increased, blood creatinine increased, asthenia, serum ferritin increased, blood bilirubin increased, hepatitis B reactivation and hyperuricaemia.

Common adverse drug reaction (incidence of $1\% \sim 10\%$) include: activated partial thromboplastin time prolonged, C-reactive protein increased, globulins decreased, interleukin level increased and cytomegalovirus infection, weight decreased, prothrombin time prolonged and thrombin time prolonged, monocyte count decreased, blood urea increased and blood phosphorus decreased, activated partial thromboplastin time shortened, brain natriuretic peptide increased, blood pressure increased, oedema peripheral, nasopharyngitis and cardiac failure, face oedema, infection, sepsis, blood creatine phosphokinase MB increased, urinary tract infection, decreased appetite, hypochlorhaemia, tumour lysis syndrome, constipation, mouth ulceration, productive cough, hypertension, headache, blood bicarbonate decreased, Epstein-Barr virus infection, fibrinogen degradation products increased, interferon gamma level increased, insomnia, international normalised ratio increased, troponin I increased, troponin T increased, chest discomfort, hepatobiliary disorders, psychiatric disorders, febrile neutropenia, hypomagnesaemia, abdominal distension, stomatitis, tachypnoea, bilirubin conjugated increased, blood lactic acid increased, blood phosphorus increased, heart rate increased, immunoglobulins decreased, white blood cell count increased, chills, coagulopathy, hyperglycaemia, hyperkalaemia, dizziness, proteinuria, bile acids increased, alpha tumour necrosis factor increased, otitis media, blood glucose increased, blood creatine phosphokinase increased, blood uric acid increased, febrile infection, electrocardiogram QT prolonged, electrocardiogram ST-T change, pancreatitis acute, red blood cell sedimentation rate increased, influenza like illness, hyperglobulinaemia, bronchitis, gastrointestinal infection, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridemia, abdominal discomfort, tongue ulceration, toothache, hypoesthesia, pleural effusion,

ventricular extrasystoles, renal impairment, cholecystitis acute, immune effector cell-associated neurotoxicity syndrome, hepatic function abnormal.

In FUMANBA-1 study, 82 patients (75.2%) were treated with systemic corticosteroids and 30 patients (27.5%) were treated with tocilizumab after receiving FUCASO infusion.

The adverse reactions with an incidence rate of $\geq 10\%$ are summarized in **Table 4** below.

Table 4. Summary of Adverse Reactions with Incidence of $\geq 10\%$ among subjects receiving FUCASO Infusion in FUMANBA-1 study

MedDRA system organ class	Number of subjects (N=109) n (%)			
Summary of Adverse Reactions by Preferred Term	All grades	Grade 3	Grade 4	Grade 5
Investigations				
Neutrophil count decreased	97(89.0%)	15(13.8%)	74(67.9%)	0
White blood cell count decreased	97(89.0%)	22(20.2%)	59(54.1%)	0
Platelet count decreased	87(79.8%)	20(18.3%)	47(43.1%)	0
Lymphocyte count decreased	82(75.2%)	25(22.9%)	39(35.8%)	0
Blood lactate dehydrogenase increased	59(54.1%)	3(2.8%)	0	0
Aspartate aminotransferase increased	49(45.0%)	14(12.8%)	2(1.8%)	0
Alanine aminotransferase increased	36(33.0%)	3(2.8%)	0	0
Blood fibrinogen decreased	31(28.4%)	4(3.7%)	0	0
Gamma-glutamyltransferase increased	31(28.4%)	14(12.8%)	2(1.8%)	0
Blood alkaline phosphatase increased	27(24.8%)	3(2.8%)	0	0
Fibrin D dimer increased	22(20.2%)	0	0	0
Alpha hydroxybutyrate dehydrogenase increased	17(15.6%)	3(2.8%)	0	0
N-terminal prohormone brain natriuretic peptide increased	16(14.7%)	1(0.9%)	0	0
Procalcitonin increased	13(11.9%)	0	0	0
Blood creatinine increased	12(11.0%)	2(1.8%)	0	0
Immune system disorders				
Cytokine release syndrome	102(93.6%)	0	1(0.9%)	0
Hypogammaglobulinaemia	69(63.3%)	6(5.5%)	0	0
General disorders and administration site conditions				
Pyrexia	103(94.5%)	23(21.1%)	1(0.9%)	0
Asthenia	12(11.0%)	0	0	0
Blood and lymphatic system disorders				
Anaemia	74(67.9%)	57(52.3%)	0	0
Hypoglobulinaemia	46(42.2%)	0	0	0
Infections and infestations				

MedDRA system organ class	Number of subjects (N=109) n (%)			
Summary of Adverse Reactions by Preferred Term	All grades	Grade 3	Grade 4	Grade 5
Pneumonia	44(40.4%)	32(29.4%)	1(0.9%)	5(4.6%)
Upper respiratory tract infection	19(17.4%)	5(4.6%)	0	0
Herpes zoster	13(11.9%)	3(2.8%)	0	0
Hepatitis B reactivation	11(10.1%)	0	0	0
Metabolism and nutrition disorders				
Hypokalaemia	46(42.2%)	13(11.9%)	2(1.8%)	0
Hypoalbuminaemia	36(33.0%)	0	0	0
Hypocalcaemia	32(29.4%)	1(0.9%)	0	0
Hyponatraemia	18(16.5%)	1(0.9%)	1(0.9%)	0
Hyperuricaemia	11(10.1%)	0	0	0
Gastrointestinal disorders				
Vomiting	30(27.5%)	0	0	0
Diarrhoea	28(25.7%)	4(3.7%)	0	0
Nausea	13(11.9%)	0	0	0
Respiratory, thoracic and mediastinal disorders				
Cough	21(19.3%)	0	0	0
Hypoxia	18(16.5%)	2(1.8%)	1(0.9%)	0
Vascular disorders				
Hypotension	16(14.7%)	2(1.8%)	0	0
Cardiac disorders				
Sinus tachycardia	15(13.8%)	0	0	0

Note: Data source: FUMANBA-1 study. Data cut-off date: May 13, 2025.

Cytokine release syndrome was graded according to ASTCT 2019, and other adverse reactions were graded according to NCI CTCAE 5.0.

6.3. Adverse Reactions/Events of Special Interest

Cytokine Release Syndrome (CRS)

In FUMANBA-1 study, 102/109 (93.6%) subjects who received FUCASO infusion developed CRS, with only one subject (0.9%) being grade 3 or higher. The median time for the first occurrence of CRS is 6.0 days after infusion (range: 1-13 days), and the median time for the duration of CRS is 5.0 days (range: 2-30 days). The main CRS related adverse events (incidence $\geq 10\%$) included pyrexia (102/109, 93.6%), blood lactate dehydrogenase increased (18/109, 16.5%), hypoxia (16/109, 14.7%), hypotension (14/109, 12.8%), aspartate aminotransferase increased (13/109, 11.9%), vomiting (12/109, 11%).

Among the 102 subjects who developed CRS, 69/102 patients (67.6%) were treated with corticosteroid, and 30/102 patients (29.4%) were treated with tocilizumab.

The monitoring and management of CRS can be found in Section 5.5. Cytokine release syndrome (CRS).

Neurotoxicity

In FUMANBA-1 study, 16/109 (14.7%) subjects who received FUCASO infusion had adverse reactions of nervous system and psychosis related to FUCASO, including headache (5/109, 4.6%), insomnia (4/109, 3.7%), dizziness (3/109, 2.8%), hypoaesthesia (2/109, 1.8%), haemorrhage intracranial, somnolence and post herpetic neuralgia (1/109, 0.9%), and 2/109 subjects (1.8%) had immune effector cell-associated neurotoxic syndrome (ICANS). Among them, 1/109 subject (0.9%) developed grade 2 ICANS 10 days after cell infusion, while the main symptoms were lethargy and wakefulness after breathing and the lasting duration was 1 day. Another 1/109 (0.9%) subject developed grade 1 ICANS 3 days after cell infusion, mainly manifested as mild drowsiness, lasting for 2 days. The ICANS outcomes of the two subjects mentioned above were all resolved. Note: ICANS was graded according to the ASTCT standard (2019).

Monitoring and management of neurotoxicity can be found in Warnings and Precautions Section 5.6. Neurotoxicity.

Hematology toxicity

Hematology toxicity includes persistent cytopenia and coagulation disorders. In the FUMANBA-1 study, 109 subjects (100%) experienced grade 3 or higher blood cell count decreased after cell infusion. By day 28 post-infusion, 70.6% (77/109) of the subjects still exhibited grade 3 or higher blood cell count decreased, including (ranged from high to low): platelet count decreased (47/109, 43.1%), neutrophil count decreased (44/109, 40.4%), haemoglobin decreased (42/109, 38.5%), white blood cell count decreased (25/109, 22.9%), and lymphocyte count decreased (24/109, 22.0%). The median time from the first occurrence of grade ≥ 3 blood cell count decreased to recovery was as follows: 7 days for haemoglobin decreased, 10 days for lymphocyte count decreased, 11 days for neutrophil count decreased, and 18 days for platelet count decreased. Coagulation disorders of grade 3 or above included blood fibrinogen decreased (5/109, 4.6%) and activated partial thromboplastin time prolonged (2/109, 1.8%).

See Warnings and Precautions Section 5.9. Prolonged Cytopenias for the monitoring and management of hematology toxicity.

Severe infections

In FUMANBA-1 study, 73/109 (67.0%) subjects developed cell infusion related infections and infectious diseases. Among them, 51/109 subjects (46.8%) were grade 3 or above, including: pneumonia (38/109, 34.9%), upper respiratory tract infection (5/109, 4.6%), infection (5/109, 4.6%), sepsis (4/109, 3.7%), herpes zoster (3/109, 2.8%), febrile infection (2/109, 1.8%), gastrointestinal infection, bacterial infection, gastroenteritis, infective exacerbation of bronchiectasis, neutropenic infection, otitis media acute, pneumonia fungal, pneumonia viral, septic shock, and sinusitis (all 1/109, 0.9%).

Note: According to the NCI CTCAE v5.0 Criteria, severe infections are defined as infections with grade ≥ 3 .

Some infections may be life-threatening or lead to death. The monitoring and management of severe infections can be found in Warnings and Precautions Section 5.7. Serious Infections.

Immunogenicity

FUCASO has the potential to induce the production of anti-drug antibodies. In FUMANBA-1 study, the immunogenicity of FUCASO was measured by determination of anti-CAR antibody in serum pre- and post-administration. 1/107 (0.9%) of patients tested positive for pre-infusion anti-CAR antibodies and post-infusion anti-CAR antibodies were detected in 27/107 (25.2%) of the patients. There is no evidence that the presence of pre-existing or post-infusion anti-CAR antibodies impact the cellular expansion, safety or effectiveness of FUCASO.

Tumor lysis syndrome (TLS)

In FUMANBA-1 study, 5/109 subjects (4.6%) developed tumor lysis syndrome, with 2/109 (1.8%) grade 4, 2/109 (1.8%) grade 3, and 1/109 (0.9%) grade 2. All of them recovered. The monitoring and management of tumor lysis syndrome can be found in the Warnings and Precautions Section 5.14. Tumor Lysis Syndrome (TLS).

Hypogammaglobulinemia

In FUMANBA-1 study, 98/109 (89.9%) subjects developed hypogammaglobulinemia (including diagnosis of hypogammaglobulinemia and laboratory IgG<500mg/dl). 96/109 subjects (88.1%) received immunoglobulin therapy during the study. The monitoring and management of hypogammaglobulinemia can be found in the Warnings and Precautions Section 5.10. Hypogammaglobulinemia.

Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS)

In FUMANBA-1 study, no subjects developed grade ≥ 3 HLH/MAS.

7. DRUG INTERACTIONS

The co-administration of agents known to inhibit T-cell function has not been formally studied. The co-administration of agents known to stimulate T-cell function has not been investigated and the effects are unknown.

HIV and the lentivirus used to make FUCASO 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 FUCASO.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

There are no available data on the use of FUCASO in pregnant women. No reproductive and developmental toxicity studies in animals have been conducted with FUCASO to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known whether FUCASO has the potential to be transferred to the fetus and causes fetal toxicity. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia and hypogammaglobulinemia.

Therefore, FUCASO is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised that there may be risks to the fetus. Pregnancy after FUCASO therapy should be discussed with the treating physician.

8.2. Lactation

There is no information regarding the presence of FUCASO 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 FUCASO and any potential adverse effects on the breastfed infant from FUCASO or from the underlying maternal condition.

8.3. Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually active females of reproductive potential should have a pregnancy test prior to starting treatment with FUCASO.

Contraception

See the package insert for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with FUCASO.

Infertility

There are no data on the effect of FUCASO on fertility.

8.4. Pediatric Use

Safety and effectiveness of FUCASO have not been established for children or adolescents under the age of 18.

8.5. Geriatric Use

In FUMANBA-1 clinical trial, all participants were 70 years old or below. There is limited experience with the use of FUCASO in elderly patients above 70 years old.

9. CLINICAL PHARMACOLOGY

9.1. Mechanism of action

FUCASO is a CAR positive T cell therapy targeting BCMA, which is expressed on the surface of normal and malignant plasma cells. The CAR construct includes an anti-BCMA scFv-targeting domain for antigen specificity, a transmembrane domain, a CD-3 zeta (CD3ζ) activation domain, and a 4-1BB costimulatory domain. Antigen-specific activation of FUCASO leads to CAR-positive T cell proliferation, cytokine release and targeted elimination of BCMA expressing cells.

9.2. Pharmacodynamics

Rapid decreases in serum levels of serum soluble BCMA (sBCMA) were observed within the first month following FUCASO infusion.

The levels of inflammatory biomarkers [IL-6, Ferritin and C-reactive protein (CRP)] increased after FUCASO infusion and peaked within 7-10 days. The peak levels were 2-15 times higher than baseline. The serum levels of all inflammatory biomarkers generally returned to baseline levels within 1–2 months post-infusion.

9.3. Pharmacokinetics

The pharmacokinetics (PK) of FUCASO was assessed in 109 adult patients with relapsed or refractory multiple myeloma in FUMANBA-1 receiving a single infusion at the target dose of 1×10^6 CAR-positive viable T cells/kg (range 70-130% except one subject who received relative dose of 65%).

Following a single infusion, FUCASO exhibited initial expansion phase followed by gradual decline. The median time of maximal expansion in peripheral blood ($T_{\max}$) occurred approximately 10 days (10-59 days) after infusion. CAR-T cells persisted in peripheral blood for more than a year in 55.4% (41/74) of subjects. A summary of $C_{\max}$, $T_{\max}$ and $AUC_{0-28\text{days}}$ of the transgene levels from FUMANBA-1 study is provided in **Table 5**.

Table 5. Pharmacokinetic Parameters of FUCASO in Patients with Relapsed/Refractory Multiple Myeloma

Pharmacokinetic Parameter	Summary Statistics	FUMANBA-1 Phase 1 (N = 17)	FUMANBA-1 Phase 2 (N = 92)	FUMANBA-1 Total (N = 109)
$C_{\max}$ (copies/ μg DNA)	Mean (SD)	87843.469 (54593.6780)	86228.971 (49133.9742)	86480.733 (49759.8242)
$T_{\max}$ (day)	Median (range)	11.9 (10, 21)	11.7 (0, 23)	11.8 (0, 23)
$AUC_{0-28\text{d}}$ (copies*day/ μg DNA)	Mean (SD)	924132.408 (931839.4542)	1025850.927 (735183.6950)	1009537.579 (765969.3263)

$AUC_{0-28\text{d}}$ = area under the curve of the transgene level from time of dose to 28 days post-infusion; $C_{\max}$ = the maximum transgene level; N = number of subjects; SD = standard deviation; $T_{\max}$ = time of maximum observed transgene level.

The pharmacokinetic parameters ($C_{\max}$ and AUC) of VCN in the peripheral blood of subjects are related to their efficacy. The median $C_{\max}$ and $AUC_{0-28\text{d}}$ of CAR-T cells in subjects who achieved response ($\geq$ PR) 3 months after infusion of this product were approximately 2-3 times higher than those in subjects who did not achieve response. The median $C_{\max}$ values were 94921.700 copies/ μg DNA (n=93) and 43344.800 copies/ μg DNA (n=16) respectively, and median $AUC_{0-28\text{d}}$ were 879819.180 day*copies/ μg DNA (n=93) and 386542.950 day*copies/ μg DNA (n=13) respectively.

The results from subjects who received corticosteroids and tocilizumab to treat CRS and neurotoxicity showed that CAR-T cells could still expand and persist after treatment with corticosteroids and tocilizumab. The median $C_{\max}$ and $AUC_{0-28\text{d}}$ of CAR-T cells in subjects treated with corticosteroids (n=82) were higher than those in subjects not receiving corticosteroids (n=27), with 2.18 times higher (100110.900 copies/ μg DNA vs 45845.600 copies/ μg DNA) for $C_{\max}$ and 2.11 times (927992.715 day*copies/ μg DNA vs 440705.920 day*copies/ μg DNA) for $AUC_{0-28\text{d}}$ respectively. The median $C_{\max}$ and $AUC_{0-28\text{d}}$ of CAR-T cells in the subjects treated with tocilizumab (n=30) were higher than those in subjects not receiving tocilizumab (n=79), with 1.67 times higher (122090.350 copies/ μg DNA vs

73014.090 copies/ μ g DNA) for $C_{\max}$ and 2.31 times (1432868.540 day*copies/ μ g DNA vs 619940.100 day*copies/ μ g DNA) for AUC_{0-28d} , respectively.

The baseline tumor burden and bridging therapy did not significantly affect the pharmacokinetics ($C_{\max}$ and AUC) of FUCASO.

Specific Populations

Age (39-70 years old), gender, mild liver dysfunction, and moderate kidney dysfunction had no significant impact on the pharmacokinetics ($C_{\max}$ and AUC) of this product. Formal renal and hepatic impairment studies of FUCASO were not conducted.

In FUMANBA-1 clinical trial, all participants were 70 years old or below. There is limited experience with the use of FUCASO in elderly patients above 70 years old.

There is no pharmacokinetic study data available for this product in the pediatric population.

10. NONCLINICAL TOXICOLOGY

The analysis of viral gene insertion site (VIS) was performed on FUCASO CAR-T cells manufactured from 3 healthy donors and 41 patients with multiple myeloma. The VIS showed good diversity, and no clone enrichment was observed. Low clone level CAR insertion was detected near related oncogenic genes.

Genotoxicity and reproductive and developmental toxicity studies have not been performed with FUCASO.

No studies have been conducted to evaluate the effects of FUCASO on fertility.

11. CLINICAL STUDIES

FUMANBA-1

FUMANBA-1 (NCT05066646) was a multicenter, open label, single arm Phase I/ II clinical study.

Phase II of the study evaluated the efficacy and safety of FUCASO at 1.0×10^6 CAR-T/kg dose level in Chinese patients who were between 18-70 years old, had received ≥ 3 lines of treatment (including chemotherapy based on proteasome inhibitor and immunomodulatory agent) and had disease progression during or within 12 months after the last line of treatment.

These patients had positive BCMA expression on the surface of bone marrow plasma cells and had measurable lesions present during screening. In addition, patients were required to have an ECOG score of 0 or 1, and a neutrophil count of $\geq 1.0 \times 10^9/L$, lymphocyte count $\geq 0.3 \times 10^9/L$, platelet $\geq 50 \times 10^9/L$, hemoglobin $\geq 60g/L$, alanine aminotransferase and aspartate transaminase $\leq 2.5 \times ULN$ and serum total bilirubin $\leq 1.5 \times ULN$, fibrinogen $\geq 1.0g/L$, activated partial thromboplastin time $\leq 1.5 \times ULN$, prothrombin time (PT) $\leq 1.5 \times ULN$, blood oxygen saturation $>91\%$, left ventricular ejection fraction $\geq 50\%$. The study excluded patients with graft-versus-host disease (GVHD) or those who need long-term use

of immunosuppressive drugs, patients who had previously received two autologous hematopoietic stem cell transplants (ASCTs) within 12 weeks prior to single blood collection, patients who had previously received allogeneic hematopoietic stem cell transplants, patients suspected or had symptoms of central nervous system invasion of plasma cell tumor, or patients with plasma cell leukemia.

Of the 101 subjects enrolled in Phase II, 100 subjects underwent leukapheresis, 94 subjects received lymphodepletion, and 92 received FUCASO infusion. Eight subjects did not receive FUCASO infusion due to withdrawal of informed consent (n=3), investigator's decision (n=4), or other (cell manufacture failure, n=1). As of data cut-off date 13 May 2025, all 92 infused subjects completed the 2-year follow-up or withdrew from the study early. The efficacy evaluable population in phase II consists of the 92 patients who received FUCASO infusion. As the data cut-off date, the median follow-up time in the Phase II trial was 36.32 months.

Of the 92 efficacy-evaluable patients, the median age was 58 years (range: 39 to 70 years), and 48.9% were male. 69 patients (75.0%) were graded as Stage II or III based on the revised International Staging System (R-ISS). High-risk cytogenetics [presence of t(4;14), t(14;16), or del(17p)] were present in 35.9% of patients. Nine patients had extramedullary disease.

The median number of prior lines of therapy was 4 (range: 3 to 14), with 33.7% of patients receiving >5 lines of therapy, 31.5% of patients had received prior autologous stem cell transplantation (ASCT) and 6.5% of patients received prior CAR-T therapy. All patients were exposed to proteasome inhibitor (PI) and immunomodulatory agents (IMiDs), 26.1% were exposed to a PI, an IMiD, and anti-CD38 antibody.

Some subjects (52.2%) received bridging therapy for control of their multiple myeloma during the manufacturing process. Bridging therapy was limited to short-term treatments that patients had previously received. The use of CD38 monoclonal antibodies as bridging therapy was not allowed. The median time from leukapheresis to FUCASO infusion was 36 days (range: 26 to 77 days). (See **Table 6**).

Lymphodepletion was completed 2-7 days before infusion with subjects receiving fludarabine (25~30mg/m²/day) and cyclophosphamide (500mg/m²/day) for 3 consecutive days. The median time from lymphodepletion to FUCASO infusion and the median of doses are shown in **Table 6**.

Table 6. Subject Treatment

Parameters	Phase II (N=92)
Bridging therapy, n (%)	48 (52.2%)
Median days from apheresis to lymphodepletion, days (range)	32 (22,73)
Median days from apheresis to FUCASO infusion, days (range)	36 (26,77)
Median days from lymphodepletion to FUCASO infusion, days (range)	5.0 (5,11)
Median dose of FUCASO infusion (range) (10 ⁶ CAR-T/kg)	0.916 (0.73,1.19)
Median duration of FUCASO administration (minutes)	11 (3,25)

CAR=Chimeric Antigen Receptor

Efficacy was established based on overall response rate (ORR) and duration of response as assessed by the Independent Review Committee (IRC) using International Myeloma Working Group (IMWG) criteria (2016). The ORR of 92 subjects at 3 months was 88.0%. Among them, 75.0% of subjects achieved very good partial response or above ($\geq$ VGPR), and 42.4% achieved stringent complete response or complete response (sCR/CR). The best ORR across all visits was 91.3%, with a $\geq$ VGPR rate of 89.1% and an sCR/CR rate of 81.5%.

Table 7. Overall response rates and complete response rates at 3-Month, and among all visits

Parameters	IRC evaluation (N=92)
At 3-Month	
ORR, n (%)	81 (88.0%)
ORR 95% CI (%)	(79.6,93.9)
$\geq$ VGPR, n (%)	69 (75.0%)
$\geq$ VGPR 95% CI (%)	(64.9,83.4)
sCR/CR, n (%)	39 (42.4%)
sCR/CR 95% CI (%)	(32.1,53.1)
Overall response rate	
ORR, n (%)	84 (91.3%)
ORR 95% CI (%)	(83.6,96.2)
$\geq$ VGPR, n (%)	82 (89.1%)
$\geq$ VGPR 95% CI (%)	(80.9,94.7)
sCR/CR, n (%)	75 (81.5%)
sCR/CR 95% CI (%)	(72.1,88.9)

IRC=Independent Review Committee; ORR=Overall Response Rate; VGPR=Very Good Partial Response; sCR=stringent Complete Response; CR=Complete Response; CI=Confidence Interval; n (%)=number and percentage.

Based on the IRC's evaluation, the median time to response (TTR) of 92 subjects was 30.0 days (range: 24 - 272), while the median duration of response (DOR) was 36.01 months.

Among the 90 MRD-evaluable subjects, 95.6% (86/90) achieved negative minimal residual disease (MRD) at least once in all visits after infusion, and the median duration of negative MRD was 36.53 months. Of the 75 subjects who achieved sCR/CR by IRC evaluation, 100% achieved negative MRD.

Table 8. Time to Response and Duration of Response based on IRC assessment

Parameters	Phase II (N=92)
Time to response (TTR) (days)	
Median (Min, Max)	30.0 (24, 272)
Duration of response (DOR) (months)	
Median (95% CI)	36.01 (23.03,46.49)

CI=confidence interval; N=number of subjects in the specified group, or the total sample

Table 9. Minimal Residual Disease (MRD)^a

Parameters	Phase II (N=92)
All subjects	n=90
MRD negativity rate in all subjects - n (%), 95% CI	86 (95.6%), (89.0,98.8)
sCR/CR subjects^b	n=75
MRD negativity rate in sCR/CR subjects - n (%), 95% CI	75 (100%), (95.2, 100)
Median duration of MRD negativity (months)	
Median value (95% CI)	36.53 (23.23, NC)

MRD=Minimal Residual Disease; sCR=stringent Complete Response; CR=Complete Response; CI=Confidence Interval; NC=not calculable; n (%)=number and percentage

^aMRD was detected using Euroflow second-generation flow cytometry with a sensitivity of 10⁻⁵.

^b75 subjects who achieved sCR/CR in IRC evaluation and had MRD test results by May 13, 2025.

12. PACK SIZE

FUCASO is supplied in a 50ml single-use CryoMACS® Freezing Bag made of EVA (ethylene vinyl acetate) and consisting of an inner freezing bag and outer overwrap bag.

13. SHELF LIFE AND IN-USE STABILITY INFORMATION

6 month.

Store and transport at < -130°C in vapor phase liquid nitrogen.

Store FUCASO in the original packaging containing the cassette protecting the infusion bag.

Thaw FUCASO prior to infusion. Infusion should begin within 20 minutes after thawing. Keep thawed FUCASO at room temperature (20°C – 25°C). The time from completion of thawing to the end of infusion should not exceed 40 minutes.

Instructions for use and handling

See Section 3.2. Administration.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements. Refer to local biosafety guidelines applicable for handling and disposal of products containing genetically-modified organisms.

FUCASO products should be transported within the facility in closed, break-proof, leak-proof containers.

Solid and liquid waste: All material having been in contact with FUCASO should be handled and disposed of as potentially infectious waste in accordance with local hospital procedures.

14. INCOMPATIBILITIES

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

15. LIST OF INGREDIENTS

- a) Multiple Electrolytes Injection (Contains Sodium chloride, Sodium gluconate, Sodium Acetate, Potassium Chloride, Magnesium Chloride, Sodium Hydroxide and hydrochloric acid if needed)
- b) Human Serum Albumin Injection (Contains Human Serum Albumin, Sodium Caprylate, sodium cetyltryptophanate and Sodium chloride)
- c) Glucose Injection (Contains Glucose, and Hydrochloric Acid if needed)
- d) Compound Amino Acid Injection (Contains Aspartic Acid, Alanine, Arginine, Cystine, Glutamic Acid, Glycine, Histidine, Isoleucine, Leucine, Lysine Acetate, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine, Sodium Metabisulfite, Glacial Acetic Acid and Water for injection)
- e) Vitamin C Injection (Contains Vitamin C, Sodium Bicarbonate, Cysteine Hydrochloride, Sodium Metabisulfite, Disodium Edetate and Water for injection)
- f) Dimethyl Sulfoxide (DMSO)

16. PRODUCT OWNER

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17. MANUFACTURER

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Version Date: 14-Sep-2026