Medicines & Healthcare products Regulatory Agency

Public Assessment Report

National Procedure

Eqjubi 600 mg concentrate for solution for infusion

sugemalimab

PLGB 54280/0003

SFL PHARMACEUTICALS DEUTSCHLAND GMBH

LAY SUMMARY
Eqjubi 600 mg concentrate for solution for infusion
sugemalimab

This is a summary of the Public Assessment Report (PAR) for Eqjubi 600 mg concentrate for solution for infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Eqjubi in this lay summary for ease of reading.

For practical information about using Eqjubi, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Eqjubi and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Eqjubi is used to treat adults with a kind of lung cancer called 'non-small cell lung cancer'. Eqjubi is used in combination with other anti-cancer medicines. It is important that the patient reads the package leaflets for the other anticancer medicines they may be receiving.

How does Eqjubi work?
Eqjubi contains the active substance sugemalimab which is a monoclonal antibody. A monoclonal antibody is a type of protein designed to recognise and attach to a specific target in the body. Eqjubi works by attaching to the target called programmed death-ligand 1 (PD-L1). This protein suppresses the body`s immune (defence) system, thereby protecting cancer cells from being attacked by the immune cells. By attaching to the protein, Eqjubi helps the immune system to fight the cancer.

How is Eqjubi used?
The pharmaceutical form of this medicine is a concentrate for solution for infusion and the route of administration is intravenous infusion (drip directly into a vein).

The recommended dose of Eqjubi is 1200 mg for individuals weighing less than115 kg, and 1500 mg for individuals weighing more than 115 kg.

Eqjubi will be given to the patient in a hospital or clinic under the supervision of an experienced doctor. The patient's doctor will give them Eqjubi through an infusion (drip) into a vein over 60 minutes every 3 weeks.

When Eqjubi is given in combination with chemotherapy for the patients' lung cancer, it will be given first followed by chemotherapy.

For further information on how Eqjubi is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Eqjubi have been shown in studies?
The benefits of Eqjubi for treatment of adults with metastatic non-small-cell lung cancer (NSCLC) is supported by clinical studies following single and multiple IV infusions. These include Phase 3 studies in participants with NSCLC (Study CS1001-301 and the pivotal Study CS1001-302).

The main study showed that Eqjubi (in combination with platinum-based chemotherapy) was more effective than placebo (a dummy treatment) in patients with Stage IV metastatic lung cancer. The main measure of effectiveness in this study was survival without worsening (progression) of the cancer.

Patients who had Eqjubi treatment lived on average for 9.0 months without the disease getting worse, compared with 4.9 months for patients who did not receive Eqjubi.

What are the possible side effects of Eqjubi?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The following side effects have been reported in clinical studies of patients treated with sugemalimab:

Very common (may affect more than 1 in 10 people):
- decreased number of red blood cells that carry oxygen around the body
- increased levels of liver enzymes known as AST, ALT in the blood
- increased levels of sugar, triglycerides, cholesterol in the blood
- decreased calcium, potassium, and sodium in the blood
- decreased levels of thyroid hormone in the blood
- increased levels of protein in the urine
- numbness, tingling or decreased touch sensation in a part of the body

Why was Eqjubi approved?
It was concluded that Eqjubi has been shown to be effective in the treatment of metastatic non-small-cell lung cancer. Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

What measures are being taken to ensure the safe and effective use of Eqjubi?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Eqjubi The RMP details the important risks of Eqjubi, how these risks can be minimised, any uncertainties about Eqjubi (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Eqjubi:

Important identified risks	Immune-related adverse reactions
Important potential risks	Reproductive and developmental toxicity
Missing information	Use in patients ≥ 75 years old

The MAH commits to the following additional risk management measures:

- Patient alert card

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Eqjubi are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Eqjubi
A marketing authorisation application for Eqjubi was received 01 November 2022 and a marketing authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 30 October 2024.

The full PAR for Eqjubi follows this summary.

This summary was last updated in January 2025.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Eqjubi 600 mg concentrate for solution for infusion (PLGB 54280/0003) could be approved.

The product is approved for the following indication:
Eqjubi in combination with platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small-cell lung cancer (NSCLC) with no known sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumour aberrations.

The active substance, sugemalimab, is a fully human immunoglobulin G4 monoclonal antibody, which binds to human programmed cell death ligand 1 (PD-L1) and blocks its interaction with PD-1 and CD80 (B7-1). By binding to PD-1 and CD80 on T cells and antigen presenting cells, PD-L1 suppresses cytotoxic T-cell activity, T-cell proliferation, and cytokine production. Sugemalimab releases the inhibition of immune responses, including activation of the anti-tumour immune response, by blocking PD-L1/PD-1 and PD-L1/CD80 interaction, without inducing antibody-dependent cell mediated cytotoxicity (ADCC).

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application. All non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

Eqjubi has been authorised as a Conditional Marketing Authorisation (CMA). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided for Eqjubi. The CMA for Eqjubi, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a full product specific waiver MHRA-100396-PIP01-21.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 22 February 2024 and 29-30 August 2024 on grounds relating to efficacy. Following provision of additional data, the CHM were reassured on the quality of the product.

A marketing authorisation application for Eqjubi was received on 1 November 2022, and marketing authorisation was granted in the Great Britain (GB, consisting of England, Scotland and Wales) on 30 October 2024.

II QUALITY ASPECTS

II.1 Introduction

The active substance is sugemalimab. 1 mL of concentrate for solution for infusion contains 30 mg of sugemalimab. Each 20 mL vial of concentrate for solution for infusion contains 600 mg of sugemalimab.

The other ingredients are histidine, histidine monohydrochloride, mannitol (E421), sodium chloride, polysorbate 80 (E433), and water for injections.

The finished product is packaged in a type 1 glass vial with an elastomeric stopper and a blue flip-off aluminium seal. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: sugemalimab

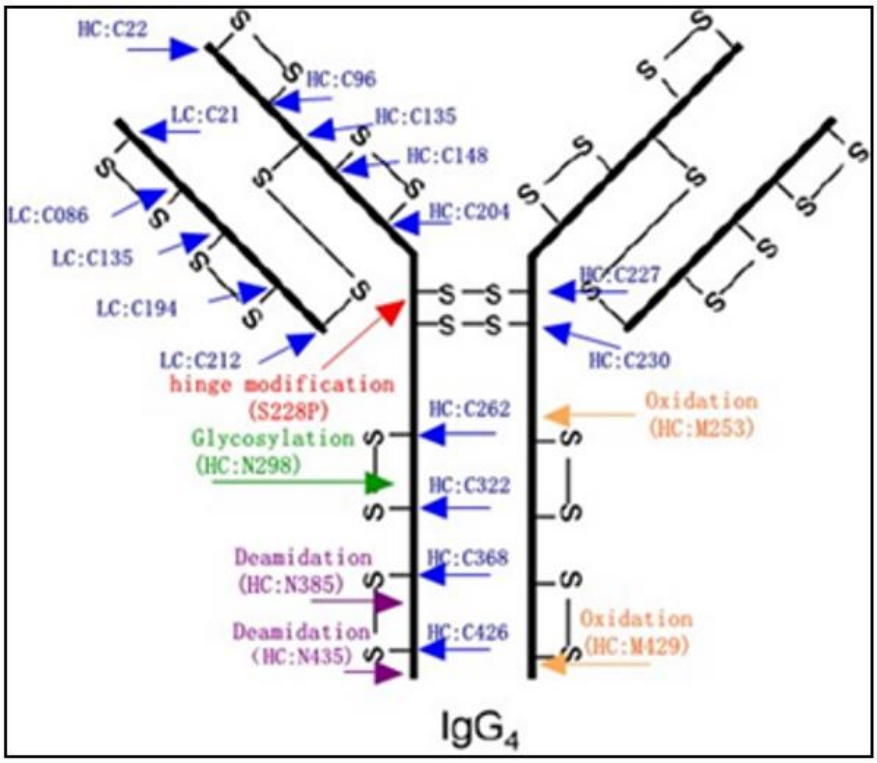
General properties

Test		Results[a]
Appearance		Colorless to slight yellow, slightly opalescent liquid
Identity	**pI**	7.3
	Peptide mapping	Comparable to reference standard
Intact molecular weight (kDa)		145.8
Deglycosylated molecular weight (kDa)		142.9
Theoretical extinction coefficient (ε_{280})		1.589 mg/mL^{-1} cm^{-1}
pH		5.5
Biological Activity		specifically binds to programmed cell death ligand 1 (PD-L1), thus blocking its ligation with PD-1.

[a] Results from clinical reference standard 3155BC180710a-RS.

Sugemalimab is a full human IgG4 monoclonal antibody composed of two λ (lambda) light chains and two heavy chains with a single disulfide bond covalently linking the heavy and light chains. Both the heavy chains are N-linked glycosylated at N298. The Fc domain of each heavy chain has mutation at Ser228Pro in the constant region. Based on the primary sequence, Sugemalimab has a theoretical molecular weight of 145.8 kDa which includes G0F/G0F glycosylation and C-terminal lysine cleavage on both heavy chains. Each light chain contains 213 amino acids and each heavy chain contains 448 amino acids. The variable regions of heavy and light chains facilitate the binding site with PD-L1 in the Fab region. Sugemalimab contains 16 disulfide bonds, including 12 intrachain disulfide bonds and 4 interchain disulfide bonds. The schematic presentation of the sugemalimab structure is shown **Error! Reference source not found.**.

Figure 1: Schematic Structure of Sugemalimab



Manufacture of the active substance has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

The molecule is suitably characterized, with typical features of a monoclonal antibody. Both product and process-related impurities are sufficiently controlled.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 30 months for the unopened vial, with the storage conditions store in a refrigerator (2°C – 8°C), do not freeze and keep the vial in the outer carton in order to protect from light, is acceptable.

Diluted medicinal product prepared for infusion

Chemical and physical in-use stability has been demonstrated for up to 48 hours at 2°C to 8°C and for up to 24 hours at room temperature (up to 25°C) from the time of preparation. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
The following non-clinical studies were submitted with this application:
In vitro binding studies
In vitro studies into the functional consequences of binding
In vivo studies in mice with implanted human tumours
Secondary pharmacodynamic studies
Pharmacokinetic studies
Tissue cross reactivity studies
General toxicity studies in cynomolgus monkeys

III.2 Pharmacology

Brief summary
Sugemalimab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody. It specifically binds to programmed cell death ligand 1 (PD-L1) blocking its interaction with PD-1 and CD80. PD-L1, when expressed on tumour cells and tumour-infiltrating immune cells, contributes to the inhibition of anti-tumour immune responses in the tumour microenvironment. Binding of PD-L1 to PD-1 and CD80 (B7.1) receptors on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production. The blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses. The evidences were presented in the dossier to show that it increased T-cell activation in vitro and inhibited tumour growth in syngeneic mouse tumour models.

Primary pharmacodynamics
Programmed cell death ligand 1 (PD-L1) binds to programmed cell death protein 1 (PD-1) and plays a major role to limit T-cell activity enabling tumour cells to evade detection by the immune system. Interactions between PD-1 expressed on activated T cells and PDL1 expressed on tumour cells downregulates immune responses and reduces anti-tumour activity. The aim of the class of drugs known as PD-1 inhibitors is to block this interaction and interfere with the action to suppress T cell-dependent immunosurveillance, leading to increased T cell activity and thereby a treatment of cancer. This is quite well established with drugs such as atezolizumab, durvalumab, nivolumab and pembrolizumab having been approved for use in patients with diverse types of cancer over the last 10 years or so as treatments for PD-L1-positive tumours.

The company set out to establish that its drug, sugemalimab, here termed WBP3155, had the intended action to bind to PD-L1 and inhibit PD1 – PDL1 interactions leading to T cell activation. Experiments were reported in Report 1001-taden WBP3155(CS1001) In Vitro Pharmacology Report.

This public assessment report describes binding studies first then presents the company's functional testing.

For this testing, a human PD-L1 expressing cell line WBP315.CHO-K1.hPro1.C11, human PD-L2 expressing cell line CHO-K1.PDL2.B6, and human CD80 expressing cell line CHOK1.CD80.B9 were constructed by the company developing the drug. Proteins used in this study were made by the developer and were: WBP315.hPro1.ECD.mFc (a fusion protein of the extracellular domain of human PD-L1 protein with mouse Fc tag) and WBP305.hPro1.ECD.mFc (a fusion protein of the extracellular domain of human PD-1 protein with mouse Fc tag). WBP315_r1.14.4 is the parental antibody of WBP315_1.14.4, the constant region of which is rat IgG1 heavy chain and lambda light chain. The antibody r1.4.1 is a rat anti-human PD-L1 antibody discovered by WuXi Biologics, which has different epitope from WBP315BMK1. The developer also made its own versions of reference anti-PD-L1 antibodies, WBP315BMK1 (synthesised from a patent) and WBP315BMK6 (also synthesised from sequences given in a patent): heavy and light chain variable region sequences of WBP315BMK6 are the same with approved anti-PD-L1 antibody Imfinzi. As a positive control antibody, the company used WBP305BMK1.IgG1 (synthesised from sequences in a patent) and also rituximab (synthesised as sequences in its patent).

Binding Methods: The first part of the study evaluated binding of anti-PD-L1 antibody to human cell surface human PD-L1, to PD-L1 from humans, cynomolgus monkey and mice, determined its affinity constant (KD) for human PD-L1 and whether the binding was competitive in nature; potential for binding to PD-L2 was also assessed. Evaluations were generated to identify the epitope on PD-L1, to which the antibody bound.

Firstly, binding of the antibody to human PD-L1 on the surface of mature human dendritic cells or of transfected Chinese hamster ovary (CHO) K-1 cells was undertaken. Briefly, 2x10(5) cells per well were exposed to different concentrations of test antibody from 0.13 – 133.4 nM, for 1 hour then a labelled goat anti-human antibody was added to the cell mix and also incubated for 1 hour and then quantified by fluorescence-based flow cytometry methods. Known anti-PD-L1 antibodies (WBP315BMK1 and WBP315BMK6) were used as positive controls and untransfected CHO-K1 cells were used as a negative control. This testing was done in triplicate.

Binding of antibody to each of human, cynomolgus monkey and mouse PD-L1 protein were compared by ELISA-based methods. For this, ELISA plates were precoated with human, cynomolgus monkey or mouse PD-L1 protein at 2 μg/ml and, after blocking with bovine serum albumin, test antibody (or the control antibodies WP315BMK1 and WBP315BMK6 and negative controls of an irrelevant (isotype) antibody and use of no antibody, were added to each reaction well. The antibody concentration was 33.35 nM and the mix was incubated for 1 hour then horseradish peroxidase-labelled goat anti-human secondary antibodies were added to each well and incubated for 1 hour. The resulting mixture was washed again, and the substrate TMB was added and the development of colour quantified by measuring absorbance at 450 nm. This testing was also done in triplicate.

A value for the binding constant of sugemalimab to human PD-L1 was determined. For this, the test antibodies (sugemalimab and positive controls antibodies known to bind to human PD-L1) were affixed to a GLM chip and PD-L1 at concentrations of 5, 2.5, 1.25, 0.625 and 0.31 nM were passed over the chip. The sample binding time was 240 s while the dissociation time was 600 s. This was also done in triplicate.

The ability of antibody to prevent binding of PD-1 to PD-L1 was tested in CHO-K1 cells. Cells, at 2x10(5)/well were mixed with antibodies at concentrations of 0.13 - 66.7 nM and then WBP305.hPro1.ECD.mFc was added and incubated for 1 hour. Cells were washed and labelled goat anti-mouse antibodies were added and incubated for a further hour and binding capacity of WBP305.hPro1.ECD.mFc to PD-L1 on the cell surface was determined by fluorimetry-based methods. This testing was done in triplicate.

Testing to show that antibody prevented binding of PD-L1 to CD80 was also done. Sugemalimab was mixed at concentrations of 3.3.35 - 133.4 nM with 10 μg/ml WBP315.hPro1.ECD.hFc t and this mixture was incubated in 96-well plates with CHO-K1.CD80.B9 cells (2x105 cells/well) for 1 hour. The cells were washed, labelled goat anti-human antibody was added and the mixture was incubated for an hour and then binding detected to determine binding capacity of WBP315.hPro1.ECD.hFc to CD80 on the cell surface by fluorescence-based flow cytometry methods. This testing was done twice.

To test if sugemalimab bound to PD-L2, the company made WBP315.CHO-K1.hPro1.C11 or CHO-K1.PDL2.B6 cells expressing human PD-L1 or PD-L2 protein. At a concentration of 2x105 cells/well each cell type was mixed with test antibody at 33.35 nM and incubated for 1

hour, then washed and the amount of bound antibody detected by use of a labelled goat anti-human antibody with fluorescence-based detection methods. This testing was done twice.

The company reported further testing into the nature of the epitope to which sugemalimab bound. SPR was used to detect whether the control antibody, WBP315BMK1, can bind to PD-L1 when sugemalimab has already bound to it. Test articles were pre-incubated with PD-L1 for 2 hours to allow binding to PD-L1 to be maximal: the mixture was then injected over the chip, pre-coated with WBP315BMK1. No signal or very low signal would be detected if the test article has same or close bin with WBP315BMK1, but strong signal would be detected if they bind to a different epitope.

Test antibodies were used at concentrations of 0.0653 – 66.7 nM and were mixed with biotin-labelled WBP315BMK1 at a constant concentration of 1 μg/ml; this mix was added to each well of 96-well plates with WBP315.CHO-K1.hPro1.C11 cells (2x105 cells/well) respectively, and incubated for 1 hour. Cells were washed and phycoerythrin (PE)-labeled streptavidin was added and the mix incubated for a further hour and binding capacity of biotin-labelled WBP315BMK1 to PD-L1 on the cell surface was. WBP315BMK1 and WBP315BMK6 were used as positive control antibodies which are known to have the same bin with WBP315BMK1. The company state this was repeated three times. The epitope was also studied by Surface Plasmon Resonance (SPR) methods. This assessment report only includes the SPR results. For this, WBP315BMK1 was injected over chips and equilibration allowed then the test antibody, mixed with 50 nM WBP315.hPro1.ECD.mFc after incubation for 2 hours was then injected onto the chip with a binding time of 100 s and dissociation time of 380 s. After each sample test, the chip was regenerated. WBP315BMK1 was use as positive control and the antibody r1.4.1 was used as negative control as it is known to have different bin from WBP315BMK1.

Results of binding: Results for binding of sugemalimab (here known as WBP3155) to human PD-L1 protein expressed by CHO-K1 cells is shown in Figure 1: an EC50 was reported of 1.10–3.09 nM. Binding to human mature dendritic cells is shown in Figure 2: this was also concentration-dependent. Binding to human, monkey or mouse PD-L1 protein as determined by ELISA is shown in Figure 3. Binding was comparable between human and monkey PD-L1, but there was no binding to mouse PD-L1 protein. The affinity constant (KD) of sugemalimab (WBP3155) at its extracellular domain target construct, WBP315.hPro1.ECD.His, was estimated at 1.38 x 10-9 M ie 1.38 nM (see Table 1).

Binding of sugemalimab to PD-L1 prevented binding of PD-1 to PD-L1 and did so in a competitive manner as shown in Figures 4 and 5. Sugemalimab (WBP315_1.14.4 / WBP3155) and control antibodies (WBP315BMK1 and WBP315BMK6) blocked binding of PD-1 with IC50s 1.93–3.87 nM. Figure 4 details results from testing with to WBP315.CHO-K1.hPro1.C11 cells and Figure 5 details results from testing with cells also expressing CD80.

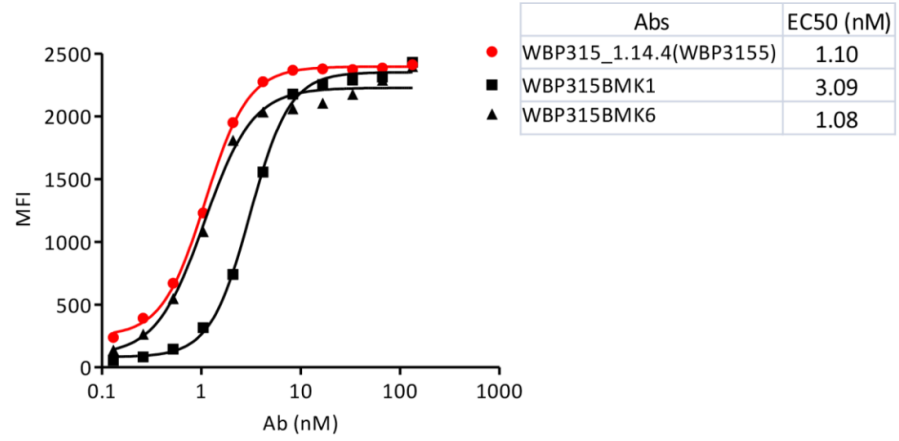


Figure 1. Binding of WBP3155 to PD-L1 protein on WBP315.CHO-K1.hPro1.C11 cell surface.

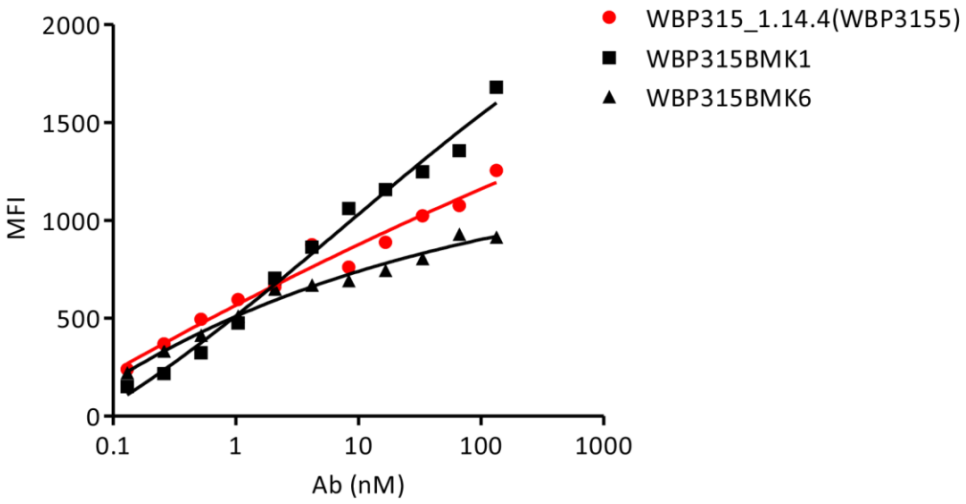


Figure 2. Binding of WBP3155 to PD-L1 protein on surface of mature dendritic cells.

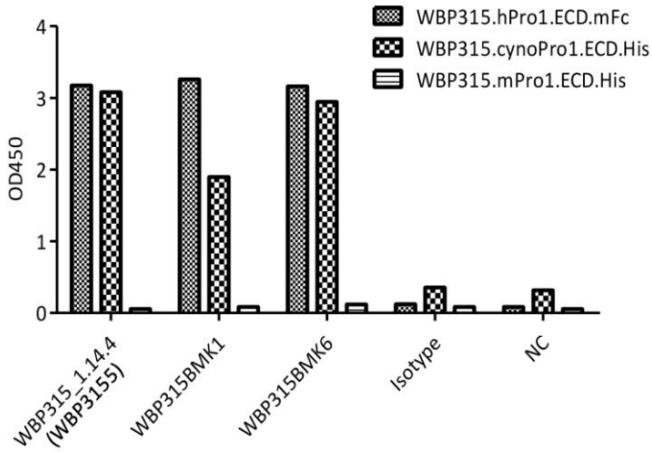


Figure 3. Binding of WBP3155 to human, cynomolgus monkey or mouse PD-L1 protein.

Table 1. Measured affinity results of WBP3155 to PD-L1 protein.

Analyte	Ligand	ka (1/Ms)	Kd (1/s)	KD (M)	Rmax (RU)	Chi^2 (RU)
WBP315.h Pro1.ECD. His	**WBP315_1.14. 4 (WBP3155)**	3.84E+05	5.28E-04	1.38E-09	238.64	4.73
	WBP315BMK1	6.80E+06	1.55E-03	2.28E-10	109.61	4.64
	WBP315BMK6	1.23E+06	2.17E-03	1.76E-09	73.18	2.77

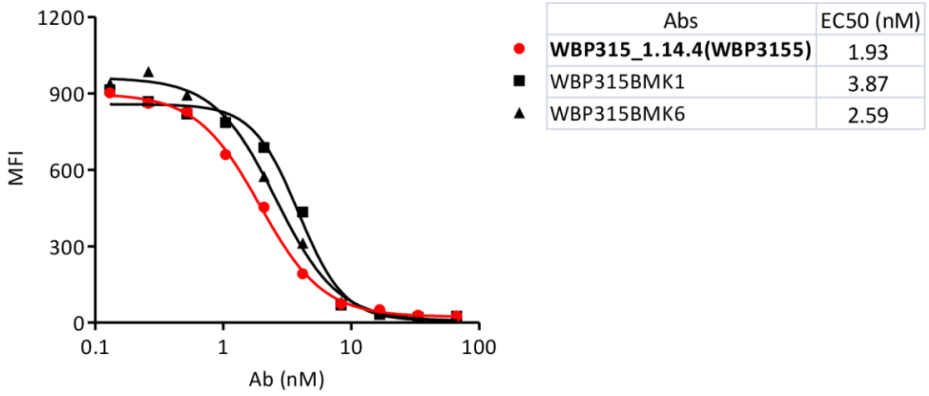


Figure 4. Competitive blocking effect of WBP3155 against binding of PD-L1 to PD-1.

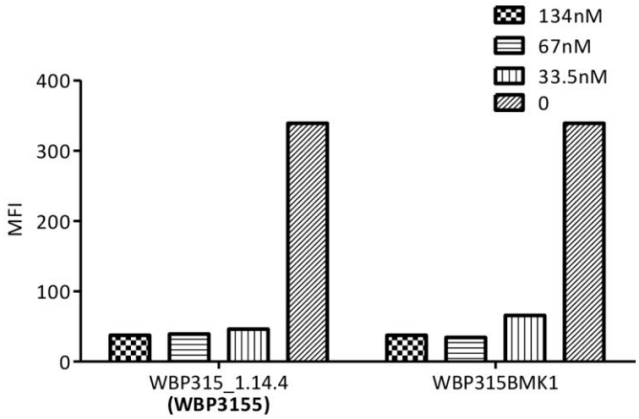


Figure 5. Competitive blocking effect of WBP3155 against binding of PD-L1 to CD80.

Binding capacity of sugemalimab (here called WBP3155) to each of human PD-L1 and PD-L2 is shown in Figure 6. It bound specifically to PD-L1 protein but did not bind to the PD-L2 protein.

When tested by SPR for binding of WBP315BMK1 to PD-L1 when it has been preincubated with sugemalimab, here called WBP3155, there was no additional binding (Figure 7) implying that the two antibodies bind to the same epitope.

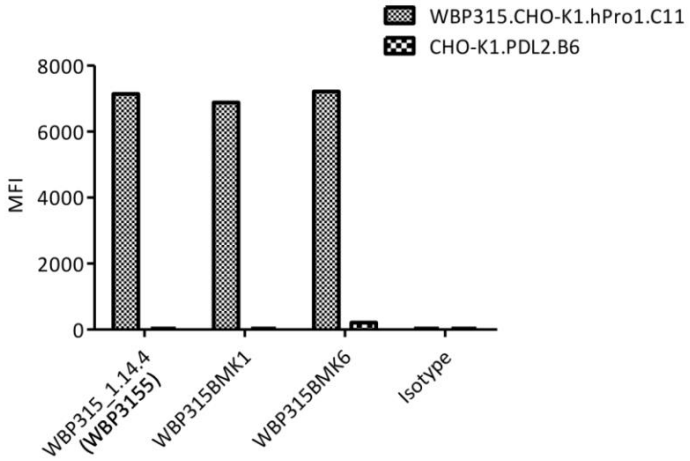


Figure 6. Binding of WBP3155 to another PD-1 Ligand, PD-L2.

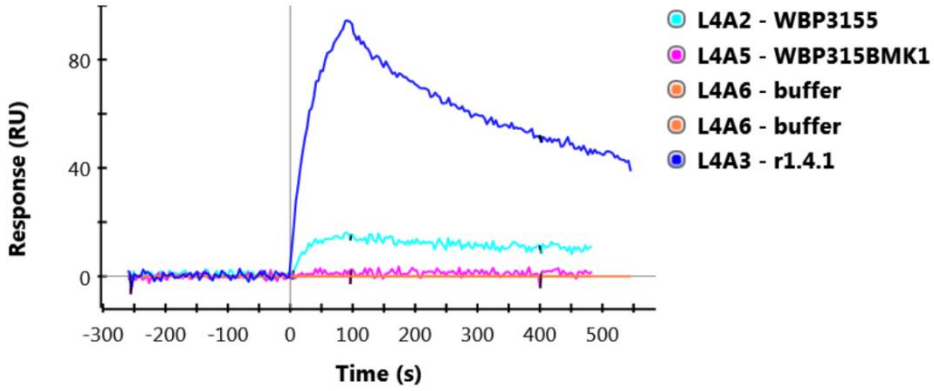


Figure 8. SPR assay of epitope binning.

In vitro function methods: A subsequent part of study evaluated functional consequences of binding by in vitro methods. This related to activation of CD4+ T lymphocytes and indicated by cell proliferation and cytokine release, and Fc-mediated antibody functions of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) of the anti-PD-L1 antibody.

Effects on proliferation of CD4+ T lymphocytes were determined by measuring IFN-γ and IL-2 in the supernatant of a mixed lymphocyte reaction (MLR) test. For this, healthy human donor-derived peripheral blood mononuclear cells (PBMCs) were used to generate dendritic cells (DCs). CD4+ T lymphocytes were separated from PBMCs with a human CD4+ T cell enrichment kit and purified CD4+ T lymphocytes and allogenic immature or mature DC (iDC or mDC) cells were co-cultured. An assay format was established which also allowed for autologous testing. CD4+T lymphocytes were added to wells and each test antibody at various concentrations were added and then suspensions of iDC or mDC cells at variable ratios were added to plates and the mixture was incubated; after 3 days the supernatant was tested for IL-2 concentration by ELISA and after 5 days, it was tested for IFN-γ concentration also by ELISA. Human IFN-γ and IL-2 levels present in the supernatants were determined by ELISA using commercially available test kits with reference to a standard curve of (IFNγ) 0.125 – 8 ng/ml and of range 0.0625 – 4 ng/m (IL-2). The report states that the experiment was repeated three times.

Cells cultured for 5 days were then used to determine proliferation level of CD4+ T lymphocytes by the ^{3}H-TDR method. For the cell proliferation assay, ^{3}H-thymidine was added to plate and then incubated with cells for 16-18 hours when the supernatant was extracted, washed and the cells harvested and after processing steps the amount of radioactivity retained in the cells was quantified by liquid scintillation counting.

To measure antibody-dependent cell-mediated cytotoxicity (ADCC), target cells (induction activated CD4+ T cells) and effector cells (PBMCs) were mixed at a ratio of 1:50. To this mixture, test antibody was added across the concentration range of 0.000067 - 67 nM. Lysis of the target cells was analysed with a commercially sourced kit. IgG1 subtype antibody WBP305BMK1.IgG1 served as a positive control of the system. Reactions were set up in triplicate for each concentration of the samples.

To measure complement-dependent cytotoxicity (CDC), target cells (induction activated CD4+ T cells) were mixed with antibody at concentrations (0.201 – 201 nM) and a 1:50 dilution of normal human serum complement was added and incubated for 2 hours. Target cell lysate was assayed using CellTiter-Glo. Rituximab and Raji target cells were used as a positive control. Reactions were set up in triplicate for each concentration of the samples.

In vitro function results: In the allogenic MLR test, T cells and antigen-presenting DC cells were co-cultured and test antibody added and the amount of human IFN-γ and IL-2 in the supernatant was quantified. Results are in Figures 9-11 which show that sugemalimab (here WBP3155) stimulated the secretion of each of IFN-γ and IL-2 from CD4+ T lymphocytes implying an effect to promote proliferation of CD4+ T lymphocytes. This effect was generally concentration-dependent. Isotype control antibodies had no effect (not shown here).

Results for testing for antibody-dependent cell-mediated cytotoxicity (ADCC) are in Figure 14 and were that PBMC did not kill PD-L1-positive immune cells in the presence of sugemalimab (WBP3155).

Results for testing for complement-dependent cell-mediated cytotoxicity (CDC) are in Figure 15 and were that sugemalimab (WBP3155) did not mediate CDC activity on activated human CD4+ T cells,
For both ADCC and CDC, the positive control antibodies elicited expected activity.

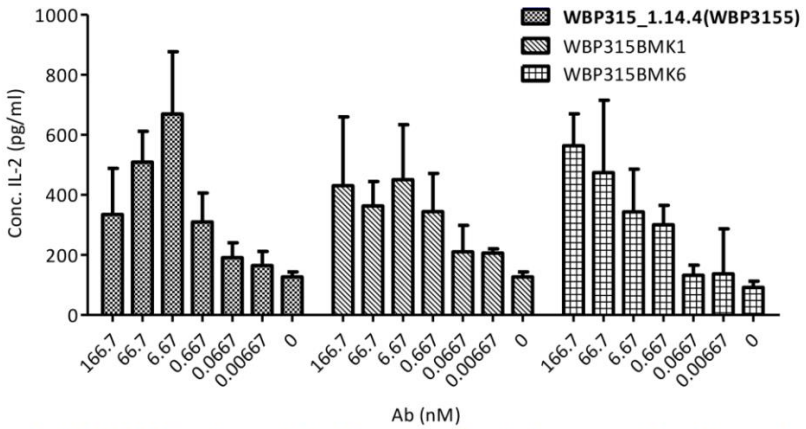


Figure 9. WBP3155 enhanced IL-2 production in human CD4+ T lymphocytes in allogenic MLR.

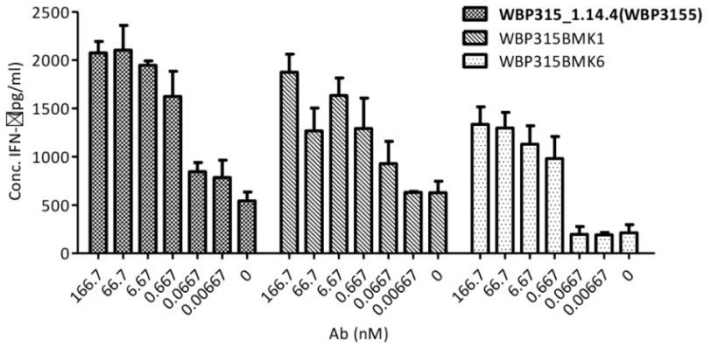


Figure 10. WBP3155 enhanced IFN-γ production in human CD4⁺ T lymphocytes in allogenic MLR.

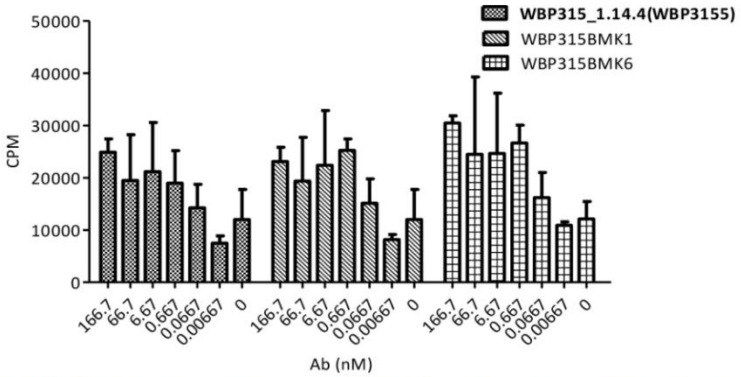


Figure 11. WBP3155 enhanced human CD4⁺ T lymphocytes proliferation in allogenic MLR.

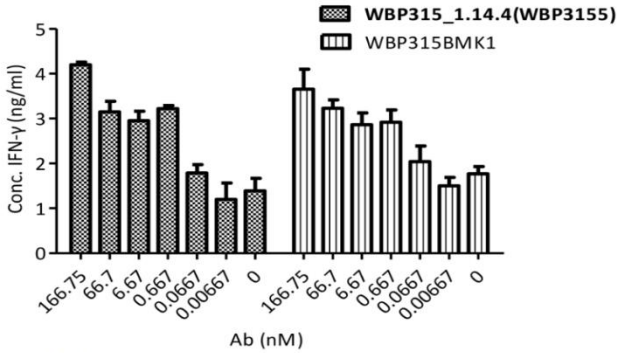


Figure 12. WBP3155 enhanced IFN-γ production in human CD4⁺ T lymphocytes

autologous antigen specific MLR.

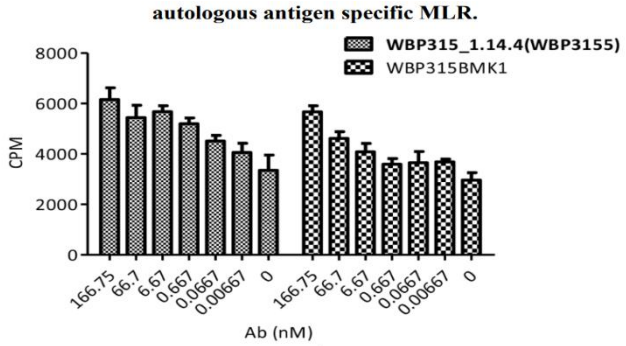


Figure 13. WBP3155 enhanced human CD4⁺ T lymphocytes proliferation in autologous antigen specific MLR.

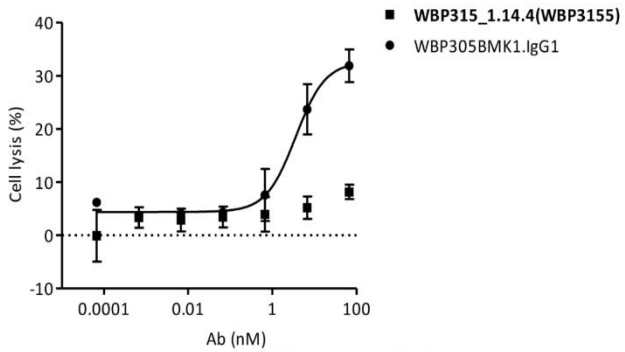


Figure 14. WBP3155 having no ADCC effect

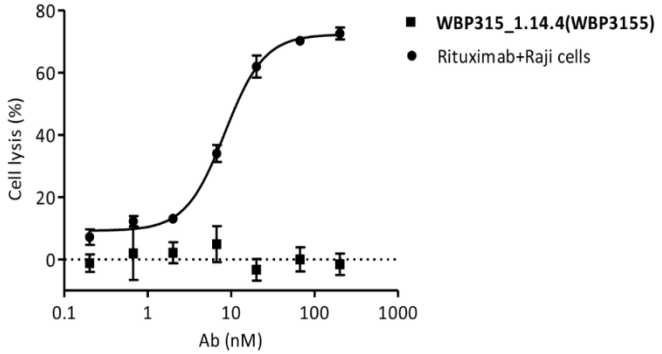


Figure 15. WBP3155 having no CDC effect.

The company concluded that sugemalimab (WBP3155) showed binding to PD-L1 on the surface of cells and that it bound to primate PD-L1 protein but not to PD-L1 of rodents. It blocked binding of human PD-L1 to human PD-1 and CD80 protein. In vitro testing indicated that it enhanced proliferation of CD4+ T lymphocytes and production of cytokines IFN-γ and IL-2. As expected for an IgG4, it lacked effector-cell functionality (no ADCC / CDC activity).

The company supplied a series of reports into the effect of sugemalimab in humanised PD-1 C57BL/6 mice bearing tumour xenografts.

Study bcg-ps-16033 sought to evaluate potential efficacy of WBP3155 as treatment of cancer in humanised PD-1 mice (C57BL/6 B-hPD-1 humanised mouse) with a subcutaneous tumour. The tumour cells were sourced commercially and were first genetically modified to express human PD-1 in place of mouse PD-1 with the human gene introduced and the murine gene knocked out.

At age ~9 weeks, 42 male mice were given a subcutaneous injection of MC38-B7Hl murine colon carcinoma cells (5x10(5)) in the right front flank. Tumour size was estimated by measuring its longest and shortest diameter and as a point where tumour volume reached 100 cubic mm mice were allocated to one of the groups as in the table below with low medium and high doses of 3, 10 (2 groups given drug from two different batches) and 30 mg/kg and controls given saline. Dosing in this study was by intraperitoneal injection every 2 days for a total of 6 doses. The first dose was given

The tumour volume and body weight were measured and recorded twice per week. The study was terminated 9 days after the last dosing: tumours were dissected from and weighed. The relative tumour growth rate (T/C) and degree of tumour growth inhibition (TGI%) were calculated.

Groups	No. Of Animal	Treatment	Dosages (mg/kg) [a]	Dosing Route	Schedule[b]
1	7	Vehicle (0.9% NaCl)	--	i.p.	Q2d×6
2	7	WBP3155 standard batch	10	i.p.	Q2d×6
3	7	WBP3155 low dose	3	i.p.	Q2d×6
4	7	WBP3155 mid dose	10	i.p.	Q2d×6
5	7	WBP3155 high dose	30	i.p.	Q2d×6

Notes:

a: Dosing volume was adjusted based on body weight (10 μL/g).

b: Q2d×6 refers to dosing every two days for a total of 6 doses..

Results: There were no unscheduled deaths. Mean tumour volumes for the groups 1 – 5 on day 25 at the end of the study were 2359, 949, 1416 and 1115 cubic mm, respectively. Sugemalimab (WBP3155) produced substantial anti-tumour activity at all doses. The TGI% values were 62.8, 42.0 and 55.4% at 3, 10 and 30 mg/kg respectively. The test batch and the standard batch had comparable anti-tumour activity at 10mg/kg. Table 1 and Figure 4 show these results.

The mean body weight and mean percent body weight change over time are shown in Figures 1 and 2 and were not affected by sugemalimab.

Table 1. Tumor growth inhibition of WBP3155 on humanized B-hPD-1 mice with murine colon cancer MC38-B7H1 tumor graft

Group	Animal number	Body weight (g)[a]		Tumor volume at 25 days after inoculation (mm^3)	Tumor growth rate T/C at 25 days after inoculation (%)	Tumor growth inhibition TGI (%)	*P*[b]
		Before dosing	19 days after dosing				
G1: Vehicle	7	27.6±1.3	28.8±1.5	2359±449	--	--	--
G2: WBP3155 standard batch	7	28.3±0.5	29.3±0.7	1241±242	52.6%	49.7%	0.049
G3: WBP3155 3mg/kg	7	28.0±0.5	29.7±0.5	949±259	40.2%	62.8%	0.019
G4: WBP3155 10mg/kg	7	27.8±0.8	30.3±1.1	1416±415	60.0%	42.0%	0.149
G5: WBP3155 30mg/kg	7	26.7±0.9	27.5±1.0	1115±297	47.3%	55.4%	0.039

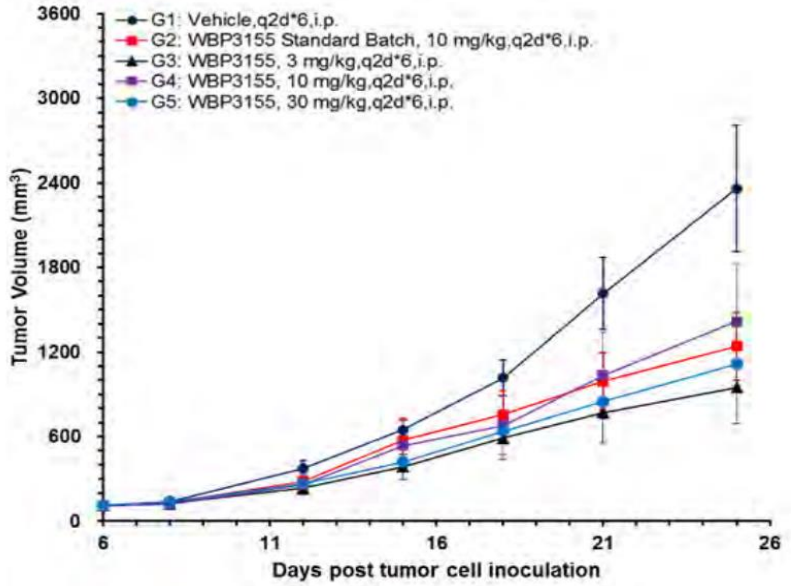
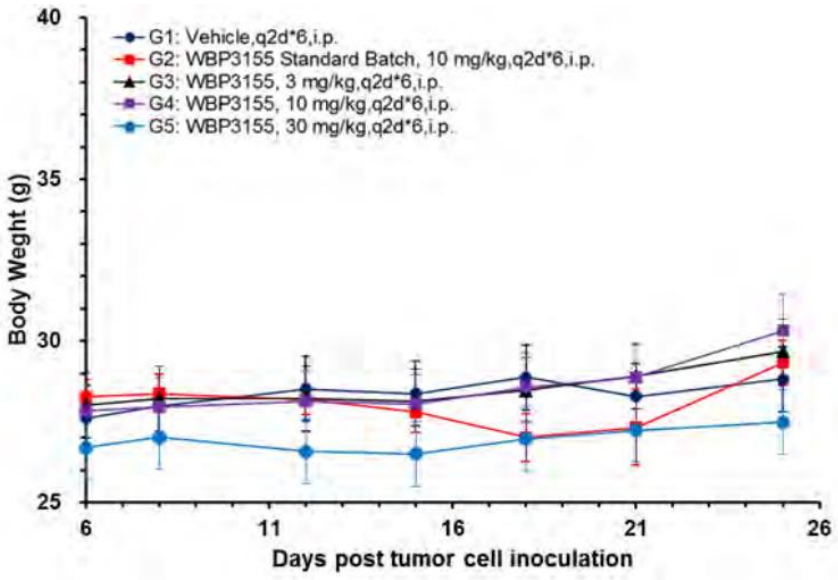


Figure 3. Tumor growth inhibition upon drug treatment



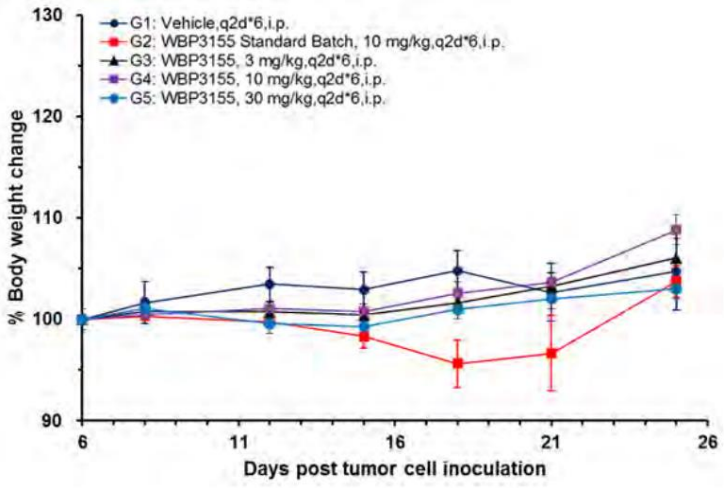


Figure 2. Mean percentage body weight change

The company concluded that sugemalimab (WBP3155) had significant tumour growth inhibition activity at all doses and it did not negatively affecting body weight or causing any obvious clinical sign.

Study 0002-16010 was a repeat of the above study (BCG-PS-16033) except that a dose of 1 mg/kg was also tested.

In brief, 53 male mice were injected with MC38-hPD-L1 tumour cells (5×10(5)) subcutaneously in their right front flank. Tumour was allowed to grow and when it reached a size of 90- 95 cubic mm, mice were randomised to 1 of 5 different groups, each with 7 mice. Remaining mice were discarded at this stage. The five groups were: vehicle control, sugemalimab (here called WBP3155) at doses of 1, 2, 3, 10 and 30 mg/kg. dosing was by intraperitoneal injection every two days for a total of six times. Tumour volume and body weight were measured and recorded twice per week and the study ran to 21 days post-grouping when tumours were dissected and weighed. Tumour growth inhibition (TGITV%) and tumour weight inhibition (TGITW%) were calculated and analysed.

Results: One mouse from group 5 was found dead on day 14 with tumours inside the peritoneum; this death was considered unrelated to treatment. One other mouse was removed from the study to prevent ongoing suffering: this was a mouse in the control group with a tumour size of 3000 cubic mm on day 20.

The tumour growth inhibition (TGITV%) was determined at the best therapeutic time point (day 18 post grouping). Sugemalimab at the doses tested showed significant anti-tumour activity (Figure 2, Tables 2 and 3). At day 18, the mean tumour volume of the control group was 1798±439 cubic mm and for the groups given 1, 2, 3, 10 and 30 mg/kg sugemalimab (WBP3155) mean tumour volumes were 1215±201, 844±162, 1061±137 and 1145±177 cubic mm respectively. Tumour growth inhibition (TGITV%) was 34.1, 55.8, 43.1 and 38.4%, respectively. At day 21, the TGITV% values were 23.9, 45.4, 34.7 and 16.8%, respectively, values which the report indicated were worse than at day 18. Between different doses, there was no difference in tumour volumes.

The mean body weight and mean percent body weight change showed no significant differences between the control group and those given sugemalimab (WBP3155) (not shown here): the report states this suggests good tolerance of the test article.

Table 2. Tumor growth inhibition of WBP3155 on humanized B-hPD-1 mice with murine colon cancer MC38-hPD-L1 tumor graft

Groups	Animal number	Tumor volume (mm^3)[a]		TGI_{TV} (%)	P^b	P^c
		Before grouping	18 days after grouping			
G1: Vehicle control	7	95±11	1798±439	--	--	--
G2: WBP3155, 1mg/kg	7	92±9	1215±201	34.1	0.232	0.029
G3: WBP3155, 3mg/kg	7	91±8	844±162	55.8	0.021	0.002
G4: WBP3155, 10mg/kg	7	91±7	1061±137	43.1	0.096	0.009
G5: WBP3155, 30mg/kg	7	95±12	1145±177	38.4	0.155	0.014

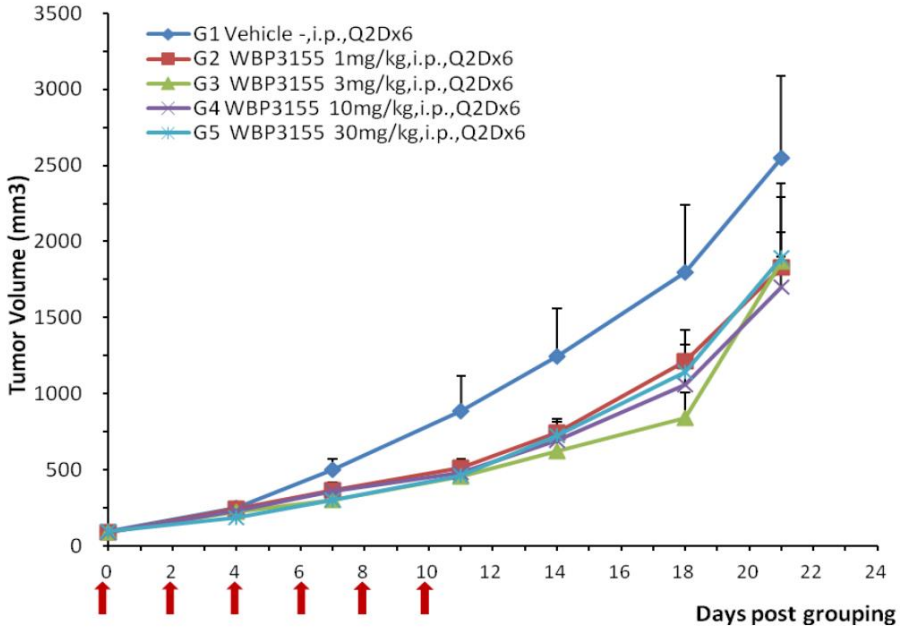


Figure 2. Tumor volume inhibition upon drug treatment

Note: Red arrow indicates dosing date

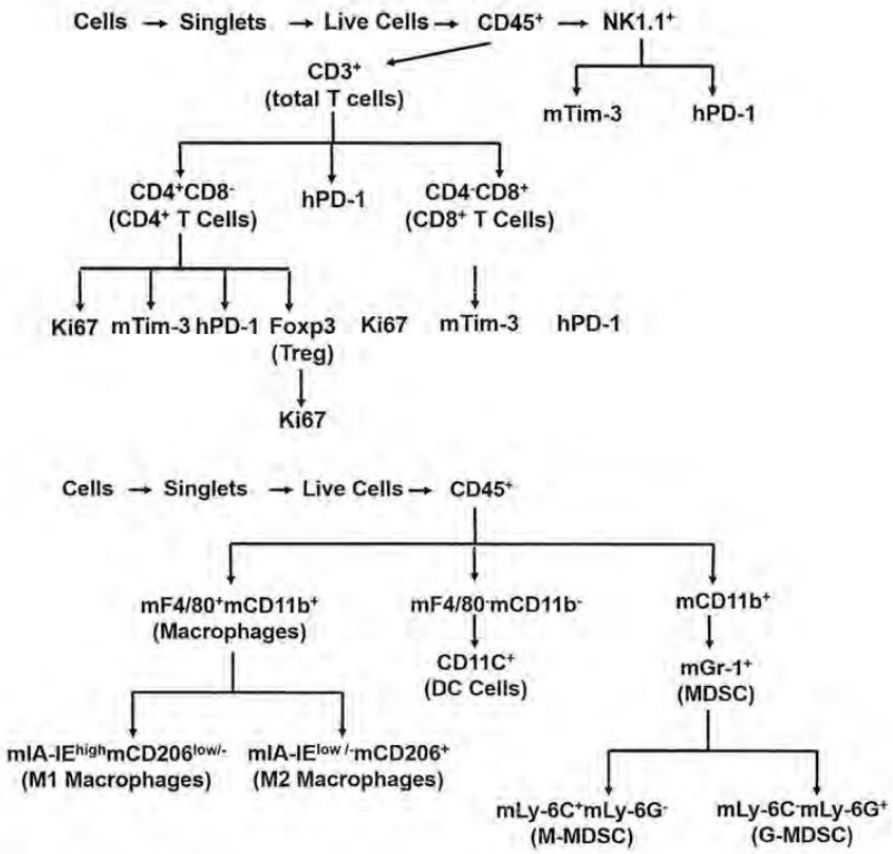
The company concluded that all doses of sugemalimab (WBP3155) had significant anti-tumour activity.

The purpose of study 193117-0123 was to test the anti-tumour activity and immunoregulatory effects of sugemalimab (here called P0l-2201) in mice implanted subcutaneously with MC38-hPD-Ll colon carcinomas. BhPD-1/hPD-Ll mice express human PDL1.

For this, B-hPD-1/hPD-Ll mice were injected subcutaneously with MC38-hPD-Ll tumour cells in the right front flank and tumour allowed to grow to ~117 cubic mm when mice were assigned to one of three study groups, with 6 mice in each group. Group 1 were given a non-

specific human IgG4 at a dose of 3 mg/kg, every 2 days for 9 doses; Group 2 were given sugemalimab (here called P0l-2201) at the same dose of 3 mg/kg, every 2 days for 9 doses; Group 3 were given sugemalimab (P0l-2201) at a dose of 3 mg/kg, twice weekly for 6 weeks. All dosing was by the intraperitoneal route.

Tumour volume and body weight were measured and recorded three times per week. The study stopped at 24 hours after the last dose of group 3 and tumours were excised from all mice and weighed and photographed and FACS analysis performed for tumour infiltrating leukocyte (TIL) analysis. The gating strategy for major cell types is shown below.



Results: There were no unscheduled deaths: body weight gradually increased indicating that dosing was tolerated. Mean tumour volumes in groups 1, 2 and 3 were 1966 ± 248, 960 ± 261 and 1055±263 cubic mm with TGI values for groups 2 and 3 of 54.4 and 49.3% (Table 1, Figure 2).

The outcome of analyses of tumour infiltrating lymphocytes (TILs) is given in Figure 3 below and indicated profound inhibition of Treg populations and increases in cytotoxic T cells/Treg ratio. Sugemalimab (P0l-2201) decreased immune-suppressive myeloid-derived suppressor cell (MDSC) and G-MDSC populations and enhanced pro-inflammatory M1 macrophages.

Table 1. Tumor growth inhibition of P01-2201 on humanized B-hPD-1/hPD-L1 mice with MC38-hPD-L1 cells

Groups	Test Articles	Dose	Tumour Volume (mm^3)[a]		TGI$_{TV}$ (%)	*P*[b]
			Before Treatment	Day 19 Post Treatment		
G1	Human IgG4	3 mg/kg	117 ± 5	1966 ± 248	-	-
G2	P01-2201	3 mg/kg	117 ± 6	960 ± 261	54.4	*0.019
G3	P01-2201	3 mg/kg	117 ± 7	1055 ± 263	49.3	*0.031

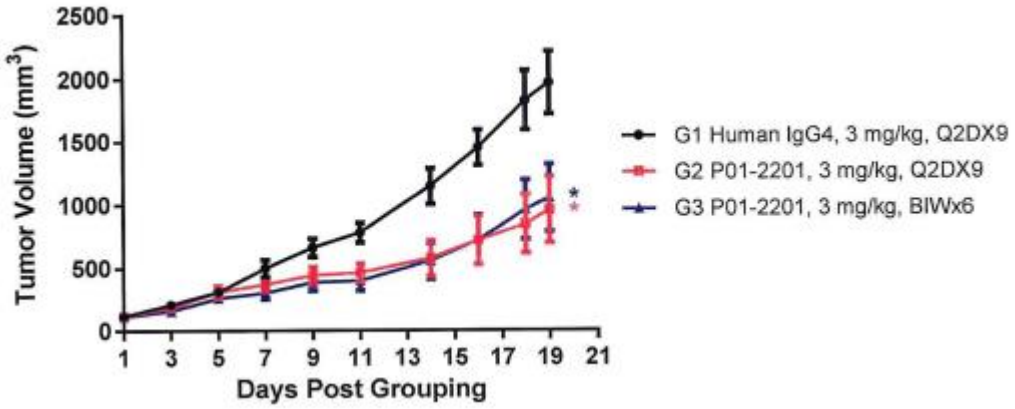


Figure 2. Tumour growth inhibition upon treatment

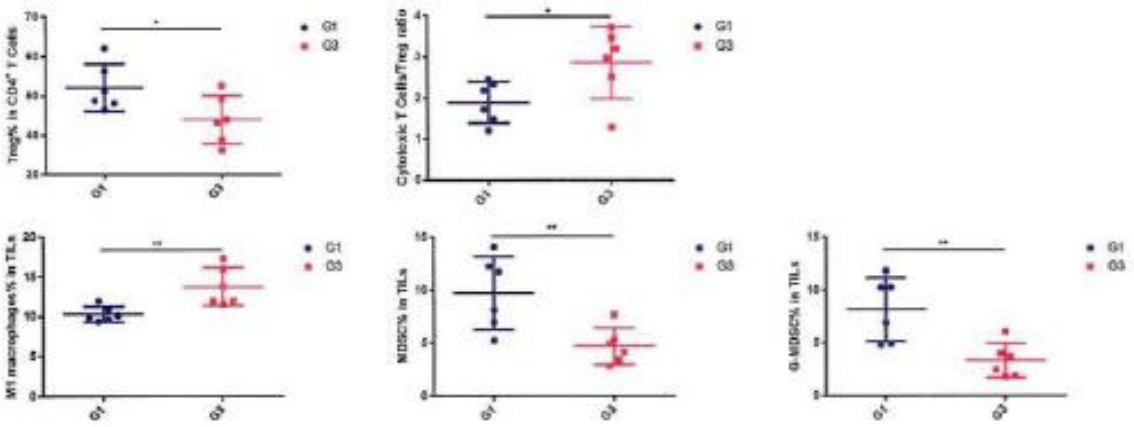


Figure 3. FACS analysis results

The company concluded that sugemalimab (POI-2201) had anti-tumour activity at 3 mg/kg as dosed in this study and did not affect body weight or induce any obvious clinical sign. It shifted the immune profile toward a more inflammatory phenotype in the tumour microenvironment.

Secondary pharmacodynamics

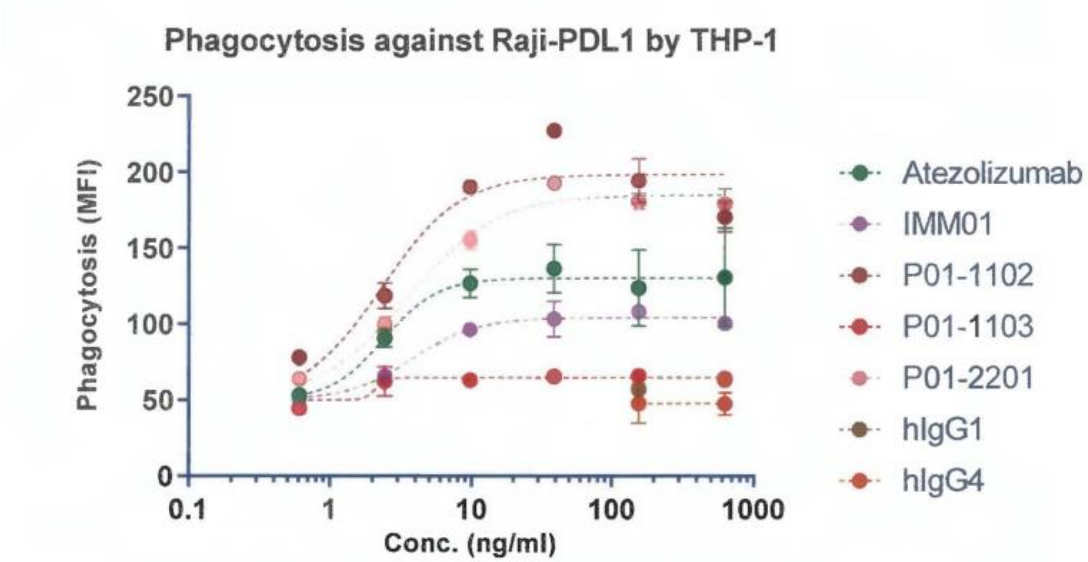
The objective of study 1001-ADCP was to test if sugemalimab had capacity to induce antibody-dependent cellular phagocytosis (ADCP).

For this, target cells (Raji-PDLl cells) labelled with a fluorescent marker were mixed with THP-1 macrophages and test antibody. In principle, in this testing, the antibody binds to ligands on the surface of the target cells and its Fc segment binds to Fc receptors on the surface of the macrophages and thereby induces macrophages to mediate phagocytosis against target cells. Fluorescence from the label in target cells and phagocytised by THP-1 cells can be detected by flow cytometry to reflect the ability of the test substances in inducing ADCP. As positive controls other antibodies, atezolizumab and IMM01, were used.

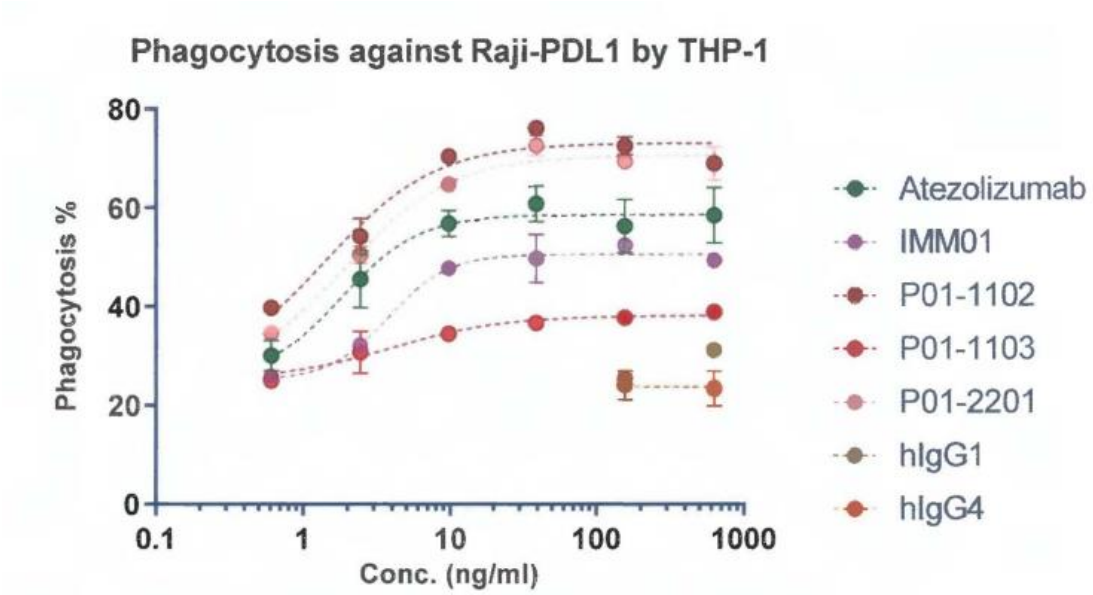
Results: Testing was done with antibodies at concentrations of 0.61 to 625 ng/ml. As shown in the figures below, there was a dose-response curve for the positive controls and the quantified mean fluorescence intensity (MFI) increased with the concentration of each of atezolizumab and of IMM01.

Sugemalimab (here called POJ-1102 and also called POl-2201) induced phagocytosis against Raji-PDLl mediated by THP-1 cells, which was more robust than that of Atezolizumab and IMMO 1 and had a maximal effect at the concentration of 39.06 ng/ml with a loss in phagocytic activity at higher concentrations. Combination of POl-1102 or POl-2201 with IMMOl did not enhance phagocytic activity compared to use of each alone. Sugemalimab is understood from this testing to have ADCP potential.

It is not clear why the same antibody, sugemalimab, is given two separate codes in this report, P01-1102 and P01-2201. However, they are different lots and were provided at different concentrations.



	Relative EC50 (ng/mL)
IMM01	3.828
Atezolizumab	2.418
P01-1102	2.335
P01-1103	~2.106
P01-2201	3.580



	Absolute EC50 (ng/mL)
IMM01	46.3
Atezolizumab	3.5
P01-1102	1.5
P01-1103	NA
P01-2201	2.2

Figure 2. EC50 Values of Antibody-Dependent Cellular Phagocytosis (ADCP) against Raji-PDL1 Cells by THP-1

Cells

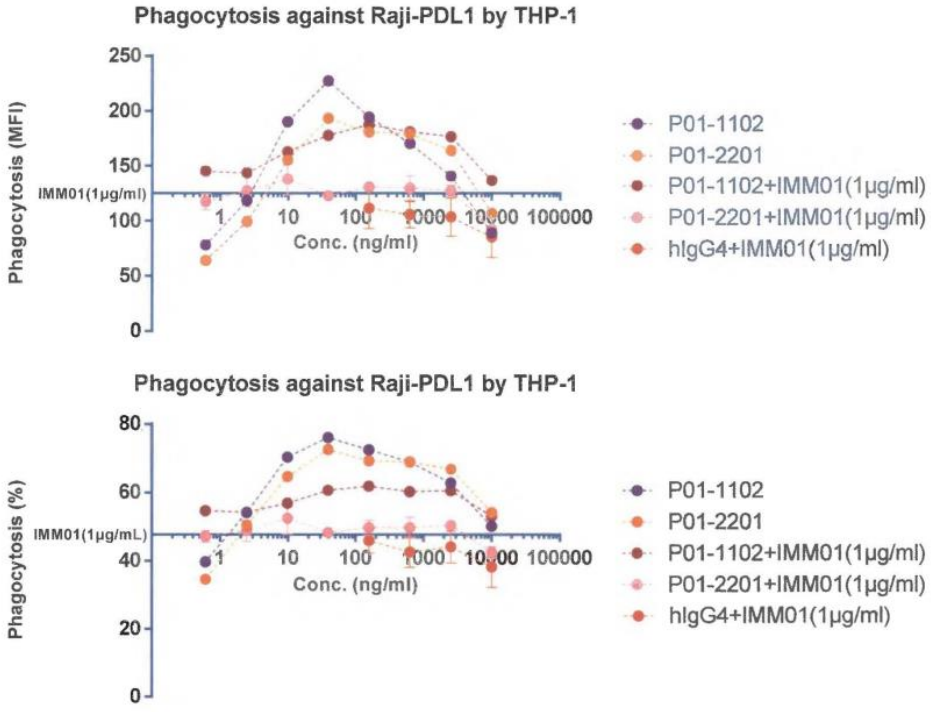


Figure 3. Antibody-Dependent Cellular Phagocytosis (ADCP) against Raji-PDL1 Cells by THP-1

Safety pharmacology
Safety pharmacology assessments were performed in 4- and 26-week GLP toxicology studies with 4-week recovery in cynomolgus monkeys. Safety pharmacology endpoints including ECG, blood pressure, heart rate, waveform abnormalities, arrythmia, respiration and neurological evaluation were assessed at baseline and intermittently throughout the treatment period using doses of sugemalimab ranging from 3 to 200 mg/kg IV infusion/week. At the highest dose tested for up to 26 weeks, sugemalimab had no effect on any of the parameters tested and all results were within normal physiological ranges.

Pharmacodynamic drug interactions
Pharmacodynamic drug-drug interaction studies were not performed.

Overall conclusions on pharmacology
Sugemalimab is an IgG4 antibody proposed as an immunotherapeutic for use in patients with cancer, specifically, in this application as treatment with platinum-based chemotherapy of metastatic non-small cell lung cancer.

Data were presented on sugemalimab and its binding to PD-L1 protein and its specificity for primate PD-L1. Sugemalimab bound to human PD-L1 expressed in PD-L1-transfected Chinese Hamster Ovary cells with an EC50 of 1.10 nM and able to engage mature human dendritic cells. It also bound to monkey PD-L1but it did not bind to PD-L1 from mice nor did it bind to human PD-L2. Sugemalimab's binding was competitive in nature.

PD-L1 may also bind to CD80, an inhibitory ligand for CTLA4 and the primary action of sugemalimab could also augment T cell function through this route.

In vivo pharmacology studies showed its potential to have anti-tumour activity in experiments in mice with implanted tumours. Tumour growth inhibition was seen at doses that had no obvious toxicity to tumour-bearing mice, as indicated by a lack of effect on bodyweights and clinical signs. These studies used colon cancer cells but the indication sought in this application is lung cancer. These colon cancer cells had been modified to express human PD-L1. This is a notable difference but the principle that the antibody can inhibit human PD-L1 to block growth of a solid tumour is established by the studies performed and there is no reason to think that this would not apply if a lung cancer had been implanted in mice.

Antitumour effects were seen with use of sugemalimab as monotherapy at doses of 3-30 mg/kg

Sugemalimab shifted the immune cell profile to an inflammatory cell phenotype with increased T cell activity: this was not noted in the toxicity studies in monkeys and the reason why this was not seen there is not understood: a question was raised to the company on this, but in these pharmacology studies, this effect was expected and was demonstrated. Secondary pharmacology studies indicated that sugemalimab acts to promote T cell proliferation and lead to increased production of IFN-γ and IL-2.

It has no ADCC or CDC effect, but potential anti-tumour activity through ADCP activity was indicated by the testing done.

Use is proposed in combination with platinum-based treatment: there were no specific pharmacodynamic drug-dug interaction studies but these are not needed: the clinical

development is based on use in patients treated with these other drugs and this absence is not a deficiency in this file.

Safety pharmacology parameters were monitored in the general toxicity studies. This is an acceptable approach. No effects on vital systems (cardiovascular, respiratory or nervous system) were noted in evaluations conducted in monkeys in general toxicity studies where doses up to 200 mg/kg were used.

Overall, these data show the modes of action of the product and indicate its potential for anti-tumour activity. Sufficient evidence is presented to support the choice of cynomolgus monkeys for toxicity studies. The interference of PD-(L)1 signalling is well-established as a means of treating cancer.

III.3 Pharmacokinetics

Pharmacokinetic studies
Methods to measure sugemalimab and anti-sugemalimab antibodies (ADA) were validated and used for serum drug concentration and ADA analysis in the cynomolgus monkey single dose pharmacokinetics (PK) study and the toxicokinetics (TK) studies incorporated in the general toxicity studies. After a single intravenous dose, sugemalimab showed target-mediated clearance, which was more significant at 10 mg/kg while became more sutured at 30 and 90 mg/kg, leading to over-proportional increase of exposure when the dose increases.

Methods of analysis
ELISA-based methods using human PD-L1 extracellular domain (ECD) and mouse anti-human IgG4 mAb as capture reagent and detection reagent, respectively were developed to measure sugemalimab concentration the serum of cynomolgus monkeys, with calibration range of 0.1 or 0.2 μg/mL to 80 μg/mL.

An acid-dissociation bridging ELISA-based three-tiered ADA assay was also developed, using biotinylated sugemalimab and digoxigeninylated sugemalimab as capture reagent and detection reagent, respectively.

These methods were considered fully validated and suitable for their intended use.

Absorption
The aim of study 201511901 was to evaluate pharmacokinetic characteristics of sugemalimab in cynomolgus monkeys, dosed once at 10, 30 or 90 mg/kg via intravenously injection. Three male and 3 female cynomolgus monkeys were used. HPLC-UV analysis confirmed that the sugemalimab concentrations in the dose formulations were all within ±20% of the nominal values. Venous blood samples of ~0.5 ml were collected prior to dosing as well as 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, 144, 312, 480, 648, 816, 984, 1152, and 1320 hr after dosing. Then serum was separated and kept frozen until bioanalysis. PK parameters, including AUC (area under concentration-time curve), Cmax (the peak or maximum concentration.), $t_{1/2}$ (terminal half-time), Vd (apparent volume of distribution), CL (clearance), MRT (mean residence time), were estimated from the serum sugemalimab concentration data. For ADA analysis, the blood samples of 1 ml were taken prior to dosing as well as 312, 648, 984, and 1320 hr after dosing.

Results: The PK parameters from this study are summarised in Table 15. There was no PK difference between male and female monkeys so results from males and females were

combined. Gender-averaged AUC values increased over-proportionally to dose. The elimination $t_{1/2}$ also increased with dose, which was 78.5, 186 or 352 hours after 10, 30 or 90 mg/kg dosing, respectively.

ADA developed in a minority of monkeys: at 10 mg/kg, 22.2% of samples from males and 22.2% of samples from females were tested positive; at 30 mg/kg, 22.2% of samples from males and 11.1% of samples females were tested positive; but at 90 mg/kg, no sample was tested positive. The company make several comments on this, most notably that the higher rate of ADA positivity at the lower dose may have contributed to the higher clearance that leading to the greater-than-dose proportional increase in sugemalimab exposure.

Table 15 Sex-averaged pharmacokinetic parameters of WBP3155 in male and female cynomolgus monkeys following single intravenous of WBP3155

PK parameters	Dose (mg/kg)								
	10			30			90		
	Mean (n=6)	SD	CV (%)	Mean (n=6)	SD	CV (%)	Mean (n=6)	SD	CV (%)
C_0 (μg/mL)	370	81.4	22.0	945	99.0	10.5	2670	215	8.05
$T_{1/2}$ (h)	78.5	39.1	49.8	186	150	80.6	352	177	50.3
V_{ss} (mL/kg)	48.7	8.11	16.7	45.9	9.16	20.0	58.8	6.89	11.7
Cl (mL/h/kg)	0.253	0.106	41.9	0.154	0.0325	21.1	0.109	0.0246	22.6
T_{last} (h)	760	330	43.4	1010	326	32.3	1320	0.00	0.00
$AUC_{0\text{-}last}$ (h*μg/mL)	44400	15800	35.6	194000	43100	22.2	769000	100000	13.0
$AUC_{0\text{-}inf}$ (h*μg/mL)	44700	15400	34.5	204000	57400	28.1	856000	173000	20.2
$MRT_{0\text{-}last}$ (h)	207	69.7	33.7	279	90.9	32.6	428	40.5	9.46
$MRT_{0\text{-}inf}$ (h)	212	64.9	30.6	325	165	50.8	567	166	29.3
$AUC_{0\text{-}inf}/AUC_{0\text{-}last}$ (%)	101	2.40	2.38	105	6.60	6.29	111	9.91	8.93

Distribution
No distribution studies were performed.

Metabolism
No metabolism studies were performed.

Excretion
No excretion studies were performed.

Pharmacokinetic drug interactions
No pharmacokinetic drug-drug interaction studies were performed.

Other pharmacokinetic studies
No other pharmacokinetic studies were performed.

Overall conclusions on pharmacokinetics
In cynomolgus monkeys, intravenous doses of 10~ 90 mg/kg were tested. The resulting estimated t1/2 ranged from 78.5 to 352 hours with an increase in exposure (AUC) that was greater than dose proportional. ADA positivity was only observed at lower dose levels with a tendency to reduce exposure. However, the ability to detect anti-sugemalimab antibodies by the bridging ELISA may have been compromised by the presence of unlabelled sugemalimab in the serum samples for ADA assay. The company consider that at 10 mg/kg, the contribution of target-mediated clearance was more significant, whereas at the higher doses, when the target became more saturated, the non-specific clearance mechanisms dominated.

Distribution studies are not required. As a biological product, this product is expected to be degraded to small peptides and amino acids and studies of routes of metabolism are not required. Direct drug-drug kinetic interactions are not anticipated because there is a high capacity to clear proteins and this product is not metabolised by cytochrome P450 enzymes, nor is it a substrate for transporter proteins. Indirect interactions whereby this product might influence the expression of these enzymes are not anticipated.

Repeated dose kinetic data were generated from general toxicity studies.

These data suffice to support the licensing of this product.

III.4 Toxicology

The toxicity studies were performed in monkeys with this species justified with reference to pharmacological studies (described above).

Tissue cross reactivity studies

An initial study evaluated the methods to be applied for use in later definitive tissue cross reactivity studies planned in tissues from humans, cynomolgus monkeys and rats (report 211-0327-IM). For this, sugemalimab and a control antibody called 135-Human Ctrl were biotinylated by a commercial kit and applied to a PD-L1 positive cell line (WBP315.CHOK1.hProl.C11) to confirm binding. Thereafter, staining of normal human placenta tissue slides was tested at concentrations of 0.5, 1, 5, 10, 25 and 50 μg/ml. Based on these investigations, the WBP315.CHO-K1.hProl.C11 cell line was considered appropriate as positive control to which biotinylated sugemalimab binds and human hypercalcaemia of malignancy factor fragment 1-34 amide was considered an appropriate negative control as there was no binding of biotinylated sugemalimab. The optimal concentration range of biotinylated sugemalimab was judged to be 1 and 10 μg/ml; at higher concentrations there was non-specific binding.

In a study to assess binding to a range of tissues from rats (211-0330-IM), no staining was noted: it was concluded that there is no cross-reactivity with rat tissues. This study did identify binding of a positive control antibody to rat CD31, confirming its suitability to identify binding if present.

In studies 211-0328-IM and 211-0329-IM, tissue cross reactivity to human and cynomolgus monkey tissues was examined. 33 human tissues and 33 monkeys were used and binding of biotinylated sugemalimab and biotinylated control article was tested. Positive and negative controls were applied and confirmed tissue suitability and specificity and sensitivity of the methods applied. The tables below list the tissues that were studied, each from 3 donors. A 6 point scale was used to describe frequency of cells that were positive, from very rare (<1%), through occasional (25-50%) to frequent (75-100%).

List of human tissues

Adrenal	Heart	Small Intestine
Bladder	Kidney (glomerulus, tubule)	Skin
Bone Marrow	Liver	Spinal Cord
Breast	Lung	Spleen
Blood cells	Lymph Node	Testis
Cerebral cortex	Striated muscle	Thymus
Cerebellum	Ovary	Thyroid
Colon	Pancreas	Tonsil
Endothelium (Aorta)	Pituitary	Ureter
Eye	Placenta	Uterus (cervix)
Fallopian Tube	Prostate	Uterus (endometrium)

List of cynomolgus monkey tissues

Adrenal Gland	Heart	Small Intestine(duodenum)
Urinary Bladder	Kidney	Skin
Bone Marrow(femur)	Liver	Spinal Cord(thoracic)
Mammary Gland	Lung	Spleen
Blood cells	Lymph Node(mesenteric)	Testis
Cerebral cortex	Skeletal Muscle	Thymus
Cerebellum	Ovary	Thyroid
Colon	Pancreas	Tonsil
Endothelium (Aorta)	Pituitary	Ureter
Eye	Prostate Gland	Uterus (cervix)
Fallopian Tube	Stomach	Uterus (endometrium)

Results: Sections of all tissue samples from three donors showed CD31 positive staining, confirming antigen expression in the tissues, implying their suitability for this study. In humans, frequent staining of biotin-labelled sugemalimab was seen at both 1 and 10 µg/ml in the membrane of trophoblastic cells of placenta. No other tissues were reported as showing any binding of sugemalimab.

In monkeys, biotinylated sugemalimab did not bind specifically to any tissues.

Single dose toxicity

In an initial study (211-0286-TX), sugemalimab was given to 1 male and 1 female cynomolgus monkey at a dose of 200 mg/kg intravenously once: the monkeys weighed 3.3 and 2.9 kg respectively. This study was not intended to be in compliance with GLP. Blood was taken for toxicokinetic evaluations at timepoints out to 672 hours (4 weeks) after dosing. From these blood samples, serum was prepared and stored frozen until analysis by ELISA: samples were also taken and used to determine presence of antibody to sugemalimab by use of a bridging ELISA prior to dosing on day 1 and again on day 29. No postmortem data were generated.

No abnormalities were recognised in measures of clinical signs, body weight or food consumption. The maximum tolerable dose was judged to be higher than the dose of 200 mg/kg used here.

The maximum concentration for serum sugemalimab was at the first timepoint, 30 minutes after the end of dosing: the table below gives other toxicokinetic data. Both monkeys showed an immune response with antibodies to sugemalimab detected in samples taken on day 29 with titres of 15,625 in the male and 390,625 in the female.

Dose (mg/kg)	Sex	Animal No.	C_0 (mg/mL)	$T_{1/2}$ (h)	AUC_{0-672h} (h*mg/mL)
200	Male	1001	5.45	374.1	564
	Female	1501	2.71	323.2	575

A second single dose general toxicity was performed in cynomolgus monkeys (211-0323-TX). This study was in compliance with GLP at a facility in China. In this study, sugemalimab was given to 1 male and 1 female cynomolgus monkey/group at doses of 0, 100, 300 or 1000 mg/kg intravenously once: body weights ranged from 3.1-4.1 kg for males and 2.9-4.0 kg for females. Monkeys were observed to day 15 after dosing when they were euthanized (by Zoletil and pentobarbital sodium overdose) and subject to gross pathological evaluations. Blood samples were not taken for toxicokinetic or immunogenicity evaluation purposes.

Again, no abnormalities were recognised in measures of clinical signs, body weight or food consumption and there were no abnormalities identified on gross pathology analyses. The maximum tolerable dose was judged to be not less than 1000 mg/kg.

Repeat-dose toxicity

Two repeat dose general toxicity studies were performed both in cynomolgus monkeys: the first was over 4 weeks (211-0324-TX) and the second (452-0092-TX) was over 26 weeks. Both studies were performed in compliance with GLP at a facility in China. Both used intravenous dosing once weekly in male and female monkeys with 5 or 6 monkeys/sex in each dose group; both studies used doses of 0, 30, 75 and 200 mg/kg sugemalimab. In the 4-week study, 5 doses were given and there was a recovery period of 4 weeks: in the 26-week study, 26 doses were given and there was also a recovery period of 4 weeks. Across both studies, a total of 44 male and 44 female monkeys were used. Ages and body weights were similar across studies and ranged 2.5 – 3.8 years old and from 2.5-3.5 kg for males and 2.5-3.5 kg for females. These studies were run at the same facility by some of the same personnel; however, there was a period of about 2 years between these studies.

In both studies, monkeys were evaluated animals were observed for mortality, clinical signs, body weights, food consumption, ophthalmic examinations, body temperatures, safety pharmacology (electrocardiography, blood pressure, heart rate, and respiratory examinations), clinical pathology (haematology, coagulation, serum chemistry, and urinalysis), immunology (anti-drug antibody analysis, B and T lymphocyte phenotyping, cytokine analysis, immunoglobin and complement concentrations analysis), toxicokinetics, organ weights and macroscopic and microscopic examinations.

Results for 4 week study: There were no unscheduled deaths and no toxicity noted on evaluations of behaviour, injection site examinations, body weight, food consumption, body temperature or clinical pathology (hematology, coagulation, serum chemistry, and urinalysis). In ophthalmological evaluations, there was one instance of retinal depigmentation at 200 mg/kg; the cause was not identified and test-article related retinal degeneration was not excluded, but this was a single case. Electrocardiography, blood

pressure, heart rate and respiration examinations and all immunological evaluations (B and T lymphocyte phenotyping, cytokine analysis, immunoglobin and complement concentrations analysis) were within normal ranges and at post-mortem, there was no indication of abnormalities on evaluations of organ weights or on macroscopic and microscopic examinations. The company set the no-adverse-effect-level (NOAEL) at 200 mg/kg/week.

No monkeys tested positive for ADA to sugemalimab in this study. In kinetic evaluations, there were no marked differences between males and females; systemic exposure increased with dose on Days 1 and 22 across 30-200 mg/kg. At the NOAEL dose, C_{max} and AUC_{0-72h} on Day 22 were 15,100 µg/ml and 653,000 h*µg/ml in males, and 12,200 ug/ml and 599,000 h*µg/ml in females.

Results for 26 week study: As in the 4 week study, this study did not identify any notable toxicity on any of the measures applied. The retinal damage seen in one monkey in the 4-week study did not occur in this study; however, one female at 200 mg/kg in this study did have a focal corneal opacity and this was not excluded because the potential test-article relationship could not be ruled out. The company set the NOAEL at 200 mg/kg/week.

No monkeys tested positive for ADA to sugemalimab in this study. In kinetic evaluations, as in the 4-week study, there were no marked differences between males and females and there was an increase in exposure with dose. At the NOAEL dose, the combined (males and females) C_{max} and AUC_{all} on Day 176 were 14,600 µg/ml and 69,600 day*µg/ml. The table in the section below gives the exposures through this study.

Toxicokinetics

There was no difference in kinetic results between the genders: the table below gives the results for C_{max} and exposures for males and female combined from the 26-week study.

Dose (mg/kg)	Study Day	C_{max} (µg/mL)	AUC_{all} (h*µg/mL)	AUC_{all} (day*µg/mL)
30	1	799	71000	2960
	85	2590	301000	12500
	176	2350	273000	11400
75	1	2220	198000	8250
	85	6970	839000	35000
	176	6500	802000	33400
200	1	5590	482000	20100
	85	14200	1620000	67500
	176	14600	1670000	69600

Interspecies comparison

The company compared exposures between monkeys given a tolerable dose (200 mg/kg) and patients given the intended therapeutic dose (1200 mg or ~20 mg/kg). Simulations were made of steady-state exposures at the proposed clinical dosing regimen of 1200 mg IV Q3W for a typical 61.5 kg (Chinese male) patient, the company noted, derived from 6 clinical studies. This gave a mean C_{max} of 577 µg/ml and a mean $_{AUC0-3w,ss}$ (AUC over a 3-week

dosing interval at steady-state) of 7,304 µgday/ml. The company concluded the toxicity data supported the proposed clinical dosing regimen with > 23- and > 9-fold exposure margins for C_{max} and AUC, respectively.

In Table 2 of the Clinical Pharmacology Summary the information copied in the table below is presented. Comparison of exposure between monkeys given 200 mg/kg and patients in cycle 4 given a dose of 1200 mg indicates C_{max} values of ~14,500 and 715 µg/ml and AUC values of 69,600 and 7,900 µgday/ml respectively: the assessor agrees that exposure in monkeys is well in excess of that expected in humans given this product as a cancer treatment at 1200 mg.

Clinical Pharmacokinetics: Extract of Table 2 from Summary of Clinical Pharmacology Studies: Summary of Sugemalimab Pharmacokinetic Parameters After Single- and Multiple-dose IV Infusion Q3W –(PK Analysis Set – Study CS1001-101a)

	3 mg/kg (N = 3)		10 mg/kg (N = 4)		20 mg/kg (N = 3)		40 mg/kg (N = 3)		1200 mg (N = 16)	
Parameter (Unit)	n	Geometric Mean (% Geo. CV)	n	Geometric Mean (% Geo. CV)	n	Geometric Mean (% Geo. CV)	n	Geometric Mean (% Geo. CV)	n	Geometric Mean (% Geo. CV)
Cycle 4										
C_{max} (µg/mL)	1	77.61 (-)	2	285.90 (31.36)	3	469.78 (14.83)	1	1187.47 (-)	14	713.64 (25.77)
$AUC_{0\text{-}21d}$ (day•µg/mL)	1	1017.55 (-)	1	3349.00 (-)	3	5178.05 (30.86)	0	-	11	8548.90 (19.28)
AUC_{tau} (day•µg/mL)	1	1016.78 (-)	1	3348.56 (-)	3	4934.00 (39.53)	1	14272.82 (-)	13	7897.90 (35.57)
$R_{acc,AUC}$	1	2.15 (-)	1	1.43 (-)	3	1.48 (11.80)	1	1.58 (-)	13	2.00 (40.34)
$R_{acc,Cmax}$	1	1.30 (-)	1	0.99 (-)	3	1.34 (15.99)	1	1.03 (-)	13	1.74 (43.87)

Genotoxicity
No genotoxicity studies were performed.

Carcinogenicity
No carcinogenicity studies were performed.

Reproductive and developmental toxicity
No reproductive or developmental toxicity studies were performed.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
No juvenile toxicity studies were performed.

Local tolerance
Separate local tolerance studies were not performed: relevant endpoints were evaluated in general toxicity studies.

Other toxicity studies
Haematocompatability
Sugemalimab was not haemolytic and did not induce red blood cell coagulation in assays using rabbit red blood cells: the concentration tested was up to 30.8 mg/ml.

Antigenicity studies
Sugemalimab was not rated as a sensitiser in a guinea pig sensitisation/anaphylaxis study.
Other studies

Specific studies into immunotoxicity, dependence, metabolites and impurities were not performed.

Overall conclusions on toxicology

Sugemalimab did not affect measures of vital functions (ECG, blood pressure, heart rate, waveforms, or respiratory and neurological evaluations) when given to cynomolgus monkeys at up to 200 mg/kg. In general toxicity studies with dosing over 26 weeks with a 4-week period after dosing ended, there was no toxicity identified that was attributed to sugemalimab. The doses used (up to 200 mg/kg intravenously) and once-weekly dosing frequency resulted in exposure in monkeys higher than that expected in patients given 1200 mg. In addition, monkeys were judged to be a suitable species in which to evaluate potential toxicity of sugemalimab, based on comparable affinity for sugemalimab binding to human and monkey PD-L1; however, there was some disparity in the tissue cross reactivity studies, where binding was present in some human tissues but not in any tissues from monkeys. However, the human tissue binding was only to placental trophoblasts. The use of monkeys in the toxicity studies is primarily supported by the in vitro binding studies presented the pharmacology section of this report.

The general toxicity studies in monkeys did not identify any toxicity. There were descriptions of each of one instance each of retinal depigmentation (in the 4-week study) and of eye focal cornea opacity in one eye (in the 26-week study). These both occurred at the top dose used but were judged by the company to be isolated instances: the MHRA assessor accepted this interpretation. The NOAEL dose was set as the highest dose of 200 mg/kg/week in both 4-week and 26-week studies.

The mode of action of the drug to inhibit PD-L1 might be expected to result in some immunological consequences. For instance, with nivolumab (anther PD-L1 targeting antibody), an increase in inflammatory cells in multiple organs was described as an expected effect, without inducing autoimmunity. No such findings of diffuse mononuclear cell infiltration were noted here. During the procedure, the company were asked to comment on this difference.

A further observation in this file is that as a single dose the drug was quite immunogenic in monkeys but when given repeatedly, there were no monkeys that tested positive for anti-drug antibody to sugemalimab.

In the single-dose toxicity study 211-0286-TX, two out of two samples were tested positive for antidrug antibodies (ADA), whereas no sample was confirmed to be ADA-positive in the dosing and recovery phases of the 4-week and 26-week cynomolgus monkey repeat-dose toxicity studies 211- 0324-TX and 452-0092-TX. The company believes that the observed differences resulted from differences in methodology (see Table 4).
In the single-dose exploratory toxicity study 211-0286-TX, the presence of ADA was evaluated by a single tier generic assay (with an arbitrary positive criterion as OD value > 2.1-fold of OD value of the pre-dose sample). No confirmation assay for the positive samples was performed. In the repeat-dose toxicity studies 211-0324-TX and 452-0092-TX, however, a fully validated multi-tiered approach (see 211-0321-AM in Appendix 2 of method validation report 211-0321-IM) was used. The first tier was a screening assay (with a floating cut point allowing 5% false positive rate) utilising a format as well as critical reagents significantly different from those of 211-0286-TX ADA assay. In case of a positive result, a confirmatory assay must be performed as the second tier to verify the specificity via

competitive inhibition using unlabelled sugemalimab (with a cut point allowing 0.1% false positive rate). In case the result from confirmatory assay is still positive, the titre assay is conducted (211-0324-TX Appendix 17 and 452-0092-TX Appendix 20). In study 211-0324-TX, 7 out of 156 samples were tested ADA-positive in the screening assay. But all these 7 samples were tested negative in the subsequent confirmation assay. Consequently, no sample was reported as ADA-positive (211- 0324-TX Appendix 17). In study 452-0092-TX, 214 samples were analysed in the screening assay and 7 of them were positive. These 7 samples were tested negative in the confirmation assay. Therefore, no sample was reported as ADA-positive (452-0092-TX Appendix 20). Considering the non-validated generic assay format and the lack of confirmation of binding specificity in study 211-0286-TX, the ADA positivity rate in this single-dose study was very likely to be overestimated.

Table 4: Comparison of ADA Assay Methodologies in the Single Dose Toxicity Study and the GLP-compliant Repeat Dose Toxicity Studies

Used in Study No.	211-0286-TX	211-0324-TX, 452-0092-TX
ADA Method No.	N/A	211-0321-AM
Method Validation Study No.	N/A	211-0321-IM
Critical Reagents	Sugemalimab (coating) Anti-monkey IgG antibody-HRP (detection)	Sugemalimab-biotin (coating to streptavidin plate) Sugemalimab-digoxigenin Anti-digoxigenin-POD (poly), Fab fragments (detection) Anti-sugemalimab antibody (positive control) Sugemalimab (inhibitor in confirmatory assay)
Number of Assay Tier(s)	1	3
Cut Point for Positive Result & Titre Calculation	Titre = Final dilution with an OD value >2.1-fold of the OD value of the corresponding pre-dose sample	Screening cut-point (SCP): OD value > 1.96-fold of the mean OD value of plate negative control samples Confirmatory cut point:>15% inhibition by unlabelled sugemalimab in confirmatory assay Titre = Dilution above SCP + (Dilution below SCP - Dilution above SCP) * (OD above SCP - SCP)/ (OD above SCP - OD below SCP)

The negative ADA results after repeated dosing might also be sign of high zone immune tolerance, which could be induced by frequent dosing. For example, in patients treated with infliximab, the incidence of ADA formation was 28% after a single dose of infliximab compared with 6% after repeated dose. The potential mechanisms include exposure-dependent activation of regulatory T cells and/or apoptosis of effector T-cells. The company's reasoning was accepted. False positive results from a single tier of testing could well explain this. Overall, this did not impede interpretation of toxicity study results.

Genotoxicity studies are not relevant for antibody product. Carcinogenicity studies are not needed for products that are intended as treatments for advanced cancer: rodent carcinogenicity studies are not relevant for this product.

The indication intended for this product is for use in combination with platinum-based chemotherapy as treatment of adults with metastatic non-small-cell lung cancer (NSCLC). Platinum-based chemotherapy is likely to be teratogenic. Other drugs with similar pharmacological actions (eg nivolumab) are known to induce reproductive toxicity – foetal loss / abortions might be expected with use of sugemalimab, based on its primary pharmacological action. As such, no reproductive toxicity studies are required. This is in line with regulatory guidance (ICH S9 Nonclinical evaluation for anticancer pharmaceuticals) where alternative approaches including literature-based assessments might be considered appropriate: the assessor considers this is appropriate and studies in pregnant monkeys given sugemalimab are not required. The PD-1/PD-L1 pathway is involved in maintenance of maternal immune tolerance to the foetus in pregnancy to allow and blocking this causes foetal loss or abortion. Sugemalimab is expected to have this same effect and it is not necessary to conduct studies in animals to demonstrate such effects. Therefore, use of this product in pregnancy should be associated with an expectation of foetal loss. Sugemalimab may be transmitted from the mother to the developing foetus. The product information warns of this effect.

In summary, the toxicity data do not identify any particular reason for concern for use of this antibody and in so far as such studies can identify potential toxicity in humans, they are considered sufficient. The absence of some inflammatory response in multiple tissues was not expected by the assessor as this has been seen with other agents acting by the same mechanism: the company commented on this apparent difference and this was concluded to be resolved. Also, there seemed to be differences across different studies in the degree to which sugemalimab induced antibodies in monkeys. The company explained this.

Regarding the GLP status, studies were conducted in China and China operates its own GLP system that is not aligned with the international system for recognition of data to which the UK adheres: nevertheless, a conclusion that these data should be disregarded and so studies must be repeated cannot be supported. The consequence of such a stance is either that further monkeys must be dosed in a study, for the sole purpose of providing data in compliance with GLP, which is not a viable conclusion. There are also data from the use of the product in patients, in both clinical trials and in regular use through commercial supply.

III.5 Ecotoxicity/Environmental Risk Assessment

In line with current regulatory guidance applicable to proteins (CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/000 corr 2)) experimental studies supporting an ERA are not required, as due to their nature they are unlikely to result in a significant risk to the environment. Sugemalimab is a monoclonal antibody and contains no novel excipients (these being histidine, mannitol, sodium chloride, polysorbate 80 and water for injection); this is acceptable.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The following clinical studies were submitted with this application:

Table 1: Clinical Studies Relevant to Clinical Pharmacology

Study Number Country Status (Data Cutoff)	Study Design	Population	Intravenous Treatment Regimen	Number of Participants Included in PopPK Analysis
CS1001-101a China Complete (30 Nov 2018)	Phase 1, open-label, dose-escalation.	Advanced solid tumours or lymphomas.	Sugemalimab 3 mg/kg Q3W	3
			Sugemalimab 10 mg/kg Q3W	4
			Sugemalimab 20 mg/kg Q3W	3
			Sugemalimab 40 mg/kg Q3W	3
			Sugemalimab 1200 mg Q3W	16
CS1001-101b[a] China Ongoing (16 Aug 2021)	Phase 1, open-label, dose-expansion.	Cohort 1: NKTL.	Sugemalimab 1200 mg Q3W	4
		Cohort 2: CC/GBC.		29
		Cohort 3: HCC (≥ 2L).		24
		Cohort 4: Any tumour with MSI-H or dMMR.		22
		Cohort 5: GC/GEJAC.	Sugemalimab 1200 mg Q3W + XELOX regimen Q3W (up to 6 cycles) Oxaliplatin: 130 mg/m² IV Day 1 Capecitabine: 1000 mg/m²/time BID oral Days 1 to 14	29
		Cohort 6: ESCC (1L).	Sugemalimab 1200 mg Q3W + Q3W (up to 6 cycles): Cisplatin: 80 mg/m² IV Day 1 5-FU: 800 mg/m²/day IV Days 1 to 5	41
		Cohort 7: ESCC (≥ 2L).	Sugemalimab 1200 mg Q3W + Docetaxel 75 mg/m², IV Q3W	4
		Cohort 8: Non-sq NSCLC.	Sugemalimab 1200 mg Q3W + Q3W (up to 6 cycles): Pemetrexed 500 mg/m² IV Day 1 Carboplatin AUC = 5 IV Day 1	21

Table 1: Clinical Studies Relevant to Clinical Pharmacology (Continued)

Study Number Country Status (Data Cutoff)	Study Design	Population	Intravenous Treatment Regimen	Number of Participants Included in PopPK Analysis
CS1001-101b[a] China Ongoing (16 Aug 2021) continued	Phase 1, open-label, dose-expansion.	Cohort 9: Sq NSCLC.	Sugemalimab 1200 mg Q3W + Q3W (up to 6 cycles): Paclitaxel: 175 mg/m²/day IV Day 1 Carboplatin AUC = 5 IV Day 1	20
		Cohort 11: HCC.	Sugemalimab 1200 mg Q3W + Lenvatinib Body weight ≥ 60 kg: 8 or 12 mg QD oral Body weight < 60 kg: 4 or 8 mg QD oral	23
CS1001-102 USA (Bridging) Complete (19 Oct 2020)	Phase 1, dose-escalation, open-label.	Advanced solid tumours or lymphomas.	Sugemalimab 10 mg/kg Q3W	12
			Sugemalimab 1200 mg Q3W	12
CS1001-201 China Ongoing (10 Nov 2021)	Phase 2, single-arm, open-label.	R/R ENKTL.	Sugemalimab 1200 mg Q3W	80
CS1001-202 China Complete (19 Feb 2020)	Phase 2, single-arm, open-label.	Relapsed or refractory classical Hodgkin lymphoma.	Sugemalimab 1200 mg Q3W	80

Table 1: Clinical Studies Relevant to Clinical Pharmacology (Continued)

Study Number Country Status (Data Cutoff)	Study Design	Population	Intravenous Treatment Regimen	Number of Participants Included in PopPK Analysis
CS1001-302 China Ongoing (22 Nov 2021)	Phase 3, randomised, double-blind, placebo-controlled, in combination with chemotherapy.	Stage IV NSCLC.	3-week treatment cycle: Sugemalimab 1200 mg Q3W and platinum-based chemotherapy	320
			3-week treatment cycle: Placebo Q3W and platinum-based chemotherapy	159[b]
CS1001-301 China Ongoing (08 Mar 2021)	Phase 3, randomised, double-blind, placebo-controlled, monotherapy.	Stage III NSCLC.	Sugemalimab 1200 mg Q3W	252
			Placebo Q3W	126[b]

[a] No participants were enrolled to cohort 10.
[b] Participants assigned to placebo were excluded from the popPK analysis.
1L = first-line; 2L = second-line; 5-FU = 5-fluorouracil; BID = twice daily; CC = cholangiocarcinoma; dMMR = deficient mismatch repair gene; ESCC = oesophageal squamous cell carcinoma; GBC = gallbladder carcinoma; GC = gastric carcinoma; GEJAC = gastroesophageal junction adenocarcinoma; HCC = hepatocellular carcinoma; IV = intravenous; MSI-H = microsatellite instability-high; NKTL = natural killer T cell lymphoma; Non-sq = non-squamous cell; NSCLC = non-small cell lung cancer; PopPK = population pharmacokinetic; Q3W = every 3 weeks; QD = once daily; R/R ENKTL = relapsed or refractory extranodal natural killer T cell lymphoma; Sq = squamous cell.
Source: CSRs as detailed in the table and PopPK/E-R Analysis Report 270593, Table 1.

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

Clinical pharmacology objectives have been implemented in 6 clinical studies following single and multiple IV infusions of 3, 10, 20, and 40 mg/kg Q3W, and 1200 mg fixed dose Q3W. These include Phase 1 studies in participants with advanced solid tumours (including NSCLC) or lymphomas (Studies CS1001-101a/b and CS1001-102), Phase 2 studies in participants with haematologic malignancies (Studies CS1001-201 and CS1001-202), and Phase 3 studies in participants with NSCLC (Study CS1001-301 and the pivotal Study CS1001-302).

The Clinical Pharmacology submission is supported by 6 clinical studies following single and multiple IV infusions of sugemalimab in patients with solid and haematologic malignancies.

Methods

Analytical methods

Standard methodology has been used for assessment of PK. Data were shown to demonstrate robustness of the assay validation.

Pharmacokinetic data analysis

Standard pharmacokinetics methods were used to derive pharmacokinetic parameters and data was summarised using standard summary statistical methods.

Evaluation and Qualification of Models

Population Pharmacokinetic Analysis

The PopPK model was developed using the individual-level concentration-time profiles from 6 clinical studies (CS1001-101a/b, CS1001-102, CS1001-201, CS1001-202, CS1001-301, and CS1001-302; **Error! Reference source not found.**). The model included PK data from 1002 participants who were Asian (Chinese; n = 978), White (n = 20), or other races (n = 4), with individual body weights ranging from 36 to 124 kg. Exposure data from weight-based dosing regimens ranging from 3 to 40 mg/kg IV Q3W, as a well as a fixed dose regimen of 1200 mg IV Q3W, were included in the analysis. A total of 7054 sugemalimab serum concentration records were obtained from the 1002 participants. Of these samples, 3999

serum concentrations were obtained from 613 participants with NSCLC, and 3055 serum concentrations were obtained from 389 participants with lymphoma or other solid tumours.

The effects of the following covariates on the PK of sugemalimab were assessed: standard demographics (body weight, age, sex, and race), albumin, markers of hepatic function (AST, ALT, and total bilirubin), markers of renal function (CRCL), disease status (Stage III/IV NSCLC, lymphomas, and other solid tumours), and ADA status and titre.

Exposure-response Analysis
For both efficacy and safety, and individual sugemalimab PK parameter estimates from the above-mentioned PopPK model were used to determine the following exposure metrics: $C_{trough,C1}$ (i.e., immediately prior to the second dose), $AUC_{tau,C1}$, and $C_{max,C1}$. Exposure metrics taken during Cycle 1 were used in the analysis due to the fact that sugemalimab displays time-dependent clearance. Using only Cycle 1 exposure metrics in the model was employed to mitigate potential bias in the estimated-exposure-response relationship inducible by this nonconstant clearance.

Exposure-efficacy Analysis
Using data from the Phase 3 study, CS1001-302 in participants with Stage IV NSCLC, the exposure-efficacy relationship of sugemalimab was explored following a dose of 1200 mg IV Q3W for the following efficacy endpoints: OR, PFS, and OS. In this analysis OR was defined via the categorisation of BOR as either "responder" (CR or PR), or "non-responder" (SD, PD, or NE). The OR and PFS endpoints were evaluated both as Investigator-assessed and by BICR.

Graphical analysis comprised boxplots of continuous exposure metrics as well as Kaplan-Meier curves stratified by exposure quartile (PFS and OS only). Logistic regression models were then used to relate OR to exposure parameters, while for PFS and OS, TTE regression models were evaluated for this purpose. For all endpoints, the effects of the following prespecified continuous or categorical covariates were evaluated in addition to sugemalimab exposure: body weight, age, sex, race (Asian vs. non-Asian), ECOG, NSCLC disease stage (Stage III versus Stage IV), squamous cell versus non-squamous cell carcinoma, baseline brain metastases, baseline tumour burden, PD-L1 expression percentage (< 1% versus < 1%), and ADA status.

Exposure-safety Analysis
Exposure-safety analysis was carried out using data from 4 clinical studies (2 Phase 1 studies, CS1001-101a/b and CS1001-102, and 2 Phase 3 studies, CS1001-301 and CS1001-302) comprising participants with Stage III or IV NSCLC, lymphomas, or other solid tumours. The effect of sugemalimab exposure across a dose range of 3 to 40 mg/kg IV Q3W (including the intended clinical dose of 1200 mg IV Q3W) was explored on the following immune-related safety endpoints: hepatitis, hyperthyroidism, hypothyroidism, pneumonitis, severe/non-severe skin adverse reactions, and hepatotoxicity-related adverse reactions. In addition, any Grade ≥ 3 sugemalimab-related TEAE was considered.

The exposure-safety analysis used the same exposure metrics as the exposure-efficacy analysis. Graphical analysis (boxplots) and logistic regression modelling were carried out to understand and characterise the relationship between sugemalimab exposure and safety events.

Exposure-response Simulations to Support Dose Selection in Non-Asian Demographic
Since all participants with NSCLC were of Asian race, simulations based upon developed exposure-response analysis were carried out to understand expected exposure-response relationships for different patient characteristics to help support dose selection in the non-Asian demographic. Specifically, these simulations accounted for differences in PK due to patient characteristics to allow for prediction of outcomes in NSCLC patients with demographics representative of the non-Asian population under the 1200 mg fixed dose IV Q3W regimen. Additionally, as in vitro data suggested 100% RO attainment at a dose of 10 mg/kg IV Q3W and at the 1200 mg fixed dose IV Q3W, the PopPK and E-R models were used to simulate the anticipated PK and resulting model-predicted efficacy of a 10 mg/kg IV Q3W regimen versus 1200 mg fixed dose IV Q3W for the non-Asian NSCLC population.

Given the lack of identification of an effect of race on sugemalimab PK in the PopPK model once body weight was included as a covariate, 1000 virtual participants were sampled with replacement from participants enrolled Study CS1001-302 in each of 3 categories. These categories were chosen to account for differences in body weight due to participant characteristics (eg, ethnic group) as follows:

- Asian: sampled from Asian participants enrolled in the clinical studies
- Non-Asian: sampled from *Normal* (70 kg [standard deviation = 15 kg]) for males and *Normal* (65 kg [standard deviation = 15 kg]) for females
- Extreme body weight: sampled from *Uniform* (90 kg, 120 kg)

The final PopPK model was used to simulate exposure metrics $AUC_{tau,C1}$, $C_{trough,C1}$, and $C_{max,C1}$ for each virtual participant under both 1200 mg IV Q3W and 10 mg/kg IV Q3W. These exposure metrics were then incorporated into the exposure-efficacy models to compute the cumulative expected probability of PFS and OS every 3 months up to 24 months.

Standard methods for population pharmacokinetic analysis and exposure-response analysis were used. The data included in this analysis was derived mainly from Asian population with <0.3% of the data derived from White and Other races populations. So, any conclusions related to the effect of race of pharmacokinetics and exposure-response analysis should be interpreted with caution.

Pharmacokinetics Properties
Following IV infusion of sugemalimab, C_{max} is reached after the EOI. After a single dose of 1200 mg IV Q3W in participants with advanced solid tumours, the geometric mean C_{max} (CV) was 422.59 μg/mL (22.76%).

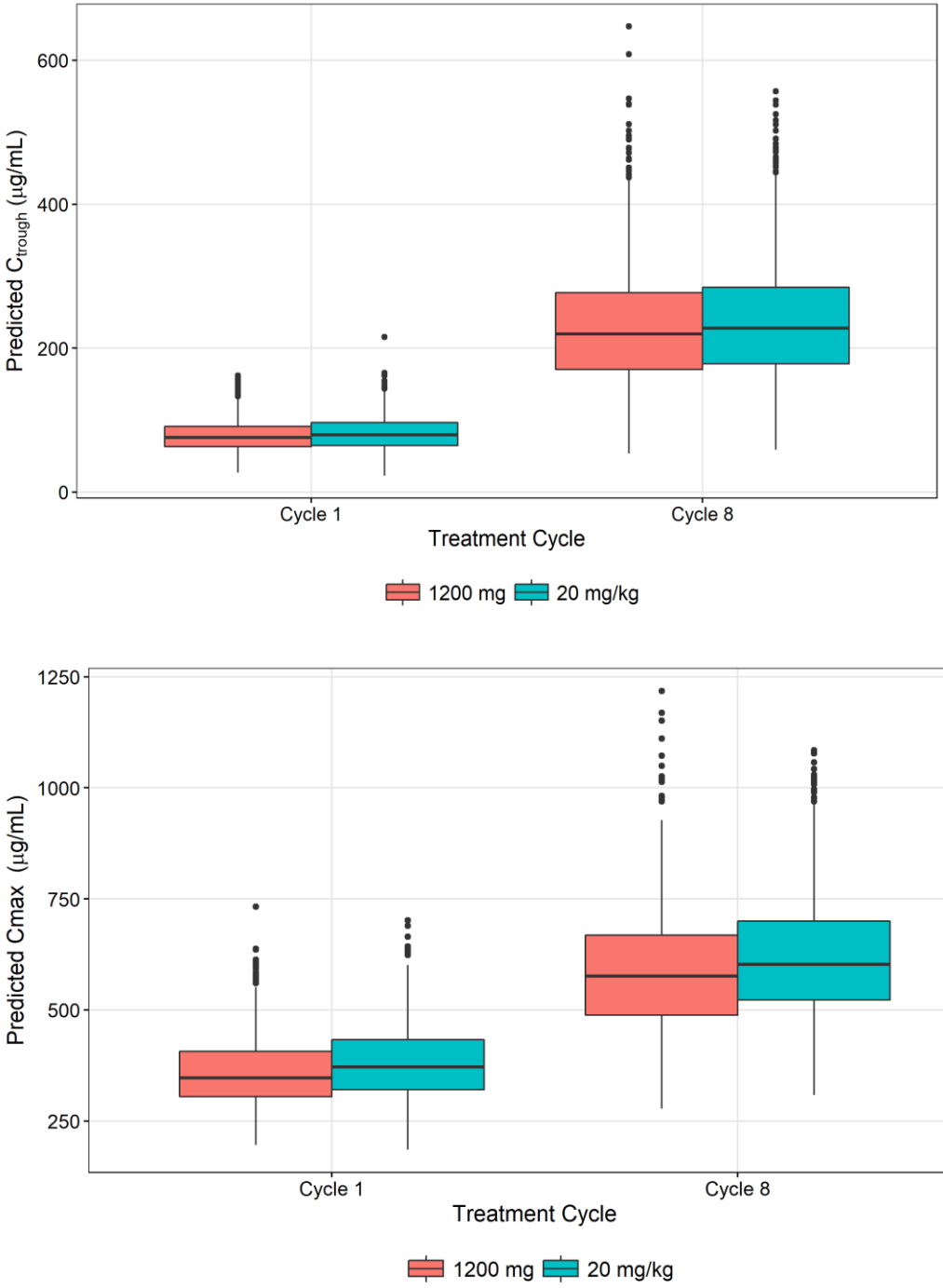
Following single- and multiple-dose IV infusions, sugemalimab exposures (AUC and C_{max}) increased in an approximately dose-proportional manner within the dose range of 3 to 40 mg/kg Q3W, including a fixed dose of 1200 mg Q3W.

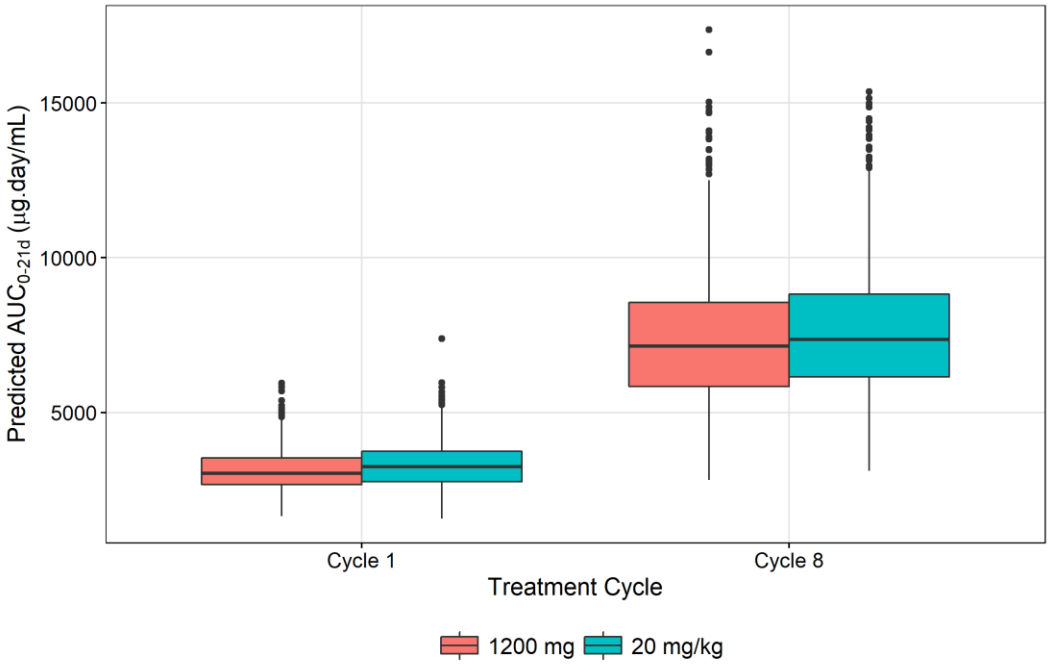
Sugemalimab exposures (C_{max} and AUC_{0-21d}) were similar for the weight-based dose of 20 mg/kg IV Q3W and the fixed dose of 1200 mg IV Q3W.

Following multiple IV infusions at the proposed therapeutic dose of 1200 mg Q3W, there was an approximately 2-fold accumulation of sugemalimab exposures (i.e., $R_{acc,Cmax}$ and $R_{acc,AUC}$ were 1.74 and 2.00, respectively).

Comparable C_{trough}, C_{max}, and $AUC_{0\text{-}21d}$ between the weight-based dose of 20 mg/kg IV Q3W and 1200 mg fixed dose IV Q3W were also observed both after a single dose in Cycle 1 and at steady state based on PopPK model simulations using virtual participants with NSCLC from Studies CS1001-301 and CS1001-302 (Figure 1).

Figure 1: Graphical Presentation (Boxplots) of Sugemalimab Simulated Trough, Maximum, and Cumulative (Over the Dosing Interval) Exposures Following IV Infusions of 20 mg/kg IV Q3W and 1200 mg Fixed Dose IV Q3W (Report 270593)





Note: Solid horizontal lines represent the median, the top and bottom of the box represent the 25th and 75th percentiles, the whiskers represent the IQR, and the circles represent outliers (≥ 1.5 × IQR).
$AUC_{0\text{-}21d}$ = area under the serum concentration-time curve for 0 to 21 days postdose; C_{max} = maximum serum concentration; C_{trough} = trough serum concentration; IQR = interquartile range; IV = intravenous; Q3W = once every 3 weeks.

Absorption
Sugemalimab is administered by IV infusion and therefore is immediately and completely bioavailable.

Influence of food
Not applicable

Distribution
Consistent with the typical limited extravascular distribution of mAbs, the Vss was small, with a geometric mean (CV%) Vss of 4.88 L (27%). As expected for an antibody, sugemalimab did not bind to plasma proteins in a specific manner.
The PopPK-estimated volume of distribution was consistent with geometric mean estimates for Vss from NCA, which ranged from 3.60 to 6.72 L after repeated 1200 mg IV Q3W doses.

Biotransformation
As an antibody, sugemalimab is catabolised through nonspecific pathways; metabolism does not contribute to its clearance.

Elimination
In the PopPK analysis, geometric mean (CV%) of total CL after a single dose was estimated to be 0.211 L/day (28.5%). At steady state (Cycle 8), geometric mean (CV%) total CL was estimated as 0.155 L/day (28.4%). The 27% decrease in mean total CL from single dose to steady state was not considered clinically meaningful. The geometric mean (CV%) t1/2

estimated from the PopPK model was approximately 17 days (25.6%) at the end of Cycle 1 and 23 days (29.6%) at steady state (Cycle 8).
The PopPK estimate of CL after a single dose was comparable to the geometric mean CL obtained by NCA after a single 1200 mg dose, which ranged from 0.176 to 0.269 L/day across studies. Similarly, the PopPK-estimated elimination t1/2 was consistent with t1/2 values estimated from NCA across studies, where the arithmetic mean t1/2 ranged from 13 to 22 days following a single IV infusion of 1200 mg fixed dose Q3W.
Time to steady state was determined using simulations from the PopPK model, which showed attainment of steady state concentrations by Cycle 8, i.e., by 24 weeks after the first dose of 1200 mg IV Q3W sugemalimab.

Dose proportionality and time dependency

- **Dose proportionality and time dependency**

Study CS1001-101, Phase 1a (Dose-escalation)
Following single IV infusions of sugemalimab at 3, 10, 20 mg/kg Q3W, 1200 mg Q3W fixed dose, and 40 mg/kg Q3W, the median t_{max} ranged from 2.05 to 4.55 hours, while mean $t_{1/2}$ ranged from 12.2 to 17.6 days. Systemic exposures of sugemalimab (C_{max} and AUC) were approximately dose-proportional over the dose range evaluated (Table 2).

Table 2: Summary of Sugemalimab Pharmacokinetic Parameters After Single- and Multiple-dose IV Infusion Q3W – (PK Analysis Set – Study CS1001-101a)

	3 mg/kg (N = 3)		10 mg/kg (N = 4)		20 mg/kg (N = 3)		40 mg/kg (N = 3)		1200 mg (N = 16)	
Parameter (Unit)	n	Geometric Mean (% Geo. CV)	n	Geometric Mean (% Geo. CV)	n	Geometric Mean (% Geo. CV)	n	Geometric Mean (% Geo. CV)	n	Geometric Mean (% Geo. CV)
Cycle 1										
C_{max} (µg/mL)	3	52.82 (15.32)	4	257.52 (25.25)	3	349.44 (13.90)	3	1278.31 (35.34)	16	422.59 (22.76)
$AUC_{0\text{-}21d}$ (day•µg/mL)	3	453.67 (10.95)	3	2099.27 (16.31)	3	3492.67 (23.82)	3	9954.30 (12.48)	15	3951.85 (17.67)
$AUC_{0\text{-}\infty}$ (day•µg/mL)	3	645.19 (19.46)	3	3195.21 (5.80)	2	5946.81 (16.16)	3	17869.92 (37.30)	16	6802.22 (32.98)
$t_{1/2}$, (day)	3	12.2 (3.32)	3	14.3 (3.59)	2	15.5 (0.07)	3	16.1 (5.66)	16	17.6 (6.24)
Cycle 4										
C_{max} (µg/mL)	1	77.61 (-)	2	285.90 (31.36)	3	469.78 (14.83)	1	1187.47 (-)	14	713.64 (25.77)
$AUC_{0\text{-}21d}$ (day•µg/mL)	1	1017.55 (-)	1	3349.00 (-)	3	5178.05 (30.86)	0	-	11	8548.90 (19.28)
AUC_{tau} (day•µg/mL)	1	1016.78 (-)	1	3348.56 (-)	3	4934.00 (39.53)	1	14272.82 (-)	13	7897.90 (35.57)
$R_{acc,AUC}$	1	2.15 (-)	1	1.43 (-)	3	1.48 (11.80)	1	1.58 (-)	13	2.00 (40.34)
$R_{acc,Cmax}$	1	1.30 (-)	1	0.99 (-)	3	1.34 (15.99)	1	1.03 (-)	13	1.74 (43.87)

Note: If the data was available, the accumulation index AUC = Cycle 4 $AUC_{0\text{-}21d}$ / Cycle 1 $AUC_{0\text{-}21d}$. Otherwise, the accumulation index AUC = Cycle 4 $AUC_{0\text{-}14d}$ / Cycle 1 $AUC_{0\text{-}14d}$. The $t_{1/2}$ is reported as arithmetic mean and standard deviation.
(-) = not applicable; $AUC_{0\text{-}\infty}$ = area under the curve from time 0 to infinity; $AUC_{0\text{-}21d}$ = area under the curve from time 0 to 21 days; AUC_{tau} = area under the serum concentration-time curve for the dosing interval C_{max} = maximum serum concentration; IV = intravenous; Geo. CV = geometric coefficient of variation; n = number of participants in analysis set; N = number of participants; PK = pharmacokinetic; Q3W = once every 3 weeks; $R_{acc,AUC}$ = accumulation ratio for AUC; $R_{acc,Cmax}$ = accumulation ratio for C_{max}; $t_{1/2}$ = elimination half-life.

The sugemalimab PK parameters median t_{max}, arithmetic mean $t_{1/2}$, geometric mean CL, and geometric mean V_{ss} were approximately similar across doses following the IV infusion of single ascending doses Q3W.

Following multiple IV infusions of sugemalimab at 3, 10, 20, and 40 mg/kg Q3W, and 1200 mg Q3W fixed dose, the systemic exposures increased in an approximately dose-proportional manner. The mean $R_{acc,AUC}$ for each group in Cycle 4 ranged from 1.43 to

2.15, and the mean $R_{acc,Cmax}$ ranged from 0.99 to 1.74. Following multiple IV infusions at the proposed therapeutic dose of 1200 mg Q3W, there was approximately 2-fold accumulation of sugemalimab exposures (i.e., mean $R_{acc,Cmax}$ and $R_{acc,AUC}$ were 1.74 and 2.00, respectively). Sugemalimab exposures (C_{max} and AUC_{0-21d}) were similar for the weight-based dose of 20 mg/kg and the fixed dose of 1200 mg in Phase 1a.

Intra- and inter-individual variability
Inter-individual variability was investigated in the population PK parameters. The applicant also provided estimates for the intra-individual variability based on the inter-occasion variability (IOV) parameter in the popPK model. IOV was 14.0% for CL and 8.5% for Vc which indicates low intra-individual variability.

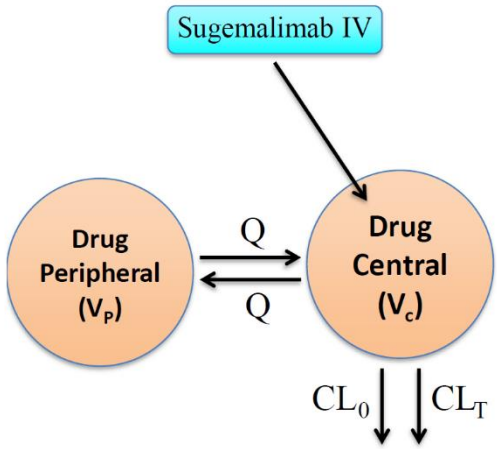
Sugemalimab is administered via IV infusion. Following administration, Cmax is reached by end of infusion. Following single and multiple administrations, sugemalimab exposure is increased in an approximately dose-proportional manner in the dose range of 3 to 40 mg/kg Q3W. The company compared the exposure after the weight adjusted dose of 20 mg/kg to the flat dose of 1200 mg and the exposure was comparable between the two doses after single and 8 cycles of multiple doses where steady state is anticipated. Sugemalimab has a small volume of distribution at steady state (Vss) of 4.88L consistent with monoclonal antibodies.

Sugemalimab is catabolised through nonspecific clearance pathways such as proteolysis. Population Pharmacokinetics analysis estimated total Clearance after a single dose to be 0.211 L/day. Population PK predicted clearance was comparable to non-compartmental analysis estimated clearance for the dose of 1200mg across studies. The t1/2 was estimated to be 13 to 22 days which was not consistent with the steady achieved by 24 weeks. Based on a t1/2 of 3 weeks, the steady state was expected to be reached by 15 weeks. For the dose of 1200 mg Q3W, there was approximately 2-fold accumulation of sugemalimab exposure. Inter-individual variability was low to moderate for clearance and central volume of distribution.

The company indicated that the reason for the longer time to reach steady state is the time dependent clearance.

Pharmacokinetics in target population
Sugemalimab pharmacokinetics were best described by a two-compartment base structural model with both stationary (time-independent) and time-dependent clearance from the central compartment. A schematic of this base structural model is given in Figure 2.

Figure 2: Schematic of the Final Population Pharmacokinetic Model (Report 270593)



CL_0 = time-independent clearance; CL_T = time-dependent clearance; IV = intravenous; Q = intercompartmental clearance; V_c = central volume of distribution; V_p = peripheral volume of distribution.

Residual variability was modelled using a multiplicative error model. Statistically significant covariates included in the final model were body weight, sex, and albumin on CL_0 and V_c, sex and time-varying ADA titre on CL_T, albumin on V_p, lymphoma disease on V_c and k_{des}, and NSCLC disease on V_p. The final PopPK model parameter estimates are presented in **Error! Reference source not found.**, and summary statistics of individual estimates of V_{ss}, CL, and $t_{1/2}$ can be found in **Error! Reference source not found.** for Cycle 1 (single dose), Cycle 4 (repeated doses), and Cycle 8 (steady state).

Table 4: Parameter Estimates for the Final Sugemalimab Population Pharmacokinetic Model (Report 270593)

Parameter	Estimate	RSE (%)	95% CI
Nonspecific time-independent clearance (CL_0, L/day)	0.149	1.4	0.145, 0.153
Effect of sex on CL_0	0.904	2.6	0.857, 0.947
Effect of weight on CL_0	0.770	7.2	0.656, 0.878
Effect of albumin on CL_0	-0.980	9.0	-1.148, -0.808
Initial time-dependent clearance (CL_T, L/day)	0.108	4.4	0.099, 0.117
Effect of sex on CL_T	0.713	6.5	0.635, 0.808
Effect of time-varying ADA titre on CL_T	0.092	15.6	0.068, 0.122
Decay coefficient of time-dependent clearance (k_{des}, 1/day)	0.0188	6.8	0.0162, 0.0212
Effect of lymphoma disease on k_{des}	0.0465	13.7	0.0349, 0.0591
Central volume of distribution (V_c, L)	3.42	1.1	3.35, 3.50
Effect of sex on V_c	0.858	2.1	0.825, 0.896
Effect of weight on V_c	0.446	9.7	0.372, 0.543
Effect of albumin on V_c	-0.332	21.5	-0.471, -0.183
Effect of lymphoma disease on V_c	0.896	2.1	0.860, 0.932
Intercompartmental clearance (Q, L/day)	0.373	8.0	0.310, 0.428
Peripheral volume of distribution (V_p, L)	0.573	22.2	0.326, 0.845
Effect of albumin on V_p	-1.40	25.2	-2.02, -0.69
Effect of NSCLC disease on V_p	3.21	23.8	2.03, 5.18
Between subject variability for CL_0	24.9	3.6	23.3, 26.7
Between subject variability for V_c	18.6	3.4	17.4, 19.8
Between subject variability for V_p	61.6	6.5	54.0, 69.4
Between subject variability for CL_T	46.3	6.5	40.0, 51.5
Between subject variability for k_{des}	104.2	5.7	93.0, 116.6
Correlation between CL_0 and V_c	0.365	12.6	0.268, 0.450
Correlation between CL_T and V_c	0.610	9.6	0.474, 0.713
Correlation between CL_T and k_{des}	0.448	15.1	0.312, 0.570
Proportional residual unexplained variability (%)	16.9	0.9	16.7, 17.2

%RSE = percent relative standard error; ADA = antidrug antibody; CI = confidence interval; NSCLC = non-small cell lung cancer.

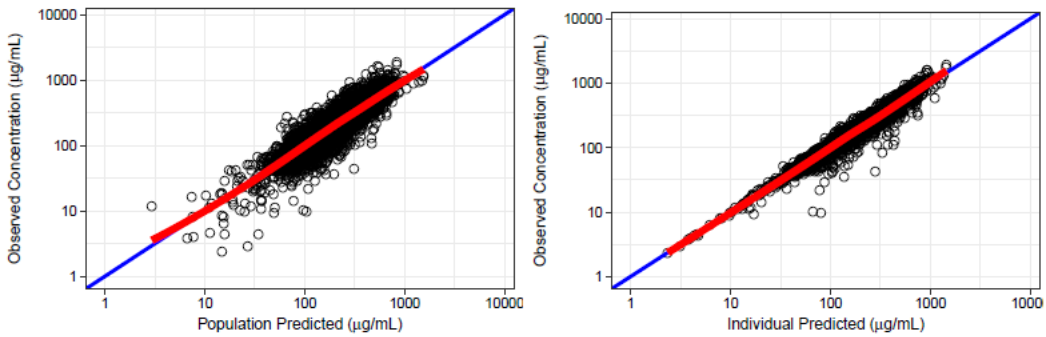
Table 5: Summary of Empirical Bayes Estimates of Pharmacokinetic Parameters by Cycle (Report 270593)

Parameter	n	Geometric Mean	Geometric Standard Deviation	Geometric CV%
CL (Cycle 1) (L/day)	1002	0.211	1.32	28.5
CL (Cycle 4) (L/day)	1002	0.168	1.34	29.5
CL (Cycle 8) (L/day)	1002	0.155	1.32	28.4
V_{ss} (L)	1002	4.88	1.30	27.0
$t_{1/2}$ (Cycle 1) (days)	1002	17.2	1.29	25.6
$t_{1/2}$ (Cycle 4) (days)	1002	21.3	1.32	28.7
$t_{1/2}$ (Cycle 8) (days)	1002	23.0	1.34	29.6

Note: V_{ss} is derived from the summation of V_c and V_p.
CL = total clearance; CV = coefficient of variation; n = number of individuals; $t_{1/2}$ = elimination half-life; V_C = central volume of distribution; V_P = peripheral volume of distribution; V_{ss} = volume of distribution at steady state.

Plots of observed versus population predicted serum concentrations and observed versus individual predicted serum concentrations for sugemalimab are presented in Figure 14. The plots of observed versus population predicted concentrations demonstrated minimal bias, with the majority of data evenly scattered around the line of unity, while the plots of observed concentrations versus the individual predicted concentrations, which account for random effects, were more tightly scattered around the line of unity. There was no obvious bias as demonstrated by the trend line for the data overlaying the line of unity.

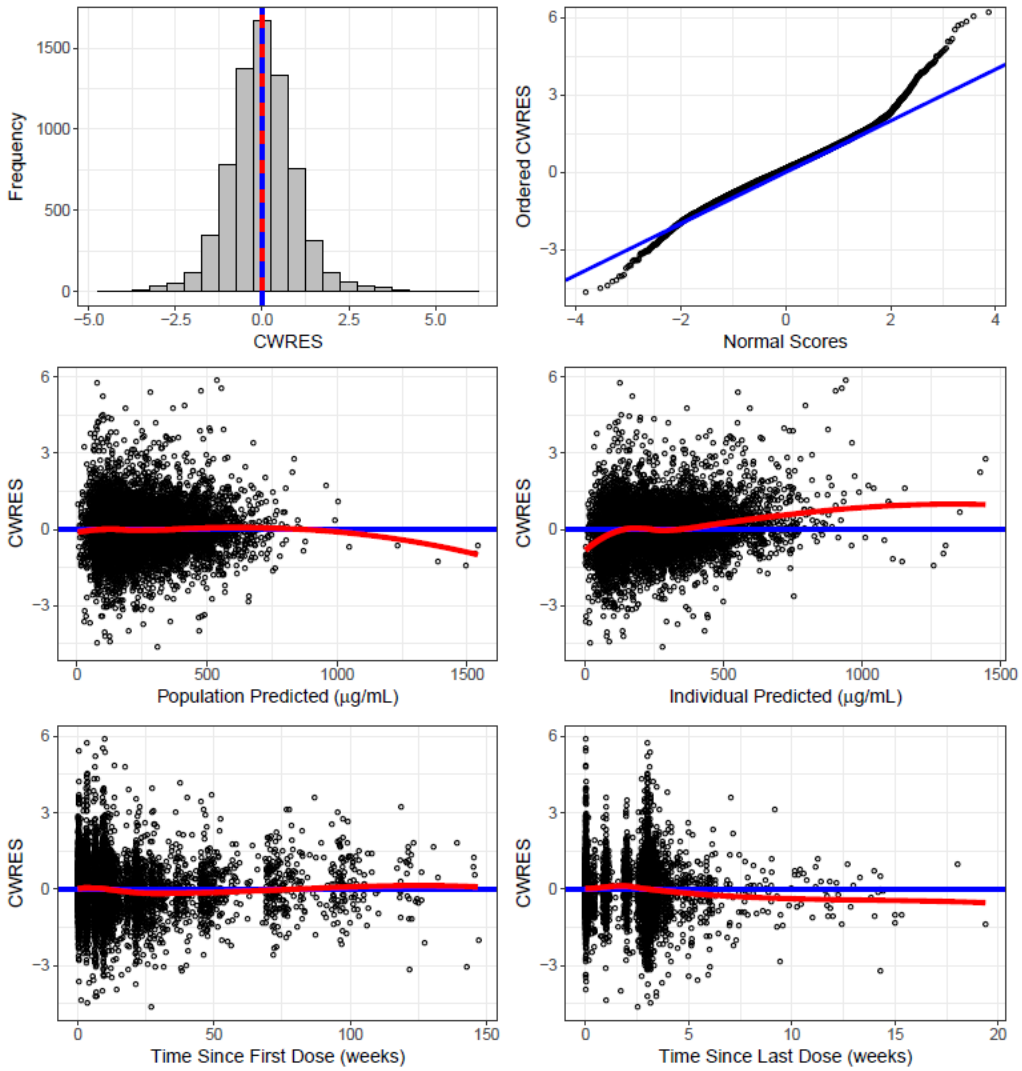
Figure 14: Goodness of Fit Plots for the Final Population PK Model



The solid blue lines represent the line of unity, the solid red lines represent the trend in the data (Loess smooth).

Additional diagnostic plots of CWRES are shown in Figure 15, which verify that the final model fitted the data with good precision and minimal bias. The quantile-quantile (QQ) plot and frequency histograms of CWRES indicate they were distributed evenly around zero with no apparent skewness. There was no bias evident in the CWRES versus time or model-predicted concentration plots.

Figure 15: CWRES Plots for the Final Population PK Model

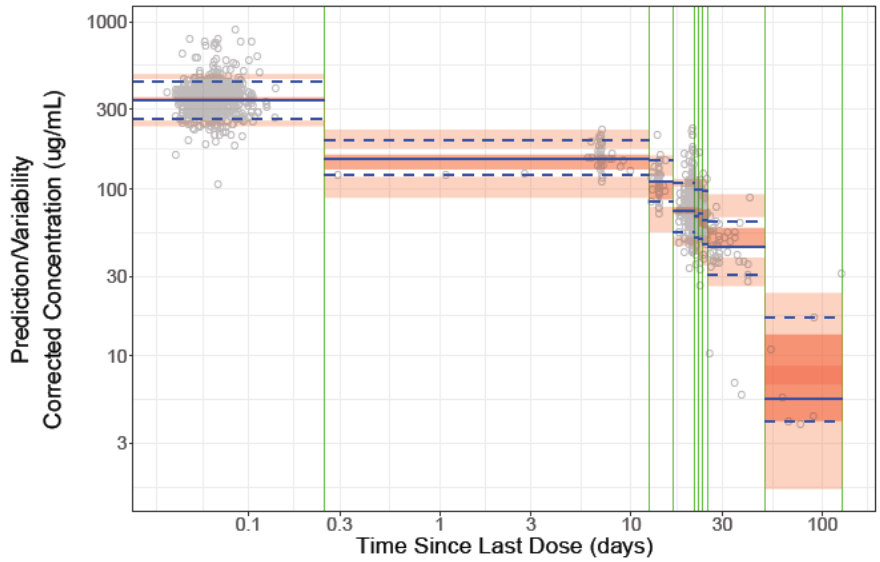


The solid blue lines represents the line of identity or zero, the red lines represents the trend in the data (Loess smooth) or the mean.

All BSV terms were distributed around zero. Individual estimates of shrinkage for CL0, CLT, Vc, Vp and kdes were 16%, 49.6%, 20.5%, 44.9% and 39.5%, respectively. The correlation between CL0, CLT and Vc, and between CLT and kdes was accounted for in the model. The variance-covariance matrix derived from NONMEM was used as a proposal uncertainty distribution for SIR to determine the true uncertainty. All SEs and 95% CIs for both the structural fixed effect and random effects parameter estimates were estimated with acceptable precision (<30%).

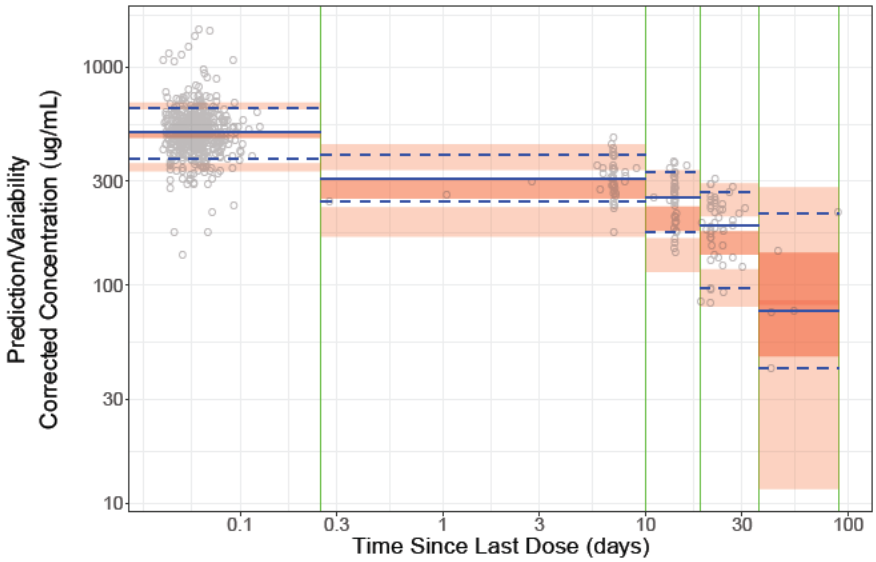
To further validate the simulation characteristics of the final model graphically, pvcVPCs stratified by disease and cycle were constructed (1000 simulated datasets) and are shown in Figures 18 – 23. These plots demonstrate that the model adequately describes the majority of the observed concentrations with an even distribution of observations above and below the 10th and 90th prediction intervals.

Figure 18: pvcVPC for the Final Population PK Model: NSCLC – Cycle 1



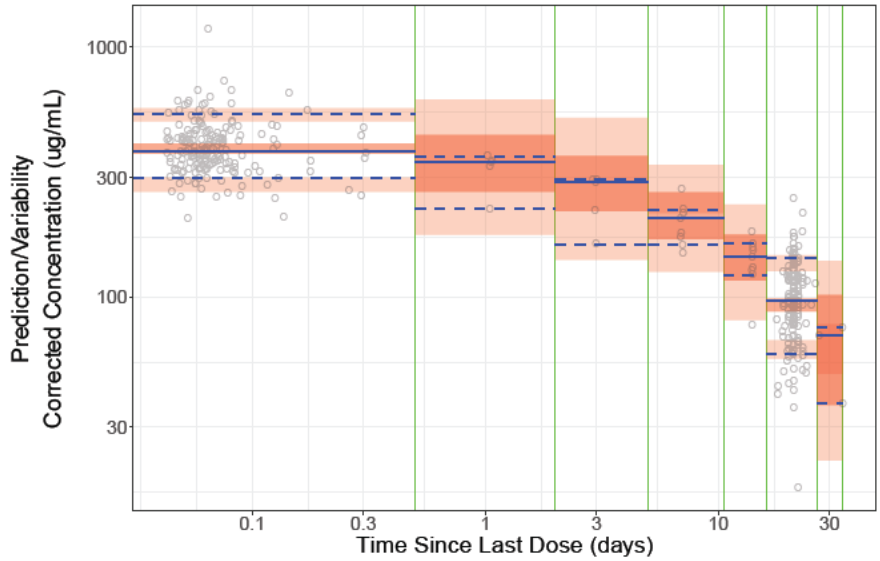
Open circles = individual observed, dashed blue lines = observed 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% prediction interval around the model predicted 10th, 50th, & 90th percentiles, green lines = bin limits. Note: Log-log scale is used.

Figure 19: pvcVPC for the Final Population PK Model: NSCLC – Cycle 4



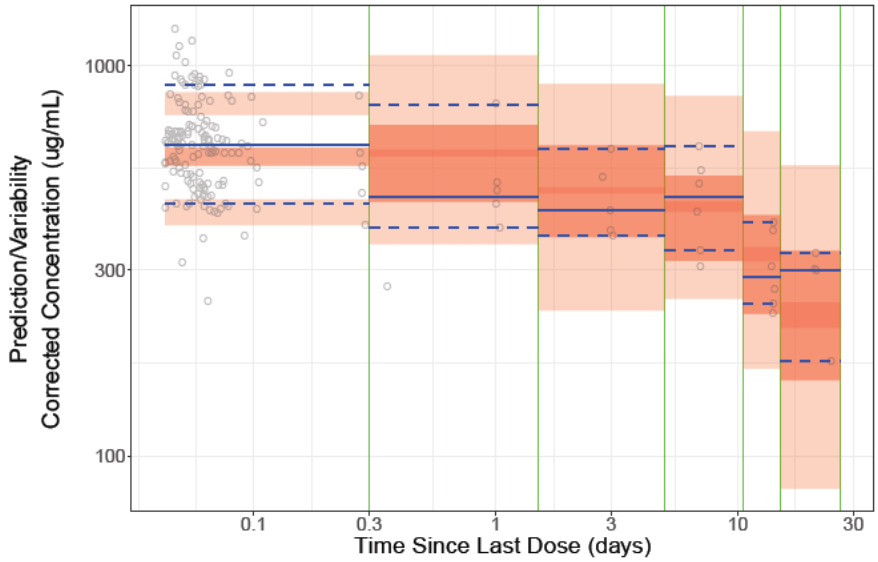
Open circles = individual observed, dashed blue lines = observed 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% prediction interval around the model predicted 10th, 50th, & 90th percentiles, green lines = bin limits. Note: Log-log scale is used.

Figure 20: pvcVPC for the Final Population PK Model: Lymphoma – Cycle 1



Open circles = individual observed, dashed blue lines = observed 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% prediction interval around the model predicted 10th, 50th, & 90th percentiles, green lines = bin limits. Note: Log-log scale is used.

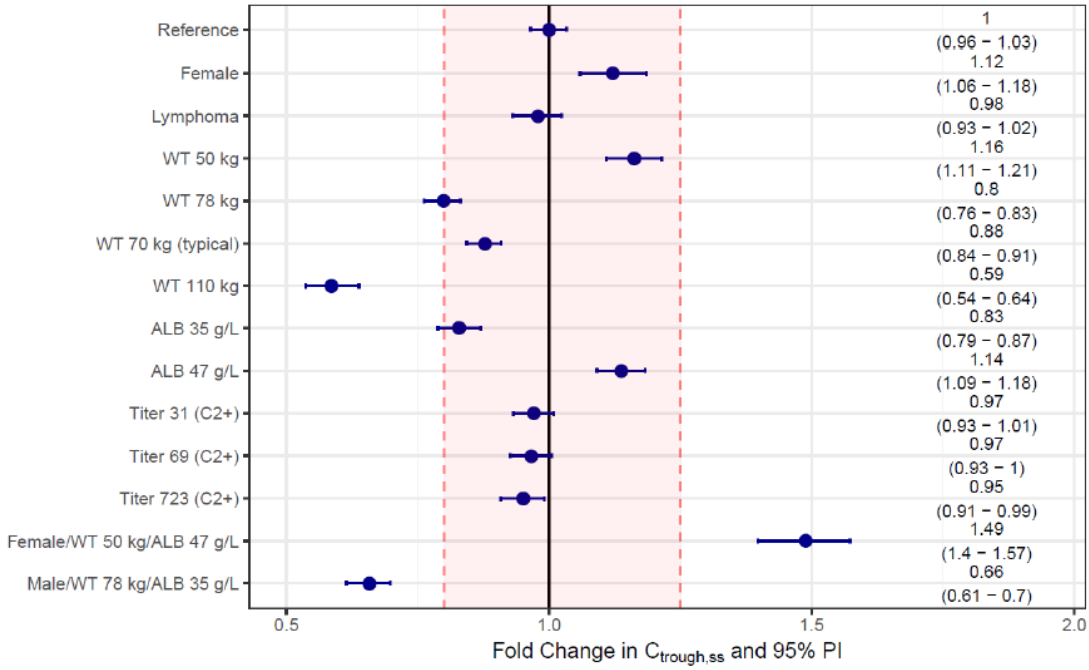
Figure 21: pvcVPC for the Final Population PK Model: Lymphoma – Cycle 4



Open circles = individual observed, dashed blue lines = observed 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% prediction interval around the model predicted 10th, 50th, & 90th percentiles, green lines = bin limits. Note: Log-log scale is used.

The impact of statistically significant covariates on model-predicted sugemalimab exposure metrics ($C_{trough,ss}$) are summarised in **Error! Reference source not found.**. The magnitude of the covariate effects on sugemalimab exposure was considered minor (generally < 20%). Extreme covariates (eg, 110 kg body weight) or the hypothetical combination of these covariates resulted in ≤ 50% change in sugemalimab exposure metrics.

Figure 2: Model-Predicted Fold Change in Sugemalimab $C_{trough,ss}$ – Cycle 8 (Report 270593)



Notes: The solid black line represents no impact of the covariate compared to the reference subject: The reference population was defined as patients with NSCLC Stage III with median weight (61 kg), median albumin (41.7 g/L) with negative ADA status receiving 1200 mg dose of sugemalimab IV every 3 weeks. The shaded red area represents the 80% to 125% range of the reference subject. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) PIs of the covariate effect based on 1000 simulated subjects within each group, including uncertainty on the fixed effect parameters.

ADA = antidrug antibody; ALB = albumin; $C_{trough,ss}$ = trough serum concentration at steady state; C2+ = ADA-positive from Cycle 2; IV = intravenous; NSCLC = non-small cell lung cancer; PI = prediction interval; Q3W = every 3 weeks; WT = weight.

Sugemalimab pharmacokinetics were best described by a two-compartment base structural model with both stationary (time-independent) and time-dependent clearance from the central compartment. The final model estimated the time independent and dependent clearance as 0.149 L/day and 0.108 L/day, respectively. The goodness of fit plots showed acceptable model fit. The company provided additional analysis to justify that the high shrinkage (35%) did not have an impact on the final model. The company's justification was acceptable.

The company used the population PK model to test the effects of different covariates and concluded that the magnitude of the covariate effects on sugemalimab exposure was minor (generally < 20%). While extreme covariates such as high body weight of 110 kg or the theoretical combination of covariates resulted in ≤ 50% change in sugemalimab exposure metrics.

Special populations

- **Impaired renal function**

The effect of renal impairment on the CL of sugemalimab was evaluated using PopPK analyses in participants with mild or moderate renal impairment compared to participants with normal renal function. The categories for renal impairment were based on estimated baseline CRCL (calculated by the Cockcroft-Gault equation; normal: ≥ 90 mL/min, mild: 60 to < 90 mL/min, and moderate: 30 to < 60 mL/min). In the analysis population, 51% of

participants had normal renal function, 42% of participants had mild renal impairment, and 7% of participants had moderate renal impairment. No participants had severe renal impairment (these subjects were excluded from clinical studies).

Overall, there was no impact of renal function on the PK of sugemalimab. Thus, no dose adjustment is necessary in patients with mild or moderate renal impairment. Sugemalimab has not been studied in participants with severe renal impairment.

- **Impaired hepatic function**

The effect of hepatic impairment on sugemalimab PK was evaluated using PopPK analyses. The covariate analysis indicated no statistically significant effect of markers of liver function (AST, ALT, and total bilirubin) on sugemalimab exposure.

- **Gender**

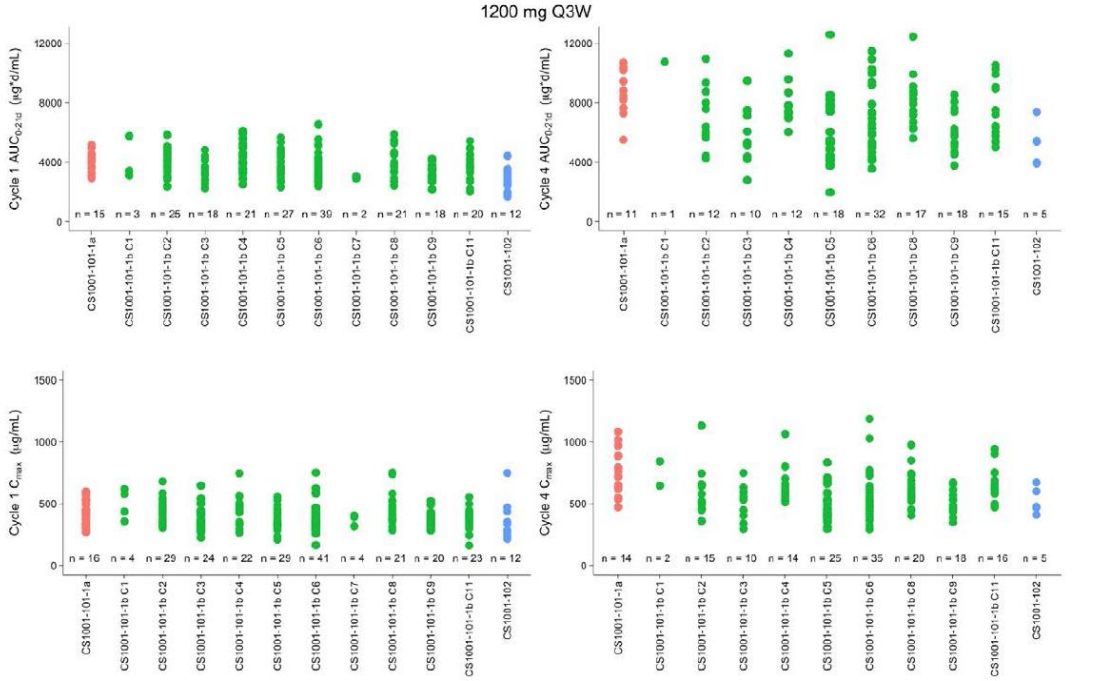
Sex was found to be a significant covariate on CL_0, CL_T, and V_c. and the magnitude of the covariate effect was lower for females relative to the reference category (males), resulting in higher predicted sugemalimab exposures in females. However, the magnitude of the effect of sex on increase in sugemalimab exposures was not considered to be clinically meaningful, as the change in sugemalimab exposure was < 20%; $AUC_{tau,ss}$, $C_{max,ss}$, and $C_{trough,ss}$ were predicted to increase by 12%, 15%, and 12%, respectively.

- **Race**

The effect of race in participants with advanced solid tumours (including NSCLC) and lymphomas receiving sugemalimab was evaluated by PopPK analysis and no impact of race was identified on the PK of sugemalimab. More specifically, there was no observed PK difference in sugemalimab between Asian and non-Asian participants.

In addition, PK parameters based on NCA of PK data following IV infusions of 1200 mg fixed dose Q3W in Asian participants (Study CS1001-101a/b) and non-Asian participants (Study CS1001-102) are presented graphically side by side in **Error! Reference source not found.**.

Figure 17: Graphical Presentation (Dot Plots) of Sugemalimab AUC and C_{max} Following IV Infusions of 1200 mg Fixed Dose Q3W in Studies CS1001-101a/b and CS1001-102 during Cycle 1 (left column) and Cycle 4 (right column)



AUC = area under the serum concentration-time curve; AUC_{0-21d} = area under the serum concentration-time curve from time 0 to 21 days postdose; C_{max} = maximum serum concentration; Cx = cohort number x; IV = intravenous; n = number of participants in analysis set; Q3W = once every 3 weeks

The data showed sugemalimab exposures (C_{max} and AUC_{0-21d}), after IV infusion of 1200 mg Q3W, were generally similar between Asian and non-Asian participants. Sugemalimab C_{max} and AUC_{0-21d} after IV infusion of 10 mg/kg Q3W, were generally similar between Asian and non-Asian participants.

- **Weight**

In the PopPK analysis, body weight was found to be a significant covariate on CL_0 and V_c. Higher (lower) body weight resulted in an increase (decrease) in both parameters relative to the median body weight of 61 kg in the analysis population. However, the magnitude of the effect of body weight on these parameters did not translate into clinically meaningful exposure differences, as the change in sugemalimab exposure was < 20% for body weights in the 10^{th} to 90^{th} percentile range of the analysis population (50 to 78 kg). At the extreme of 110 kg, model-predicted sugemalimab $AUC_{tau,ss}$, $C_{max,ss}$, and $C_{trough,ss}$ were reduced by 35%, 30%, and 41%, respectively, when compared to the median participant weight of 61.5 kg.

- **Age**

The impact of age (range 18 to 78 years) was examined as a covariate in the PopPK analysis across the Phase 1 to 3 clinical studies. Overall, no impact of age was identified in the PopPK analysis. Thus, no dose adjustment of sugemalimab is warranted based on age.

- **Albumin**

Albumin was found to be a significant covariate on CL_0, V_c, and V_p; however, the magnitude of the effect of albumin level on these parameters translated into < 20% exposure differences and thus were not considered clinically meaningful. At an albumin level of 47 g/L, predicted $AUC_{tau,ss}$, $C_{max,ss}$, and $C_{trough,ss}$ were 11%, 8%, and 14% higher, respectively, compared with exposures predicted at the median albumin level of 41.9 g/L. At an albumin level of 35 g/L,

$AUC_{tau,ss}$, $C_{max,ss}$, and $C_{trough,ss}$ were 14%, 10%, and 17% lower, respectively, compared with exposures predicted at the median albumin level.

- **Disease Status**

PopPK analysis demonstrated that disease status (i.e., lymphomas versus NSCLC or other solid tumours) was a statistically significant covariate in the sugemalimab model. Sugemalimab V_c and V_p were higher in participants with NSCLC or other solid tumours as compared to participants with lymphoma (3-fold and 10% higher in V_c and V_p, respectively). Changes in predicted sugemalimab exposures were < 20% and were not considered clinically meaningful: 7% lower $C_{max,ss}$, 8% lower $AUC_{tau,ss}$, and 2% higher $C_{trough,ss}$ were predicted in participants with NSCLC or other solid tumours relative to participants with lymphoma.

- **Antidrug Antibody Titre**

Time-varying ADA titre was found to be a significant covariate on CL_T. The CL_T increased over 9% with a one-log increase in ADA titre over baseline, implying lower predicted sugemalimab exposure with increases in ADA titre. However, the resulting effect of ADA titre on sugemalimab did not lead to clinically meaningful differences in sugemalimab exposures, as predicted exposure differences were < 20%: for titres as high as the 90^{th} percentile in the ADA-positive population, median $AUC_{tau,ss}$, $C_{max,ss}$, and $C_{trough,ss}$ were predicted to decrease by only 4%, 3%, and 5%, respectively.

The company indicated that mild and moderate renal impairment and mild hepatic impairment are not expected to affect sugemalimab exposure and indicated in the SmPC that Sugemalimab has not been studied in patients with severe renal impairment and patients with moderate or severe hepatic impairment which is acceptable. The effects of gender, weight, albumin, ADA titre and disease state were significant on sugemalimab exposure but the company considered these effects not to be clinically meaningful. The company concluded that race and age have no impact on sugemalimab exposure, however, the number of subjects from non-asian origin is very limited to draw any conclusion with regard to the effect of race.

Interactions

No formal drug-drug interaction studies have been conducted with sugemalimab. PK drug-drug interaction of sugemalimab with other therapeutics is not anticipated given that sugemalimab (a mAb) is not cleared via hepatic or renal pathways; instead, the primary elimination pathways are protein catabolism. As such, sugemalimab is not expected to induce or inhibit the major drug metabolising cytochrome P450 pathways.
Sugemalimab PK parameters were not affected by coadministration with combination therapies.

Overall conclusions on pharmacokinetics

The Clinical Pharmacology submission is supported by 6 clinical studies following single and multiple IV infusions sugemalimab in patients with solid and haematologic malignancies. Standard pharmacokinetics methods were used to derive pharmacokinetic parameters and data was summarised using standard summary statistical methods. Standard methods for population pharmacokinetic analysis and exposure-response analysis were used. The data included in this analysis was derived mainly from Asian population with <0.3% of the data derived from White and Other races populations. So, any conclusions related to the effect of race of pharmacokinetics and exposure-response analysis should be interpreted with caution.

Sugemalimab is administered via IV infusion. Following administration, Cmax is reached by end of infusion. Following single and multiple administrations, sugemalimab exposure is

increased in an approximately dose-proportional manner in the dose range of 3 to 40 mg/kg Q3W. The company compared the exposure after the weight adjusted dose of 20 mg/kg to the flat dose of 1200 mg and the exposure was comparable between the two doses after single and 8 cycles of multiple doses where steady state is anticipated. Sugemalimab has small volume of distribution at steady state (Vss) of 4.88L consistent with monoclonal antibodies.

Sugemalimab is catabolised through nonspecific clearance pathways such as proteolysis. Population Pharmacokinetics analysis estimated total Clearance after a single dose to be 0.211 L/day. Population PK predicted clearance was comparable to non-compartmental analysis estimated clearance for the dose of 1200 mg across studies. The t1/2 was estimated to be 13 to 22 days which was not consistent with the steady achieved by 24 weeks. Based on a t1/2 of 3 weeks, the steady state was expected to be reached by 15 weeks. For the dose of 1200 mg Q3W, there was approximately 2-fold accumulation of sugemalimab exposure.

Inter-individual variability was low to moderate for clearance and central volume of distribution. Sugemalimab pharmacokinetics were best described by a two-compartment base structural model with both stationary (time-independent) and time-dependent clearance from the central compartment. The final model estimated the time independent and dependent clearance as 0.149 L/day and 0.108 L/day, respectively. The goodness of fit plots showed acceptable model fit. The company used the population PK model to test the effects of different covariates and concluded that the magnitude of the covariate effects on sugemalimab exposure was minor (generally < 20%). While extreme covariates such as high body weight of 110 kg or the theoretical combination of covariates resulted in ≤ 50% change in sugemalimab exposure metrics.

IV.3 Pharmacodynamics

Mechanism of action

Sugemalimab is a full-length, fully human IgG4 (s228p) mAb. It specifically binds to PD-L1, thus blocking its ligation with PD-1. When expressed on tumour cells and tumour-infiltrating immune cells, PD-L1 can contribute to the inhibition of an anti-tumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and CD80 (B7.1) receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation, and cytokine production. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing ADCC. PD-L1 blockade with sugemalimab led to increased T-cell activation in vitro and decreased tumour growth in syngeneic mouse tumour models. Given its mechanism of action and the established clinical benefit of immune checkpoint inhibitors, sugemalimab has proven to be efficacious in the first-line treatment of metastatic NSCLC

Pharmacodynamics and Pharmacokinetics-Pharmacodynamics (PK/PD)

Exposure-Response for Efficacy

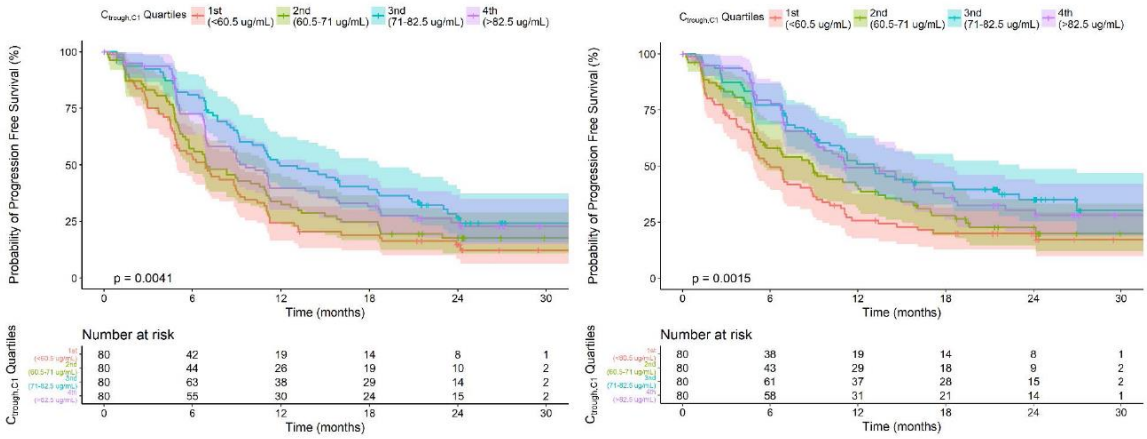
Overall Response

Graphical analysis for OR suggest no relationship between Cycle 1 sugemalimab exposure ($AUC_{tau,C1}$, $C_{max,C1}$, or $C_{trough,C1}$) and BOR (Investigator-assessed or BICR . In the final logistic regression models for overall response, there was no statistically significant relationship present between sugemalimab exposure ($C_{trough,C1}$) and probability of response as measured by BOR (PR versus SD + PD + NE), for either Investigator-assessed (P = 0.085) or BICR (P = 0.155) response.

Progression-free Survival

Graphical analysis for PFS indicated a possible relationship between $C_{trough,C1}$ and PFS, as assessed by both the Investigator and BICR (Kaplan-Meier curves by quartiles of $C_{trough,C1}$; **Error! Reference source not found.**). The TTE model for PFS as assessed by the Investigator showed an estimated 9.2% reduction in the hazard of disease progression or death per increase in $C_{trough,C1}$ of 10 µg/mL, while the model for PFS as assessed by BICR showed an estimated 12.4% reduction in the hazard of disease progression or death per increase in $C_{trough,C1}$ of 10 µg/mL, indicating an improvement in PFS with increasing sugemalimab Cycle 1 trough concentration.

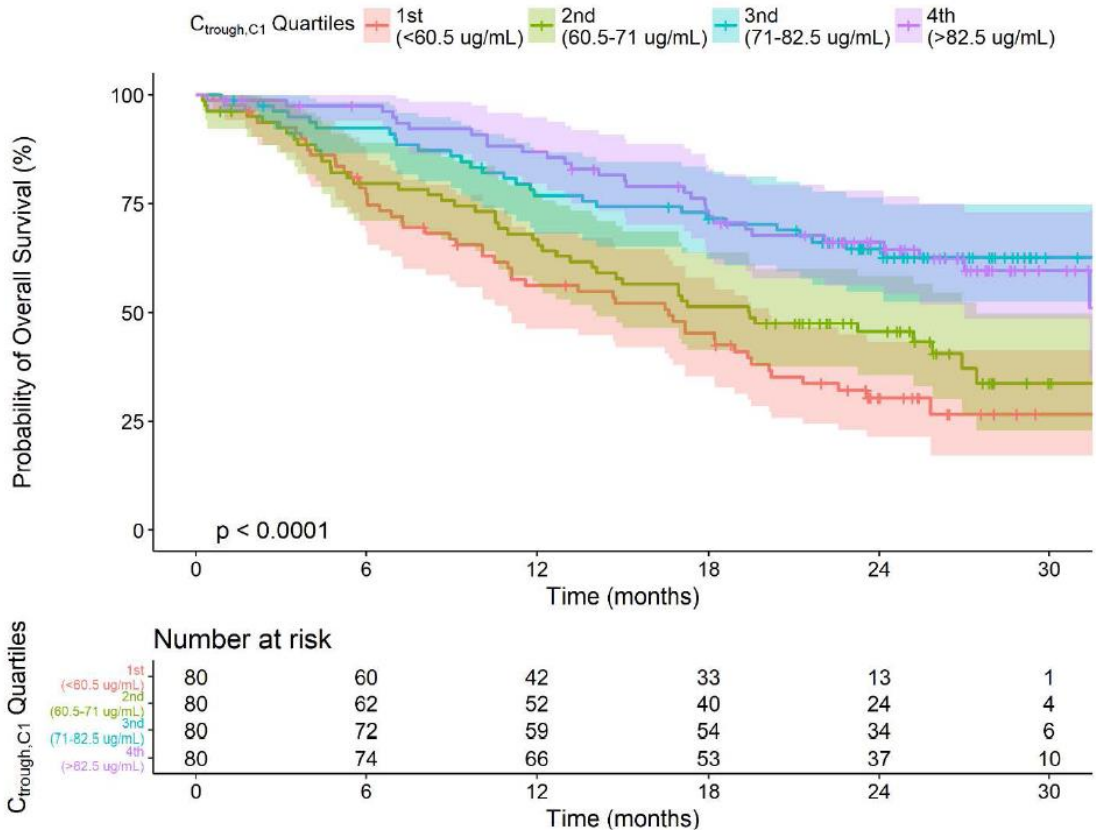
Figure 3: Progression-free Survival by Quartiles of $C_{trough,C1}$ (Report 270593) Investigator-assessed (left figure) and BICR-assessed (right figure)



Note: Solid lines represent Kaplan-Meier curves, shaded areas represent 95% CI, and *P* value is derived from a log-rank test.
BICR = blinded independent central review; CI = confidence interval; $C_{trough,C1}$ = trough serum concentration in Cycle 1.

The graphical analysis using Kaplan-Meier plots for OS indicated a possible relationship present between sugemalimab exposure ($C_{trough,C1}$) and OS (**Error! Reference source not found.**). The TTE model for OS confirmed the conclusions of the graphical analysis, with higher exposures ($C_{trough,C1}$) resulting in improvement in OS, as there was an estimated 20.2% reduction in the hazard of death per 10 µg/mL increase in sugemalimab Cycle 1 trough concentration

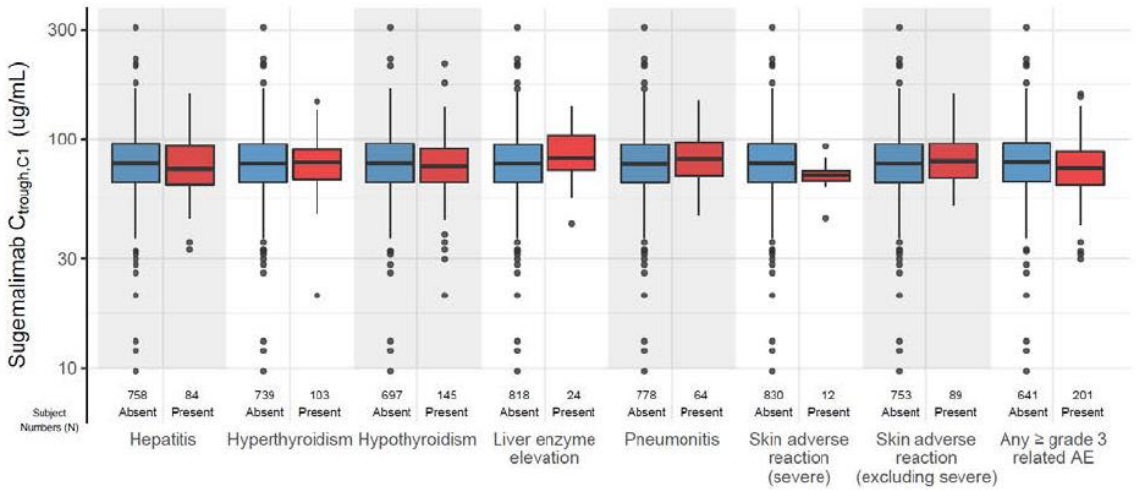
Figure 4: Overall Survival by Quartiles of $C_{trough,C1}$ (Report 270593)



Exposure-Safety Analyses

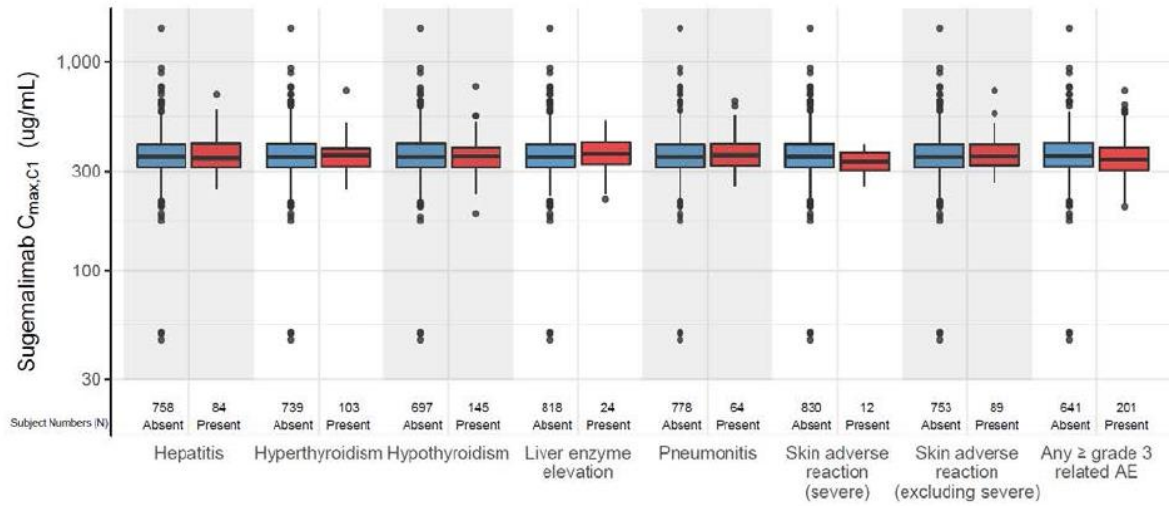
Boxplots of exposure-response analyses for safety suggested no relationships between any metric of sugemalimab exposure ($C_{trough,C1}$, $AUC_{tau,C1}$, or $C_{max,C1}$) and increased risk of TEAEs of interest (any Grade ≥ 3 sugemalimab-related AE, immune-related hepatitis, immune-related hypothyroidism, immune-related hyperthyroidism, liver enzyme elevation, immune-related pneumonitis, immune-related skin adverse reactions (severe), and immune-related skin adverse reactions, excluding severe [**Error! Reference source not found.**, **Error! Reference source not found.**, and **Error! Reference source not found.**]). Graphical analyses were supported by logistic regression models that demonstrated no relationship between the risk of any safety event and any sugemalimab exposure metric.

Figure 5: Boxplots of Sugemalimab $C_{trough,C1}$ by Adverse Events (Report 270593)



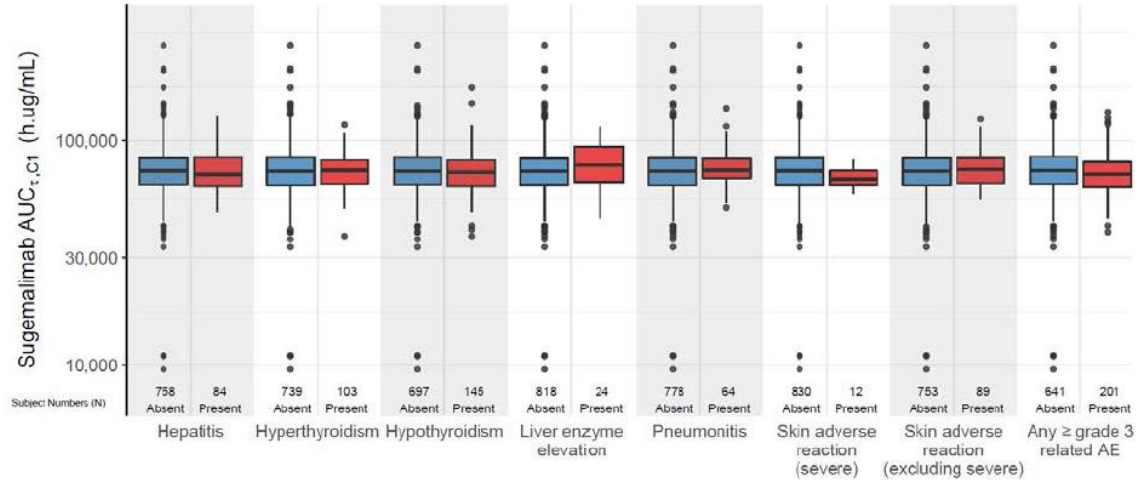
Note: Solid horizontal lines represent the median, the top and bottom of the box represent the 25th and 75th percentiles, the whiskers represent the IQR, and the circles represent outliers (≥ 1.5 × IQR). The number below each box specifies the number of subjects per group.
$C_{trough,C1}$ = trough serum concentration in Cycle 1; IQR = interquartile range.

Figure 6: Boxplots of Sugemalimab $C_{max,C1}$ by Adverse Events (Report 270593)



Note: Solid horizontal lines represent the median, the top and bottom of the box represent the 25th and 75th percentiles, the whiskers represent the IQR, and the circles represent outliers (≥ 1.5 × IQR). The number below each box specifies the number of subjects per group.
AE = adverse event; $C_{max,C1}$ = maximum serum concentration in Cycle 1; IQR = interquartile range.

Figure 7: Boxplots of Sugemalimab $AUC_{tau,C1}$ by Adverse Events (Report 270593)



Note: Solid horizontal lines represent the median, the top and bottom of the box represent the 25th and 75th percentiles, the whiskers represent the IQR, and the circles represent outliers (≥ 1.5 × IQR). The number below each box specifies the number of subjects per group.
AE = adverse event; $AUC_{\tau,C1}$ = $AUC_{tau,C1}$ = area under the serum concentration-time curve for the dosing interval in Cycle 1; IQR = interquartile range.

Dose Rationale

The optimal dose and dosing schedule for sugemalimab were initially evaluated in the Phase 1 Study CS1001-101a and confirmed in Study CS1001-102. The studies were conducted in China and the US, respectively.

The proposed therapeutic dose of 1200 mg fixed IV Q3W is based on the following:
1. Results from early phase clinical Studies CS1001-101a/b and CS1001-102, and confirmation from the Phase 3 clinical studies in participants with NSCLC
2. In vitro activity and clinical PK and pharmacodynamics (RO) characteristics of sugemalimab
3. PopPK and exposure-response analyses

Results from Early Phase Clinical Studies

Study CS1001-101a/b, First in Human Study (China)

RO was tested on whole blood samples of 6 participants at the fixed 1200 mg dose group in this study to evaluate the pharmacodynamic characteristics of sugemalimab. All 6 participants reached 100% RO on Day 1 of Cycle 2 and Cycle 4.

The selection of a fixed dose of 1200 mg IV infusion Q3W for subsequent studies was mainly based on the following data from Study CS1001-101a:
The fixed dose of 1200 mg IV Q3W had an acceptable safety and tolerability profile. No DLT event occurred, and no MTD was obtained. The PK results showed that the exposure of sugemalimab was proportional to the dose at the dose level of 3 to 40 mg/kg (including the fixed dose of 1200 mg). In addition, the exposure of sugemalimab at a fixed dose of 1200 mg IV Q3W was similar to that of the weight-based dose of 20 mg/kg IV Q3W.

Study CS1001-102 (US)

As Study CS1001-101a/b showed similar exposures between 20 mg/kg IV Q3W and 1200 mg fixed dose IV Q3W, a second study, CS1001-102, was conducted in the US to evaluate a lower dose of 10 mg/kg IV Q3W and 1200 mg fixed dose IV Q3W. Following single and

repeated IV infusions of sugemalimab at a 10 mg/kg IV Q3W or 1200 mg fixed dose IV Q3W, sugemalimab systemic exposures (C_{max} and AUC) were generally comparable with the data from Study CS1001-101a/b. RO was tested in 7 evaluable participants in this study (3 in the 10 mg/kg group and 4 in the fixed 1200 mg dose group) to evaluate the pharmacodynamic characteristics of sugemalimab. All 7 participants reached 100% RO (pharmacodynamics) at the predose on Day 1 of Cycle 2. A consistently high level of RO (76% to 100%) was shown in the 3 participants at the predose on Day 1 of Cycle 4.

Phase 3 Clinical Studies in Participants with Non-small Cell Lung Cancer
The findings of the Phase 3 studies demonstrated a favourable benefit-risk profile for the fixed dose of 1200 mg IV Q3W.

In Vitro Activity and Clinical Pharmacokinetic Characteristics
As observed in clinical Studies CS1001-101a/b and CS1001-102, participants who received 1200 mg IV Q3W maintained geometric mean $C_{trough,ss}$ serum concentrations of 211.79 μg/mL (CV = 65%) (**Error! Reference source not found.**) and 152 μg/mL (CV = 33%) (**Error! Reference source not found.**), respectively. These concentrations are > 60-fold higher than the projected target serum concentration (2.54 μg/ml) from in vitro studies.

The RO (pharmacodynamic) data from Studies CS1001-101 and CS1001-102 further confirmed that at 1200 mg IV Q3W, receptors are fully (100%) occupied throughout the dose interval.

Population Pharmacokinetic and Exposure-Response Analyses
In the PopPK and E-R analyses, simulations demonstrated that there was no difference in median PFS (Investigator-assessed) or median OS between Asian and non-Asian participants. In the PopPK model, body weight was identified as a statistically significant covariate on both CL_0 and Vc; however, the magnitudes of these body weight effects on model-predicted steady-state sugemalimab exposure metrics was generally less than 20% (Section **Error! Reference source not found.**), and therefore not considered clinically meaningful based upon typical 80% to 125% acceptance criteria.

Although both 10 mg/kg IV Q3W and 1200 mg fixed dose IV Q3W reached 100% RO in Study CS1001-102, E-R simulations showed that a regimen of 1200 mg IV Q3W resulted in 10.2% longer median PFS (Investigator-assessed), 14.5% longer median PFS (BICR-assessed), and 20.7% longer median OS at 12 months compared to 10 mg/kg IV Q3W in non-Asian participants.

Immunogenicity
Immunogenicity of sugemalimab was assessed following IV infusion of 10, 20, and 40 mg/kg Q3W, and 1200 mg fixed dose Q3W in Study CS1001-101a/b, following IV infusion of 10 mg/kg Q3W and 1200 mg fixed dose Q3W in Study CS1001-102, as well as in Studies CS1001-201, CS1001-202, CS1001-301 and CS1001-302 following IV infusion of 1200 mg fixed dose Q3W.

Overall, these ADA data from the 6 clinical studies indicated low treatment-induced immunogenicity potential following IV infusion of 10 mg/kg, 20 mg/kg, 40 mg/kg Q3W, and 1200 mg fixed dose Q3W sugemalimab in participants with various tumours.

The applicant has revised the Summary Table (Table 21) as requested and presented

immunogenicity data from all studies by taking account of the standardised terminology (and provided definitions) used to categorise the ADA response. A figure showing ADA titre profiles for all ADA +ve patients has also been included.

Table 21: Summary ADA/NAb Results of All Studies

	101 Ia/Ib (N=226)	102 (N=19)	201 (N=75)	202 (N=80)	301 (N=246)	302 (N=309)	Total (N=955)
ADA Status	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ADA Positive [1]	26 (11.5)	1 (5.3)	5 (6.7)	2 (2.5)	26 (10.6)	53 (17.2)	109 (11.8)
Treatment Emergent-Positive [2]	12 (5.3)	0	3 (4.0)	1 (1.3)	14 (5.7)	28 (9.1)	58 (6.1)
Treatment Induced Persistent	2 (0.9)	0	1 (1.3)	0	7 (2.8)	12 (3.9)	22 (2.3)
Treatment Induced Transient	12 (5.3)	0	2 (2.7)	1 (1.3)	6 (2.4)	14 (4.5)	31 (3.7)
Treatment-Enhanced	2 (0.9)	0	0	0	1 (0.4)	2 (0.6)	5 (0.5)
Non-Treatment Emergent-Positive [3]	10 (4.4)	1 (5.3)	2 (2.7)	1 (1.3)	12 (4.9)	25 (8.1)	51 (5.3)
NAb Positive	1 (0.4)	NA	1 (1.3)	NA	4 (1.6)	5 (1.6)	11(1.2)

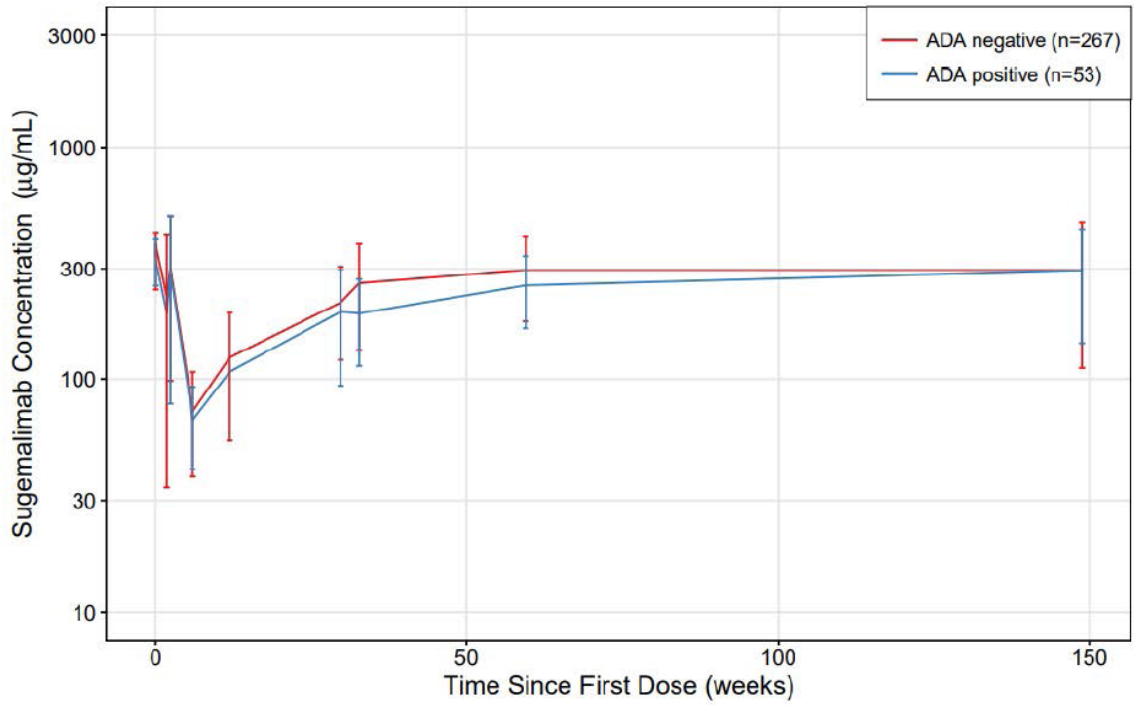
[1] At least one baseline or post-baseline ADA test result is positive.
[2] Includes treatment enhanced positive and treatment induced positive.
[3] Baseline ADA is positive and all post-baseline ADA titer results are not greater than 4 x baseline value, or baseline is positive and all post-baseline are negative or missing.
Data cut-off date for Study 101-1a: 16AUG2021; 101-1b: 16AUG2021; 102: 08FEB2021; 201: 10NOV2021; 202: 19FEB2020; 301: 08MAR2021; 302:22NOV2021.

Impact of Immunogenicity on Pharmacokinetics, Safety, and Efficacy

A total of 1471 immunogenicity samples (from 309 participants) were collected in the pivotal Phase 3 Study CS1001-302 in participants with NSCLC. In this study, the total positive rate of sugemalimab was 9.0%, including 28 participants. Among them, 26 participants (8.4%) were drug-induced positive participants, 2 participants (0.6%) were drug-enhanced positive participants, and 25 participants (8.1%) were non-drug-related positive participants.

The effect of ADA status on PK in Study CS1001-302 following 1200 mg IV Q3W across the entire study duration is presented in **Error! Reference source not found.**. The effect of ADA status on PK is shown for each of the other studies for participants receiving the 1200 mg IV Q3W dose across the entire study duration. In these figures, the mean (± standard deviation) serum concentration-time profiles of sugemalimab are displayed by ADA status (positive versus negative). The concentrations of sugemalimab were generally comparable between ADA-negative and ADA-positive subjects, indicating that the presence of ADA did not influence the PK of sugemalimab.

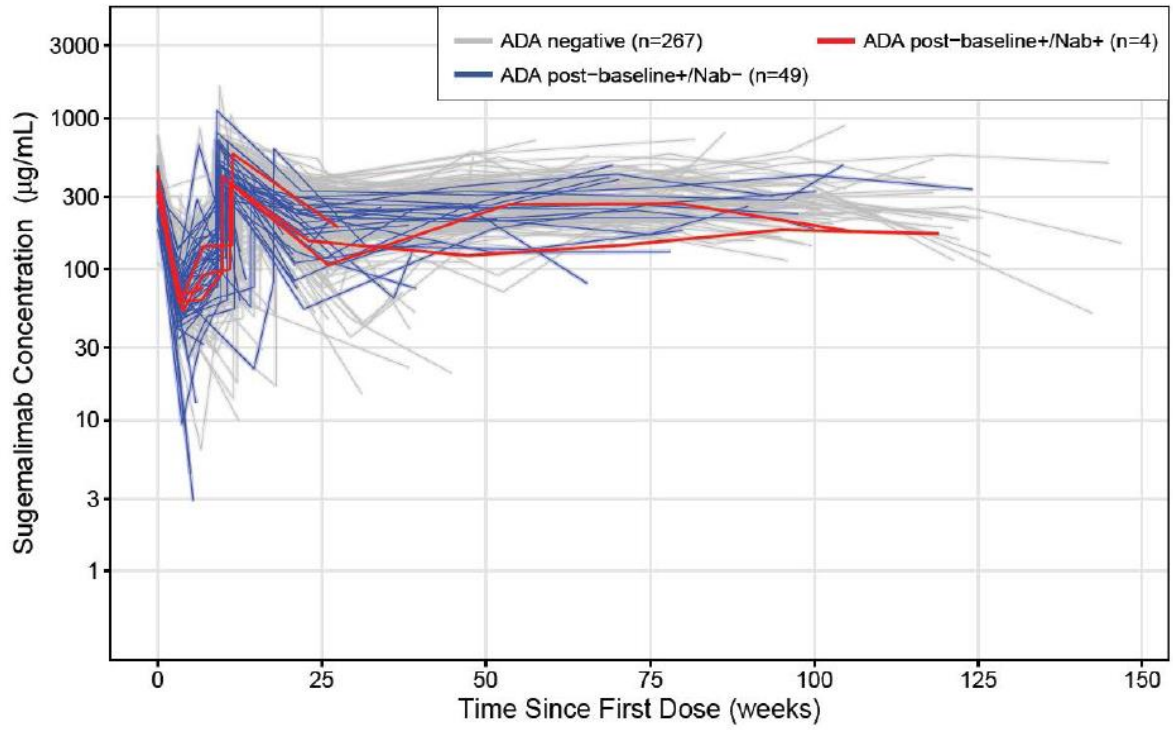
Figure 19: Mean (± SD) Sugemalimab Concentrations in the Pivotal Phase 3 Study CS1001-302, Stratified by ADA Status, After Administration of Sugemalimab 1200 mg IV Q3W (Report 270593)



ADA = antidrug antibody; IV = intravenous; Q3W = once every 3 weeks; SD = standard deviation.

The effect of NAb status on PK in Study CS1001-302 following 1200 mg IV Q3W across the entire study duration is presented in **Error! Reference source not found.**. The effect of NAb status on PK is also shown for each of the other studies in which NAb was determined (Studies CS1001-101b, CS1001-201, and CS1001-301) across the entire study duration, for participants receiving 1200 mg IV Q3W. Individual serum concentration-time profiles of sugemalimab are displayed by ADA (post baseline) and NAb status (positive versus negative). The serum concentrations of sugemalimab were generally comparable between NAb-positive and NAb-negative participants, indicating that the presence of NAb did not influence the PK of sugemalimab.

Figure 20: Individual Serum Concentration-time Profiles by Antidrug Antibody Status and Neutralising Antibody Status in Study CS1001-302 (Report 270593)

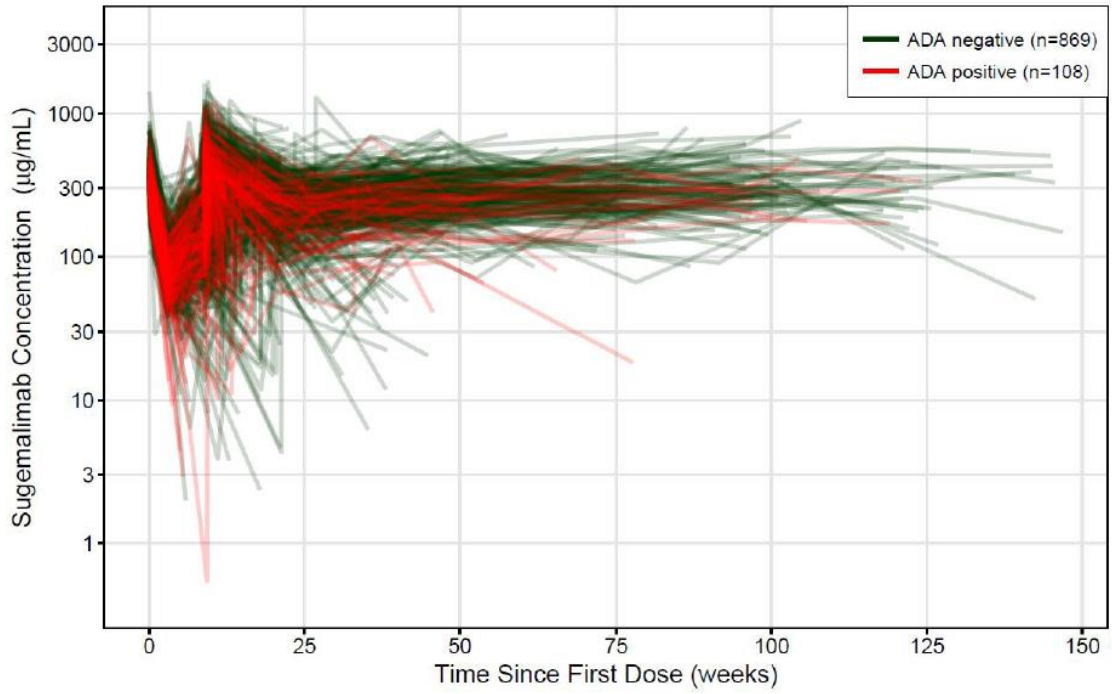


ADA = antidrug antibody; Nab = neutralising antibody.

Cross-Study Immunogenicity Assessment – Impact of Immunogenicity on Pharmacokinetics

Across the clinical studies, positive ADA status after administration of sugemalimab 1200 mg IV Q3W did not affect sugemalimab PK, as the distribution of pooled concentration-time profiles of all ADA-positive participants receiving this dose lay generally within the distribution of ADA-negative subjects (**Error! Reference source not found.**). This was consistent with summary-level data from the individual studies, which showed comparable mean (± standard deviation) concentration-time profiles between ADA-positive and ADA-negative participants. As discussed, while time-varying ADA titre was identified as a statistically significant covariate on time-dependent clearance through PopPK modelling, the resultant effects on sugemalimab exposure were < 20%, regardless of ADA titre level.

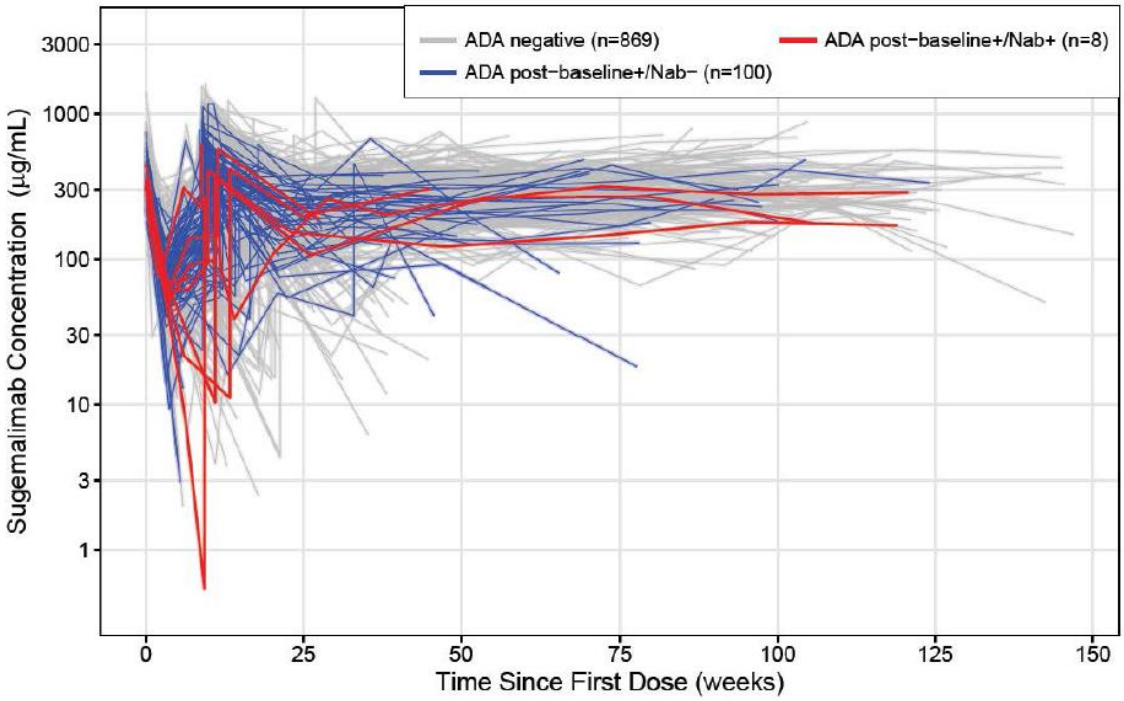
Figure 21: Individual Sugemalimab Concentrations Across Studies CS1001-101a, CS1001-101b, CS1001-102, CS1001-201, CS1001-202, CS1001-301, and CS1001-302, Stratified by ADA Status, After Administration of Sugemalimab 1200 mg IV Q3W (Report 270593)



ADA = antidrug antibody; IV = intravenous; Q3W = once every 3 weeks.

Similarly, across the clinical studies, positive NAb status after administration of sugemalimab 1200 mg IV Q3W did not affect sugemalimab PK, as the distribution of pooled concentration-time profiles of all NAb-positive participants receiving the 1200 mg dose lay within the distribution of NAb-negative subjects (**Error! Reference source not found.**).

Figure 22: Individual Serum Concentration-time Profiles by Antidrug Antibody Status and Neutralising Antibody Status Following a 1200 mg Fixed Dose IV Q3W, Across Studies CS1001-101a, CS1001-101b, CS1001-102, CS1001-201, CS1001-202, CS1001-301, and CS1001-302 (Report 270593)



ADA = antidrug antibody; IV = intravenous; Nab = neutralising antibody; Q3W = once every 3 weeks.

Impact of Immunogenicity on Efficacy

In the exposure-efficacy analyses, Kaplan-Meier curves showed that stratification by presence/absence of ADA did not have an observable effect on either PFS (Investigator-assessed and BICR) or OS.

Impact of Immunogenicity on Safety

There was no evidence of an impact of immunogenicity on safety.

Overall conclusions on pharmacodynamics

Exposure response analysis for efficacy found no relationship between Cycle 1 sugemalimab exposure and BOR (best overall response) or BICR (blinded independent central review). The time to event (TTE) model for progression free survival (PFS) as assessed showed an estimated 9.2% reduction in the hazard of disease progression or death per increase in $C_{trough,C1}$ of 10 µg/mL, while the model for PFS as assessed by BICR showed an estimated 12.4% reduction in the hazard of disease progression or death per increase in $C_{trough,C1}$ of 10 µg/mL, indicating an improvement in PFS with increasing sugemalimab Cycle 1 trough concentration. The TTE model for OS showed that higher exposures as measure by Ctrough at cycle 1 resulting in improvement in OS with an estimated 20.2% reduction in the hazard of death per 10 µg/mL increase in sugemalimab Cycle 1 trough concentration. No relationship was found between sugemalimab exposure and safety events. The company indicated that the receptor occupancy (RO) are fully (100%) occupied throughout the dose interval for the 1200 mg IV Q3W dose. Although the company indicated that sugemalimab exposure was comparable at a 10 mg/kg IV Q3W or 1200 mg fixed dose IV Q3W, and RO in both arms was 100%, the company then indicated that , exposure response simulations showed that a

regimen of 1200 mg IV Q3W resulted in 10.2% longer median PFS (Investigator-assessed), 14.5% longer median PFS (BICR-assessed), and 20.7% longer median OS at 12 months compared to 10 mg/kg IV Q3W in non-Asian participants.

The applicant provided simulations for exposure based on Ctrough, AUC and Cmax in weight bands of 5 Kg across body weight ranging from 80 to 150 Kg. The applicant used stringent bioequivalence (BE) limits of 80-125% to compare the simulated exposure to the reference exposure in the pivotal study CS1001-302 with a dose of 1200 mg Q3W and actual weight range of 41-96 kg. The simulations showed that the 1200 mg dose was able to maintain the exposure within the BE limits up to the weight band of 110-115, whereas as the 1500 mg dose maintained the exposure within the BE limits in the weight band 115 to 150 Kg. Based on these simulations, the dosing regimen of 1200 mg Q3W for individuals weighing ≤115 kg and 1500 mg Q3W for those weighing >115 kg is acceptable.

ADA did not appear to have impact of PK, efficacy or safety.

ADA (anti-drug antibody) assays

A standard 3-tiered strategy which includes screening and confirmatory methods for assessment of ADA followed by evaluation of ADA titre and neutralization potential has been used.

All data requested for ADA assays was provided along with sufficient supporting information.

IV.4 Clinical efficacy

In support of the application, the following was submitted:

Phase/Study Identifier; Country(ies)	Objective(s) of the Study (Key Endpoints)	Study Design and Type of Control	Diagnosis of Participants	No. of Participants per Cohort	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment per Protocol	Study Status; Type of Report; DCO/LPLV
5.3.3.2 Reports of Human Pharmacokinetic (PK) Studies – Patient PK and Initial Tolerability Study Reports							
Phase 1; CS1001-101 1a; NCT03312842; China	Safety and tolerability, MTD, and RP2D	Open-label, dose-exploration, not controlled	Participants with metastatic or locally advanced unresectable solid tumours or lymphoma with at least 1 lesion	Sugemalimab: 29	Sugemalimab; 3, 10, 20, and 40 mg/kg or 1200 mg single dose every 3 weeks; IV	Up to 2 years	Completed; Full CSR; LPLV: 30 Nov 2018
Phase 1; CS1001-101 1b; NCT03312842; China	Preliminary efficacy (ORR, DCR, DoR, PFS, OS, and Epstein-Barr virus DNA levels)	Open-label, dose-expansion, not controlled	Participants with metastatic or locally advanced unresectable solid tumours or NKTL	Sugemalimab: 217[a]	Sugemalimab as a monotherapy or in combination with chemotherapy drugs, radiation therapy, or targeted therapy; 1200 mg single dose every 3 weeks[b]; IV	Up to 2 years[c]	Ongoing; Full CSR; DCO: 16 Aug 2021
Phase 1; CS1001-102; NCT03744403; US	Safety, tolerability, and RP2D	Open-label, dose-escalation, not controlled	Participants with metastatic or locally advanced unresectable solid tumours	Sugemalimab: 24	Sugemalimab; 10 mg/kg or 1200 mg single dose every 3 weeks; IV	Up to 2 years	Completed; Full CSR; LPLV: 19 Oct 2020
5.3.5.1 Reports of Efficacy and Safety Studies – Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication							
Phase 3; CS1001-302; NCT03789604; China	Efficacy (PFS and OS)	Randomised, double-blind, placebo-controlled	Participants with metastatic (Stage IV) NSCLC	Sugemalimab: 320 Placebo: 159	Sugemalimab in combination with platinum-based chemotherapy; 1200 mg single dose every 3 weeks; IV	Up to 2 years	Ongoing; Full CSR; DCO: 22 Nov 2021

Phase/Study Identifier; Country(ies)	Objective(s) of the Study (Key Endpoints)	Study Design and Type of Control	Diagnosis of Participants	No. of Participants per Cohort	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment per Protocol	Study Status; Type of Report; DCO/LPLV
5.3.5.4 Reports of Efficacy and Safety Studies – Other Study Reports							
Phase 2; CS1001-201; NCT03595657; China, US[d]	Efficacy (ORR)	Open-label, not controlled	Participants with relapsed or refractory extranodal NKTL	Sugemalimab: 80	Sugemalimab; 1200 mg single dose every 3 weeks; IV	Up to 2 years	Ongoing; Abbreviated CSR; DCO: 10 Nov 2021
Phase 2; CS1001-202; NCT03505996; China	Efficacy (ORR)	Open-label, not controlled	Participants with relapsed or refractory classical Hodgkin lymphoma	Sugemalimab: 81	Sugemalimab; 1200 mg single dose every 3 weeks; IV	Up to 2 years	Ongoing; Full CSR; DCO: 19 Feb 2020
Phase 3; CS1001-301; NCT03728556; China	Efficacy (PFS, OS)	Randomised, double-blind, placebo-controlled	Participants with locally advanced unresectable Stage III NSCLC	Sugemalimab: 255 Placebo: 126	Sugemalimab as a consolidation therapy; 1200 mg single dose every 3 weeks; IV	Up to 2 years	Ongoing; Full CSR DCO: 08 Mar 2021

[a] There were 217 participants enrolled into Cohort 1 to Cohort 9 and Cohort 11. No participant was enrolled into Cohort 10. The data for Cohort 12 and Cohort 13 were not included in the CSR.
[b] Data from Cohort 12 (1800 mg every 4 weeks) were not included in the CSR.
[c] Participants who had completed 2 years of study treatment, after consultation with the Investigator and the Sponsor, may have continued treatment until the participant experienced an intolerable adverse reaction, progressive disease, withdrawal of ICF, lost to follow-up, death, or study termination, whichever occurred first.
[d] No US participants were enrolled.
CS1001 = sugemalimab; CSR = clinical study report; DCO = data cutoff date (for ongoing studies); DCR = disease control rate; DNA = deoxyribonucleic acid; DoR = duration of response; ICF=informed consent form; IV = intravenous; LPLV = last participant last visit (for completed studies); MTD = maximum tolerated dose; NKTL = natural killer/T-cell lymphoma; No. = number; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK=pharmacokinetic(s); RP2D = recommended Phase 2 dose; US = United States.

All the studies were conducted in China, except for Study CS1001-201 which was conducted in the US and China, and Study CS1001-102, which was conducted in the US to bridge PK data collected from the Asian population.

The pivotal study for this application is Study CS1001-302. It is an ongoing multicentre, randomized, double-blind, placebo-controlled Phase 3 study of platinum-based chemotherapy with or without sugemalimab in patients with Stage IV non-small cell lung cancer (NSCLC) without EGFR mutation, ALK fusion, ROS1 fusion or RET fusion.

Supportive evidence of sugemalimab's use in combination with platinum-based chemotherapy comes from an additional 41 patients with NSCLC in Cohorts 8 and 9 of the Phase 1b part of Study CS1001-101.

Other studies relevant to this application are:

CS1001-101 1a – dose escalation part of the sugemalimab first-in-human study

CS1001-102 – a bridging study conducted in the US, entitled 'A Phase I, Open-label, Multiple-Dose, Dose-Escalation Study of Sugemalimab in Subjects with Advanced Solid Tumours'.

CS1001-301 – an ongoing randomized, double-blind, placebo-controlled, Phase III study to evaluate the efficacy and safety of sugemalimab as consolidation therapy in patients with locally advanced/unresectable (Stage III) non-small cell lung cancer that had not progressed after prior concurrent/sequential chemoradiotherapy. This study, in which sugemalimab was given as a single agent, contributes additional safety data.

Apart from CS1001-102 which was conducted in the US, the studies were conducted in China.

There are 2 ongoing Phase 2 (CS1001-201 and -202) studies which are of less relevance to this application and have not been assessed.

Dose-response studies (Study CS1001-101 & Study CS1001-102)

Study CS1001-101 1a

Study CS1001-101 is a Phase 1a/1b, first-in-human, open-label study of sugemalimab in participants with advanced solid tumours or lymphomas.

The Phase 1a dose-escalation part (using 3+3 dose escalation design) of the study is completed and the Phase 1b dose-expansion part of the study is ongoing.

The study is conducted in centres in China.

Only Phase 1a part is covered in this section.

Study Start Date for Phase 1a (First subject signed the Informed Consent Form): 12 Oct 2017

Data Cut-off Date for Phase 1a: 30 Nov 2018

Methods

- **Objectives**

Primary Objectives

- To evaluate the safety, tolerability of sugemalimab.
- To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of sugemalimab.

Secondary Objectives

- To describe the PK profiles of sugemalimab.
- To preliminarily evaluate the anti-tumour efficacy of sugemalimab.
- To evaluate the immunogenicity of sugemalimab.

Exploratory Objectives

- To explore the pharmacodynamic profiles of sugemalimab.
- To evaluate the potential predictive biomarkers, including:
    - ➢Expression of programmed death ligand-1 (PD-L1) in tissues
    - ➢Tumour mutational burden (TMB)
- To assess the relationship between drug exposure and toxicity as well as efficacy

- **Study Participants**

Main inclusion criteria

1. Males or females, aged 18-75 years (inclusive)
2. Histologically or cytologically confirmed advanced or metastatic tumours (unresectable)
3. Progressed since the last anti-tumour therapy, or had no available standard treatment or had refused standard therapy
4. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
5. At least one measurable lesion that had not been previously treated with local therapy per RECIST v1.1 (solid tumours) [bone metastases alone or central nervous system (CNS)metastases alone were not accepted as measurable lesions]; or subjects had at least one evaluable or measurable lesion per the Lugano classification (lymphoma).
6. Subjects should provide tumour tissue samples for biomarker analysis. The sample may be formalin-fixed, paraffin-embedded or, if the subject had no archival tumour tissue sample, he/she must be willing to undergo a tumour lesion biopsy within 42 days prior to treatment initiation to obtain the corresponding tumour samples (the number of samples obtained depended on the biopsy).

Main exclusion criteria

1. Received any antibody/drug targeting T-cell co-regulatory proteins (immune checkpoints), including anti-programmed death factor-1 (PD-1), PD-L1 antibodies, etc.
2. Received systemic anti-tumour therapy within 14 days prior to starting study treatment.
3. Received glucocorticoids (prednisone > 10 mg/day or equivalent dose of other similar drugs) or other immunosuppressants within 14 days prior to the administration of the investigational product.
4. Major surgeries or radical radiotherapy within 28 days, had palliative radiotherapy within 14 days, or received radiopharmaceuticals (strontium, samarium, etc.) within 56 days prior to starting study treatment.
5. Received Chinese herbal medicines or traditional Chinese medicinal products within 7 days prior to starting study treatment.
6. History of interstitial lung disease, chemical pneumonitis, pneumonitis allergic, connective tissue disease pneumonia, pulmonary fibrosis, acute lung disorder, etc. (except for local interstitial pneumonia induced by radiotherapy), or uncontrolled systemic diseases, including diabetes mellitus, hypertension, etc.
7. Active or history of autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, autoimmune thyroid disease, vasculitis, psoriasis, etc.) or at risk (e.g., organ transplant requiring immunosuppressive therapy). However, subjects with the following diseases were allowed to be enrolled after further screening: type I diabetes, hypothyroidism managed with hormone replacement therapy only, skin diseases not requiring systemic treatment (such as vitiligo, psoriasis, or alopecia), or diseases not expected to recur in the absence of external triggering factors.
8. Active infection requiring systemic treatment within 2 weeks prior to starting study treatment.
9. Previous solid organ transplant.
10. Subjects with immune-related adverse events (irAEs) ≥ Grade 3 after prior immunotherapy.

11. Known serious allergic reactions to monoclonal antibodies (CTCAE v4.03 ≥ Grade3), and those with a history of uncontrolled allergic asthma.

- **Definitions and Excerpt from dose escalation rules**

DLT was defined as follows:

Non-haematological toxicities:

1. ≥ Grade 4 Toxicities
2. ≥ Grade 3 immune-related adverse events (irAEs), including: immune-related pneumonia, colitis, etc., were detailed in Section 18.5 of the Annex of the study protocol
3. Grade 3 toxicities (regardless of duration), with the following exceptions: diarrhoea, nausea, vomiting, or electrolyte abnormalities that recovered to ≤ Grade 2 within 3 days
4. Grade 3 tumour flare lasting ≥ 7 days (defined as local pain, irritation, or rash localized at sites of known or suspected tumours)

Haematological toxicities:

1. Grade 4 neutropenia that lasted for > 5 days
2. Febrile neutropenia [defined as absolute neutrophil count (ANC) < 1000/mm3 with a single temperature rising to 38.3°C or the temperature of 38°C for > 1 hour]
3. Grade 3 neutrophils reduced with infection
4. Grade 3 platelets decreased with haemorrhage
5. Grade 4 platelets decreased
6. Grade 4 anaemia (life-threatening)

And other toxicities of any grade that required premature discontinuation of the subject after discussion by the investigators and the sponsors.

Definition of the MTD: the highest dose at which ≤ 1/6 subjects experienced a DLT and for which escalation could not be made further in a dose group with at least 6 subjects evaluable for DLTs.

Excerpt from dose escalation rules

For the 3, 10, 20, 40 mg/kg and 1200 mg fixed dose groups, 3 subjects were enrolled in each dose level as the first batch:

- If none of the 3 subjects in a dose group experienced a DLT within 21 days after the first dose, 3 new subjects would be enrolled into the next pre-specified escalation dose group. At the same time, the subjects in this dose group may continue treatment at the current dose.

-The MTD was not reached at 10 mg/kg (Group 2), then 3 additional subjects were enrolled into the next escalation dose of 20 mg/kg (Group 3). At the same time, 3 additional subjects were enrolled to evaluate the safety and PK of the fixed dose of 1200 mg (Group 5) corresponding to the 20 mg/kg dose (calculated with a body weight of 60 kg). The selection of the fixed dose was decided by the SMC based on available study data.

a) If 2 or more of the 3 subjects enrolled in the 1200 mg dose group (Group 5) experienced 2 or more DLTs, the SMC would decide whether to continue the exploration of the fixed dose based on available study information.

b) If 1 of the 3 subjects enrolled in the 1200 mg (Group 5) dose group experienced one DLT, 3 new subjects would be enrolled to that dose group; if 1 or more of the 3 new subjects experienced DLTs, the SMC would decide whether to continue the exploration of the fixed dose based on available study information.

- If the MTD was still not reached at 40 mg/kg dose group (Group 4), the SMC (Safety Monitoring Committee) would decide whether to continue the dose-escalation and the specific dose based on the available safety, efficacy, and PK data.

When the RP2D was determined, this dose group should be supplemented to 10 subjects.

If the fixed dose of 1200 mg was selected as the RP2D, the corresponding 1200 mg dose group would also be supplemented to 10 subjects. If ≥ 1/3 of subjects experienced DLTs in the first treatment cycle during the expansion to 10 subjects of the RP2D group, the SMC would determine whether the dose group was safe.

Results

Twenty-nine subjects with solid tumours or lymphomas were enrolled into 1 of 5 sugemalimab dose groups [i.e., Phase 1a doses: 3 mg/kg (n=3), 10 mg/kg (n=4), 20 mg/kg (n=3), 40 mg/kg (n=3), and 1200 mg fixed dose (n=16)] in a 3+3 dose-escalation design.

Sugemalimab was given by intravenous infusion over 60 to 120 minutes every 21 days.

Table CE2: Demographic and Baseline Characteristics

Characteristic (Unit)	3 mg/kg (N = 3)	10 mg/kg (N = 4)	20 mg/kg (N = 3)	40 mg/kg (N = 3)	1200 mg (N = 16)	Total (N = 29)
Age (yrs)						
n	3	4	3	3	16	29
Mean (SD)	50.3 (12.2)	53.8 (5.0)	69.0 (5.6)	44.7 (9.5)	51.9 (16.2)	53.0 (14.1)
Median	53.0	53.5	70.0	45.0	49.0	53.0
Min, Max	37, 61	49, 59	63, 74	35, 54	23, 75	23, 75
Sex						
Male	1 (33.3)	3 (75.0)	2 (66.7)	1 (33.3)	11 (68.8)	18 (62.1)
Female	2 (66.7)	1 (25.0)	1 (33.3)	2 (66.7)	5 (31.3)	11 (37.9)
Weight at Baseline (kg)						
n	3	4	3	3	16	29
Mean (SD)	54.0 (6.2)	64.7 (9.8)	54.1 (2.9)	63.3 (5.0)	58.5 (9.2)	58.93 (8.6)
Median	56.0	63.0	54.0	63.8	62.1	59.2
Min, Max	47.0, 59.0	54.7, 78.0	51.3, 57.0	58.0, 68.0	41.0, 70.0	41.0, 78.0
BMI（kg/m^2）						
n	3	4	3	3	16	29
Mean (SD)	19.9 (2.8)	22.0 (2.4)	20.4 (0.9)	23.4 (1.9)	21.1 (2.7)	21.3 (2.5)
Median	21.1	21.2	20.6	22.7	21.5	21.2
Min, Max	16.7, 21.9	20.3, 25.5	19.4, 21.2	21.8, 25.6	14.9, 24.8	14.9, 25.6
ECOG at Baseline						
0	1 (33.3)	1 (25.0)	0	0	2 (12.5)	4 (13.8)
1	2 (66.7)	3 (75.0)	3 (100)	3 (100)	14 (87.5)	25 (86.2)

Source: Table 14.1.2a.
Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; n = number of subjects; N = number of subjects in the analysis set.

The median and mean weight of patients was 59.2 kg (range 41 – 78) and 58.9 kg (SD 8.6), respectively.

Adverse events

Table CE3: Summary of AEs in Study CS1001-101 (DCO - 30 Nov 2018)

Classification	3 mg/kg (N = 3) n (%)	10 mg/kg (N = 4) n (%)	20 mg/kg (N = 3) n (%)	40 mg/kg (N = 3) n (%)	1200 mg (N = 16) n (%)	Total (N = 29) n (%)
TEAE	3 (100)	4 (100)	3 (100)	3 (100)	16 (100)	29 (100)
Treatment-related TEAEs	3 (100)	4 (100)	3 (100)	2 (66.7)	15 (93.8)	27 (93.1)
Grade 3/4/5 TEAEs	1 (33.3)	3 (75.0)	2 (66.7)	0	7 (43.8)	13 (44.8)
Grade 3/4/5 treatment-related TEAEs	0	0	1 (33.3)	0	2 (12.5)	3 (10.3)
SAE	0	2 (50.0)	1 (33.3)	0	3 (18.8)	6 (20.7)
Treatment-related SAEs	0	0	0	0	0	0
DLT	0	0	0	0	0	0
TEAEs leading to permanent discontinuation	0	0	0	0	2 (12.5)	2 (6.9)
TEAEs leading to dose reduction	0	0	0	0	0	0
TEAEs leading to infusion interruption of study medication	0	0	0	0	0	0
TEAEs leading to delay of treatment cycles	2 (66.7)	2 (50.0)	2 (66.7)	0	7 (43.8)	13 (44.8)
TEAEs leading to death	0	0	0	0	0	0
irAE	0	1 (25.0)	3 (100)	0	3 (18.8)	7 (24.1)
Infusion-related TEAEs	0	0	0	0	0	0

Source: Table 14.3.3.1a.
Abbreviations: AE = adverse event; DLT = dose limiting toxicity; irAE = immune-related adverse event; n = number of subjects; N =number of subjects; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table CE4: Summary of TEAEs by PTs with an Overall Incidence of ≥ 10.0%

MedDRA PT	3 mg/kg (N = 3) n (%)	10 mg/kg (N = 4) n (%)	20 mg/kg (N = 3) n (%)	40 mg/kg (N = 3) n (%)	1200 mg (N = 16) n (%)	Total (N = 29) n (%)
Number of subjects with at least one TEAE	3 (100)	4 (100)	3 (100)	3 (100)	16 (100)	29 (100)
Investigations						
Blood bilirubin increased	2 (66.7)	0	1 (33.3)	1 (33.3)	4 (25.0)	8 (27.6)
Alanine aminotransferase increased	1 (33.3)	0	1 (33.3)	0	5 (31.3)	7 (24.1)
Aspartate aminotransferase increased	2 (66.7)	0	1 (33.3)	0	4 (25.0)	7 (24.1)
Bilirubin conjugated increased	2 (66.7)	0	1 (33.3)	1 (33.3)	3 (18.8)	7 (24.1)
White blood cell count decreased	1 (33.3)	0	1 (33.3)	1 (33.3)	4 (25.0)	7 (24.1)
Blood creatine phosphokinase increased	0	1 (25.0)	0	0	2 (12.5)	3 (10.3)
Renal and urinary disorders						
Proteinuria	1 (33.3)	2 (50.0)	2 (66.7)	1 (33.3)	7 (43.8)	13 (44.8)
Blood and lymphatic system disorders						
Anaemia	3 (100)	1 (25.0)	1 (33.3)	0	9 (56.3)	14 (48.3)
Gastrointestinal disorders						
Nausea	2 (66.7)	1 (25.0)	1 (33.3)	0	1 (6.3)	5 (17.2)
Constipation	0	0	0	0	3 (18.8)	3 (10.3)
Vomiting	0	2 (50.0)	1 (33.3)	0	0	3 (10.3)
General disorders and administration site conditions						
Fatigue	1 (33.3)	1 (25.0)	1 (33.3)	0	1 (6.3)	4 (13.8)
Metabolism and nutrition disorders						
Decreased appetite	2 (66.7)	0	2 (66.7)	0	2 (12.5)	6 (20.7)
Respiratory, thoracic and mediastinal disorders						
Cough	1 (33.3)	0	0	0	4 (25.0)	5 (17.2)
Infections and infestations						
Upper respiratory tract infection	1 (33.3)	0	1 (33.3)	0	1 (6.3)	3 (10.3)
Skin and subcutaneous tissue disorders						
Pruritis	0	0	1 (33.3)	1 (33.3)	1 (6.3)	3 (10.3)
Rash	1 (33.3)	0	1 (33.3)	1 (33.3)	0	3 (10.3)
Endocrine disorders						
Hypothyroidism	0	1 (25.0)	2 (66.7)	0	1 (6.3)	4 (13.8)

Source: Table 14.3.3.2a.
The version of MedDRA was 20.0.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; N = number of subjects in the analysis set; PT = preferred term; TEAE = treatment-emergent adverse event.

Table CE5: Summary of TEAEs with the Highest CTCAE Grade of Grade 3 or Higher

MedDRA SOCs MedDRA PTs	3 mg/kg (N = 3) n (%)	10 mg/kg (N = 4) n (%)	20 mg/kg (N = 3) n (%)	40 mg/kg (N = 3) n (%)	1200 mg (N = 16) n (%)	Total (N = 29) n (%)
Number of subjects with at least one ≥ Grade 3 TEAE	1 (33.3)	3 (75.0)	2 (66.7)	0	7 (43.8)	13 (44.8)
Blood and lymphatic system disorders						
Anaemia	0	0	0	0	2 (12.5)	2 (6.9)
Investigations						
Bilirubin conjugated increased	1 (33.3)	0	0	0	0	1 (3.4)
Blood creatine phosphokinase increased	0	0	0	0	1 (6.3)	1 (3.4)
Platelet count decreased	0	0	1 (33.3)	0	0	1 (3.4)
Renal and urinary disorders						
Renal failure	0	0	0	0	1 (6.3)	1 (3.4)
Gastrointestinal disorders						
Ascites	0	1 (25.0)	0	0	0	1 (3.4)
Gastric hemorrhage	0	1 (25.0)	0	0	0	1 (3.4)
Gastrointestinal haemorrhage	0	0	0	0	1 (6.3)	1 (3.4)
Musculoskeletal and connective tissue disorders						
Bone pain	0	1 (25.0)	0	0	0	1 (3.4)
Neck Pain	0	0	0	0	1 (6.3)	1 (3.4)
Metabolism and nutrition disorders						
Hypokalaemia	0	0	0	0	1 (6.3)	1 (3.4)
Infections and infestations						
Pulmonary tuberculosis	0	0	0	0	1 (6.3)	1 (3.4)
Hepatobiliary disorders						
Liver function abnormal	0	0	0	0	1 (6.3)	1 (3.4)
Surgical and medical procedures						
Tumour excision	0	0	1 (33.3)	0	0	1 (3.4)
Vascular disorders						
Hypertension	0	0	0	0	1 (6.3)	1 (3.4)

Source: Table 14.3.3.11a.

A total of 8 deaths occurred during this study, none was attributable to sugemalimab.

Table CE6: Treatment-Emergent Adverse Events Leading to Drug Interruption/Treatment Delay

System Organ Class Preferred Term	3 mg/kg (N=3) n (%)	10 mg/kg (N=4) n (%)	20 mg/kg (N=3) n (%)	40 mg/kg (N=3) n (%)	1200 mg (N=16) n (%)	Total (N=29) n (%)
Number of Subjects with at least one TEAE Leading to Study Drug Interruption/ Treatment Cycle Delay/ Dose Reduction	2 (66.7)	2 (50.0)	2 (66.7)	0	7 (43.8)	13 (44.8)
Investigations	2 (66.7)	1 (25.0)	1 (33.3)	0	1 (6.3)	5 (17.2)
Bilirubin conjugated increased	1 (33.3)	0	0	0	1 (6.3)	2 (6.9)
Aspartate aminotransferase increased	1 (33.3)	0	0	0	0	1 (3.4)
Blood bilirubin increased	1 (33.3)	0	0	0	0	1 (3.4)
Blood bilirubin unconjugated increased	0	0	0	0	1 (6.3)	1 (3.4)
Platelet count decreased	0	0	1 (33.3)	0	0	1 (3.4)
Weight decreased	0	1 (25.0)	0	0	0	1 (3.4)
Gastrointestinal disorders	0	2 (50.0)	0	0	1 (6.3)	3 (10.3)
Abdominal pain	0	1 (25.0)	0	0	0	1 (3.4)
Ascites	0	1 (25.0)	0	0	0	1 (3.4)
Constipation	0	0	0	0	1 (6.3)	1 (3.4)
Faeces discoloured	0	0	0	0	1 (6.3)	1 (3.4)
Gastric haemorrhage	0	1 (25.0)	0	0	0	1 (3.4)
Intestinal obstruction	0	1 (25.0)	0	0	0	1 (3.4)
Renal and urinary disorders	0	0	0	0	2 (12.5)	2 (6.9)
Haemorrhage urinary tract	0	0	0	0	1 (6.3)	1 (3.4)
Renal failure	0	0	0	0	1 (6.3)	1 (3.4)
Blood and lymphatic system disorders	0	0	0	0	1 (6.3)	1 (3.4)
Anaemia	0	0	0	0	1 (6.3)	1 (3.4)
Cardiac disorders	0	0	0	0	1 (6.3)	1 (3.4)
Supraventricular extrasystoles	0	0	0	0	1 (6.3)	1 (3.4)
Infections and infestations	0	0	0	0	1 (6.3)	1 (3.4)
Pneumonia	0	0	0	0	1 (6.3)	1 (3.4)
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (6.3)	1 (3.4)
Neck pain	0	0	0	0	1 (6.3)	1 (3.4)
Surgical and medical procedures	0	0	1 (33.3)	0	0	1 (3.4)
Tumour excision	0	0	1 (33.3)	0	0	1 (3.4)

SOURCE: Listing 16.2.7.2.1a
MedDRA version 20.0 was used to code adverse events.
The cut-off date for the data included in this report was 30 Nov 2018.

Table CE7: Treatment-Emergent Adverse Events Leading to Drug Permanently Discontinued

System Organ Class Preferred Term	3 mg/kg (N=3) n (%)	10 mg/kg (N=4) n (%)	20 mg/kg (N=3) n (%)	40 mg/kg (N=3) n (%)	1200 mg (N=16) n (%)	Total (N=29) n (%)
Number of Subjects with at least one TEAE Leading to Study Drug Withdrawn	0	0	0	0	2 (12.5)	2 (6.9)
Hepatobiliary disorders	0	0	0	0	1 (6.3)	1 (3.4)
Hepatic function abnormal	0	0	0	0	1 (6.3)	1 (3.4)
Infections and infestations	0	0	0	0	1 (6.3)	1 (3.4)
Pulmonary tuberculosis	0	0	0	0	1 (6.3)	1 (3.4)

SOURCE: Listing 16.2.7.2.5a
MedDRA version 20.0 was used to code adverse events.
The cut-off date for the data included in this report was 30 Nov 2018.

Table CE8: Summary of Immune-Related TEAEs by SOCs and PTs

MedDRA SOCs MedDRA PTs	3 mg/kg (N = 3) n (%)	10 mg/kg (N = 4) n (%)	20 mg/kg (N = 3) n (%)	40 mg/kg (N = 3) n (%)	1200 mg (N = 16) n (%)	Total (N = 29) n (%)
Number of subjects with at least one irTEAE	0	1 (25.0)	3 (100)	0	3 (18.8)	7 (24.1)
Endocrine disorders						
Hypothyroidism	0	1 (25.0)	2 (66.7)	0	1 (6.3)	4 (13.8)
Adrenal insufficiency	0	1 (25.0)	0	0	0	1 (3.4)
Hyperthyroidism	0	0	1 (33.3)	0	0	1 (3.4)
Investigations						
Blood creatine phosphokinase MB increased	0	0	0	0	1 (6.3)	1 (3.4)
Blood creatine phosphokinase increased	0	0	0	0	1 (6.3)	1 (3.4)
Blood thyroid stimulating hormone decreased	0	0	1 (33.3)	0	0	1 (3.4)
Blood thyroid stimulating hormone increased	0	0	0	0	1 (6.3)	1 (3.4)
Thyroxine free increased	0	0	1 (33.3)	0	0	1 (3.4)
Tri-iodothyronine free increased	0	0	1 (33.3)	0	0	1 (3.4)
Skin and subcutaneous tissue disorders						
Pruritis	0	0	1 (33.3)	0	1 (6.3)	2 (6.9)
Rash	0	0	1 (33.3)	0	0	1 (3.4)
Infections and infestations						
Pneumonia	0	0	0	0	1 (6.3)	1 (3.4)

MTD was not reached.

DLT events or significant safety concerns did not occur in any dose group during the study. Therefore, all escalation doses were completed as planned, and the fixed dose of 1200 mg was determined as the RP2D based on the then available safety, preliminary clinical efficacy, and PK profiles of sugemalimab.

PK results

Due to the limitations of blood sampling time points, the clearance rate constant (kel) could not be accurately calculated by non-compartmental model, making it impossible to calculate PK parameters related to the clearance rate constant (e.g., t1/2, Vss, CL, AUC0-∞, etc.).

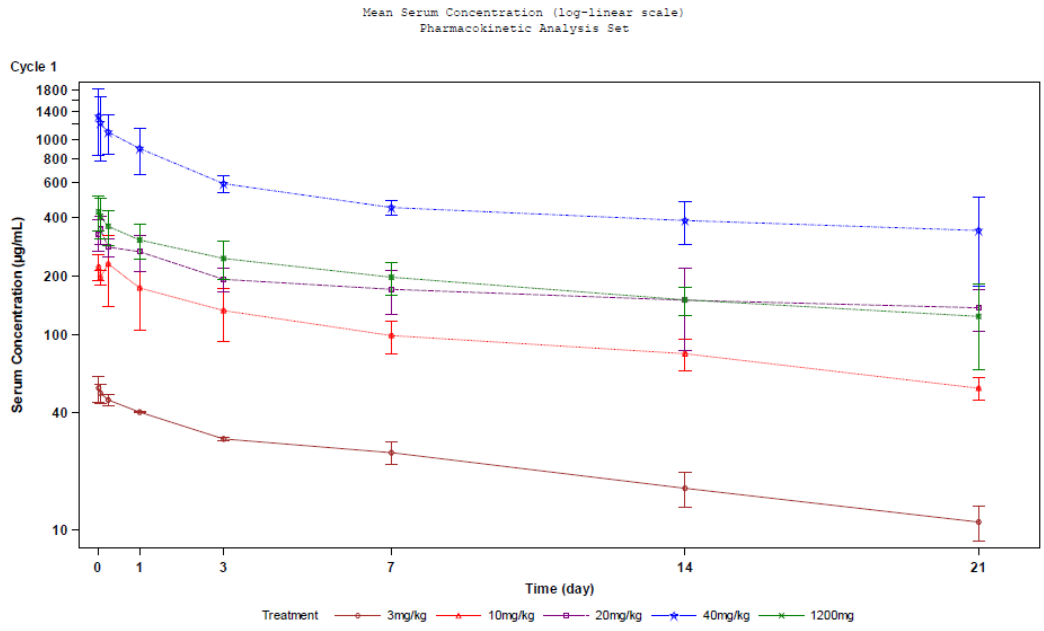
After a single IV infusion of CS1001 in each dose group, the geometric means (geometric CV) for Cmax were 52.82 μg/mL (15.32%), 257.52 μg/mL (25.25%), 349.44 μg/mL (13.90%), 1278.31 μg/mL (35.34%) and 422.59 μg/mL (22.76%), respectively; the geometric means (geometric CV) for AUC0-21d were 453.67 days • μg/mL (10.95%), 2099.27 days • μg/mL (16.31%), 3492.67 days • μg/mL (23.82%), 9954.30 days • μg/mL (12.48%) and 3951.85 days • μg/mL (17.67%), respectively.

After multiple doses, in Cycle 4, the geometric means (geometric CV) for Cmax were 77.61 μg/mL (-), 285.90 μg/mL (31.36%), 469.78 μg/mL (14.83%), 1187.47 μg/mL (-) and 713.64 μg/mL (25.77%), respectively; the geometric means (geometric CV) for AUC0-tau were 1016.78 days • μg/mL (-), 3348.56 days • μg/mL (-), 4934.00 days • μg/mL (39.53%), 1427282 days • μg/mL (-) and 7897.90 days • μg/mL (35.57%), respectively. The geometric means (geometric CV) for CLss were 0.139 L/day (-), 0.233 L/day (-), 0.224 L/day (47.659%), 0.179 L/day (-) and 0.152 L/day (35.574%), respectively.

In Cycle 4, the geometric means for AUC accumulation index were 2.15, 1.43, 1.48, 1.58 and 2.00 for the 3 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, and 1200 mg fixed dose groups, respectively; and the geometric means for Cmax accumulation index were 1.30, 0.99, 1.34, 1.03 and 1.74, respectively.

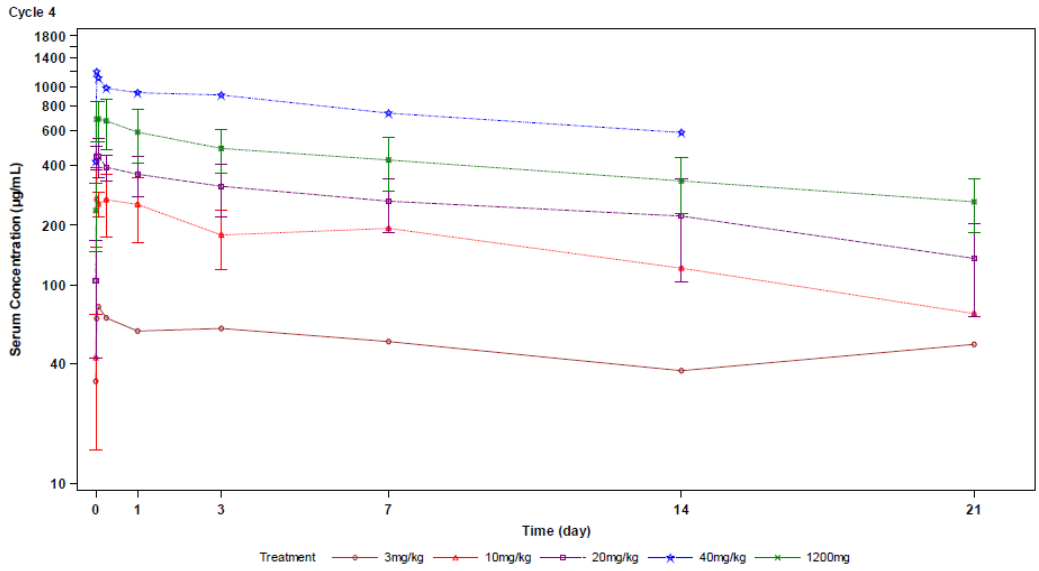
Based on the above results, the extent of *in vivo* exposure of CS1001 increased with the increase of dose.

Figure CE1: Mean serum concentration at cycle 1 for each dose group (log-linear scale)



SOURCE: Listing 16.2.5.2.1a

Figure CE2: Mean serum concentration at cycle 4 for each dose group (log-linear scale)



PD and Biomarker results

No PD-L1 RO (receptor occupancy) results or biomarker test results were available.

Efficacy results

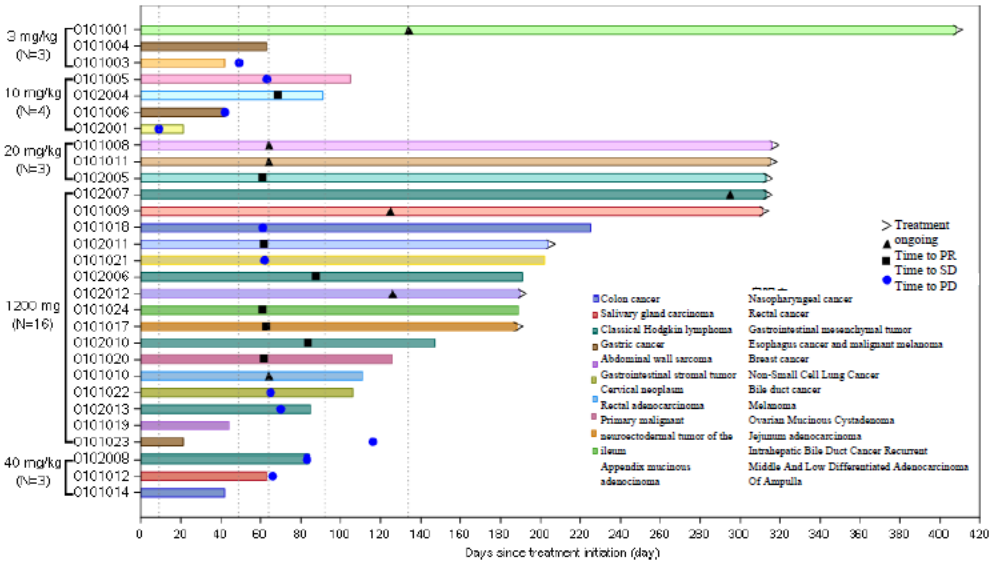
Table CE9: Summary of Objective Response in Part 1a of CS1001-101 (DCO: 30 Nov 2018)

	3 mg/kg (N = 3)	10 mg/kg (N = 4)	20 mg/kg (N = 3)	40 mg/kg (N = 3)	1200 mg (N = 16)	Total (N = 29)
Category of Best Response [n (%)] [1]						
CR	0	0	0	0	0	0
PR	1 (33.3)	0	2 (66.7)	0	4 (25.0)	7 (24.1)
SD	0	1 (25.0)	1 (33.3)	0	6 (37.5)	8 (27.6)
PD	1 (33.3)	3 (75.0)	0	2 (66.7)	5 (31.3)	11 (37.9)
N/A[2]	1 (33.3)	0	0	1 (33.3)	1 (6.3)	3 (10.3)
ORR [1]	1 (33.3)	0	2 (66.7)	0	4 (25.0)	7 (24.1)
95% CI (%)[4]	-	-	-	-	-	(10.3, 43.5)
Confirmed ORR[1,5]	1 (33.3)	0	2 (66.7)	0	3 (18.8)	6 (20.7)
95% CI (%) [4]	-	-	-	-	-	(8.0, 39.7)
DCR [1]	1 (33.3)	1 (25.0)	3 (100)	0	10 (62.5)	15 (51.7)
95% CI (%)[4]	-	-	-	-	-	(32.5, 70.6)
DOR (months)[6]						
Median (95% CI)[3]	- (-, -)	- (-, -)	- (6.2, -)	- (-, -)	- (-, -)	- (6.2, -)
Min, Max	8.7, 8.7	-, -	6.2, 7.8	-, -	0.03, 4.4	0.03, 8.7

Source: Table 14.2.1a.
Abbreviations: CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

1. ORR referred to the proportion of individual subjects who achieved CR or PR in terms of BOR. DCR referred to the proportion of individual subjects who achieved CR, PR, or SD in terms of BOR;
2. Subjects who had no post-baseline tumor assessments;
3. The 95% CI of the median was obtained according to the Kaplab-Meier method;
4. The 95% CIs for ORR and DCR were obtained by the one-sample Clopper-Pearson method;
5. Confirmed objective response (CR or PR) referred to subjects who achieved CR or PR for multiple times after the first observed response. Confirmed ORR referred to the proportion of subjects who achieved confirmed CR or PR. This rule applied only to patients who had tumor assessments as per RECSIT;
6. DOR is defined as the time from the first observed response to the first observed PD or death, whichever occurs earlier. Subjects were censored at the time of the last tumor assessment if no PD or death was observed after response.

Figure CE3: Bar Charts of Treatment Duration, Individual BOR, PD by Dose Group (DCO: 30 Nov, 2018)



Immunogenicity results

The overall ADA positive rate for all subjects was 20.7% (overall positivity was defined as a situation where a subject had a negative ADA result at baseline and had at least one positive ADA result post-baseline; or a subject had a positive ADA result at baseline with an increase in titre post-baseline).

Table CE10: Summary of the Immunogenicity of CS1001-ADAAS (DCO: 30 Nov, 2018)

Visit	3 mg/kg (N = 3) n (%)	10 mg/kg (N = 4) n (%)	20 mg/kg (N = 3) n (%)	40 mg/kg (N = 3) n (%)	1200 mg (N = 16) n (%)	Total (N = 29) n (%)
Baseline						
Positive	0	0	0	0	2 (12.5)	2 (6.9)
Negative	3 (100)	4 (100)	3 (100)	3 (100)	14 (87.5)	27 (93.1)
Missing	0	0	0	0	0	0
C2D1						
Positive	0	1 (25.0)	0	0	3 (18.8)	4 (13.8)
Negative	3 (100)	2 (50.0)	3 (100)	3 (100)	12 (75.0)	23 (79.3)
Missing	0	1 (25.0)	0	0	1 (6.3)	2 (6.9)
C4D1						
Positive	0	2 (50.0)	2 (66.7)	0	2 (12.5)	6 (20.7)
Negative	1 (33.3)	0	1 (33.3)	1 (33.3)	12 (75.0)	15 (51.7)
Missing	2 (66.7)	2 (50.0)	0	2 (66.7)	2 (12.5)	8 (27.6)
C5D1						
Positive	0	1 (25.0)	2 (66.7)	0	1 (6.3)	4 (13.8)
Negative	1 (33.3)	0	1 (33.3)	0	10 (62.5)	12 (41.4)
Missing	2 (66.7)	3 (75.0)	0	3 (100)	5 (31.3)	13 (44.8)
C7D1						
Positive	0	0	0	0	1 (6.3)	1 (3.4)
Negative	1 (33.3)	0	3 (100)	0	9 (56.3)	13 (44.8)
Missing	2 (66.7)	4 (100)	0	3 (100)	6 (37.5)	15 (51.7)
C10D1						
Positive	0	0	0	0	0	0
Negative	1 (33.3)	0	3 (100)	0	4 (25.0)	8 (27.6)
Missing	2 (66.7)	4 (100)	0	3 (100)	12 (75.0)	21 (72.4)
C13D1						
Positive	0	0	0	0	0	0
Negative	1 (33.3)	0	2 (66.7)	0	2 (12.5)	5 (17.2)
Missing	2 (66.7)	4 (100)	1 (33.3)	3 (100)	14 (87.5)	24 (82.8)
C16D1						
Positive	0	0	0	0	0	0
Negative	1 (33.3)	0	0	0	0	1 (3.4)
Missing	2 (66.7)	4 (100)	3 (100)	3 (100)	16 (100)	28 (96.6)
Overall[1]						
Positive	0	2 (50.0)	2 (66.7)	0	2 (12.5)	6 (20.7)
Negative	3 (100)	1 (25.0)	1 (33.3)	3 (100)	12 (75.0)	20 (69.0)
Non-drug-induced	0	0	0	0	1 (6.3)	1 (3.4)
No post-baseline assessment	0	1 (25.0)	0	0	1 (6.3)	2 (6.9)

Source: Table 14.5.1a.
Abbreviations: n = number of subjects; N = number of subjects in the analysis set.

Summary:

In the dose escalation period (Phase 1a) of Study CS1001-101, sugemalimab doses of 3 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg and a fixed dose of 1200 mg were studied.

All patients were Asians. MTD was not reached. No DLTs were reported.

There was no obvious trend to suggest that adverse events (common or Grade ≥3) are dose-dependent. Dose-dependence was observed for PK – serum concentration of sugemalimab increased with increasing doses.

The PK (exposure and half-life) of the 1200 mg fixed dose and the 20 mg/kg were similar. This was an expected observation since the median weight of the patients in the fixed dose 1200 mg group was 62.1kg, which equates to 19.3 mg/kg (i.e.. ~20 mg/kg).

The fixed dose of 1200 mg sugemalimab was chosen to be the RP2D.

Most patients (16/29) received the fixed dose of 1200 mg. In this group, the top 10 most frequently observed adverse events (in order of decreasing frequency) were anaemia, proteinuria, increased ALT, increased AST, increased bilirubin, decreased WBC, cough, constipation, decreased appetite, increased CPK. The most common ≥Grade 3 adverse event was anaemia. Adverse events were manageable.

An immunogenicity assessment found ADA in 12.5% (2/16) in the 1200 mg fixed dose group.

- **Study CS1001-102**

Title: Phase I, open-label, dose-escalation study of sugemalimab in subjects with advanced solid tumours.

This study was designed based on 3 + 3 dose escalation scheme to evaluate 2 dose levels sequentially: 10 mg/kg and a fixed dose of 1200 mg.

It was conducted at 2 sites in the US to bridge the PK data collected from an Asian population and has been completed.

Study Start Date (First subject enrolled): 04 Dec 2018

Last Patient Last Visit: 19 Oct 2020

Methods

- **Objectives**

The objectives were the same as for Study CS1001-101, the first-in-human study.

- **Study Participants**

The inclusion and exclusion criteria were essentially the same as for Study CS1001-101, the first-in-human study.

Results

Twenty-four subjects with solid tumours were enrolled into 1 of 2 sugemalimab dose groups - 10 mg/kg (n=12) or 1200 mg fixed dose (n=12).

Sugemalimab was given by intravenous infusion over 60 to 120 minutes every 21 days.

Table CE11: Demographic and Baseline Characteristics

	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Sex			
Male	6 (50.0%)	4 (33.3%)	10 (41.7%)
Female	6 (50.0%)	8 (66.7%)	14 (58.3%)
Age (Years)			
n	12	12	24
Mean (SD)	65.9 (6.78)	60.5 (12.80)	63.2 (10.39)
Median	66.5	61.0	64.0
Min, Max	56, 76	31, 76	31, 76
Age Category (Years)			
18-<45	0	1 (8.3%)	1 (4.2%)
45-<65	5 (41.7%)	6 (50.0%)	11 (45.8%)
≥ 65	7 (58.3%)	5 (41.7%)	12 (50.0%)
Race			
White	10 (83.3%)	10 (83.3%)	20 (83.3%)
Black or African American	1 (8.3%)	2 (16.7%)	3 (12.5%)
Other	1 (8.3%)	0	1 (4.2%)
Ethnicity			
Hispanic or Latino	1 (8.3%)	0	1 (4.2%)
Not Hispanic or Latino	11 (91.7%)	12 (100.0%)	23 (95.8%)
Height (cm)			
n	12	12	24
Mean (SD)	166.63 (9.679)	165.88 (9.744)	166.25 (9.506)
Median	167.50	165.10	165.10
Min, Max	148.6, 180.0	150.0, 182.9	148.6, 182.9
Weight (kg)			
n	12	12	24
Mean (SD)	81.54 (22.653)	83.09 (24.505)	82.32 (23.092)
Median	74.00	87.20	81.00
Min, Max	53.0, 122.4	36.0, 124.0	36.0, 124.0
BMI (kg/m^2)			
n	12	12	24
Mean (SD)	29.114 (6.4817)	29.806 (7.5800)	29.460 (6.9063)
Median	27.724	30.097	30.091
Min, Max	21.50, 41.04	14.98, 45.55	14.98, 45.55
ECOG Performance Status			
0	1 (8.3%)	2 (16.7%)	3 (12.5%)
1	11 (91.7%)	10 (83.3%)	21 (87.5%)

The median and mean weight of patients in US was 81.0 kg (range 36 – 124) and 82.3 kg (SD 23.1), respectively.

Adverse events

Table CE13: Most Common (Total Incidence ≥ 5%) Treatment-Emergent Adverse Event by Preferred Term

MedDRA Preferred Term	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Number of patients with at least TEAE	12 (100.0%)	12 (100.0%)	24 (100.0%)
Nausea	6 (50.0%)	3 (25.0%)	9 (37.5%)
Fatigue	6 (50.0%)	2 (16.7%)	8 (33.3%)
Abdominal pain	1 (8.3%)	5 (41.7%)	6 (25.0%)
Blood alkaline phosphatase increased	4 (33.3%)	2 (16.7%)	6 (25.0%)
Abdominal distension	2 (16.7%)	3 (25.0%)	5 (20.8%)
Constipation	3 (25.0%)	2 (16.7%)	5 (20.8%)
Vomiting	2 (16.7%)	3 (25.0%)	5 (20.8%)
Dehydration	1 (8.3%)	3 (25.0%)	4 (16.7%)
Gastrooesophageal reflux disease	3 (25.0%)	1 (8.3%)	4 (16.7%)
Hypokalaemia	1 (8.3%)	3 (25.0%)	4 (16.7%)
Ascites	1 (8.3%)	2 (16.7%)	3 (12.5%)
Aspartate aminotransferase increased	2 (16.7%)	1 (8.3%)	3 (12.5%)
Blood bilirubin increased	1 (8.3%)	2 (16.7%)	3 (12.5%)
Decreased appetite	3 (25.0%)	0	3 (12.5%)
Performance status decreased	2 (16.7%)	1 (8.3%)	3 (12.5%)
Pneumonia	2 (16.7%)	1 (8.3%)	3 (12.5%)
Proteinuria	1 (8.3%)	2 (16.7%)	3 (12.5%)
Pyrexia	2 (16.7%)	1 (8.3%)	3 (12.5%)
Anaemia	2 (16.7%)	0	2 (8.3%)
Dysphagia	1 (8.3%)	1 (8.3%)	2 (8.3%)
Dyspnoea	1 (8.3%)	1 (8.3%)	2 (8.3%)
Hypercalcaemia	1 (8.3%)	1 (8.3%)	2 (8.3%)
Hypophosphataemia	1 (8.3%)	1 (8.3%)	2 (8.3%)
Influenza like illness	1 (8.3%)	1 (8.3%)	2 (8.3%)
Neck pain	2 (16.7%)	0	2 (8.3%)
Pruritus	2 (16.7%)	0	2 (8.3%)
Sepsis	0	2 (16.7%)	2 (8.3%)
Small intestinal obstruction	1 (8.3%)	1 (8.3%)	2 (8.3%)
Weight decreased	1 (8.3%)	1 (8.3%)	2 (8.3%)

Table CE14: Summary of TEAEs with the Highest CTCAE Grade of Grade 3 or Higher

MedDRA System Organ Class MedDRA Preferred Term	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Number of patients with at least one event	5 (41.7%)	9 (75.0%)	14 (58.3%)
Gastrointestinal disorders	**2 (16.7%)**	**3 (25.0%)**	**5 (20.8%)**
Abdominal pain	1 (8.3%)	1 (8.3%)	2 (8.3%)
Ascites	0	2 (16.7%)	2 (8.3%)
Small intestinal obstruction	1 (8.3%)	1 (8.3%)	2 (8.3%)
Nausea	1 (8.3%)	0	1 (4.2%)
Small intestinal perforation	0	1 (8.3%)	1 (4.2%)
Infections and infestations	**2 (16.7%)**	**2 (16.7%)**	**4 (16.7%)**
Pneumonia	2 (16.7%)	0	2 (8.3%)
Sepsis	0	2 (16.7%)	2 (8.3%)
Investigations	**1 (8.3%)**	**2 (16.7%)**	**3 (12.5%)**
Aspartate aminotransferase increased	0	1 (8.3%)	1 (4.2%)
Blood alkaline phosphatase increased	1 (8.3%)	0	1 (4.2%)
Blood bilirubin increased	0	1 (8.3%)	1 (4.2%)
International normalised ratio increased	0	1 (8.3%)	1 (4.2%)
Metabolism and nutrition disorders	**1 (8.3%)**	**2 (16.7%)**	**3 (12.5%)**
Hypokalaemia	0	2 (16.7%)	2 (8.3%)
Hypophosphataemia	1 (8.3%)	1 (8.3%)	2 (8.3%)
Hypercalcaemia	0	1 (8.3%)	1 (4.2%)
Hyperglycaemia	1 (8.3%)	0	1 (4.2%)
Blood and lymphatic system disorders	**1 (8.3%)**	**1 (8.3%)**	**2 (8.3%)**
Anaemia	1 (8.3%)	0	1 (4.2%)
Iron deficiency anaemia	0	1 (8.3%)	1 (4.2%)
General disorders and administration site conditions	**1 (8.3%)**	**1 (8.3%)**	**2 (8.3%)**
Performance status decreased	1 (8.3%)	1 (8.3%)	2 (8.3%)
Product issues	**0**	**1 (8.3%)**	**1 (4.2%)**
Device dislocation	0	1 (8.3%)	1 (4.2%)
Renal and urinary disorders	**0**	**1 (8.3%)**	**1 (4.2%)**
Acute kidney injury	0	1 (8.3%)	1 (4.2%)
Vascular disorders	**1 (8.3%)**	**0**	**1 (4.2%)**
Hypertension	1 (8.3%)	0	1 (4.2%)

A total of 14 (58.3%) deaths occurred during this study, including 12 (50.0%) due to disease progression and 2 (8.3%) due to AE. One patient died of pneumonia (in the 10 mg/kg group), and one died of acute kidney injury (in the 1200 mg group). The investigator assessed the SAE of pneumonia as not related to study drug or study procedure. The SAE of acute kidney injury was assessed by investigator as possibly related to study drug.

Table CE15: Treatment-Emergent Adverse Events Leading to Drug Interruption

MedDRA System Organ Class MedDRA Preferred Term	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Number of patients with at least one event	0	2 (16.7%)	2 (8.3%)
Infections and infestations	**0**	**1 (8.3%)**	**1 (4.2%)**
Sepsis	0	1 (8.3%)	1 (4.2%)
Metabolism and nutrition disorders	**0**	**1 (8.3%)**	**1 (4.2%)**
Hypercalcaemia	0	1 (8.3%)	1 (4.2%)

Table 16: Treatment-Emergent Adverse Events Leading to Drug Permanently Discontinued

MedDRA System Organ Class MedDRA Preferred Term	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Number of patients with at least one event	1 (8.3%)	3 (25.0%)	4 (16.7%)
General disorders and administration site conditions	**1 (8.3%)**	**1 (8.3%)**	**2 (8.3%)**
Performance status decreased	1 (8.3%)	1 (8.3%)	2 (8.3%)
Investigations	**0**	**1 (8.3%)**	**1 (4.2%)**
Aspartate aminotransferase increased	0	1 (8.3%)	1 (4.2%)
Blood bilirubin increased	0	1 (8.3%)	1 (4.2%)
Renal and urinary disorders	**0**	**1 (8.3%)**	**1 (4.2%)**
Acute kidney injury	0	1 (8.3%)	1 (4.2%)

No immune-related adverse event or infusion-related adverse event was reported in this study.

MTD was not reached.

DLT events or significant safety concerns did not occur.

PK results

After single dose administration, the maximum concentrations of sugemalimab in the 10 mg/kg and 1200 mg groups were 261.1 and 346.0 μg/mL, respectively. The CL and elimination half-life were approximately 13.65/12.29 mL/h and 11.64/17.40 days after 10 mg/kg or 1200 mg single dose administration of CS1001 in Cycle 1.

After multiple administrations at the 10 mg/kg or 1200 mg dose level, the average trough concentrations were 94.38 and 157.9 μg/mL, respectively. The accumulation index for AUC and Cmax were around 2.

Table CE17: Summary of Sugemalimab Pharmacokinetic Parameters After Single- and Multiple-dose IV Infusion

PK Parameter (Unit)	10 mg/kg (N = 12)		1200 mg (N = 12)	
	n	Geometric Mean (Geomean % CV)	n	Geometric Mean (Geomean % CV)
Cycle 1				
C_{max} (µg/mL)	12	254 (22.85)	12	323 (38.33)
$AUC_{0\text{-}21d}$ (day•µg/mL)	12	1870 (20.03)	12	2680 (28.49)
$t_{1/2}$ (day)	12	11.6 (5.94)	11	17.4 (7.59)
Cycle 4				
C_{max} (µg/mL)	2	331 (60.61)	5	516 (20.34)
$AUC_{0\text{-}21d}$ (day•µg/mL)	2	2920 (77.5)	5	5070 (26.8)
$R_{acc,AUC}$	2	2.012 (69.66)	5	1.660 (21.89)
$R_{acc,Cmax}$	2	1.650 (60.33)	5	1.503 (15.53)

Note: $t_{1/2}$ is presented as arithmetic mean and standard deviation.
$AUC_{0\text{-}21d}$ = area under the curve from time 0 to 21 days; C_{max} = maximum serum concentration; Geo. CV = geometric coefficient of variation; IV = intravenous; n = number of participants in analysis set; PK = pharmacokinetic(s); Q3W = once every 3 weeks; $R_{acc,AUC}$ = accumulation ratio for AUC; $R_{acc,Cmax}$ = accumulation ratio for C_{max}; $t_{1/2}$ = elimination half-life.
Source: Clinical Study Report CS1001-102, Table t_pk_param_PKAS.

Figure CE4: Mean serum concentration at cycle 1 for each dose group in Study CS1001-102 (log-linear scale)

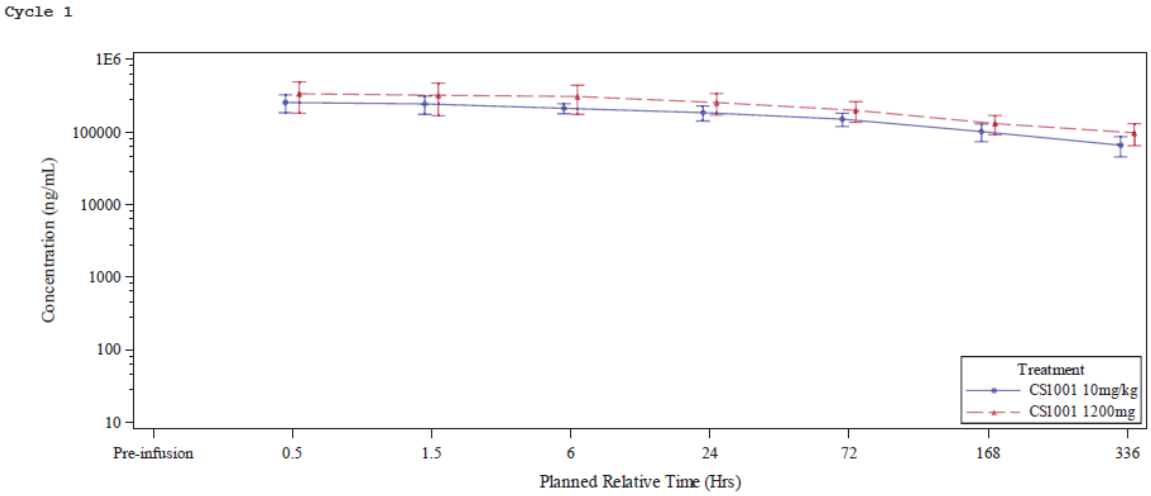
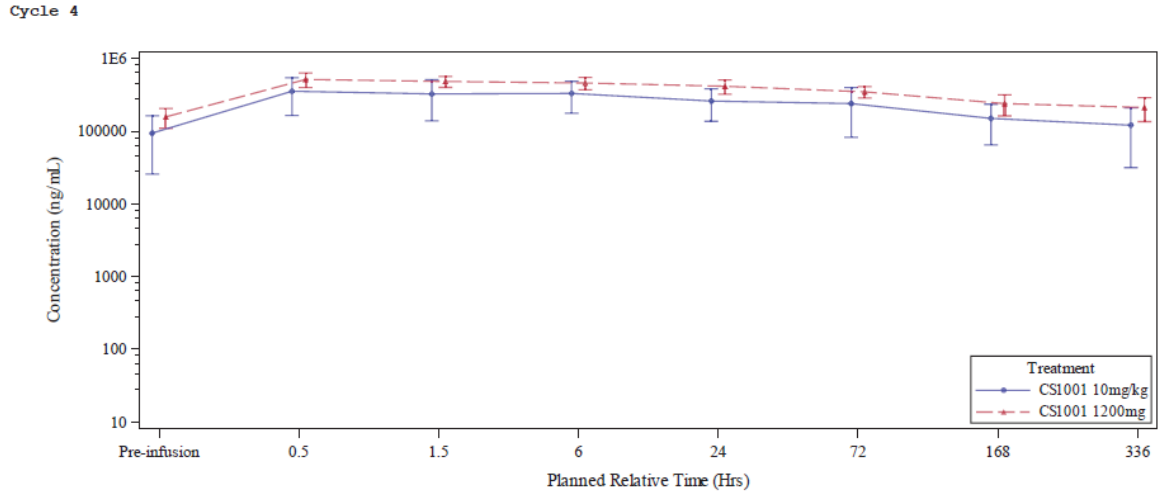


Figure CE5: Mean serum concentration at cycle 4 for each dose group (log-linear scale)

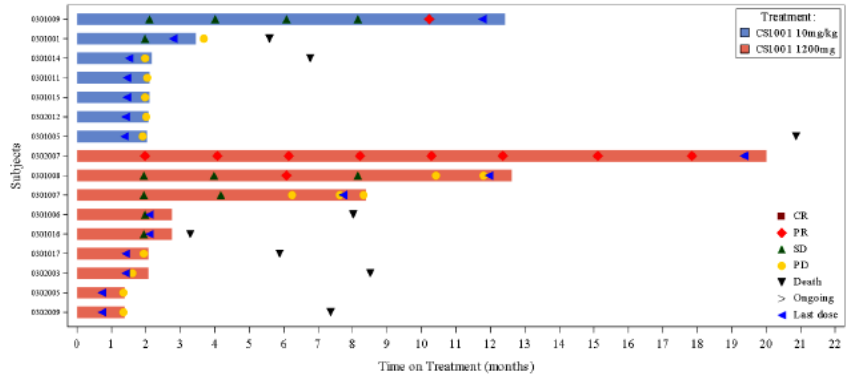


Efficacy results

Table CE18: Best overall response assessed by investigator

	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Objective Response Rate (CR+PR)	0	1 (8.3%)	1 (4.2%)
95% CI	[NE, NE]	[0.2%, 38.5%]	[0.1%, 21.1%]
Best Overall Response			
Complete Response (CR)	0	0	0
95% CI	[NE, NE]	[NE, NE]	[NE, NE]
Partial Response (PR)	0	1 (8.3%)	1 (4.2%)
95% CI	[NE, NE]	[0.2%, 38.5%]	[0.1%, 21.1%]
Stable Disease (SD)	2 (16.7%)	4 (33.3%)	6 (25.0%)
95% CI	[2.1%, 48.4%]	[9.9%, 65.1%]	[9.8%, 46.7%]
Progressive Disease (PD)	5 (41.7%)	4 (33.3%)	9 (37.5%)
95% CI	[15.2%, 72.3%]	[9.9%, 65.1%]	[18.8%, 59.4%]
Not Evaluable (NE)	0	0	0
Not Applicable	5 (41.7%)	3 (25.0%)	8 (33.3%)
Disease Control Rate (CR+PR+SD)	2 (16.7%)	5 (41.7%)	7 (29.2%)
95% CI	[2.1%, 48.4%]	[15.2%, 72.3%]	[12.6%, 51.1%]

Figure CE6: Swimmer Plot of Treatment Duration, Overall Response and Progression



Immunogenicity results

Among all 19 patients who were evaluable for immunogenicity, the overall ADA positive rate was 5.3%.

Table CE19: Summary of the Immunogenicity

	CS1001 10 mg/kg (N=9)	CS1001 1200 mg (N=10)	Total (N=19)
Baseline			
n	9	10	19
ADA positive	0	1 (10.0%)	1 (5.3%)
ADA negative	9 (100.0%)	9 (90.0%)	18 (94.7%)
Post-Baseline			
n	9	10	19
ADA positive	0	1 (10.0%)	1 (5.3%)
ADA negative	9 (100.0%)	9 (90.0%)	18 (94.7%)
ADA Status			
Treatment-induced ADA positive	0	0	0
Treatment-enhanced ADA positive	0	1 (10.0%)	1 (5.3%)
Treatment-unaffected ADA	0	0	0

Abbreviation: ADA = Anti-Drug Antibody.
Treatment-induced ADA positive was defined as patients who had a baseline-negative ADA result and developed ADA at any time after initial drug administration.
Treatment-enhanced ADA positive was defined as patients who had a baseline-positive ADA result in whom the assay signal was enhanced (greater than baseline titer by =0.60 titer units) at any time after initial drug administration.
Treatment-unaffected ADA was defined as patients with a baseline-positive ADA result and available post-baseline ADA result(s), none of which was enhanced (greater than baseline).
Source: Table t_im_SA

Summary:

CS1001-102 was conducted in the US in non-Asian patients with the intention of ethnic bridging as well as dose-finding. Two dose levels were investigated: 10 mg/kg and a fixed dose of 1200 mg (the selected RP2D from Study CS1001-101).

The study was initiated based on the selected RP2D of 1200 mg. The company state that the PK of monoclonal antibodies in general have been extensively studied and were shown to be similar across various populations and racial groups (accounting for differences in metabolism, pharmacogenetic variations, etc). The PK of mAbs targeting PD-1/L1 show saturating PK. In light of these considerations, it was deemed sufficient by the company to explore only two dose levels (RP2D and a lower dose of 10 mg/kg for further investigation of the optimal dose).

Twelve patients were entered into each of the 2 groups.

The median weight of patients in Study CS1001-102 was 74.0 kg (53.0, 122.4) in the 10 mg/kg arm and 87.2 kg (36.0, 124.0) in the 1200 g fixed dose arm. The company provided an analysis of weight against (a) PK / PD parameters, (b) type and severity of adverse events, (c) ORR (overall response rate) and DoR (duration of response) for each patient in the 1200 mg fixed dose group, as for Study CS1001-101.

As per the requirements, the company stratified several indicators (PK parameters, AE, Efficacy) by body weight, conducting both binary and four-category classifications. In summary, no significant differences were observed across various weight intervals for each indicator after stratification by body weight.

MTD was not reached.

No DLTs were reported.

The most frequent adverse events were nausea, fatigue, abdominal pain, increased ALP, abdominal distension, constipation, vomiting, dehydration, gastro-oesophageal reflux and hypokalaemia.

There was a slightly higher proportion of Grade 3-4 adverse events and treatment discontinuation in the 1200 mg fixed dose group than the 10 mg/kg group.

C_{max} and AUC were higher in the 1200 mg fixed dose group compared to the 10 mg/kg group, although not by much. Not surprisingly, comparison between studies revealed less separation of the PK curves between these 2 dose levels in non-Asians than Asians from Study CS1001-101, since the corresponding weight-base dose in the 1200 mg fixed dose group with patients' mean weight of 83 kg worked out to be ~15 mg/kg.

No conclusion was drawn from this cross-study comparison and small number of patients (total of 12 non-Asians patients).

Ethnic bridging between non-Asians and Asians was not demonstrated.

Only one patient (1200 mg fixed dose group) achieved a partial response. At the 1200 mg fixed dose, there were more responders in Asians (25% [4/16] Study CS1001-101a) than non-Asians (8.3% [1/12] Study CS1001-102).

Of the 2 dose levels investigated, the 1200 mg fixed dose was selected as the RP2D. It is agreed that this dose group was overall better than the 10 mg/kg dose, but this study was not considered adequate as a dose-finding study as it was not possible to conclude from this study that the chosen RP2D of sugemalimab has been thoroughly investigated in non-Asians.

Proposed dose

The Applicant provided simulations for exposure based on Ctrough, AUC and Cmax in weight bands of 5 Kg across body weight ranging from 80 to 150 kg.

Based on these simulations, the recommended dose of sugemalimab is 1200 mg once every 3 weeks for individual weighing ≤115 kg and 1500 mg Q3W for those weighing >115 kg.

The proposed posology is acceptable; the Applicant used stringent bioequivalence (BE) limits of 80-125% to compare the simulated exposure to the reference exposure in the pivotal study CS1001-302 with a dose of 1200 mg Q3W and actual weight range of 41-96 kg.

Main study (Study CS1001-302)

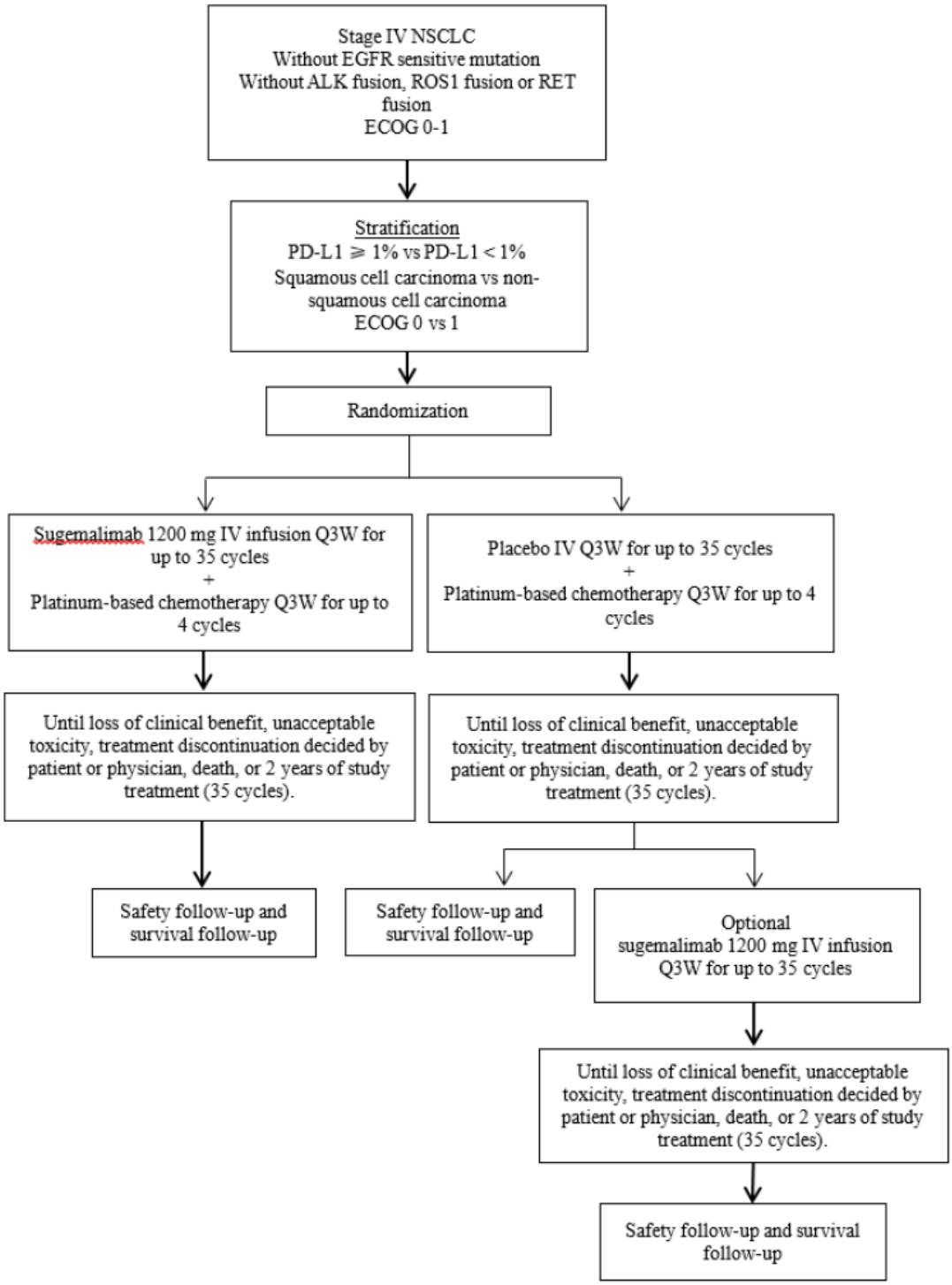
Title: A Multicentre, Randomized, Double-Blind, Phase III Study of Platinum-Based Chemotherapy With or Without Sugemalimab in Patients with Stage IV Non-Small Cell Lung Cancer

This ongoing study is conducted in China. It commenced on 13 December 2018 (first patient first visit).

Data cut-off date for the final PFS (progression free survival) analyses was 15 March 2021.

Data cut-off date for the interim OS (overall survival) analyses was 22 November 2021.

Figure CE7: Study schema



Enrolment to Study CS1001-302 (GEMSTONE-203) is completed.

Study CS1001-302 is an ongoing Phase 3 randomized, double-blind, placebo-controlled study that compared the efficacy and safety of sugemalimab versus placebo as first-line treatment, in combination with standard chemotherapy regimens followed by maintenance sugemalimab/placebo, for patients with metastatic NSCLC without EGFR mutation, ALK fusion, ROS1 fusion or RET fusion.

After chemotherapy, sugemalimab or placebo continued until disease progression, unacceptable toxicity, patient withdrawal of informed consent, death or completion of 2 years of treatment (35 cycles).

Eligible patients who progressed could enter the cross-over phase to receive open-label sugemalimab monotherapy for up to 35 cycles.

Methods

- **Study Participants**

Main inclusion criteria:

- 18 years of age or older
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1
- Histologically or cytologically confirmed as locally advanced or metastatic NSCLC (Including patients relapsed after previous surgical treatment or with newly diagnosed stage IIIB/IV.
- Not received any systemic treatment
- EGFR sensitive mutations (including exon 19 deletion (Ex19del) or L858R, one mutation alone or coexisting with other EGFR mutations) confirmed on tumour sample or blood sample by central laboratory testing
- Measurable disease

Main exclusion criteria:

Received any of the following treatments:

- any EGFR tyrosine kinase inhibitor in the past

- undergone major surgery within 4 weeks before the first administration of the study drug

- received more than 30% bone marrow irradiation or received extensive radiotherapy within 4 weeks before the first administration of the study drug

- used potent inhibitors or inducers of CYP3A4 or drugs with a narrow therapeutic window that are sensitive substrates of CYP3A4 within 7 days before the first administration of the study drug

Spinal cord compression or brain metastasis, unless asymptomatic, conditions stable, and not requiring steroid therapy for at least 2 weeks prior to the first administration of the study treatment

Any serious or poorly controlled systemic diseases, such as poorly controlled high blood pressure, active bleeding constitution, or active infection

Clinically significant heart disease and prolonged QT interval (QTc)

History of interstitial lung disease

Insufficient bone marrow reserve or organ function

- **Treatments**

Patients were randomized in a 2:1 ratio to receive either sugemalimab + chemotherapy or placebo + chemotherapy.

Sugemalimab 1200 mg or matching placebo was administered over 60 minutes on Day 1 of each treatment cycle, every 3 weeks (21 days, Q3W) until progression of disease or occurrence of unacceptable toxicity, study withdrawal, or death.

The selection of platinum-based chemotherapy was based on the participant's histopathological subtype (pemetrexed and carboplatin for non-squamous NSCLC and paclitaxel and carboplatin for squamous NSCLC).

Chemotherapy for non-squamous cell carcinoma: treatment cycle: 21 days (3 weeks)

Pemetrexed: 500 mg/m2, on Day 1 of each cycle for 4 cycles. After that, pemetrexed maintenance treatment at 500 mg/m2 Q3W was allowed.

Carboplatin: AUC = 5 mg/mL/min (calculated according to Calvert formula, dose not to exceed 750 mg), on Day 1 of each cycle for 4 cycles.

Chemotherapy for squamous cell carcinoma: treatment cycle: 21 days (3 weeks)

Paclitaxel: 175 mg/m2, IV infusion on Day 1 of each cycle for up to 4 cycles.

Carboplatin: AUC = 5 mg/mL/min (calculated according to Calvert formula, dose not to exceed 750 mg), on Day 1 of each cycle for 4 cycles.

- **Objectives and Endpoints**

Primary objectives:	**Primary endpoint:**
To compare efficacy between sugemalimab in combination with platinum-based chemotherapy and placebo in combination with platinum-based chemotherapy	PFS assessed by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary objectives:	**Secondary endpoints:**
To compare the efficacy between sugemalimab in combination with platinum-based chemotherapy and placebo in combination with platinum-based chemotherapy	• Overall survival (OS) • PFS assessed by BICR according to RECIST v1.1 • PFS in patients with PD-L1≥1% evaluated by investigators according to RECIST v1.1 • Objective response rate (ORR) and duration of response (DoR) assessed by investigators according to RECIST v1.1
To evaluate safety and tolerability of sugemalimab in combination with platinum-based chemotherapy and placebo in combination with platinum-based chemotherapy	Treatment emergent adverse events, vital signs, physical examination, electrocardiogram (ECG), laboratory tests (including chemistry, hematology and urinalysis), etc.
To characterize the pharmacokinetics (PK) and immunogenicity of sugemalimab	• Peak and trough serum concentrations of sugemalimab • Number and percentage of patients who develop anti-sugemalimab antibody (ADA)
To evaluate the efficacy of sugemalimab monotherapy in patients who experienced progressive disease after assigned to the placebo group in the double-blind phase	• ORR, DoR, progression free survival (PFS) assessed by the investigators according to RECIST v1.1 and OS

- **Tumour response assessment**

Baseline tumour assessment was carried out at screening and within 14 days prior to any study treatment.

Patients were evaluated at week 6 (± 7 days), week 12 (± 7 days) after the first dose, and then every 9 weeks (± 7 days) with radiological imaging for the first year of treatment; and every 12 weeks (± 7 days) thereafter, until progression of disease, lost to follow-up, death, or end of study, whichever occurred first.

- **Sample size**

A total of 480 subjects are planned to be randomized in this study.

A total of 360 PFS events are required to detect a maximum HR of 0.80 with 89% power.

Sample size and number of events needed were estimated based upon the following assumptions:

− Hazard ratio (HR) of PFS: 0.70.

− Two-sided significance level: 0.05.

− Randomization ratio: 2:1.

− Median PFS in control group is 6 months. Time-to- event data follows exponential distribution.

− The average enrolment rate is around 22 subjects per month, the enrolment duration will be about 21.8 months.

− An interim analysis was planned to be conducted when approximately 70% of data is available. Type I error was planned to be controlled using Lan-DeMets method with approximate O'Brien-Fleming boundary.

− The drop-out rate of PFS is 5% every 12 months. The required sample size and number of events for PFS required at the interim and final analysis are summarised below.

	Sample size	Number of events	Time (months)	Boundary of hazard ratio	Boundary of P value	Power
PFS						
Interim analysis	465	252	21	0.722	0.0148	0.60
Final analysis	480	360	29	0.800	0.0455	0.89

A total of 360 OS events are required to detect a maximum HR 0.777 with 80% power.

Sample size and number of events needed were estimated based upon the following assumptions:

− OS HR is 0.72, the median OS in control group is 12 months.

− Two-sided significance level is 0.05. Time-to-event data follows exponential distribution.

− An interim analysis will be conducted when 70% of data is available. Type I error will be controlled using Lan-DeMets method with approximately Pocock boundary.

− The drop-out rate of OS is 2% every 12 months. The required sample size and number of events for OS required at the interim and final analysis are summarised below.

	Sample size	Number of events	Time (months)	Boundary of hazard ratio	Boundary of P value	Power
OS						
Interim analysis	480	252	28	0.759	0.0395	0.66
Final analysis	480	360	43	0.777	0.0243	0.80

The sample size is reasonable given the assumptions made.

The use of Lan-DeMets method with approximate O'Brien-Fleming boundary to control the type error is acceptable. This method uses spending functions to set boundaries for group sequential trials and allows interim analyses to be conducted at non-equal intervals, while controlling the error rate at the interim analyses.

- **Randomisation**

Patients were randomised 2:1 to receive sugemalimab in combination with platinum-based chemotherapy (referred to as "sugemalimab group") or placebo in combination with chemotherapy (referred to as "placebo group").

Randomisation was stratified by:

- Performance status (0 or 1)
- Histological type (squamous cell carcinoma or Non-squamous cell carcinoma)
- PD-L1 expression (≥1% or <1%)

In this study, the proportion of patients with squamous cell carcinoma will not exceed 40%. The proportion of subjects with PD-L1 < 1% was planned to be no more than 40% in subjects with both

squamous cell carcinoma and non-squamous cell carcinoma.

Stratified block randomization by IVRS/IWRS was used.

The randomisation scheme is acceptable. Equal randomisation is the most statistically efficient ratio as it maximises the power for a given sample size. However, the use of unequal randomisation ratio is understood in this context. Factors used to stratify patients were adjusted for in the primary analysis in line with the recommendation in the CHMP Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013)

- **Blinding (masking)**

Study CS1001-302 adopted a double-blind design. Investigators, subjects and the Sponsor were blinded to the exact PD-L1 expression value of randomized subjects throughout the study.

This was a double-blind study although immune-related adverse effects of sugemalimab would have given clues to investigators, which could have introduced potential bias. For the primary endpoint, both investigator assessed and BICR assessed PFS, ORR, DOR were reported. This approach is supported.

- **Statistical methods**

Statistical Analysis Software (SAS) version 9.4 or above was used for all data analysis and programming.

Primary analysis

Progression-free survival (PFS) is defined as the time from the date of randomisation to disease progression or death whichever occurs first. Subjects without event (no disease progression or death) were censored at the date of "last tumour assessment". Subjects without post-baseline tumour assessment were censored at the date of randomisation.

Stratified log-rank test was used to compare the PFS difference between the two treatment groups. Stratified Cox regression model was used to estimate the efficacy (tie issue were handled with the Efron's approach), PFS HR and its 95% confidence interval, and the unstratified HR and its 95% confidence interval were provided as well. The stratification factors are the same as those for randomization. The order of the three stratification factors is specified as ECOG PS, PD-L1 expression value, and histology type. If number of subjects in any strata doesn't meet the requirement of analysis method, for example less than 10 subjects, the associated strata was combined.

Non-parametric Kaplan Meier method was used to estimate median PFS, PFS at different time points and their 95% CIs (by Brookmeyer Crowley method). A Kaplan Meier curve was used to visually describe PFS over time.

The primary analysis methods are acceptable. These are standard methods for the analysis and description of time-to-events data. The censoring rules are in line with the Appendix 1 to the CHMP guideline on the evaluation of anticancer medicinal products in man (CHMP/EWP/205/95 REV. 3).

Secondary analysis

• Overall survival (OS): Overall survival is defined as the time from the randomization date to all-cause death date. Subjects alive were censored at the last known alive date. For OS analysis, subjects without any data after baseline were censored at the date of randomization. The statistical analysis method for OS is the same as that for the primary efficacy endpoint.

• Progression-free survival (PFS, assessed by BICR according to RECIST v1.1): The statistical analysis methods for this endpoint is the same as that for the primary efficacy endpoint.

• PD-L1 ≥ 1% PFS (assessed by the investigator per RECIST v1.1): The analysis method for this endpoint is consistent with the statistical analysis method for the primary efficacy endpoint.

• Objective response rate (ORR, assessed by the investigator according to RECIST v1.1): the number and percentage of subjects who achieve objective tumour response (CR or PR). A subject included in ORR analysis but without post-baseline tumour assessment were considered as a non-responder. All randomized subjects with a measurable baseline lesion were included in ORR analysis set.

Stratified Mantel-Haenszel test was used to compare ORR difference between two treatment groups. Normal approximation to binomial distribution was used to calculate 95% CI for ORR difference between two groups. Clopper Pearson method was used to calculate the ORR and its 95% CI of each group.

• Duration of repose (DOR, assessed by the investigator according to RECIST v1.1): Duration of response for responders (CR or PR) was defined as the time between the date of the earliest qualified response and the date of progressive disease or all-cause-death, whichever occurs first. The duration of response was analysed in the investigator-assessed complete or partial responders. This analysis set is not determined by randomization, and therefore, all statistical analyses are descriptive analyses.

Kaplan Meier method was used to estimate median DOR. Kaplan Meier curve was provided to visually describe DOR changes over time. Subjects who are alive without progression after meeting the criteria of response were censored on the date of last evaluable tumour assessment. If no tumour assessment is performed after the first occurrence of CR or PR, DOR was censored at the date of CR or PR.

• Objective response rate (ORR, assessed by BICR according to RECIST v1.1): the number and percentage of subjects who achieve objective tumour response (CR or PR). A subject included in ORR analysis but without post-baseline tumour assessment will be considered as a non-responder. All randomised subjects with a measurable baseline lesion were included in ORR analysis set. Stratified Mantel-Haenszel test was used to compare ORR difference between two treatment groups. Normal approximation to binomial distribution was used to calculate 95% CI for ORR difference between two groups. Clopper Pearson method will be used to calculate the ORR and its 95% CI of each group.

• Duration of repose (DOR, assessed by BICR according to RECIST v1.1): Duration of response for responders (CR or PR) is defined as the time between the date of the earliest qualified response and the date of progressive disease or all-cause death, whichever occurs first. The duration of response was analysed in the investigator-assessed complete or partial responders. This analysis set is not determined by randomisation, and therefore, all statistical analyses are descriptive analyses.

Kaplan Meier method was used to estimate median DOR. Kaplan Meier curve was provided to visually describe DOR changes over time. Subjects who are alive without progression after meeting the criteria of response were censored on the date of last evaluable tumour assessment. If no tumour assessment is performed after the first occurrence of CR or PR, DOR were to be censored at the date of CR or PR.

The efficacy endpoints in the cross-over phase were analysed in subjects who have at least one dose of CS1001 in cross-over phase, have not taken any CS1001 in the double-blind treatment phase and are assessed as PD by the investigator per RECIST v1.1. The tumour

assessment baseline of cross-over phase was defined as the last tumour assessment prior to CS1001 administration.

• Objective response rate (ORR, assessed by the investigator according to RECIST v1.1): the number and percentage of subjects who achieve objective tumour response (CR or PR). Subjects with measurable lesion were considered as responders if the first CR or PR is confirmed in ≥ 4 weeks. Clopper Pearson method was used to calculate the ORR and its 95% CI.

• Duration of response (DOR, assessed by the investigator according to RECIST v1.1): Duration of response for responders (CR or PR) is defined as the time between the date when subject is confirmed to meet criteria of response and the date of PD or all-cause death, whichever occurs first. The duration of response was analysed in the investigator-assessed and confirmed complete or partial responders. All statistical analyses are descriptive analyses.

Kaplan Meier method was used to estimate median DOR. Kaplan Meier curve was provided to visually describe DOR changes over time. For subjects who are alive without progression following the qualified response, duration of response were censored on the date of last evaluable tumour assessment. If no tumour assessment was performed after the confirmed CR or PR, DOR were censored at the date of CR or PR confirmation.

• Progression-free survival (PFS) (assessed by the investigator according to RECIST v1.1): the time from the first CS1001 dose date in the cross-over phase till progressive disease or death, whichever occurs first. Subjects without event (no disease progression or death) were censored at the date of "last tumour assessment". Subjects without tumour assessment after baseline were censored at the date of the first CS1001 dose in the cross-over phase. Kaplan Meier method was used to estimate median PFS, PFS at different time points and their 95% CIs (by Brookmeyer Crowley method). Kaplan Meier curve was provided to visually describe PFS changes over time.

• Overall survival (OS) (assessed by the investigator according to RECIST v1.1): the time from the first CS1001 administration in the cross-over phase till all-cause death. Subjects alive were censored at the date of last known alive. For OS analysis, subjects without any data after baseline were censored at the date of the first CS1001 dose in the cross-over phase. Non-parametric Kaplan Meier method was used to estimate median OS, PFS at different time points and their 95% CIs (by Brookmeyer Crowley method). Kaplan Meier curve was provided to visually describe OS changes over time.

The above secondary analyses are supported. These are standard methods for the analysis of binary and time-to-events data. It is expected that no sign of detrimental effect on OS should be present when PFS is selected as the primary endpoint.

High concordance between investigator assessed and blinded independent central review (BICR) assessed PFS, ORR, and DOR will strengthen the evidence from this study.

For ORR, the handling of patients without postbaseline data as non-responder is generally supported.

Sensitivity analysis

1) Sensitivity analysis was performed when more than 5% of subjects in either treatment group use unallowed anti-neoplastic treatment. Subjects who have used unallowed anti-neoplastic treatment before PFS (assessed by the investigator according to RECIST v1.1) were censored on the last tumour assessment day before the use of unallowed anti-neoplastic treatment. Subjects without any tumour assessment after the baseline were censored at the date of randomization.
2) Subjects who have missed two or more consecutive tumour assessments before PFS event (assessed by the investigator according to RECIST v1.1) were censored before the last tumour assessment date prior to the PFS event (assessed by the investigator according to RECIST v1.1). Subjects without any tumour assessment after the baseline were censored at the date of randomisation.
3) The stratification factors collected by EDC were used in the sensitivity analysis for the primary efficacy endpoint (assessed by the investigator according to RECIST v1.1) and OS. The primary endpoint and OS were analysed using an unstratified Cox regression model.

Sensitivity analyses were carried out on PD-L1 ≥ 1% PFS (assessed by the investigator per RECIST v1.1), PD-L1 ≥ 1% PFS (assessed by BICR per RECIST v1.1), and PFS (assessed by BICR per RECIST v1.1), in a manner consistent with PFS as assessed by the investigator per RECISTv1.1.

4) The effect of COVID-19 on PFS (assessed by the investigator per RECIST v1.1) and PFS (assessed by BICR per RECIST v1.1) was analysed in the following aspects: patients who have a delay of chemotherapy administration > 3 weeks due to COVID-19 (the delay duration will be calculated as per IxRS scheduled visit date) in the double-blind treatment phase with CS1001/placebo in combination with chemotherapy; all patients who have a delay of CS1001/placebo administration > 9 weeks due to COVID-19 (the delay duration were calculated as per IxRS scheduled visit date) were censored before the last tumour assessment date prior to the COVID-19. The start date of COVID-19 is set as January 22, 2020. Patients without any tumour assessment after the baseline were censored at the date of randomization.

5) Sensitivity analyses of OS were carried out according to methods of IPCW (Inverse Probability of Censoring Weighting), RPSFT (Rank Preserving Structural Failure Time) and AFT (Two-stage Accelerated Failure Time) for patients who received PD-(L) 1 Class non-protocol antineoplastic therapy or cross-over treatment.

The following sensitivity analyses of OS was performed: patients who used PD-(L) 1 Class unallowed antineoplastic therapy prior to death will be censored on the day they receive PD-(L) 1 Class unallowed antineoplastic therapy (including CS1001 when they entered the cross-over phase).

The sensitivity analyses are supported.

Subgroup analysis

Subgroup analyses were performed for the primary efficacy endpoint, providing a forest plot containing each subgroup factor, including demographics (age [< 65 years; ≥ 65 years], sex, smoking status) and stratification factors (ECOG PSPS [0; 1], tumour pathological histological type [squamous; non-squamous], brain metastasis [yes; no], liver metastasis [yes; no], and previous antineoplastic therapy [yes; no] and Central lab tested PD-L1 expression value [PD-L1 ≥ 1%; 50%>PD-L1 ≥ 1%; or PD-L1 ≥ 1%; PD-L1 < 1%]).

In addition, further analyses were performed in the following subgroups for PD-L1 ≥ 1% PFS (assessed by the investigators according to RECIST v1.1), PD-L1 ≥ 1% PFS (assessed by BICR according to RECIST v1.1) and PFS (assessed by BICR according to RECIST v1.1), using the same statistical methods as the primary efficacy analysis. Subgroup factors include demographic (age [< 65 years; ≥ 65 years], sex, smoking status) and stratification factors (ECOG PS [0; 1], tumour pathological histological type [squamous; non-squamous], PD-L1 expression value [PD-L1≥50%; 50%>PD-L1≥1%], brain metastasis [yes; no], liver metastasis [yes; no], previous antineoplastic therapy [yes; no]). The concordance of the findings across subgroups will be then assessed.

Subgroup analyses were performed for OS, providing a forest plot containing each subgroup factor including demographics (age [< 65 years; ≥ 65 years], sex, smoking status) and stratification factors (ECOG PS [0; 1], tumour pathological histological type [squamous; non-squamous], PD-L1 expression value [PD-L1≥50%; 50%>PD-L1≥1%; PD-L1 < 1%], brain metastasis [yes; no], liver metastasis [yes; no], previous antineoplastic therapy [yes; no]).

Subgroup analyses were performed for objective response rate assessed by the investigators according to RECIST v1.1 and by BICR according to RECIST v1.1, providing a forest plot containing factors for each subgroup, including demographic (age [< 65 years; ≥ 65 years], sex, smoking status) and stratification factors (ECOG PS [0; 1], tumour pathological histological type [squamous; non-squamous], PD-L1 expression value [PD-L1≥50%; 50%>PD-L1≥1%; PD-L1 < 1%]), brain metastasis (yes; no), liver metastasis (yes; no), and previous antineoplastic therapy (yes; no).

Kaplan-Meier curves were plotted to visually depict the change in PFS over time according to tumour pathological histological type (squamous; non-squamous) or PD-L1 expression value (PD-L1 ≥ 1%; 50%>PD-L1 ≥ 1%; or PD-L1 ≥ 1%; PD-L1 < 1%) for PFS assessed by the investigators according to RECIST v1.1 and PFS assessed by BICR according to RECIST v1.1.

Kaplan-Meier curves were plotted to visually depict the change in OS over time according to tumour pathological histological type (squamous; non-squamous) or PD-L1 expression value (PD-L1 ≥ 1%; 50%>PD-L1 ≥ 1%; or PD-L1 ≥ 1%; PD-L1 < 1%).

The subgroup analyses are supported. In particular, consistency of treatment effects across the subgroups defined by stratification factors used to randomise participants will strengthen the evidence from this study.

Additional analyses

The relationship between different cut-off values of PD-L1 and efficacy, such as PD-L1 < 1%, 50%>PD-L1≥1%, and ≥ 50%, was explored by treatment group.

Disease progression assessed by the investigator per RECIST v1.1 with time point of assessment, and disease progression assessed by BICR per RECIST v1.1 with time point of assessment was analysed for concordance; a shift table of objective response as assessed by the investigator and objective response as assessed by BICR was provided.

The approach to explore the sensitivity of the study results to various thresholds of PD-L1 is supported.

Adjustment for multiplicity

Sequential testing was planned to be performed if PFS (as assessed by the investigators according to RECIST v1.1) analysis result shows that the null hypothesis, i.e. CS1001 is superior to placebo, is rejected. Sequential testing method was adopted to control overall type I error (two-sided 5% significance level) as follows:

1) OS

2) PD-L1 ≥ 1% PFS (as assessed by the investigators according to RECIST v1.1)

3) ORR (as assessed by the investigators according to RECIST v1.1)

The use of sequential testing to control the type I error at two-sided 5% significance level is considered acceptable.

Interim analyses

PFS interim analysis: PFS interim analysis was planned to be conducted when approximately 252 PFS events (70% of data information) are observed or when the last subject is randomised, whichever occurs later. The interim analysis was to be conducted at around 21 months after the first patient randomisation. The final PFS analysis was planned to be carried out when 360 PFS events occur, which is estimated to be at 29 months after the first patient randomisation. Lan-DeMets method with approximate O'Brien-Fleming boundary was used to control two-sided type I error within 0.05.

If the interim or final PFS analysis shows positive result, OS was planned to be tested under the significance level of 0.05.

OS interim analysis: OS interim analysis was planned to be conducted when approximately 252 OS events (70% of data information) are observed or when the last subject is randomised, whichever occurs later. This was estimated to be around 28 months after the first subject randomisation. The final OS analysis was planned to be performed when 360 deaths occur, which was estimated to be around 43 months after the first subject randomisation. The interim OS analysis could be carried out at the same time as the final PFS analysis. Lan-DeMets method with approximate Pocock boundary was planned to be used to control type I error.

An iDMC will monitor the data for interim PFS efficacy analysis and make recommendations to sponsor according to the pre-defined boundaries.

The strategy to control the type I error as a result of performing interim analyses is acceptable. With O'Brien-Fleming boundary, the results will have to be extremely compelling in order to trigger termination of the study. Whereas Pocock boundaries will provide a reasonable chance of an early stop by spending more alpha. The use of alpha spending function provides flexibility in terms of number and time of interim analyses.

- **Analysis sets**

PFS and OS efficacy analyses were based upon the ITT set (as defined below). ORR analysis was based upon ITT set with measurable baseline lesion. DOR analysis was based upon ITT set who achieve objective response. All analysis sets were confirmed prior to database lock.

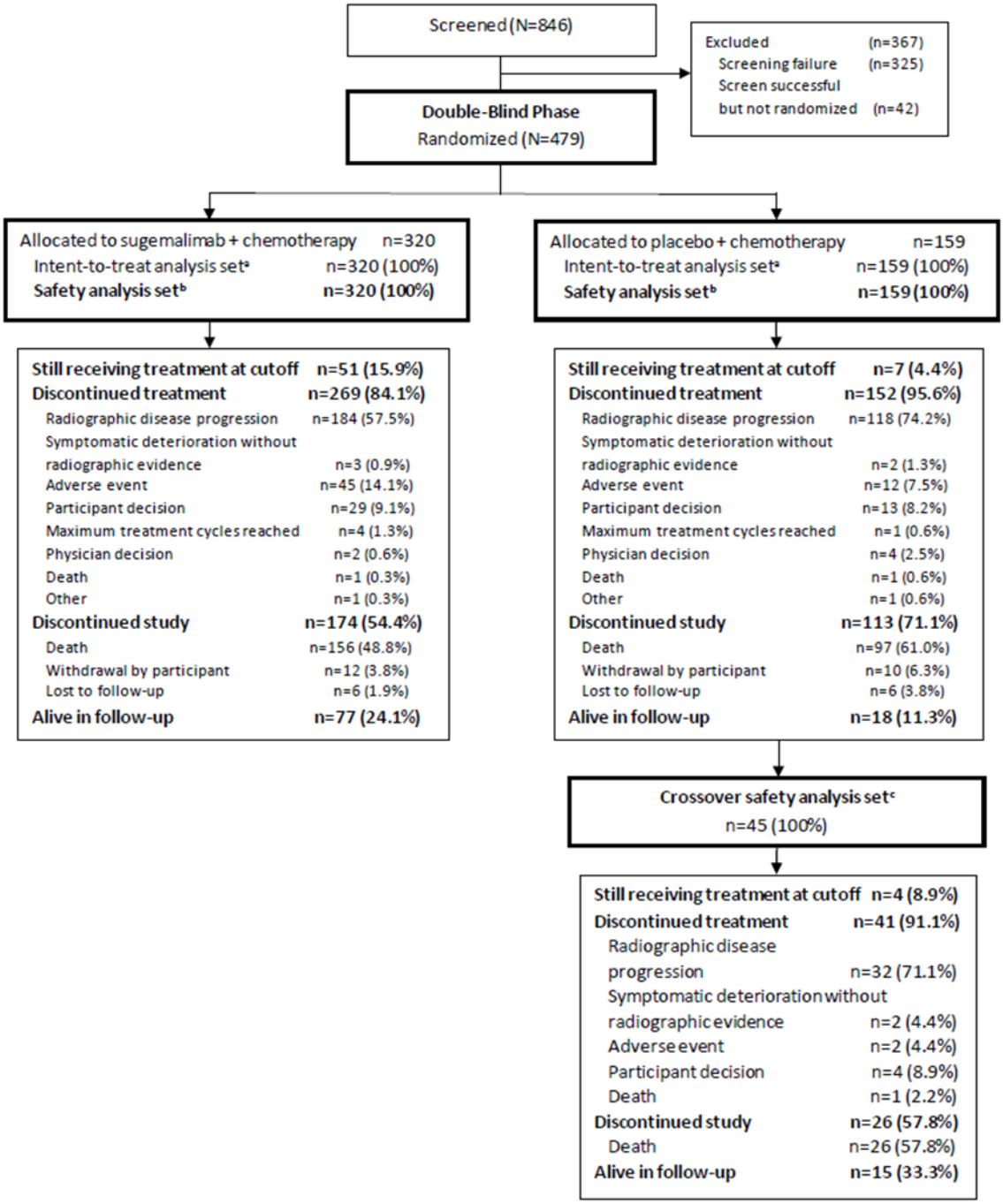
Analysis sets	Study endpoints applicable to the analysis sets	Description
Intent-to-treat (ITT) set	Primary and secondary efficacy endpoints	Including all randomized patients; these patients were grouped by the assigned treatment at randomization. Patient disposition, demographics, and other baseline characteristics, PFS and OS efficacy analysis were based upon the ITT set. ORR analysis was based upon ITT set with measurable disease at baseline. DOR analysis was based upon ITT set who achieved objective response.
Safety analysis set (SAS)	Secondary safety endpoints	Including patients who received at least one dose of any study treatment. Randomized patients who had not received any dose of study treatment would not be included in the SAS. For safety analysis, patients were grouped according to sugemalimab treatment (including those who receive sugemalimab by mistake) or no sugemalimab treatment. The safety analyses were based upon the SAS.
Efficacy Analysis Set - Cross-over	Secondary efficacy endpoints in cross-over phase	Including patients who had at least one dose of sugemalimab in cross-over phase, had not taken any sugemalimab in the double-blind phase and were assessed as PD by the investigator per RECIST v1.1.
Safety Analysis Set – Cross-over	Secondary safety endpoints in cross-over phase	Including patients who had at least one dose of sugemalimab in cross-over phase, had not taken any sugemalimab in the double-blind phase and were assessed as PD by the investigator per RECIST v1.1.

The analysis sets are appropriately defined.

Results

- **Participant flow**

Figure CE8: Summary of Patient Disposition – Study CS1001-302



[a] All participants who were randomised into the study.
[b] All participants who were randomised and received at least one dose of the study drug.
[c] All participants who entered the crossover phase, did not take any sugemalimab during the double-blind phase (ie, placebo group), and received at least one dose of sugemalimab monotherapy during the crossover phase.
CSR = clinical study report
Sources: Study CS1001-302 CSR, Table t_ds_ALL, Table t_ds_cross_ALL, Table t_pop_IT, and Table t_pop_cross_SA

Of the 846 patients screened, 479 were randomized: Sugemalimab + chemo arm = 320; Placebo + chemo arm = 159.

Most screening failures were due eligibility criteria not being met.

At the date of data cut-off, a higher proportion of patients remained on treatment in the sugemalimab arm (sugemalimab 15.9% v. placebo 4.4%).

A higher proportion of patients discontinued treatment due to adverse events in the sugemalimab arm than the placebo arm (14.1% v. 7.5%).

- **Conduct of the study**

Changes to the protocol

The original protocol was dated 02 August 2018. It was amended three times [07 Dec 2018 (v1.1), 25 Dec 2019 (v1.2) and 07 Apr 2020 (v2.0)]. The Statistical Analysis Plan (SAP version 1.1, dated 22 April 2021) was prepared according to the Protocol Version 2.0.

The company summarised the key changes to the protocol in each version, together with the number of patients enrolled when each amendment was implemented. The changes do not raise any concern.

Protocol deviations

Table CE20: Summary of Important Protocol Deviation -- Intent-to-Treat Analysis Set

Deviation Category Types of the Deviations	Sugemalimab +Chemotherapy N=320	Placebo +Chemotherapy N=159
Number of Patients with at Least One Important Protocol Deviation	**15(4.7%)**	**7(4.4%)**
Number of Patients with at Least One Important Protocol Deviation due to COVID-19	**2 (0.6%)**	**1 (0.6%)**
Overall Total Number of Important Protocol Deviations	**18**	**11**
Important Protocol Deviation Category		
Concomitant Medication Criteria	5(1.6%)	2(1.3%)
Efficacy Criteria	2(0.6%)	2(1.3%)
Eligibility and Entry Criteria	3(0.9%)	1(0.6%)
IP Compliance	4(1.3%)	2(1.3%)
Other Criteria	1(0.3%)	0
Study Procedures Criteria	1(0.3%)	1(0.6%)

Source: Table t_dv_IT_3 and Table t_dv_covid_IT_3
Sugemalimab + chemotherapy is the sugemalimab group, and placebo + chemotherapy is the placebo group.
[Source: ...\PRODUCTION\TABLES\OSIA_TABLE\T_DV_IT.SAS] IQVIA 11JAN2022

(Efficacy criteria referred to missed / missing tumour assessments.)

Protocol deviations were reported with similar proportion between the two arms. These were relatively low and unlikely to have had an impact on the outcome of the trial.

It noted that some protocol deviations relate eligibility criteria. The company provided more details on the reasons leading to protocol deviations related to inclusion/exclusion criteria and further information on the follow-up status of patients with these deviations.

- **Baseline data**

Demographic and disease characteristics

Table CE21: Demographics and baseline characteristics in Study CS1001-302

	Sugemalimab + Chemotherapy (N = 320)	**Placebo + Chemotherapy (N = 159)**	**Total (N = 479)**
Age (years)			
Mean (SD)	61.1 (7.89)	61.5 (8.20)	61.3 (7.98)
Median	62.0	64.0	63.0
Min, max	29, 75	36, 75	29, 75
Age Category (years), n (%)			
< 65	202 (63.1)	91 (57.2)	293 (61.2)
≥ 65	118 (36.9)	68 (42.8)	186 (38.8)
Sex, n (%)			
Male	254 (79.4)	129 (81.1)	383 (80.0)
Female	66 (20.6)	30 (18.9)	96 (20.0)
Race, n (%)			
Asian	320 (100.0)	159 (100.0)	479 (100.0)
Ethnicity, n (%)			
Non-Hispanic or Latino	320 (100.0)	159 (100.0)	479 (100.0)
Weight at Baseline (kg)			
Mean (SD)	62.488 (9.7117)	64.131 (8.8530)	63.033 (9.4578)
Median	61.000	64.000	62.000
Min, max	41.00, 96.00	44.00, 88.00	41.00, 96.00
ECOG Performance Status at Baseline, n (%)			
0	59 (18.4)	25 (15.7)	84 (17.5)
1	261 (81.6)	134 (84.3)	395 (82.5)
Tobacco Use, n (%)			
Never	88 (27.5)	40 (25.2)	128 (26.7)
Current or former	232 (72.5)	119 (74.8)	351 (73.3)

CSR = clinical study report; ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; max = maximum; min = minimum; SD = standard deviation

Source: Study CS1001-302 CSR, Table t_dm_IT

Table CE22: Baseline Disease Characteristics in Study CS1001-302

	Sugemalimab + Chemotherapy (N = 320)	**Placebo + Chemotherapy (N = 159)**
Time Since Initial Diagnosis (years)[a]		
Mean (SD)	0.318 (0.9997)	0.434 (1.1909)
Median	0.079	0.079
Min, max	0.02, 9.67	0.02, 9.61
Histology Type, n (%)		
Squamous cell carcinoma	129 (40.3)	63 (39.6)
Non-squamous cell carcinoma	191 (59.7)	96 (60.4)
Stage at Screening[b], n (%)		
IV	320 (100.0)	159 (100.0)
Baseline Liver Metastases, n (%)		
Yes	39 (12.2)	18 (11.3)
No	281 (87.8)	141 (88.7)
Baseline Brain Metastases, n (%)		
Yes	50 (15.6)	17 (10.7)
No	270 (84.4)	140 (88.1)
PD-L1 Expression Level (From Central Laboratory), n (%)		
≥ 1%	196 (61.3)	95 (59.7)
< 1%	124 (38.8)	64 (40.3)

[a] Time since initial diagnosis (years) = (date of randomisation - date of initial diagnosis + 1) / 365.25.

[b] Cancer stage at Screening (Stage IV) includes Stage IV, Stage IVA, Stage IVB, and Stage IVC.

CSR = clinical study report; ITT = intent-to-treat; max = maximum; min = minimum; PD-L1 = programmed death ligand-1; SD = standard deviation

Sources: Study CS1001-302 CSR, Table t_dm_dx_IT and Table t_dm_biom_IT

Baseline demographics and disease characteristics were well-matched between the 2 arms of the study.

All patients were Asians; the study was conducted in China.

The median age was 63 years.

Most patients were male (80.0% overall), current or former smokers (73.3% overall) with PS 1 (82.5% overall).

All patients had stage IV disease.

The median time from the initial diagnosis of NSCLC to enrolment in the study was 0.079 years (or 4.12 weeks) in both arms.

About 60% of patients had non-squamous cell carcinoma, and the rest had squamous cell carcinoma.

About 60% of patients had tumours with ≥1% PD-L1 expression.

Prior antitumour therapies

The majority of participants had not received any prior antitumour drug treatment (303 [94.7%] participants in the sugemalimab group and 144 [90.6%] participants in the placebo group). In the sugemalimab group, 17 (5.3%) participants received prior antitumour therapies that were adjuvant therapies. In the placebo group, 15 (9.4%) participants received antitumour therapies, most of which were adjuvant therapies (13 [8.2%] participants). No participant had received prior chemotherapy for Stage IV NSCLC.

In the sugemalimab group and placebo group, 270 (84.4%) and 135 (84.9%) participants, respectively, underwent prior cancer-related surgery, and 15 (4.7%) and 8 (5.0%) participants, respectively, received radiotherapy.

Table CE23: Prior Treatment History of NSCLC in Study CS1001-302

	Sugemalimab + Chemotherapy (N = 320) n (%)	**Placebo + Chemotherapy (N = 159) n (%)**	**Total (N = 479) n (%)**
Received Any Antitumour Drug Treatment Regimen in the Past?[a]			
Yes	17 (5.3)	15 (9.4)	32 (6.7)
No	303 (94.7)	144 (90.6)	447 (93.3)
Treatment Setting			
Adjuvant therapy	17 (5.3)	13 (8.2)	30 (6.3)
Neoadjuvant therapy	0	1 (0.6)	1 (0.2)
Other	1 (0.3)	2 (1.3)	3 (0.6)
Had Any Previous Cancer-Related Surgery?			
Yes	270 (84.4)	135 (84.9)	405 (84.6)
No	49 (15.3)	24 (15.1)	73 (15.2)
Have Received Any Radiotherapy?			
Yes	15 (4.7)	8 (5.0)	23 (4.8)

	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)	Total (N = 479) n (%)
No	305 (95.3)	151 (95.0)	456 (95.2)
Treatment Setting[b]			
Adjuvant	4 (1.3)	1 (0.6)	5 (1.0)
Palliative	6 (1.9)	3 (1.9)	9 (1.9)
Definitive	2 (0.6)	2 (1.3)	4 (0.8)
Other	3 (0.9)	2 (1.3)	5 (1.0)

[a] Participants for whom no prior treatment data were collected were considered not to have received the corresponding treatment in the past.

[b] Associated with radiotherapy.

CSR = clinical study report; ITT = intent-to-treat; NSCLC = non-small cell lung cancer

Source: Study CS1001-302 CSR, Table t_dm_pth_IT

93.3% of patients had not had any systemic treatment at the time of study entry; the remaining patients were exposed to systemic therapies mainly in the adjuvant setting, ie. patients received first-line systemic treatment for metastatic disease within the trial.

It is noted that 405 out of 479 patients (84.6%) had 'any previous cancer-related surgery'. The Company has below provided details, such as type of surgery, indication, time from surgery to entry into trial, etc..

Previous cancer-related surgery has been summarised in Table 39. The majority of the prior cancer related surgery/procedures was performed for disease diagnosis purposes (78.7%).

This is consistent with exclusion criterion no. 3 in Study CS1001-302, which excluded patients who had major surgery other than a diagnostic biopsy within 4 weeks prior to the first dose of study treatment.

Forty-five (9.4%) patients had undergone curative surgery for early stage NSCLC, when they were first diagnosed. These patients had metastatic Stage IV NSCLC at the time of enrolment in Study CS1001-302.

For 16 patients the surgical purpose was recorded as "palliative", for 5 patients the surgical purpose was recorded as "other" and for 7 patients the surgical purpose was recorded as "unknown".

Table 39: Prior Cancer-Related Surgery in Study CS1001-302

	Sugemalimab+ Chemotherapy N=320	Placebo+ Chemotherapy N=159	Total N=479
Any Prior Cancer-Related Surgery/Procedure Performed?			
Yes	270 (84.4%)	135 (84.9%)	405 (84.6%)
No	49 (15.3%)	24 (15.1%)	73 (15.2%)
Procedure Intent			
Diagnosis	251 (78.4%)	126 (79.2%)	377 (78.7%)
Curative	26 (8.1%)	19 (11.9%)	45 (9.4%)
Palliative	11 (3.4%)	5 (3.1%)	16 (3.3%)
Unknown	5 (1.6%)	2 (1.3%)	7 (1.5%)
Other	3 (0.9%)	2 (1.3%)	5 (1.0%)

Source: Module 5.3.5.1 CS1001-302-e3-16-2-04a Listing l_cm_ppr_IT

- **Outcomes and estimation**

At the time of the data cut-off date of 22 Nov 2021, 320 participants had received sugemalimab treatment for a median (range) duration of 7.15 (0.2 to 34.7) months; and 159 participants had received placebo treatment for a median (range) duration of 4.60 (0.3 to 31.8) months.

Exposure to chemotherapy was comparable between the 2 treatment groups, with 80.3% of participants in the sugemalimab group and 78.0% of participants in the placebo group completing the protocol-defined maximum of 4 cycles.

<u>Primary efficacy endpoint</u> – Progression-free survival (PFS) by investigator assessment

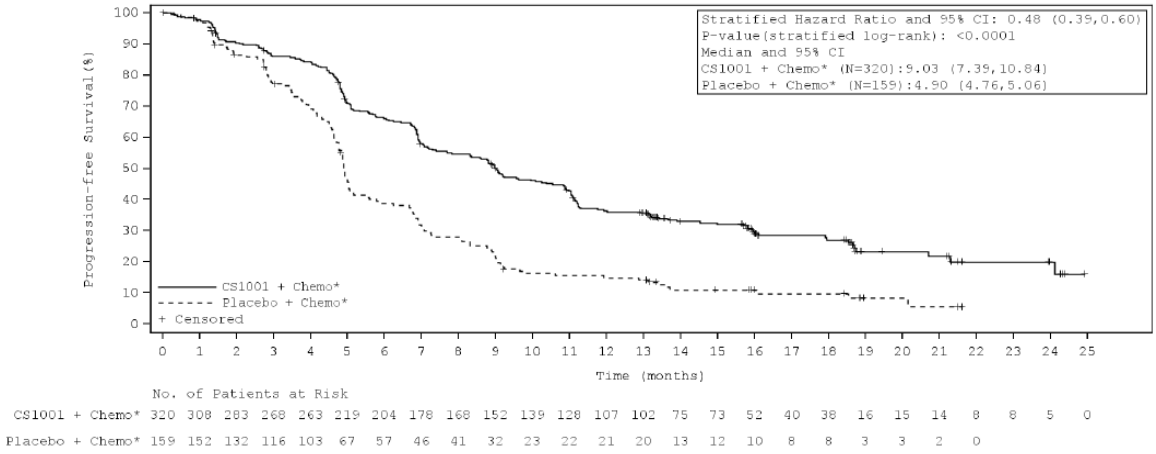
The study met its primary endpoint.

Table CE24: Summary for PFS Assessed by Investigator—Intent-to- Treat Analysis Set—PFS Final Analysis (DCO date: 15 March 2021)

	Sugemalimab +Chemotherapy N=320	Placebo +Chemotherapy N=159
Patients with Event	**223(69.7%)**	**135(84.9%)**
Death	33(10.3%)	10(6.3%)
Progressive Disease	190(59.4%)	125(78.6%)
Patients Censored	**97(30.3%)**	**24(15.1%)**
Progression-Free Survival (months)		
Median [a]	9.03	4.90
95% CI [a]	(7.39, 10.84)	(4.76, 5.06)
25% and 75% Percentiles [a]	4.83,18.69	3.48,8.77
Range	0.0 + to 24.9 +	0.0 + to 21.6 +
Stratified Analysis [b]		
P-Value (Log-Rank)	<0.0001	
Hazard Ratio	0.48	
95% CI	(0.39,0.60)	
Unstratified Analysis		
P-Value (Log-Rank)	<0.0001	
Hazard Ratio	0.50	
95% CI	(0.40,0.62)	
Progression-Free Survival Rate [c]		
6 Months	66.0%	38.7%
95% CI	(60.5%,71.0%)	(30.9%,46.5%)
Difference	27.3%	
95% CI	(17.8%,36.7%)	
9 Months	50.1%	21.7%
95% CI	(44.4%,55.5%)	(15.5%,28.7%)
Difference	28.3%	
95% CI	(19.7%,37.0%)	
12 Months	36.4%	14.8%
95% CI	(31.0%,41.8%)	(9.7%,21.1%)
Difference	21.5%	
95% CI	(13.6%,29.4%)	
15 Months	32.1%	10.9%
95% CI	(26.8%,37.5%)	(6.4%,16.7%)
Difference	21.2%	
95% CI	(13.8%,28.6%)	
18 Months	27.0%	9.7%
95% CI	(21.7%,32.6%)	(5.3%,15.5%)
Difference	17.3%	
95% CI	(9.9%,24.8%)	
21 Months	21.7%	5.5%
95% CI	(15.9%,28.2%)	(1.7%,12.9%)
Difference	16.2%	
95% CI	(7.9%,24.5%)	
24 Months	19.9%	-
95% CI	(13.8%,26.9%)	(-,-)
Difference	-	
95% CI	(-,-)	

Source: Table t_ef_tte_pfs_inv_all_IT_2
Sugemalimab + chemotherapy is the sugemalimab group, and placebo + chemotherapy is the placebo group.
The Lan-DeMets O'Brien–Fleming P-value boundary is 0.0188 (two-sided).
[a] Summaries of progression-free survival (median, percentiles) are Kaplan-Meier estimates. Confidence interval for the median is computed using the method of Brookmeyer and Crowley.
[b] The stratification factors are ECOG Performance Status, Histology Type, and PD-L1 from IxRS.
[c] Confidence intervals for event-free rates are computed using variances from the Greenwood method.
+ is for the minimum or maximum value from censored patients.
[Source: ...\PRODUCTION\TABLES\PFSFA_TABLE\T_EF_TTE_PFS_INV_ALL_IT.SAS] IQVIA 18MAY2021

Figure CE9: Kaplan-Meier Plot of PFS Assessed by Investigator—Intent-to-Treat Analysis Set—PFS Final Analysis



PFS interim analysis was planned to be conducted when approximately 252 PFS events, which corresponds to a two-sided p-value boundary of 0.0148. A total of 358 events were reported and the corresponding two-sided p-value boundary was reported to be 0.0188.

The study met its primary endpoint, which was investigator-assessed PFS.

A statistically significant increase ($p<0.0001$) in PFS was seen with sugemalimab compared to placebo.

Median (95% CI) PFS by investigator assessment was 9.03 (7.39, 10.84) months in the sugemalimab arm and 4.90 (4.76, 5.06) months in the placebo arm.

The HR for disease progression or death was 0.48 (95% CI: 0.39, 0.60).

The company has presented details of the reasons for censoring**.** For both PFS, OS, and DoR, the most common reason for censoring is the patients being alive without the event of interest. For all of these outcomes, the higher proportions of patients alive without the events of interest favour the study drug.

Secondary efficacy endpoint – PFS assessed by BICR

For sugemalimab in combination with chemotherapy vs placebo in combination with chemotherapy, the stratified HR for PFS was 0.56 (95% CI: 0.45-0.71, nominal p <0.0001), the risk of PD or death was reduced by 44%, and median PFS (95% CI) was 9.30 months (8.34, 11.10) and 5.06 months (4.86, 6.80) in the 2 groups, respectively.

Table CE25: Concordance Analysis between the Blinded Independent Central Review Determined and the Investigator Determined Progressive Disease Status— PFS Final Analysis

	CS1001+Chemotherapy N=320	Placebo+Chemotherapy N=159
Patients Included in the Analysis[a]	308	153
PD Occurrence		
Concordance	234(76.0%)	107(69.9%)
PD per Investigator and PD per BICR	131(42.5%)	84(54.9%)
No PD per Investigator and No PD per BICR	103(33.4%)	23(15.0%)
Discordance	74(24.0%)	46(30.1%)
PD per Investigator and No PD per BICR	59(19.2%)	41(26.8%)
No PD per Investigator and PD per BICR	15(4.9%)	5(3.3%)
PD Occurrence and Timing of PD		
Concordance	189(61.4%)	85(55.6%)
PD per Investigator and PD per BICR, Dates within 7 Weeks	86(27.9%)	62(40.5%)
No PD per Investigator and No PD per BICR	103(33.4%)	23(15.0%)
Discordance	119(38.6%)	68(44.4%)
PD per Investigator and No PD per BICR	59(19.2%)	41(26.8%)
No PD per Investigator and PD per BICR	15(4.9%)	5(3.3%)
PD per Investigator and PD per BICR, Dates Differ by > 7 Weeks	45(14.6%)	22(14.4%)
Differences in Timing between Investigator and BICR PD Dates > 7 Weeks		
Investigator PD Earlier than BICR PD	2(0.6%)	0
> 7 to 14 Weeks	1(0.3%)	0
> 14 to 21 Weeks	0	0
> 21 Weeks	1(0.3%)	0
Investigator PD Later than BICR PD	43(14.0%)	22(14.4%)
> 7 to 14 Weeks	27(8.8%)	17(11.1%)
> 14 to 21 Weeks	6(1.9%)	4(2.6%)
> 21 Weeks	10(3.2%)	1(0.7%)

Abbreviations: BICR = Blinded Independent Central Review; PD = Progressive Disease
[a] is defined as patients evaluable for concordance, which includes intent-to-treat patients with both investigator and BICR evaluated post-baseline tumor assessments available.
Percentages are based on the number of patients included in the analysis.

[Source: ...\PRODUCTION\TABLES\PFSFA_TABLE\T_EF_PFS_CONCORD_IT.SAS] IQVIA 18MAY2021

<u>Secondary efficacy endpoint – PFS based on PD-L1 expression level as assessed by investigators</u>

In patients with PD-L1 ≥1%, median PFS (95% CI) was 10.87 months (8.90, 11.27) in the sugemalimab arm and 4.90 months (4.70, 5.85) in the placebo arm. HR for the unstratified analysis of PFS assessed by investigators was 0.46 (95% CI: 0.35-0.62).

In patients with PD-L1 <1%, median PFS (95% CI) was 7.39 months (6.80, 8.97) in the sugemalimab arm and 4.93 months (3.98, 5.78) in the placebo arm. HR for the unstratified analysis of PFS assessed by investigators was 0.55 (95% CI: 0.40-0.77).

BICR assessment was basically consistent with investigator assessment.

Figure CE10: Kaplan-Meier Plot of PFS as assessed by investigator for patients with PD-L1≥1% - Final Analysis

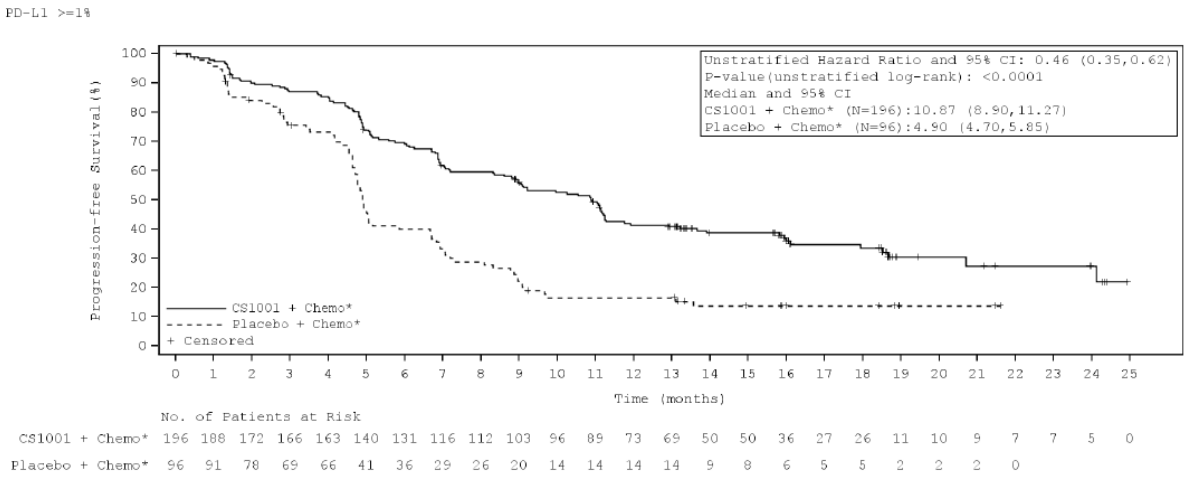
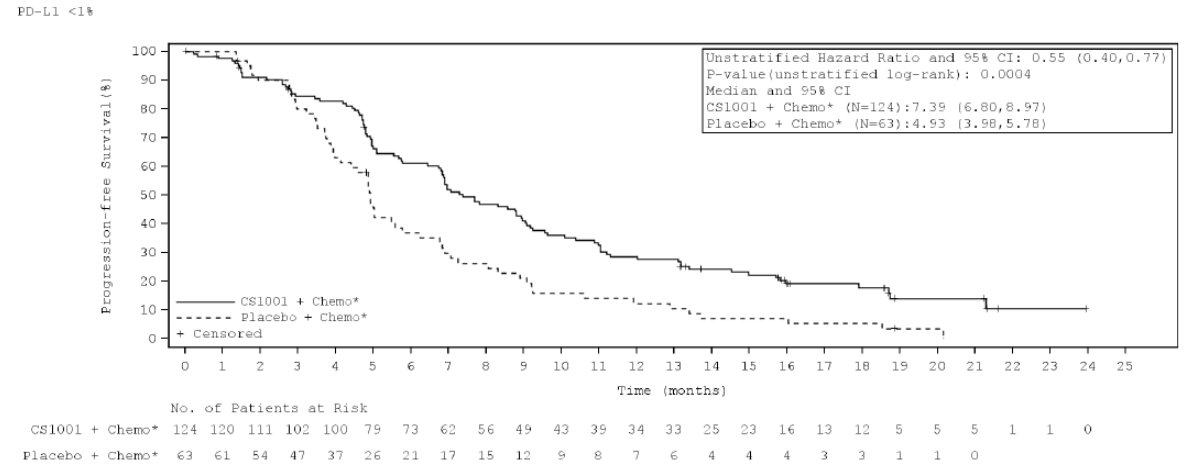


Figure CE11: Kaplan-Meier Plot of PFS as assessed by investigator for patients with PD-L1<1% - Final Analysis



Patients in the sugemalimab arm whose tumour had PD-L1 expression ≥1% had longer median PFS (10.87 months) compared to those with PD-L1 expression level of <1% (7.39 months). The KM curve suggests departure from the proportional hazard in the subgroup of patients with PD-L1 expression level of <1%, therefore the results should be interpreted with caution.

Despite a lower PFS in those with PD-L1 expression <1% on sugemalimab, its addition to chemotherapy was still better compared to placebo.

The company reported the proportions of concordance/discordance by treatment group, time and occurrence of PD. The company was requested to provide a summary of overall concordance between investigator and BICR assessed PFS The level of agreement between investigator and BICR assessed PFS and ORR is considered moderate.

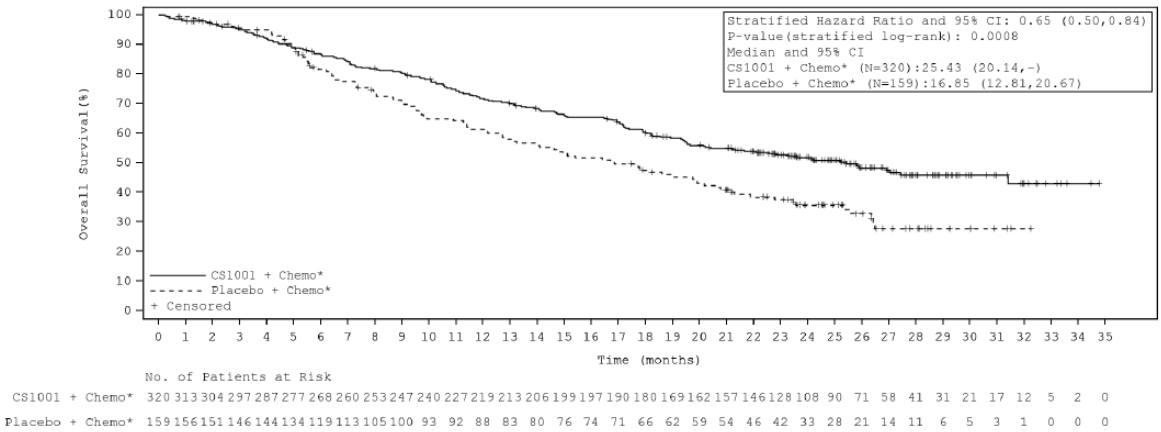
The company presented landmark analyses for PFS and OS by PD-L1 subgroups. For PFS, results based on assessment by investigator and BICR were provided. In the sugemalimab group, median PFS and OS for patients with PD-L1 ≥1% was significantly better than for patients with PD-L1 <1%. Given that patients with PD-L1 <1% in the sugemalimab group fared better than those in the placebo group, the use of sugemalimab for all-comers can be accepted.

Secondary efficacy endpoint – Overall survival (OS)

The protocol pre-specified OS interim analysis (data cut-off 22 November 2021) was performed with a median follow-up of 25.43 and 24.94 months for the sugemalimab and placebo group, respectively.

The median OS (95% CI) was 25.43 months (20.14, NR) in the sugemalimab group, and the median OS (95% CI) in the placebo group was 16.85 months (12.81, 20.67), with a HR of 0.65, 95% CI: 0.50, 0.84, stratified two-sided log-rank test p =0.0008.

Figure CE12: Kaplan-Meier Plot of OS (DCO: 22 Nov 2022)



Interim overall survival data demonstrated better survival in the sugemalimab arm compared to placebo. However, the Kaplan-Meir curve suggests departure from proportional hazards assumption, therefore the results should be interpreted with caution.

Secondary efficacy endpoints – Overall response rate (ORR) and Duration of response (DoR) as assessed by investigator

Table CE26: ORR investigator assessment (DCO: 22 Nov 2022)

	Sugemalimab +Chemotherapy N=320	Placebo +Chemotherapy N=159
Objective Response Rate (CR+PR)	203(63.4%)	64(40.3%)
95% CI [a]	(57.9%,68.7%)	(32.6%,48.3%)
Difference in Objective Response Rates [b]	23.2%	
95% CI	(13.9%,32.5%)	
P-Value (CMH)	<0.0001	
Best Overall Response [c]		
Complete Response (CR)	0	0
95% CI [a]	(0.0%,1.1%)	(0.0%,2.3%)
Partial Response (PR)	203(63.4%)	64(40.3%)
95% CI [a]	(57.9%,68.7%)	(32.6%,48.3%)
Stable Disease (SD)	81(25.3%)	73(45.9%)
95% CI [a]	(20.6%,30.4%)	(38.0%,54.0%)
Progressive Disease (PD)	22(6.9%)	15(9.4%)
95% CI [a]	(4.4%,10.2%)	(5.4%,15.1%)
Not Evaluable (NE)	2(0.6%)	1(0.6%)
Not Applicable (NA)	12(3.8%)	6(3.8%)

Table CE27: DoR by investigator assessment

	Sugemalimab +Chemotherapy N=203	Placebo +Chemotherapy N=64
Patients with Response (CR+PR)	**203(100.0%)**	**64(100.0%)**
Number of Patient with Events	**144(70.9%)**	**56(87.5%)**
Progressive Disease	133(65.5%)	53(82.8%)
Death	11(5.4%)	3(4.7%)
Number of Patients Censored	**59(29.1%)**	**8(12.5%)**
Duration of Response (months)		
Median [a]	9.92	4.44
95% CI [a]	(8.57, 13.24)	(3.52, 6.08)
25% and 75% Percentiles [a]	4.93,31.51	3.48,7.82
Range	0.7 to 31.5	0.0 + to 26.0 +

ORR in the sugemalimab arm was better than in the placebo arm (Sugemalimab 63.4% v. Placebo 40.3%).

DoR in the sugemalimab arm was longer compared to the Placebo arm (median duration (95% CI) 9.92 (8.57, 13.24) months v. 4.44 (3.52, 6.08) months).

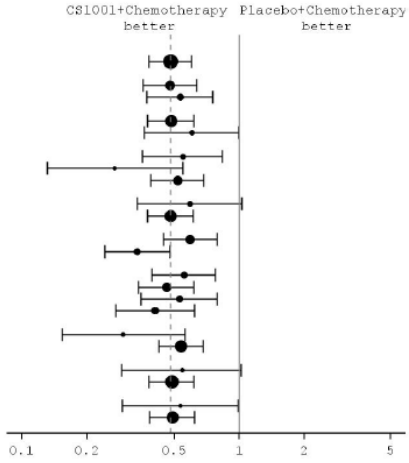
- **Ancillary analyses**

Subgroup analyses

Subgroup analyses of PFS confirm the consistency of effect for sugemalimab compared with placebo.

Figure CE13: Forest Plot of PFS by investigator assessment by subgroup – Final analysis

Baseline Risk Factor	CS1001+ Chemotherapy (n=320) Event/n	Median	Placebo+ Chemotherapy (n=159) Event/n	Median	Hazard Ratio(95% CI)
All Patients	223/320	9.03	135/159	4.90	0.48 (0.39, 0.60)
Age(yrs)					
<65 years	142/202	9.17	78/91	4.93	0.48 (0.36, 0.63)
>= 65 years	81/118	8.61	57/68	4.90	0.53 (0.38, 0.75)
Sex					
Male	176/254	8.87	111/129	4.90	0.48 (0.38, 0.62)
Female	47/66	9.03	24/30	5.49	0.60 (0.37, 0.99)
Smoking Status					
Never	65/88	9.03	34/40	4.93	0.55 (0.36, 0.83)
Current	22/35	12.02	15/16	4.60	0.27 (0.13, 0.55)
Former	136/197	8.80	86/103	4.93	0.52 (0.39, 0.68)
ECOG					
0	41/59	10.86	19/25	4.90	0.59 (0.34, 1.02)
1	182/261	8.54	116/134	4.90	0.48 (0.38, 0.61)
Histology Type					
NSQ	128/191	9.56	78/96	5.85	0.59 (0.45, 0.79)
SQ	95/129	8.31	57/63	4.76	0.34 (0.24, 0.48)
PD-L1					
<1%	100/124	7.39	57/64	4.93	0.56 (0.40, 0.77)
>=1%	123/196	10.87	78/95	4.90	0.46 (0.35, 0.62)
>=1% and <50%	66/92	8.80	39/48	4.83	0.53 (0.35, 0.79)
>=50%	57/104	12.91	39/47	5.06	0.41 (0.27, 0.62)
Brain Metastases					
Yes	33/50	8.94	17/17	4.53	0.29 (0.15, 0.56)
No	190/270	9.03	116/140	4.93	0.54 (0.43, 0.68)
Liver Metastases					
Yes	30/39	6.05	16/18	3.88	0.54 (0.29, 1.02)
No	193/281	9.20	119/141	4.93	0.49 (0.39, 0.61)
Prior Cancer Therapy					
Yes	22/34	8.94	20/24	4.86	0.53 (0.29, 0.98)
No	201/286	9.03	115/135	4.93	0.49 (0.39, 0.62)



Subgroup analyses supported consistency of the PFS result.

Improvement in median PFS in favour of sugemalimab was demonstrated in all subgroups.

- **Summary of main efficacy results**

Table CE28: Efficacy Summary

	Sugemalimab+ Chemotherapy N=320	Placebo+ Chemotherapy N=159
Progression-Free Survival Assessed by Investigator (months)		
Median[a]	9.03	4.90
2-sided P-value (Stratified Log-Rank Test)	<0.0001	
Hazard Ratio (Stratified Cox Regression)	0.49	
95% CI	(0.40,0.61)	
Progression-Free Survival Assessed by Blinded Independent Central Review (months)		
Median[a]	9.33	5.06
2-sided P-value (Stratified Log-Rank Test)	<0.0001	
Hazard Ratio (Stratified Cox Regression)	0.57	
95% CI	(0.46,0.71)	
Progression-Free Survival with PD-L1≥1% from IxRS Assessed by Investigator (months)		
Median[a]	10.91	4.90
2-sided P-value (Unstratified Log-Rank Test)	<0.0001	
Hazard Ratio (Unstratified Cox Regression)	0.48	
95% CI	(0.36,0.63)	
Overall Survival		
Median[a]	25.43	16.85
2-sided P-value (Stratified Log-Rank Test)	0.0008	
Hazard Ratio (Stratified Cox Regression)	0.65	
95% CI	(0.50,0.84)	
Objective Response Assessed by Investigator [b]		
n	320	159
Responder[c]	203(63.4%)	64(40.3%)
Difference in Objective Response Rates (95% CI)	23.2% (13.9%,32.5%)	
2-sided P-value (Stratified CMH Test)	<0.0001	
Duration of Response Assessed by Investigator (months)		
Median[a]	9.92	4.44

Supportive studies (Cohorts 8 & 9 of the Phase 1b part of Study CS1001-101)

- **Part 1b of Phase 1 (dose expansion)**

The primary objective of Phase 1b was to evaluate the anti-tumour effect of sugemalimab used as a single agent and in combination with other therapies in patients with various tumour types.

This part of the study is ongoing.

First patient enrolled: 04 May 2018

Data cut-off date: 16 August 2021

It consisted of several cohorts (Cohort 1 to Cohort 13). Of these, patients and treatment in Cohorts 8 and 9 most closely resembled those of the pivotal study.

Cohorts 8 and 9 of Study CS1001-101b studied the preliminary antitumour efficacy in participants with newly diagnosed advanced (Stage IIIB) or metastatic (Stage IV) NSCLC. The 2 cohorts enrolled participants with non-squamous NSCLC and squamous NSCLC,

respectively. Similar to Study CS1001-302, the participants with squamous NSCLC received sugemalimab plus platinum-based chemotherapy consisting of carboplatin and paclitaxel as first-line treatment for up to 6 cycles and then sugemalimab for up to 2 years. The participants with NSCLC with non-squamous histology received sugemalimab in combination with carboplatin and pemetrexed for up to 6 cycles, followed by sugemalimab in combination with pemetrexed for up to 2 years.

Efficacy evaluation parameters included ORR, DoR, DCR, PFS, and OS (all evaluated by the investigator).

At the date of data cut-off on 16 August 2021, 41 patients were enrolled into Cohorts 8 (n=21) and 9 (n=20).

Efficacy results for Cohorts 8 and 9

Of the 21 participants in Cohort 8 (non-squamous NSCLC cohort), the confirmed ORR was 38.1% (95% CI: 18.1%, 61.6%) with a median (range) DoR of 11.32 months (1.77, 30.32). Nine participants had SD (stable disease). Median PFS was 6.5 months (4.4, 12.9). OS was 25.7 months (10.4, -).

Of the 20 participants in Cohort 9 (squamous NSCLC cohort), the confirmed ORR was 70.0% (95% CI: 45.7%, 88.1%), with a median DoR (range) of 18.15 months (2.04, 27.73). Four participants had SD. Median PFS was 13.24 months (8.2, -). OS was 30.85 (15.24, -).

Cohorts 8 and 9 of the Phase 1b part of Study CS1001-101 indicated that good responses could be achieved with sugemalimab in combination with chemotherapy in patients with squamous cell and non-squamous cell NSCLC.

Overall conclusions on clinical efficacy

The data support the efficacy of sugemalimab in combination with platinum-based chemotherapy as first-line treatment for patients with metastatic NSCLC without EGFR mutation, ALK fusion, ROS1 fusion or RET fusion.

IV.5 Clinical safety

Safety data of sugemalimab at the recommended fixed dose of 1200 mg iv infusion every 3 weeks in combination with platinum-based chemotherapy in lung cancer patients came mainly from the pivotal study CS1001-302 (n=320 in sugemalimab + chemotherapy arm; n=159 in placebo +chemotherapy arm). There were an additional 138 patients with various tumour types from Phase 1b of the open-label study CS1001-101.

Table CS1: Clinical Studies Included in the Sugemalimab Combination Therapy Pool

Treatment Received	Indication	Study Number	Other Drugs in Combination With Sugemalimab	Number of Participants Treated	Total Number of Participants Treated
Sugemalimab 1200 mg IV Q3W in Combination With Chemotherapy	NSCLC	CS1001-302 (double-blind phase)	Non-squamous NSCLC: pemetrexed and carboplatin Squamous NSCLC: paclitaxel and carboplatin	320	435
		CS1001-101b	Cohort 8 (non-squamous NSCLC[a], 1L): pemetrexed and carboplatin Cohort 9 (squamous NSCLC, 1L): paclitaxel and carboplatin	41	
	Other indications (non-NSCLC)	CS1001-101b	Cohort 5 (GAC/GEJAC, 1L): oxaliplatin and capecitabine Cohort 6 (ESCC, 1L): cisplatin and 5-fluorouracil Cohort 7 (ESCC, ≥ 2L): docetaxel	74	
Sugemalimab 1200 mg IV Q3W in Combination With Targeted Therapy	HCC[b]	CS1001-101b	Cohort 11 (HCC, 1L): lenvatinib	23	23

The safety database of sugemalimab in combination platinum-based chemotherapy for patients with squamous and non-squamous non-small cell lung cancer (NSCLC) includes a total of 361 patients (320 patients from CS1001-302 and 41 from CS1001-101b).

This section will mainly focus on observations from CS1001-302, the pivotal Phase 3 study, since it contributes the majority of patients and allows direct comparison of sugemalimab with placebo.

Patient exposure

Demographics and disease characteristics

Baseline demographic characteristics and disease characteristics were similar between the 2 treatment arms.
See under Clinical Efficacy for details.

Extent of exposure

At the time of the data cut-off date of 22 Nov 2021, 320 participants had received sugemalimab treatment for a median (range) duration and cycle of 7.15 (0.2 to 34.7) months and 10.0 (1 to 49) cycles; and 159 participants had received placebo treatment for a median (range) duration and cycle of 4.60 (0.3 to 31.8) months and 6.0 (1 to 44) cycles. Exposure to chemotherapy was comparable between the 2 treatment groups, with 80.3% of participants in the sugemalimab group and 78.0% of participants in the placebo group completing the protocol-defined maximum of 4 cycles.
During the crossover phase of the study, 45 participants had received sugemalimab monotherapy for a median (range) duration and cycle of 4.30 (0.4 to 16.6) months and 6.0 (1 to 24) cycles.

Table CS2: Summary of Exposure to Sugemalimab or Placebo - Study CS1001-302

	Sugemalimab + Chemotherapy (N = 320)	**Placebo + Chemotherapy (N = 159)**
Treatment Duration (months)		
Mean (SD)	11.04 (9.156)	6.29 (6.155)
Median	7.15	4.60
Min, max	0.2, 34.7	0.3, 31.8
Number of Cycles		
Mean (SD)	14.9 (12.64)	8.5 (8.37)
Median	10.0	6.0
Min, max	1, 49	1, 44
Total Cumulative Dose (mg)		
Mean (SD)	17910.0 (15173.01)	10218.7 (10042.44)
Median	12000.0	7200.0
Min, max	1200, 58800	1200, 52800
Participants who completed 4 cycles of chemotherapy (including pemetrexed, paclitaxel, and carboplatin), %	80.3	78.0

Treatment duration is defined as minimum of (treatment end date of study drug - treatment start date of study drug + 21, clinical cutoff date - treatment start date of study drug + 1, study discontinue date - treatment start date of study drug + 1) / 30.4375.
Total cumulative dose is defined as the sum of actual dosage administered during each cycle.
CSR = clinical study report; max = maximum; min = minimum; SD = standard deviation
Source: Study CS1001-302 CSR, Table t_ex_cs_SA

The median time of exposure to sugemalimab was 7.15 months (10 cycles) and to placebo was 4.60 months (6 cycles).
In both arms of the study, approximately 80% of patients completed 4 cycles of platinum-based chemotherapy.

Adverse events

Table CS3: Overview of Treatment-Emergent Adverse Events in Study CS1001-302

	Sugemalimab + Chemotherapy (N = 320) n (%)	**Placebo + Chemotherapy (N = 159) n (%)**
Number of Participants With		
Any TEAE	**319 (99.7)**	**157 (98.7)**
Any TEAE of Grade ≥ 3	207 (64.7)	99 (62.3)
Any serious TEAE	110 (34.4)	49 (30.8)
Any TEAE leading to permanent discontinuation from any treatment	62 (19.4)	18 (11.3)
Any TEAE leading to permanent discontinuation from sugemalimab/placebo	45 (14.1)	12 (7.5)
Any TEAE leading to infusion interrupted from any treatment	8 (2.5)	4 (2.5)
Any TEAE leading to infusion interrupted from sugemalimab/placebo	2 (0.6)	0
Any TEAE leading to treatment cycle delayed from any treatment	144 (45.0)	61 (38.4)
Any TEAE leading to treatment cycle delayed from sugemalimab/placebo	144 (45.0)	59 (37.1)
Any TEAE leading to death	20 (6.3)	9 (5.7)
Any Treatment-Related TEAE	**317 (99.1)**	**153 (96.2)**
Sugemalimab/placebo-related TEAE	264 (82.5)	103 (64.8)
Carboplatin-related TEAE	316 (98.8)	152 (95.6)
Pemetrexed-related TEAE	187 (58.4)	92 (57.9)
Paclitaxel-related TEAE	129 (40.3)	61 (38.4)
Any treatment-related TEAE of Grade ≥ 3	185 (57.8)	92 (57.9)
Sugemalimab/placebo-related TEAE of Grade ≥ 3	95 (29.7)	39 (24.5)
Carboplatin-related TEAE of Grade ≥ 3	169 (52.8)	85 (53.5)
Pemetrexed-related TEAE of Grade ≥ 3	97 (30.3)	48 (30.2)
Paclitaxel-related TEAE of Grade ≥ 3	80 (25.0)	42 (26.4)
Any treatment-related serious TEAE	78 (24.4)	31 (19.5)
Sugemalimab/placebo-related serious TEAE	53 (16.6)	16 (10.1)
Carboplatin-related serious TEAE	57 (17.8)	26 (16.4)
Pemetrexed-related serious TEAE	38 (11.9)	21 (13.2)
Paclitaxel-related serious TEAE	23 (7.2)	8 (5.0)
Any treatment-related TEAE leading to death	11 (3.4)	2 (1.3)
Infusion-Related Reaction TEAE	**12 (3.8)**	**8 (5.0)**
Immune-Related AEs by Investigator Assessment[a]	**114 (35.6)**	**26 (16.4)**

[a] Immune-related AEs by Sponsor assessment are provided in Study CS1001-302 CSR, Section 12.1.8.

Treatment-emergent adverse event is defined as any adverse event that occurred or worsened on or after the start of study treatment.
NCI-CTCAE version 4.03.
"Related" is defined as the relationship to the study drug is related or missing.
AE = adverse event; CSR = clinical study report; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event
Sources: Study CS1001-302 CSR, Table t_ae_sum_SA and Module 5.3.5.3, Study CS1001-302 Adhoc, Table 3.2.8.3.1.

Notable differences between the sugemalimab (S) + chemotherapy arm and placebo (P) + chemotherapy arm from the table above are:
-Any TEAE leading to permanent discontinuation from any treatment 19.4% v 11.3% (S v P)
-Any TEAE leading to permanent discontinuation from sugemalimab/placebo 14.1% v 7.5%
-Sugemalimab/placebo-related TEAE 82.5% v 64.8%
-Sugemalimab/placebo-related serious TEAE 16.6% v 10.1%
-Any treatment-related TEAE leading to death 3.4% v 1.3%
-Immune-Related AEs by Investigator Assessment 35.6% v 16.4%
Not surprisingly, a greater proportion of patients in the sugemalimab arm experienced immune-related AEs.

Common adverse events

Table CS4: Common Adverse Events Reported in ≥ 10% of Subjects (by Preferred Term) in Study CS1001-302

System Organ Class Preferred Term	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)
Number of Participants With at Least One Event	**319 (99.7)**	**157 (98.7)**
Investigations	**282 (88.1)**	**138 (86.8)**
Neutrophil count decreased	186 (58.1)	94 (59.1)
White blood cell count decreased	180 (56.3)	94 (59.1)
Aspartate aminotransferase increased	114 (35.6)	43 (27.0)
Alanine aminotransferase increased	112 (35.0)	53 (33.3)
Platelet count decreased	108 (33.8)	63 (39.6)
Weight increased	76 (23.8)	15 (9.4)
Gamma-glutamyltransferase increased	48 (15.0)	25 (15.7)
Weight decreased	40 (12.5)	24 (15.1)
Blood bilirubin increased	28 (8.8)	17 (10.7)
Blood and Lymphatic System Disorders	**261 (81.6)**	**120 (75.5)**
Anaemia	245 (76.6)	113 (71.1)
Leukopenia	33 (10.3)	14 (8.8)
Metabolism and Nutrition Disorders	**210 (65.6)**	**97 (61.0)**
Decreased appetite	92 (28.8)	41 (25.8)
Hypoalbuminaemia	59 (18.4)	29 (18.2)
Hyponatraemia	46 (14.4)	10 (6.3)
Hyperglycaemia	45 (14.1)	19 (11.9)
Hypokalaemia	44 (13.8)	17 (10.7)
Hypercholesterolaemia	38 (11.9)	9 (5.7)
Gastrointestinal Disorders	**185 (57.8)**	**93 (58.5)**
Nausea	77 (24.1)	43 (27.0)
Constipation	75 (23.4)	43 (27.0)
Vomiting	44 (13.8)	23 (14.5)
Diarrhoea	32 (10.0)	16 (10.1)
General Disorders and Administration Site Conditions	**182 (56.9)**	**84 (52.8)**
Asthenia	56 (17.5)	29 (18.2)
Pyrexia	55 (17.2)	32 (20.1)
Fatigue	42 (13.1)	8 (5.0)
Skin and Subcutaneous Tissue Disorders	**134 (41.9)**	**58 (36.5)**
Alopecia	62 (19.4)	33 (20.8)
Rash	59 (18.4)	17 (10.7)
Musculoskeletal and Connective Tissue Disorders	**118 (36.9)**	**48 (30.2)**
Arthralgia	45 (14.1)	12 (7.5)
Pain in extremity	24 (7.5)	17 (10.7)
Infections and Infestations	**112 (35.0)**	**42 (26.4)**
Pneumonia	43 (13.4)	21 (13.2)
Upper respiratory tract infection	34 (10.6)	9 (5.7)
Endocrine Disorders	**45 (14.1)**	**7 (4.4)**
Hypothyroidism	35 (10.9)	3 (1.9)

Treatment-emergent adverse event is defined as any adverse event that occurred or worsened on or after the start of study treatment.
The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 24.0.
CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities;
PT = preferred term; SOC = system organ class
Source: Study CS1001-302 CSR, Table t_ae_SA

Adverse Events of ≥ Grade 3 in Study CS1001-302

Table CS5: Grade ≥ 3 Adverse Events Reported in ≥ 5% of Subjects in Either Arm (by Preferred Term) in Study CS1001-302

System Organ Class Preferred Term	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)
Number of Participants With at Least One Event	**207 (64.7)**	**99 (62.3)**
Investigations	**140 (43.8)**	**70 (44.0)**
Neutrophil count decreased	104 (32.5)	53 (33.3)
White blood cell count decreased	46 (14.4)	27 (17.0)
Platelet count decreased	34 (10.6)	16 (10.1)
Blood and Lymphatic System Disorders	**72 (22.5)**	**30 (18.9)**
Anaemia	48 (15.0)	18 (11.3)
Infections and Infestations	**25 (7.8)**	**10 (6.3)**
Pneumonia	16 (5.0)	9 (5.7)

Source: Study CS1001-302 CSR, Table t_ae_grd_SA

Treatment-Related Treatment-Emergent Adverse Events

Table CS6: Sugemalimab- or Placebo-related Adverse Events Reported in ≥ 5% of Subjects (by Preferred Term) in Either Arm in Study CS1001-302

System Organ Class Preferred Term	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)
Number of Participants With at Least One Event	**264 (82.5)**	**103 (64.8)**
Investigations	**179 (55.9)**	**70 (44.0)**
Aspartate aminotransferase increased	84 (26.3)	26 (16.4)
Alanine aminotransferase increased	80 (25.0)	29 (18.2)
Neutrophil count decreased	56 (17.5)	32 (20.1)
White blood cell count decreased	53 (16.6)	26 (16.4)
Gamma-glutamyltransferase increased	33 (10.3)	8 (5.0)
Platelet count decreased	30 (9.4)	18 (11.3)
Blood bilirubin increased	22 (6.9)	9 (5.7)
Blood creatinine increased	19 (5.9)	4 (2.5)
Blood and Lymphatic System Disorders	**105 (32.8)**	**37 (23.3)**
Anaemia	92 (28.8)	33 (20.8)
Metabolism and Nutrition Disorders	**89 (27.8)**	**28 (17.6)**
Decreased appetite	27 (8.4)	13 (8.2)
Hyperglycaemia	25 (7.8)	5 (3.1)
Hypoalbuminaemia	18 (5.6)	3 (1.9)
General Disorders and Administration Site Conditions	**82 (25.6)**	**21 (13.2)**
Fatigue	30 (9.4)	3 (1.9)
Asthenia	25 (7.8)	8 (5.0)
Pyrexia	16 (5.0)	3 (1.9)
Skin and Subcutaneous Tissue Disorders	**72 (22.5)**	**18 (11.3)**
Rash	46 (14.4)	11 (6.9)
Gastrointestinal Disorders	**62 (19.4)**	**26 (16.4)**
Nausea	17 (5.3)	7 (4.4)
Endocrine Disorders	**44 (13.8)**	**7 (4.4)**
Hypothyroidism	34 (10.6)	3 (1.9)
Hyperthyroidism	20 (6.3)	1 (0.6)

Source: Study CS1001-302 CSR, Table t_ae_rel_cs_SA

Grade 3 to 5 Treatment-Related Treatment-Emergent Adverse Events

During the double-blind phase of the study, Grade 3 to 5 sugemalimab- or placebo-related TEAEs were reported in 95 (29.7%) and 39 (24.5%) participants, respectively.

The most frequently reported Grade 3 to 5 sugemalimab- or placebo-related TEAEs by PT were neutrophil count decreased (27 [8.4%] and 20 [12.6%] participants, respectively), white blood cell count decreased and anaemia (14 [4.4%] and 7 [4.4%] participants each, respectively), and platelet count decreased (10 [3.1%] and 5 [3.1%] participants, respectively).

All other Grade ≥ 3 sugemalimab- or placebo-related TEAEs by PT were reported in < 2% of participants each in both treatment groups.
Grade 4 sugemalimab- or placebo-related TEAEs were reported in 17 (5.3%) and 11 (6.9%) participants, respectively; and the most frequently reported Grade 4 sugemalimab- or placebo-related TEAE by PT was neutrophil count decreased (8 [2.5%] and 8 [5.0%] participants, respectively).
Grade 5 (fatal) sugemalimab- or placebo-related TEAEs were reported in 7 (2.2%) participants in the sugemalimab group and 1 (0.6%) participant in the placebo group.

Summary:
The most common adverse events (≥ 20%) in the sugemalimab + chemotherapy arm were anaemia (76.6%), decreased neutrophil count (58.1%), increased AST (35.6%), increased ALT (35.0%), decreased platelet count (33.8%), decreased appetite (28.8%), nausea (24.1%), weight increased (23.8%) and constipation (23.4%).

Of the very common adverse events (≥10%) in Study CS1001-302, the following were reported with > 5% difference between the two arms of the study. Except for decreased platelet count, they were all more frequent in the sugemalimab + chemotherapy arm:

Increased weight 14.4% (23.8 v 9.4)
Hypothyroidism 9% (10.9 v 1.9)
Increased AST 8.6% (35.6 v 27.0)
Hyponatraemia 8.1% (14.4 v 6.3)
Fatigue 8.1% (13.1 v 5.0)
Rash 7.7% (18.4 v 10.7)
Arthralgia 6.6% (14.1 v 7.5)
Hypercholesterolaemia 6.2% (11.9 v 5.7)
Decreased platelet count 5.8% (33.8 v 39.6)
Anaemia 5.6% (76.6 v 71.1)

Very common adverse events which occurred more frequently in the sugmalimab arm than in the placebo arm were mostly related to expected immune checkpoint-inhibitor-induced toxicities. However, the cause of increased weight is puzzling. The company has provided detail of causes of ‘increased weight’ in the study and explained the difference observed in the sugemalimab arm (23.8%) and placebo arm (9.4 %).

From the list of AEs provided, more cases of oedema (peripheral oedema, face oedema and peripheral swelling) were observed in the sugemalimab arm than the placebo arm. However, it is agreed that increased weight was overall likely attributable to response to treatment.

The treatment-related adverse events which were considered related to sugemalimab or placebo and had >5% difference in incidence between the 2 arms were increased AST increased (26.3% vs 16.4%), anaemia (28.8% vs 20.8%), hypothyroidism (10.6% vs 1.9%), fatigue (9.4% vs 1.9%), rash (14.4% vs 6.9%), alanine aminotransferase increased (25.0% vs 18.2%), gamma-glutamyltransferase increased (10.3% vs 5.0%), and hyperthyroidism (6.3% vs 0.6%).

Adverse events of Grade 3 or more affecting at least 5% of patients were mainly haematological and were likely a result of the chemotherapy component of treatment. The company has provided a table of ≥Grade 3 adverse events, in decreasing order of frequency, seen in at least 2% (≥2%) of patients.

TEAEs Grade 3–5 for Study CS1001-302 with a cut-off of at least 2% of patients per PT are presented in Table 51. The most common Grade 3 to 5 TEAEs in this study (affecting ≥ 5% of patients in either group) were neutrophil count decreased (32.5% sugemalimab vs. 33.3% placebo), white blood cell count decreased (14.4% vs. 17.0%), anaemia (15.0% vs. 11.3%), platelet count decreased (10.6% vs.10.1%), and pneumonia (5.0% vs. 5.7%).

Table 51: Treatment-emergent Adverse Events Grade 3-5 in ⩾2% Patients in either Group per Preferred Term in Study CS1001-302 (Data cut-off 22 Nov 2021)

MedDRA System Organ Class MedDRA Preferred Term	Sugemalimab+ Chemotherapy N=320	Placebo+ Chemotherapy N=159
Number of Patients with at Least One Event	**207 (64.7%)**	**99 (62.3%)**
Neutrophil count decreased	104 (32.5%)	53 (33.3%)
Anaemia	48 (15.0%)	18 (11.3%)
White blood cell count decreased	46 (14.4%)	27 (17.0%)
Platelet count decreased	34 (10.6%)	16 (10.1%)
Pneumonia	16 (5.0%)	9 (5.7%)
Neutropenia	12 (3.8%)	7 (4.4%)
Hyponatraemia	11 (3.4%)	1 (0.6%)
Gamma-glutamyltransferase increased	9 (2.8%)	3 (1.9%)
Lymphocyte count decreased	9 (2.8%)	3 (1.9%)
Death	7 (2.2%)	3 (1.9%)
Hepatic function abnormal	7 (2.2%)	2 (1.3%)
Febrile neutropenia	7 (2.2%)	1 (0.6%)
Hypertriglyceridaemia	7 (2.2%)	1 (0.6%)
Alanine aminotransferase increased	3 (0.9%)	4 (2.5%)

Source: Module 5.3.5.1 CS1001-302-e3-csr Table t_ae_grd_SA
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class; NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events.
Treatment-Emergent Adverse Event (TEAE) is defined as any AE that occurred or worsened on or after the start of study treatment.
MedDRA version 24.0.
NCI-CTCAE version 4.03.
Patient is counted only once at the highest grade for unique SOC or preferred term.

Adverse events of special interest (AESI)

Immune-related adverse events (irAEs) were adverse events of special interest (AESIs). Based on the characteristics of irAEs of similar drugs, and the characteristics of irAEs described in guidelines and literature, a listing of 24 categories of MedDRA preferred terms (PTs) were selected by CStone Pharmaceuticals to search for and identify irAEs. The 24 categories of AESI are:

Category of Adverse Events of Special Interest	Category of Adverse Events of Special Interest
Immune-related hepatitis	Immune-related renal insufficiency
Immune-related pneumonitis	Immune-related hypophysitis
Immune-related colitis	Immune-related myasthenic syndrome and myasthenia gravis
Immune-related nephritis (including renal failure)	Immune-related meningoencephalitis and encephalitis
Immune-related thyroid disorders (including thyroid function increased, thyroid function decreased, and thyroiditis)	Immune-related myocarditis
Immune-related diabetes mellitus	Immune-related vasculitis
Serious immune-related skin adverse reactions	Immune-related ocular toxicity
Immune-related pancreatitis	Immune-related myositis
Immune-related Guillain-Barre syndrome and demyelinating lesions	Immune-related skin adverse reactions (except serious events)
Immune-related haemolytic anaemia	Immune-related pancytopenia or bilineage cytopenia
Immune-related thrombocytopenic purpura	Immune-related arthritis
Immune-related rhabdomyolysis and myopathy	Immune-related upper gastrointestinal disorder

Table CS7: Overall Summary of Adverse Event of Special Interest (DCO: 22 Nov 2021)

AESI Category: All

	CS1001+Chemotherapy N=320	Placebo+Chemotherapy N=159
Number of Patients with at Least One Event	84(26.3%)	7(4.4%)
Number of Patients with at Least One		
Grade 3-5 Event	17(5.3%)	0
Serious Event	17(5.3%)	1(0.6%)
Investigator Assessed as irAE	69(21.6%)	5(3.1%)
Event Leading to Drug Permanently Discontinued	9(2.8%)	0
Event Leading to Drug Interruption	24(7.5%)	2(1.3%)
Event Leading to Death	1(0.3%)	0
Event Treated with Systemic Corticosteroid	30(9.4%)	2(1.3%)
Event Treated with High Dose Systemic Corticosteroid	18(5.6%)	2(1.3%)

Abbreviations: NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; irAE = immune related adverse event; AESI = Adverse Event of Special Interest.
MedDRA version 24.0.
NCI-CTCAE version 4.03.
Drug in this table indicates CS1001/Placebo; Drug interruption includes action taken associated with infusion interrupted or treatment cycle delayed.

Table CS8: Immune-related AEs by Category and NCI-CTCAE Grade in Study CS1001-302

Category	NCI-CTCAE Grade	Sugemalimab +Chemotherapy N=320	Placebo +Chemotherapy N=159
Number of Patients with at Least One Event	**Any Grade**	**84(26.3%)**	**7(4.4%)**
	1	37(11.6%)	5(3.1%)
	2	30(9.4%)	2(1.3%)
	3	13(4.1%)	0
	4	3(0.9%)	0
	5	1(0.3%)	0
Hypothyroidism	**Any Grade**	**35(10.9%)**	**1(0.6%)**
Overall	1	19(5.9%)	1(0.6%)
	2	16(5.0%)	0
	3	0	0
	4	0	0
	5	0	0

Skin adverse reaction (excluding severe)	**Any Grade**	**26(8.1%)**	**2(1.3%)**
Overall	1	15(4.7%)	2(1.3%)
	2	11(3.4%)	0
	3	0	0
	4	0	0
	5	0	0
Hyperthyroidism	**Any Grade**	**24(7.5%)**	**2(1.3%)**
Overall	1	23(7.2%)	1(0.6%)
	2	1(0.3%)	1(0.6%)
	3	0	0
	4	0	0
	5	0	0
Hepatitis	**Any Grade**	**6(1.9%)**	**0**
Overall	1	0	0
	2	0	0
	3	5(1.6%)	0
	4	1(0.3%)	0
	5	0	0
Pneumonitis	**Any Grade**	**6(1.9%)**	**2(1.3%)**
Overall	1	0	1(0.6%)
	2	3(0.9%)	1(0.6%)
	3	2(0.6%)	0
	4	0	0
	5	1(0.3%)	0
Severe Skin Adverse Reactions	**Any Grade**	**5(1.6%)**	**0**
Overall	1	0	0
	2	0	0
	3	5(1.6%)	0
	4	0	0
	5	0	0
Diabetes Mellitus	**Any Grade**	**5(1.6%)**	**0**
Overall	1	4(1.3%)	0
	2	0	0
	3	0	0
	4	1(0.3%)	0
	5	0	0
Nephritis (including renal failure)	**Any Grade**	**3(0.9%)**	**0**
Overall	1	0	0
	2	2(0.6%)	0
	3	1(0.3%)	0
	4	0	0
	5	0	0
Arthritis	**Any Grade**	**3(0.9%)**	**0**
Overall	1	0	0
	2	3(0.9%)	0
	3	0	0
	4	0	0
	5	0	0
Thyroiditis	**Any Grade**	**2(0.6%)**	**1(0.6%)**
Overall	1	2(0.6%)	1(0.6%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0

Colitis	**Any Grade**	**1(0.3%)**	**0**
Overall	1	1(0.3%)	0
	2	0	0
	3	0	0
	4	0	0
	5	0	0
Pancreatitis	**Any Grade**	**1(0.3%)**	**0**
Overall	1	0	0
	2	0	0
	3	0	0
	4	1(0.3%)	0
	5	0	0
Adrenal Insufficiency	**Any Grade**	**1(0.3%)**	**0**
Overall	1	1(0.3%)	0
	2	0	0
	3	0	0
	4	0	0
	5	0	0
Myocarditis	**Any Grade**	**1(0.3%)**	**0**
Overall	1	0	0
	2	1(0.3%)	0
	3	0	0
	4	0	0
	5	0	0
Ocular Toxicities	**Any Grade**	**1(0.3%)**	**0**
Overall	1	1(0.3%)	0
	2	0	0
	3	0	0
	4	0	0
	5	0	0

Source: Table t_ae_aesi_sicat_pt_ctc_SA_3
Sugemalimab +chemotherapy is the sugemalimab group, Placebo +chemotherapy is the placebo group.
Abbreviations: NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities.
MedDRA version 24.0.
NCI-CTCAE version 4.03.
Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
For the category overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade was reported.
[Source: ...\PRODUCTION\TABLES\OSIA_TABLE\T_AE_AESI_SICAT_PT_CTC_SA.SAS] IQVIA 17FEB2022

Immune-related Endocrine Disorders

Hypothyroidism

Immune-related hypothyroidism occurred in 35 (10.9%) patients receiving sugemalimab in combination with chemotherapy, versus 1 (0.6%) patient receiving placebo in combination with chemotherapy.

In the sugemalimab group, all immune-related hypothyroidism were of Grade 1-2. Immune-related hypothyroidism led to drug interruption in 5 (1.6%) patients, and no patients permanently discontinued sugemalimab due to this TEAE.

The median time to onset of immune-related hypothyroidism was 135.0 days (range: 19 - 607 days), and median duration was 143.0 days (range: 7 - 788+ days).

As of the data cut-off date, 23 of the total 35 patients received thyroid therapy. Immune-related hypothyroidism was resolved in 12 of the 35 patients, not resolved in 17 patients, and resolving in the remaining 6 patients as of the data cut-off date.

Hyperthyroidism
Immune-related hyperthyroidism occurred in 24 (7.5%) patients of patients receiving sugemalimab in combination with chemotherapy, versus 2 (1.3%) patients receiving placebo in combination with chemotherapy.

In the sugemalimab group, all immune-related hyperthyroidism reported were of Grade 1-2, with the majority being of Grade 1 (23 of 24 patients). No patients permanently discontinued sugemalimab or had drug interrupted due to the immune-related hyperthyroidism.

The median time to onset of immune-related hyperthyroidism was 88.0 days (range: 41 – 620 days), and median duration was 44.0 days (range: 22 - 484+ days).

As of the data cut-off date, 2 of the total 24 patients received thyroid therapy. Immune-related hyperthyroidism was resolved in 20 of the 24 patients, not resolved in 3 patients, resolving in 1 patient as of the data cut-off date.

Diabetes Mellitus
Immune-related diabetes mellitus occurred in 5 (1.6%) patients receiving sugemalimab in combination with chemotherapy, versus no patients receiving placebo in combination with chemotherapy.

In the sugemalimab group, 4 (1.3%) patients experienced Grade 1 TEAE, and the rest 1 (0.3%) reported Grade 4 TEAE. Immune-related diabetes mellitus led to drug interruption in 1 (0.3%) patient, and no patients permanently discontinued sugemalimab due to this TEAE. The median time to onset of immune-related diabetes mellitus was 561.0 days (range: 44 – 891 days), and median duration was not reached (range: 63 - 190+ days).

As of the data cut-off date, 1 of the total 5 patients received the drug used in diabetes. Immune-related diabetes mellitus was resolved in 2 of the 5 patients, and not resolved in 3 patients as of the data cut-off date.

Thyroiditis
Immune-related thyroiditis occurred in 2 (0.6%) patients receiving sugemalimab in combination with chemotherapy, versus 1 (0.6%) patient receiving placebo in combination with chemotherapy.

In the sugemalimab group, both immune-related thyroiditis reported were of Grade 1 (PT: immune-mediated thyroiditis and anti-thyroid antibody positive). No patients permanently discontinued sugemalimab or had drug interruption due to the immune-related thyroiditis. The time to onset of immune-mediated thyroiditis and positive antithyroid antibody was 167 days and 99 days, respectively. Immune-related thyroiditis was resolved in 1 patient after taking thyroid therapy, it was not resolved in the other 1 patient who did not receive thyroid therapy.

Immune-related Skin Adverse Reactions

Skin Adverse Reactions (Excluding Severe)

Immune-related skin adverse reactions (excluding severe) occurred in 26 (8.1%) patients receiving sugemalimab in combination with chemotherapy, versus 2 (1.3%) patients receiving placebo in combination with chemotherapy.

In the sugemalimab group, all events were of Grade 1-2. Immune-related skin adverse reactions (excluding severe) led to drug interrupted in 5 (1.6%) patients, and no patients permanently discontinued sugemalimab due to this TEAE.

The median time to onset of immune-related skin adverse reactions (excluding severe) was 143.0 days (range: 6 - 909 days), and median duration was 13.5 days (range: 4 - 659+ days). As of the data cutoff date, systemic corticosteroids were required in 1.9% (6/320) of patients, and 0.3% (1/320) of patients required treatment of high-dose (≥40 mg prednisone or equivalency daily) systemic corticosteroids.

Immune-related skin adverse reactions (excluding severe) resolved in 17 of the 26 patients, were resolving in 7 patients, and not resolved in 2 patients as of the data cutoff date.

Severe Skin Adverse Reactions

Immune-related severe skin adverse reactions occurred in 5 (1.6%) patients who received sugemalimab in combination with chemotherapy, versus no patients receiving placebo in combination with chemotherapy.

In the sugemalimab group, all events were of Grade 3. Immune-related skin adverse reactions led to drug interrupted in 4 (1.3%) patients, and led to sugemalimab permanently discontinued in 1 (0.3%) patient.

The median time to onset of immune-related severe skin adverse reactions was 133.0 days (range: 19 - 430 days), and median duration was 77.5 days (range: 12 - 522+ days).
As of the data cutoff date, systemic corticosteroids were required in 0.9% (3/320) of patients, and 0.6% (2/320) of patients required treatment of high-dose (≥40 mg prednisone or equivalency daily) systemic corticosteroids.

Immune-related severe skin adverse reactions resolved in 4 patients, and not resolved in 1 patient as of the data cutoff date.

Immune-related Hepatitis

Immune-related hepatitis occurred in 6 (1.9%) patients receiving sugemalimab in combination with chemotherapy, versus no patient receiving placebo in combination with chemotherapy.

In the sugemalimab group, the majority of events were of Grade 3 (5, 1.6%), 1 (0.3%) patient reported a Grade 4 event. Immune-related hepatitis led to drug interruption in 4 (1.3%) patients, and led to sugemalimab permanently discontinued in 3 (0.9%) patients.

The median time to onset of immune-related hepatitis was 121.5 days (range: 18 - 652 days), and median duration was 56.0 days (range: 5 - 777+ days).

As of the data cutoff date, systemic corticosteroids were required in 1.6% (5/320) of patients, and 1.6% (5/320) of patients required treatment of high-dose (≥40 mg prednisone or equivalency daily) systemic corticosteroids.
Immune-related hepatitis was resolved in 2 of the 6 patients, was resolving in 1 patient, and was not resolved in 3 patients as of the data cutoff date.

Immune-related Pneumonitis
Immune-related pneumonitis occurred in 6 (1.9%) patients receiving sugemalimab in combination with chemotherapy, versus 2 (1.3%) patients receiving placebo in combination with chemotherapy.

In the sugemalimab group, the events were of Grade 3 (2, 0.6%), Grade 2 (3, 0.9%) and Grade 5 (1, 0.3%). Immune-related pneumonitis led to sugemalimab permanently discontinued in 4 (1.3%) patients, led to drug interruption in 3 (0.9%) patients, and led to death in 1 (0.3%) patient.

The median time to onset of immune-related pneumonitis was 125.0 days (range: 78 - 371 days), and median duration was not reached (range: 18 - 558+ days).

As of the data cutoff date, systemic corticosteroids were required in 1.9% (6/320) of patients, and 1.9% (6/320) of patients required treatment of high-dose (≥40 mg prednisone or equivalency daily) systemic corticosteroids.

Immune-related pneumonitis was resolved in 2 of the 6 patients, resolving in 1 patient, was not resolved in 2 patients, and led to death in 1 patient as of the data cutoff date.

Immune-related Nephritis (Including Renal Failure)
Immune-related nephritis (including renal failure) occurred in 3 (0.9%) patients receiving sugemalimab in combination with chemotherapy, versus no patients receiving placebo in combination with chemotherapy.

In the sugemalimab group, the events were of Grade 3 (1, 0.3%) and Grade 2 (2, 0.6%). Immune-related nephritis (including renal failure) led to sugemalimab permanently discontinued in 1 (0.3%) patient, and led to drug interruption in 1 (0.3%) patient.

The median time to onset of immune-related pneumonitis was 241.0 days (range: 133 – 291 days), and median duration was not reached (range: 72 - 592+ days).

As of the data cutoff date, systemic corticosteroids were required in 0.9% (3/320) of patients, and 0.6% (2/320) of patients required treatment of high-dose (≥40 mg prednisone or equivalency daily) systemic corticosteroids.

Immune-related Arthritis
Immune-related arthritis occurred in 3 (0.9%) patients receiving sugemalimab in combination with chemotherapy, versus no patients receiving placebo in combination with chemotherapy. In sugemalimab group, all the events were Grade 2. Immune-related arthritis led to drug interruption in 2 (0.6%) patients, and no patients permanently discontinued sugemalimab due to this TEAE.

The median time to onset of immune-related arthritis was 207.0 days (range: 140 - 366 days), and median duration was not reached (range: 50 - 515+ days).

As of the data cutoff date, systemic corticosteroids were required in 0.9% (3/320) of patients, and no patients required treatment of high-dose (≥40 mg prednisone or equivalency daily) systemic corticosteroids.

Immune-related arthritis was resolved in 1 of the 3 patients, was resolving in 1 patient, not resolved in the remaining 1 patient as of the data cutoff date.

Immune-related Pancreatitis, Myocarditis, Colitis, Adrenal Insufficiency and Ocular Toxicities

Each of these immune-related adverse event was experienced by 1 patient receiving sugemalimab and chemotherapy.

The most commonly observed immune-related adverse reactions were hypothyroidism, skin reaction and hyperthyroidism.

Only immune-related adverse reactions were considered AESI by the company.

Sugemalimab is an anti PD-L1 monoclonal antibody. There were no mechanistic reasons or class effects to suggest that sugemalimab causes AESI other than immune-related AE. The company did not identify any non-immune-related AESI.

Serious adverse events and deaths

Serious adverse events

Serious TEAEs were reported in 110 (34.4%) participants in the sugemalimab group and 49 (30.8%) participants in the placebo group.
The most frequently reported serious TEAE by PT was pneumonia, which occurred in 18 (5.6%) participants in the sugemalimab group and 12 (7.5%) participants in the placebo group.

Table CS9: Serious Treatment-Emergent Adverse Events (at Least 2% of Participants in Either Treatment Group by Preferred Term) in Study CS1001-302

System Organ Class Preferred Term	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)
Number of Participants With at Least One Event	**110 (34.4)**	**49 (30.8)**
Infections and Infestations	**27 (8.4)**	**12 (7.5)**
Pneumonia	18 (5.6)	12 (7.5)
Blood and Lymphatic System Disorders	**21 (6.6)**	**9 (5.7)**
Anaemia	11 (3.4)	5 (3.1)
Investigations	**19 (5.9)**	**9 (5.7)**
Platelet count decreased	10 (3.1)	5 (3.1)
Neutrophil count decreased	6 (1.9)	4 (2.5)
General Disorders and Administration Site Conditions	**13 (4.1)**	**5 (3.1)**
Death	7 (2.2)	3 (1.9)

Source: Study CS1001-302 CSR, Table t_ae_sae_SA

Serious TEAEs considered related to any treatment were reported in 78 (24.4%) participants in the sugemalimab group and 31 (19.5%) participants in the placebo group. Of these, serious TEAE considered related to sugemalimab or placebo as assessed by investigators were reported in 53 (16.6%) and 16 (10.1%) participants, respectively.

Table CS10: Sugemalimab- or Placebo-Related Serious Treatment-Emergent Adverse Events (at Least 1% of Participants in Either Treatment Group by Preferred Term) in Study CS1001-302

System Organ Class Preferred Term	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)
Number of Participants With at Least One Event	**53 (16.6)**	**16 (10.1)**
Blood and Lymphatic System Disorders	**12 (3.8)**	**5 (3.1)**
Anaemia	6 (1.9)	3 (1.9)
Respiratory, Thoracic and Mediastinal Disorders	**11 (3.4)**	**1 (0.6)**
Immune-mediated lung disease	4 (1.3)	0
Hepatobiliary Disorders	**8 (2.5)**	**1 (0.6)**
Hepatic function abnormal	5 (1.6)	1 (0.6)
Investigations	**8 (2.5)**	**3 (1.9)**
Platelet count decreased	3 (0.9)	2 (1.3)
Infections and Infestations	**5 (1.6)**	**3 (1.9)**
Pneumonia	4 (1.3)	3 (1.9)

Source: Study CS1001-302 CSR, Table t_ae_ser_evt_cs_SA

Of the 320 patients in the sugemalimab arm, 34.4% (110 patients) had an SAE. However, only 53 of these 110 patients were considered to have drug-related SAEs.
SAEs attributable to sugemalimab were mainly immune-mediated lung disease and hepatic function abnormalities.

Only SAEs of at least 2 % have been listed. The company subsequently provided a table of SAEs that list all events with >1% in either arm of Study CS1001-302 (Table 52).

Table 52: Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% Patients in either group in Study CS1001-302 (Data cutoff 22 Nov 2021)

MedDRA System Organ Class MedDRA Preferred Term	Sugemalimab+ Chemotherapy N=320	Placebo+ Chemotherapy N=159
Number of Patients with at Least One Event	**110 (34.4%)**	**49 (30.8%)**
Infections and infestations	**27 (8.4%)**	**12 (7.5%)**
Pneumonia	18 (5.6%)	12 (7.5%)
Blood and lymphatic system disorders	**21 (6.6%)**	**9 (5.7%)**
Anaemia	11 (3.4%)	5 (3.1%)
Myelosuppression	5 (1.6%)	1 (0.6%)
Febrile neutropenia	4 (1.3%)	0
Investigations	**19 (5.9%)**	**9 (5.7%)**
Platelet count decreased	10 (3.1%)	5 (3.1%)
Neutrophil count decreased	6 (1.9%)	4 (2.5%)
White blood cell count decreased	4 (1.3%)	1 (0.6%)
Alanine aminotransferase increased	2 (0.6%)	2 (1.3%)
Respiratory, thoracic and mediastinal disorders	**15 (4.7%)**	**9 (5.7%)**
Immune-mediated lung disease	4 (1.3%)	0
Haemoptysis	1 (0.3%)	3 (1.9%)
Pleural effusion	1 (0.3%)	2 (1.3%)
General disorders and administration site conditions	**13 (4.1%)**	**5 (3.1%)**
Death	7 (2.2%)	3 (1.9%)
Gastrointestinal disorders	**8 (2.5%)**	**5 (3.1%)**
Gastrointestinal disorder	0	2 (1.3%)
Hepatobiliary disorders	**8 (2.5%)**	**2 (1.3%)**
Hepatic function abnormal	5 (1.6%)	2 (1.3%)
Nervous system disorders	**7 (2.2%)**	**3 (1.9%)**
Cerebral infarction	6 (1.9%)	1 (0.6%)

Source: Module 5.3.5.1 CS1001-302 CSR Table t_ae_sae_SA
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class.
Treatment-Emergent Adverse Event (TEAE) is defined as any AE that occurred or worsened on or after the start of study treatment.
MedDRA version 24.0.
The patient is counted only once per unique SOC and once per unique preferred term within SOC.

Note is made of a higher frequency of cerebral infarcts in the sugemalimab arm compared to placebo arm (1.9% v. 0.6%, respectively). There was no other thrombotic SAE with incidence of >1%.

Deaths

As of the data cutoff date of 22 Nov 2021, death was reported in 156 (48.8%) participants in the sugemalimab group and 97 (61.0%) participants in the placebo group in Study CS1001-302.

Table CS11: Summary of deaths in Study CS1001-302

	Sugemalimab + Chemotherapy (N = 320) n (%)	**Placebo + Chemotherapy (N = 159) n (%)**
Number of Participant Deaths	**156 (48.8)**	**97 (61.0)**
Primary Cause of Death		
Adverse event	13 (4.1)	7 (4.4)
Disease under study	117 (36.6)	81 (50.9)
Other	26 (8.1)	9 (5.7)

During the study, TEAEs leading to death were reported in 20 participants in the sugemalimab group (all during the double-blind phase) and 10 participants in the placebo group (9 participants during the double-blind phase and 1 participant during the crossover phase).

Table CS12: Treatment-Emergent Adverse Events Leading to Death in Study CS1001-302

System Organ Class Preferred Term	**Sugemalimab + Chemotherapy (N = 320) n (%)**	**Placebo + Chemotherapy (N = 159) n (%)**
Number of Participants With at Least One Event	**20 (6.3)**	**9 (5.7)**
General Disorders and Administration Site Conditions	**7 (2.2)**	**4 (2.5)**
Death	7 (2.2)	3 (1.9)
Multiple organ dysfunction syndrome	0	1 (0.6)
Infections and Infestations	**5 (1.6)**	**2 (1.3)**
Pneumonia	3 (0.9)	2 (1.3)
Septic shock	2 (0.6)	0
Nervous System Disorders	**4 (1.3)**	**1 (0.6)**
Cerebral infarction	3 (0.9)	0
Haemorrhage intracranial	1 (0.3)	0
Epilepsy	0	1 (0.6)
Respiratory, Thoracic and Mediastinal Disorders	**3 (0.9)**	**0**
Respiratory failure	2 (0.6)	0
Immune-mediated lung disease	1 (0.3)	0
Blood and Lymphatic System Disorders	**1 (0.3)**	**0**
Myelosuppression	1 (0.3)	0
Cardiac Disorders	**1 (0.3)**	**0**
Cardiac failure	1 (0.3)	0
Gastrointestinal Disorders	**1 (0.3)**	**0**
Abdominal pain	1 (0.3)	0
Metabolism and Nutrition Disorders	**0**	**1 (0.6)**
Diabetic ketoacidosis	0	1 (0.6)
Psychiatric Disorders	**0**	**1 (0.6)**
Completed suicide	0	1 (0.6)

There were proportionately more deaths in the placebo arm.
The main cause of death was disease progression.
Deaths due to adverse events were about the same for each arm of the study (sugemalimab 4.1% v. placebo 4.4%). There were, however, a higher percentage of deaths due to 'other' causes in the sugemalimab arm (8.1%, n=26).

Laboratory findings

Haematology

In the sugemalimab group and the placebo group, the most common haematology abnormalities from baseline Grade 0-2 to post-baseline Grade 3-4 was low neutrophil count (109, 34.1% vs 60, 37.7%). The incidence of haematological abnormalities from baseline Grade 0-2 to post-baseline Grade 3-4 was basically similar between the 2 groups, with a difference of less than or equal to 4.0%.

Table CS14: Laboratory Abnormalities Worsening from Baseline for Haematology

		Sugemalimab +Chemotherapy N=320		Placebo +Chemotherapy N=159	
Parameter	Directionality	All Grades	Grade 3-4	All Grades	Grade 3-4
Hemoglobin (g/L)	Low	261(81.6%)	47(14.7%)	124(78.0%)	17(10.7%)
	High	6(1.9%)	0	1(0.6%)	0
Platelets (10^9/L)	Low	120(37.5%)	35(10.9%)	66(41.5%)	19(11.9%)
Leukocytes (10^9/L)	Low	201(62.8%)	54(16.9%)	104(65.4%)	32(20.1%)
Neutrophils (10^9/L)	Low	206(64.4%)	109(34.1%)	107(67.3%)	60(37.7%)
Lymphocytes (10^9/L)	Low	148(46.3%)	22(6.9%)	60(37.7%)	14(8.8%)
	High	11(3.4%)	2(0.6%)	3(1.9%)	2(1.3%)

Source: Table t_lb_wors_hemo_SA_3
Laboratory results are graded using Common Terminology Criteria for Adverse Events version 4.03. Sugemalimab+chemotherapy is the sugemalimab group, Placebo +chemotherapy is the placebo group.
[Source: ...\PRODUCTION\TABLES\OSIA_TABLE\T_LB_WORS_HEMO_SA.SAS] IQVIA 11JAN2022

Biochemistry

In the sugemalimab group and the placebo group, the incidence of serum chemistry abnormalities from baseline Grade 0-2 to post-baseline Grade 3-4 was basically similar between the 2 groups, with a difference of less than or equal to 2.3%. In the sugemalimab group, the most frequently reported serum chemistry abnormalities from baseline Grade 0-2 to post-baseline Grade 3-4 were low blood sodium (17, 5.3%), high blood glucose (13, 4.1%), and high gamma-glutamyltransferase (13, 4.1%). In the placebo group, the most frequently reported serum chemistry abnormalities from baseline Grade 0-2 to post-baseline Grade 3-4 were high gamma-glutamyltransferase increased (9, 5.7%), high blood glucose (9, 5.7%), and low blood sodium (7, 4.4%).

Table CS15: Laboratory Abnormalities Worsening from Baseline for Chemistry

Parameter	Directionality	Sugemalimab +Chemotherapy N=320		Placebo +Chemotherapy N=159	
		All Grades	Grade 3-4	All Grades	Grade 3-4
Albumin (g/L)	Low	113(35.3%)	0	51(32.1%)	0
Alanine Aminotransferase (IU/L)	High	131(40.9%)	6(1.9%)	57(35.8%)	5(3.1%)
Alkaline Phosphatase (IU/L)	High	66(20.6%)	5(1.6%)	33(20.8%)	2(1.3%)
Aspartate Aminotransferase (IU/L)	High	143(44.7%)	5(1.6%)	54(34.0%)	3(1.9%)
Gamma Glutamyl Transferase (IU/L)	High	121(37.8%)	13(4.1%)	60(37.7%)	9(5.7%)
Calcium (mmol/L)	Low	39(12.2%)	2(0.6%)	10(6.3%)	2(1.3%)
	High	38(11.9%)	0	27(17.0%)	2(1.3%)
Total Cholesterol (mmol/L)	High	120(37.5%)	2(0.6%)	49(30.8%)	1(0.6%)
Creatine Kinase (IU/L)	High	31(9.7%)	0	9(5.7%)	0
Creatinine (µmol/L)	High	263(82.2%)	6(1.9%)	115(72.3%)	1(0.6%)
Glucose (mmol/L)	Low	19(5.9%)	0	5(3.1%)	0
	High	154(48.1%)	13(4.1%)	67(42.1%)	9(5.7%)
Phosphate (mmol/L)	Low	53(16.6%)	9(2.8%)	20(12.6%)	3(1.9%)
Magnesium (mmol/L)	Low	86(26.9%)	0	21(13.2%)	1(0.6%)
	High	29(9.1%)	4(1.3%)	12(7.5%)	2(1.3%)
Potassium (mmol/L)	Low	62(19.4%)	10(3.1%)	20(12.6%)	4(2.5%)
	High	17(5.3%)	1(0.3%)	9(5.7%)	0
Sodium (mmol/L)	Low	85(26.6%)	17(5.3%)	36(22.6%)	7(4.4%)
	High	29(9.1%)	1(0.3%)	4(2.5%)	0
Bilirubin (µmol/L)	High	34(10.6%)	5(1.6%)	15(9.4%)	2(1.3%)

Source: Table t_lb_wors_chem_SA_3
Laboratory results are graded using Common Terminology Criteria for Adverse Events version 4.03. [Source: ...\PRODUCTION\TABLES\OSIA_TABLE\T_LB_WORS_CHEM_SA.SAS] IQVIA 11JAN2022

Liver function tests

In the sugemalimab group and the placebo group, 6 (1.9%) and 1 (0.6%) patient reported alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3 × ULN and total bilirubin ≥1.5 × ULN, respectively, but none of these patients reported (ALP) <2 × ULN. No events of discontinuation of sugemalimab or placebo due to TEAEs of ALT and/or AST increased, or total bilirubin increased alone were reported.

Table CS16: Liver Function Laboratory Findings

Liver Function Laboratory Findings	Sugemalimab +Chemotherapy N=320	Placebo +Chemotherapy N=159
ALT and/or AST>3×ULN, and TBIL≥2×ULN and ALP<2×ULN	**0**	**0**
ALT and/or AST>3×ULN, and TBIL≥2×ULN	**6(1.9%)**	**1(0.6%)**
ALT and/or AST>3×ULN, and TBIL≥1.5×ULN	**6(1.9%)**	**1(0.6%)**
ALT and/or AST		
>3×ULN	31(9.7%)	16(10.1%)
≥5×ULN	9(2.8%)	6(3.8%)
≥10×ULN	2(0.6%)	2(1.3%)
≥20×ULN	0	0
ALT		
>3×ULN	29(9.1%)	15(9.4%)
≥5×ULN	6(1.9%)	5(3.1%)
≥10×ULN	1(0.3%)	1(0.6%)
≥20×ULN	0	0
AST		
>3×ULN	16(5.0%)	8(5.0%)
≥5×ULN	5(1.6%)	3(1.9%)
≥10×ULN	1(0.3%)	2(1.3%)
≥20×ULN	0	0
TBIL		
≥1.5×ULN	9(2.8%)	4(2.5%)
≥2×ULN	7(2.2%)	2(1.3%)
ALP		
≥1.5×ULN	40(12.5%)	24(15.1%)

Source: Table t_lb_liver_SA_3

Abbreviations: ALP = Alkaline Phosphatase; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; TBIL = Total Bilirubin; ULN = Upper Limits of Normal.

Number of patients with post-baseline test results (or combination of test results from the same visit) that met the predetermined criteria are counted.

[Source: ...\PRODUCTION\TABLES\OSIA_TABLE\T_LB_LIVER_SA.SAS] IQVIA 11JAN2022

Haematological abnormalities were common and found with similar frequencies in both arms.

Apart from raised transaminases, the biochemical abnormalities which showed an obvious difference between the sugemalimab (S) arm and placebo (P) arm were:

Increased creatinine 82.2% v. 72.3% (S v. P)
Hypomagnesaemia 26.9% v. 13.2%
Hypokalaemia 19.4% v. 12.6%
Hypocalcaemia 12.2% v. 6.3%
Hypernatraemia 9.1% v. 2.5%
Hypoglycaemia 5.9% v. 3.1%

The potential Hy's Law case was defined as subjects with concurrent elevation in transaminases and bilirubin meeting the laboratory criteria: bilirubin > 2 × ULN and ALT/AST >3 × ULN without concomitant elevated alkaline phosphatase (ALP > 2 × ULN). No case met the definition of Hy's Law in Study CS1001-302.
For the patients with concomitant elevated ALP (> 2 × ULN) and raised bilirubin and transaminases (n=6 [1.9%] in the sugemalimab arm, n=1 [0.6%] in the placebo arm), the Clinical Study report mentioned that 'medical history and chemotherapy were considered to be key contributory factors'. However, the difference in percentages between the 2 arms would suggest that sugemalimab caused more drug-induced liver abnormality, otherwise percentages in the two arms would be expected to be similar.

Safety in special populations

Age, Sex and Weight
For Study CS1001-302, subgroup analyses by sex, age group, weight quartile, tumour histology type, PD-L1 expression value (< 1% or ≥ 1%), and ADA status showed that the observed differences were not considered clinically meaningful.

Race, Ethnicity
All patients in Study CS1001-302 were Asians.

Efficacy and safety of sugemalimab in combination with platinum-based chemotherapy in patients with NSCLC has been studied in Asian patients only.

There are no efficacy and safety data of this combination in non-Asian patients. Whilst efficacy and safety of a checkpoint inhibitor with chemotherapy are known from already approved agents, such as pembrolizumab and atezolizumab, there is concern about whether sugemalimab at the proposed fixed dose of 1200 mg would result in the similar efficacy because of inadequate dose-finding and bridging investigations. As such, response to sugemalimab at the proposed dose + chemotherapy cannot be anticipated / extrapolated, and further studies in non-Asian patients are required.

Large molecules mainly do not affect transporters and specific metabolic pathways as do small molecules. MAbs are eliminated via proteolytic catabolism, which is a non-specific immunoglobulin elimination pathway, and intracellular degradation after binding to their targets. It is not anticipated that there is an interaction of sugemalimab with chemotherapeutic drugs or any impact of sugemalimab on exposure of the chemotherapeutic drug in different populations.

In a meta-analysis investigating the effects of ethnic disparities on clinical outcomes of ICIs monotherapy among patients with NSCLC, Asian individuals with NSCLC exhibited comparable response rates and survival benefits to their Western counterparts, despite variations in epidemiology, genetic susceptibility, and molecular profiles.

A meta-analysis included 11 ICI trials focusing on metastatic non-small cell lung cancer (mNSCLC) submitted to the FDA between 2014 and 2018. The meta-analysis included pooled results of 286 Asians and 2214 non-Asians with mNSCLC receiving either 1st-line combination of ICI with chemotherapy (1L-C) or chemotherapy alone (Table 5). Although Asians appear to have better prognosis than non-Asians, the magnitude of 1L-C ICI treatment effect relative to chemo was similar for Asian and non-Asian patients.

The characteristics of sugemalimab include linear pharmacokinetics (PK) within the range of 3-40 mg/kg, a relatively flat exposure-response profile encompassing efficacy and safety, a broad therapeutic dose range, the absence of metabolism pathways, intravenous administration ensuring high bioavailability with no dietary absorption effects, low likelihood of protein binding, and minimal potential for drug-drug interactions (DDI). These features align with guidelines ICH E5, indicating that sugemalimab is ethnically insensitive.

In summary, the company believes that the efficacy and safety in non-Asian patients would be similar to that observed in Study CS1001-302.

Table 5: Meta-analyses of NSCLC Trials

Treatment setting and population	N	OS		PFS	
		Medians (months)	HR (95% CI)	Medians (months)	HR (95% CI)
1L-C Asians: ICI vs. chemo	286	24.0 vs 20.9	0.72 (0.48, 1.07)	7.0 vs 5.8	0.72 (0.55, 0.96)
1L-C non-Asians: ICI vs. chemo	2214	19.5 vs 13.4	0.68 (0.60, 0.78)	8.1 vs 5.8	0.62 (0.56, 0.69)

Abbreviations: ICI: Immune checkpoint inhibitors, chemo: chemotherapy, 1L-C: 1st line Combination with chemotherapy
Source: Chang, Gong et al. 2019

The company conducted a further comprehensive analysis to address the concern about the optimal dose for GB patients and proposes a dose adjustment for patients weighing more than 115 kg based on PK exposure matching. As the dose regimen of 1200 mg Q3W had demonstrated the efficacy and safety in the confirmatory CS1001-302 study, the exposure following 1200 mg Q3W in the study CS1001-302 was used as the reference for comparison. The analysis includes results of simulations from the population PK model and the exposure-response relationship, which support that a dose increase to 1500 mg for patients >115 kg and a dose of 1200 mg for patients ≤115 kg could ensure comparable exposure.

The company provided simulations for exposure based on Ctrough, AUC and Cmax in weight bands of 5 Kg across body weight ranging from 80 to 150 Kg. The company used stringent bioequivalence (BE) limits of 80-125% to compare the simulated exposure to the reference exposure in the pivotal study CS1001-302 with a dose of 1200 mg Q3W and actual weight range of 41-96 kg. The simulations showed that the 1200 mg dose was able to maintain the exposure within the BE limits up to the weight band of 110-115, whereas as the 1500 mg dose maintained the exposure within the BE limits in the weight band 115 to 150 Kg. Based on these simulations, the dosing regimen of 1200 mg Q3W for individuals weighing ≤115 kg and 1500 mg Q3W for those weighing >115 kg is acceptable.

Immunological events

Table CS17: Summary of Immunogenicity Incidence Combination Therapy - ADA Immunogenicity Analysis Set

	Sugemalimab + Chemotherapy						
	NSCLC						
ADA Status	302 NSCLC (N=309) n (%)	101b NSCLC (N=41) n (%)	Total (N=350) n (%)	Other Indications (non-NSCLC) (N=68) n (%)	Total (N=418) n (%)	Sugemalimab + Targeted Therapy (N=20) n (%)	Total (N=438) n (%)
Baseline							
n	309	41	350	68	418	20	438
ADA Positive	27 (8.7)	1 (2.4)	28 (8.0)	7 (10.3)	35 (8.4)	2 (10.0)	37 (8.4)
ADA Negative	282 (91.3)	40 (97.6)	322 (92.0)	61 (89.7)	383 (91.6)	18 (90.0)	401 (91.6)
Post-Baseline							
n	309	41	350	68	418	20	438
ADA Positive	44 (14.2)	2 (4.9)	46 (13.1)	9 (13.2)	55 (13.2)	3 (15.0)	58 (13.2)
ADA Negative	265 (85.8)	39 (95.1)	304 (86.9)	59 (86.8)	363 (86.8)	17 (85.0)	380 (86.8)
ADA Status							
ADA Negative [1]	256 (82.8)	38 (92.7)	294 (84.0)	56 (82.4)	350 (83.7)	17 (85.0)	367 (83.8)
ADA Positive [2]	53 (17.2)	3 (7.3)	56 (16.0)	12 (17.6)	68 (16.3)	3 (15.0)	71 (16.2)
Treatment Emergent-Positive [3]	28 (9.1)	2 (4.9)	30 (8.6)	5 (7.4)	35 (8.4)	2 (10.0)	37 (8.4)
Treatment Induced Persistent	12 (3.9)	0	12 (3.4)	1 (1.5)	13 (3.1)	0	13 (3.0)
Treatment Induced Transient	14 (4.5)	2 (4.9)	16 (4.6)	4 (5.9)	20 (4.8)	1 (5.0)	21 (4.8)
Treatment-Enhanced	2 (0.6)	0	2 (0.6)	0	2 (0.5)	1 (5.0)	3 (0.7)
Non-Treatment Emergent-Positive [4]	25 (8.1)	1 (2.4)	26 (7.4)	7 (10.3)	33 (7.9)	1 (5.0)	34 (7.8)

Note: ADA Immunogenicity Analysis Set includes patients who received at least 1 dose of study drug with baseline and at least one post-baseline anti-Sugemalimab antibody data available.
[1] All baseline and post-baseline ADA test results are negative.
[2] At least one baseline or post-baseline ADA test result is positive.
[3] Includes treatment enhanced positive and treatment induced positive
[4] Baseline ADA is positive and all post-baseline ADA titer results are not greater than 4 x baseline value, or baseline is positive and all post-baseline are negative or missing.
Data cut-off date for Study 101-1a: 16AUG2021; 101-1b: 16AUG2021; 102: 08FEB2021; 201: 10NOV2021; 202: 19FEB2020; 301: 08MAR2021; 302: 22NOV2021.

AEs leading to dose reduction and treatment interruption

Treatment interruption

2.5% of patients in both the sugemalimab arm (n=8) and placebo arm (n=4) experienced adverse events which led to infusion of treatment being interrupted.
Of the 8 events in the sugemalimab arm, 2 caused infusion of sugemalimab to be interrupted (tachycardia and infusion-related reaction).
Infusion of placebo was not interrupted by adverse events.

Dose reduction

There was no dose reduction, only dose delays.

Treatment delay

Table CS18: TEAEs Leading to Sugemalimab Treatment Cycle Delayed by System Organ Class and Preferred Term Combination Therapy

	Sugemalimab + Chemotherapy						
	NSCLC						
System Organ Class Preferred Term	302 NSCLC (N=320) n (%)	101b NSCLC (N=41) n (%)	Total (N=361) n (%)	Other Indications (non-NSCLC) (N=74) n (%)	Total (N=435) n (%)	Sugemalimab + Targeted Therapy (N=23) n (%)	Total (N=458) n (%)
Number of patients with at least one TEAE leading to sugemalimab treatment cycle delayed	144 (45.0)	21 (51.2)	165 (45.7)	35 (47.3)	200 (46.0)	5 (21.7)	205 (44.8)
Blood and lymphatic system disorders	48 (15.0)	5 (12.2)	53 (14.7)	8 (10.8)	61 (14.0)	1 (4.3)	62 (13.5)
Anaemia	42 (13.1)	1 (2.4)	43 (11.9)	2 (2.7)	45 (10.3)	0	45 (9.8)
Thrombocytopenia	1 (0.3)	3 (7.3)	4 (1.1)	3 (4.1)	7 (1.6)	1 (4.3)	8 (1.7)
Neutropenia	4 (1.3)	0	4 (1.1)	3 (4.1)	7 (1.6)	0	7 (1.5)
Myelosuppression	0	2 (4.9)	2 (0.6)	1 (1.4)	3 (0.7)	0	3 (0.7)
Febrile neutropenia	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Leukocytosis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Leukopenia	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Neutrophilia	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Cardiac disorders	9 (2.8)	0	9 (2.5)	0	9 (2.1)	0	9 (2.0)
Arrhythmia	4 (1.3)	0	4 (1.1)	0	4 (0.9)	0	4 (0.9)
Atrial fibrillation	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Bradyarrhythmia	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Immune-mediated myocarditis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Palpitations	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Ventricular fibrillation	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Ear and labyrinth disorders	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Vertigo	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Endocrine disorders	5 (1.6)	0	5 (1.4)	0	5 (1.1)	0	5 (1.1)
Hypothyroidism	5 (1.6)	0	5 (1.4)	0	5 (1.1)	0	5 (1.1)
Eye disorders	1 (0.3)	2 (4.9)	3 (0.8)	0	3 (0.7)	0	3 (0.7)
Dry eye	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Glaucoma	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Keratitis	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Gastrointestinal disorders	9 (2.8)	1 (2.4)	10 (2.8)	1 (1.4)	11 (2.5)	0	11 (2.4)
Diarrhoea	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Vomiting	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Constipation	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Functional gastrointestinal disorder	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Ileus	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Intestinal perforation	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Nausea	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Oesophageal food impaction	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Pancreatitis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Proctitis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)

Upper gastrointestinal haemorrhage	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
General disorders and administration site conditions	16 (5.0)	1 (2.4)	17 (4.7)	3 (4.1)	20 (4.6)	0	20 (4.4)
Fatigue	5 (1.6)	0	5 (1.4)	1 (1.4)	6 (1.4)	0	6 (1.3)
Pyrexia	3 (0.9)	1 (2.4)	4 (1.1)	1 (1.4)	5 (1.1)	0	5 (1.1)
Asthenia	4 (1.3)	0	4 (1.1)	0	4 (0.9)	0	4 (0.9)
Malaise	2 (0.6)	0	2 (0.6)	1 (1.4)	3 (0.7)	0	3 (0.7)
Face oedema	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Influenza like illness	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Hepatobiliary disorders	6 (1.9)	0	6 (1.7)	0	6 (1.4)	0	6 (1.3)
Hepatic function abnormal	5 (1.6)	0	5 (1.4)	0	5 (1.1)	0	5 (1.1)
Hepatitis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Infections and infestations	18 (5.6)	4 (9.8)	22 (6.1)	4 (5.4)	26 (6.0)	0	26 (5.7)
Pneumonia	12 (3.8)	1 (2.4)	13 (3.6)	1 (1.4)	14 (3.2)	0	14 (3.1)
Conjunctivitis	0	3 (7.3)	3 (0.8)	0	3 (0.7)	0	3 (0.7)
Upper respiratory tract infection	0	0	0	3 (4.1)	3 (0.7)	0	3 (0.7)
Anal fungal infection	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Bronchitis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Gastroenteritis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Herpes zoster	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Influenza	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Nasopharyngitis	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Peritonitis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Pneumonia bacterial	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Urinary tract infection	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Investigations	62 (19.4)	12 (29.3)	74 (20.5)	25 (33.8)	99 (22.8)	3 (13.0)	102 (22.3)
Neutrophil count decreased	19 (5.9)	5 (12.2)	24 (6.6)	12 (16.2)	36 (8.3)	0	36 (7.9)
Platelet count decreased	18 (5.6)	5 (12.2)	23 (6.4)	12 (16.2)	35 (8.0)	0	35 (7.6)
White blood cell count decreased	22 (6.9)	1 (2.4)	23 (6.4)	7 (9.5)	30 (6.9)	0	30 (6.6)
Alanine aminotransferase increased	7 (2.2)	4 (9.8)	11 (3.0)	2 (2.7)	13 (3.0)	1 (4.3)	14 (3.1)
Aspartate aminotransferase increased	7 (2.2)	3 (7.3)	10 (2.8)	0	10 (2.3)	1 (4.3)	11 (2.4)
Blood creatinine increased	5 (1.6)	1 (2.4)	6 (1.7)	1 (1.4)	7 (1.6)	0	7 (1.5)
Gamma-glutamyltransferase increased	5 (1.6)	2 (4.9)	7 (1.9)	0	7 (1.6)	0	7 (1.5)
Amylase increased	1 (0.3)	0	1 (0.3)	3 (4.1)	4 (0.9)	0	4 (0.9)
Blood bilirubin increased	2 (0.6)	0	2 (0.6)	1 (1.4)	3 (0.7)	1 (4.3)	4 (0.9)
Blood alkaline phosphatase increased	2 (0.6)	1 (2.4)	3 (0.8)	0	3 (0.7)	0	3 (0.7)
Lymphocyte count decreased	3 (0.9)	0	3 (0.8)	0	3 (0.7)	0	3 (0.7)
Transaminases increased	3 (0.9)	0	3 (0.8)	0	3 (0.7)	0	3 (0.7)
Alanine aminotransferase	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Bilirubin conjugated increased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Biopsy lung	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Blood creatine phosphokinase MB increased	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Blood creatine phosphokinase increased	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Blood glucose increased	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Brain natriuretic peptide increased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
C-reactive protein increased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Creatinine renal clearance decreased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Electrocardiogram Q wave abnormal	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Granulocyte count decreased	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Lipase increased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Myocardial necrosis marker increased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Myoglobin blood increased	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Procalcitonin increased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Total bile acids increased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Troponin T increased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Weight decreased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Metabolism and nutrition disorders	12 (3.8)	0	12 (3.3)	2 (2.7)	14 (3.2)	0	14 (3.1)
Decreased appetite	4 (1.3)	0	4 (1.1)	0	4 (0.9)	0	4 (0.9)
Hyperglycaemia	3 (0.9)	0	3 (0.8)	1 (1.4)	4 (0.9)	0	4 (0.9)
Hyponatraemia	1 (0.3)	0	1 (0.3)	1 (1.4)	2 (0.5)	0	2 (0.4)
Hypercalcaemia	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)

Hypoalbuminaemia	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Hypochloraemia	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Hypokalaemia	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Hypoproteinaemia	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Type 2 diabetes mellitus	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	4 (1.3)	0	4 (1.1)	0	4 (0.9)	0	4 (0.9)
Muscular weakness	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Arthritis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Immune-mediated arthritis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Nervous system disorders	3 (0.9)	2 (4.9)	5 (1.4)	1 (1.4)	6 (1.4)	0	6 (1.3)
Cerebral infarction	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Dizziness	0	2 (4.9)	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Hypoaesthesia	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Neuropathy peripheral	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Psychiatric disorders	0	2 (4.9)	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Depressive symptom	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Mental disorder	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Renal and urinary disorders	8 (2.5)	0	8 (2.2)	0	8 (1.8)	0	8 (1.7)
Renal failure	3 (0.9)	0	3 (0.8)	0	3 (0.7)	0	3 (0.7)
Proteinuria	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Chronic kidney disease	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Haematuria	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Renal impairment	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Reproductive system and breast disorders	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Benign prostatic hyperplasia	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	10 (3.1)	1 (2.4)	11 (3.0)	2 (2.7)	13 (3.0)	0	13 (2.8)
Pneumonitis	2 (0.6)	0	2 (0.6)	2 (2.7)	4 (0.9)	0	4 (0.9)
Dyspnoea	3 (0.9)	0	3 (0.8)	0	3 (0.7)	0	3 (0.7)
Haemoptysis	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Immune-mediated lung disease	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Bronchostenosis	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Hiccups	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Skin and subcutaneous tissue disorders	10 (3.1)	0	10 (2.8)	0	10 (2.3)	1 (4.3)	11 (2.4)
Rash	6 (1.9)	0	6 (1.7)	0	6 (1.4)	1 (4.3)	7 (1.5)
Dermatitis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Eczema	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Henoch-Schonlein purpura	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Rash maculo-papular	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Urticaria	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Vascular disorders	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Deep vein thrombosis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Internal haemorrhage	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)

Note:
MedDRA version 24.1.
TEAE: Treatment-emergent adverse event.
A patient with multiple conditions within a category (SOC or PT) is counted only once within that category.
The percentages are calculated based on the number of safety analysis set.
Data cut-off date for Study 101-1a: 16AUG2021; 101-1b: 16AUG2021; 102: 08FEB2021; 201: 10NOV2021; 202: 19FEB2020; 301: 08MAR2021; 302: 22NOV2021.

Treatment delays due to adverse events were reported in 45.0% in the sugemalimab arm and 38.4% in the placebo arm.
The most common adverse events that led to delay in sugemalimab being given in Study CS1001-302 were haematological - anaemia (13.1%), decreased WBC (6.9%), decreased neutrophil count (5.9%), decreased platelet count (5.6%).

Discontinuation due to AEs
The incidence of TEAEs leading to discontinuation of sugemalimab or placebo was higher in the sugemalimab group compared with the placebo group (45 [14.1%] vs 12 [7.5%] participants).

The most frequently reported (≥ 1% of participants) TEAEs leading discontinuation of sugemalimab or placebo by PT were pneumonia (6 [1.9%] and 3 [1.9%] participants, respectively) and death (4 [1.3%] and 2 [1.3%] participants, respectively); the remaining TEAEs leading to permanent discontinuation of sugemalimab or placebo by PT occurred in < 1% of participants each.

Table CS19: Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Sugemalimab or Placebo Treatment (at Least 2 Participants in Either Treatment Group by Preferred Term) in Study CS1001-302

System Organ Class Preferred Term	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)
Number of Participants With at Least One Event	**45 (14.1)**	**12 (7.5)**
Infections and Infestations	**8 (2.5)**	**3 (1.9)**
Pneumonia	6 (1.9)	3 (1.9)
Septic shock	2 (0.6)	0
General Disorders and Administration Site Conditions	**7 (2.2)**	**3 (1.9)**
Death	4 (1.3)	2 (1.3)
Pyrexia	2 (0.6)	0
Respiratory, Thoracic and Mediastinal Disorders	**7 (2.2)**	**0**
Immune-mediated lung disease	3 (0.9)	0
Respiratory failure	2 (0.6)	0
Hepatobiliary Disorders	**5 (1.6)**	**1 (0.6)**
Hepatic function abnormal	3 (0.9)	1 (0.6)
Cardiac Disorders	**3 (0.9)**	**1 (0.6)**
Cardiac failure	2 (0.6)	0
Blood and Lymphatic System Disorders	**2 (0.6)**	**2 (1.3)**
Myelosuppression	2 (0.6)	0
Vascular Disorders	**2 (0.6)**	**0**
Venous thrombosis limb	2 (0.6)	0

Source: Study CS1001-302 CSR, Table t_ae_disc_cs

Sugemalimab-related TEAEs leading to treatment discontinuation was due to death in 5 participants: pneumonia and respiratory failure, abdominal pain, cardiac failure, immune-mediated lung disease, and death in 1 participant each. The TEAE of immune-mediated lung disease was considered an investigator-assessed irAE of immune-related pneumonitis. No participant had placebo-related TEAEs leading to treatment discontinuation that resulted in death.

Table CS20: TEAEs Leading to Sugemalimab Treatment Discontinuation by System Organ Class and Preferred Term Combination Therapy

	Sugemalimab + Chemotherapy						
	NSCLC						
System Organ Class Preferred Term	302 NSCLC (N=320) n (%)	101b NSCLC (N=41) n (%)	Total (N=361) n (%)	Other Indications (non-NSCLC) (N=74) n (%)	Total (N=435) n (%)	Sugemalimab + Targeted Therapy (N=23) n (%)	Total (N=458) n (%)
Number of patients with at least one TEAE leading to sugemalimab treatment discontinuation	45 (14.1)	8 (19.5)	53 (14.7)	17 (23.0)	70 (16.1)	4 (17.4)	74 (16.2)
Blood and lymphatic system disorders	2 (0.6)	0	2 (0.6)	1 (1.4)	3 (0.7)	0	3 (0.7)
Myelosuppression	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Anaemia	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Cardiac disorders	3 (0.9)	0	3 (0.8)	0	3 (0.7)	0	3 (0.7)
Cardiac failure	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Arrhythmia	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Congenital, familial and genetic disorders	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Tracheo-oesophageal fistula	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Endocrine disorders	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Hypothyroidism	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Eye disorders	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Vision blurred	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Gastrointestinal disorders	3 (0.9)	0	3 (0.8)	2 (2.7)	5 (1.1)	0	5 (1.1)
Abdominal pain	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Abdominal pain upper	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Diarrhoea	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Gastrointestinal haemorrhage	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Nausea	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Obstruction gastric	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Vomiting	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
General disorders and administration site conditions	7 (2.2)	0	7 (1.9)	4 (5.4)	11 (2.5)	0	11 (2.4)
Death	4 (1.3)	0	4 (1.1)	0	4 (0.9)	0	4 (0.9)
Asthenia	0	0	0	2 (2.7)	2 (0.5)	0	2 (0.4)
Pyrexia	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Multiple organ dysfunction syndrome	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Oedema peripheral	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Pain	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Hepatobiliary disorders	5 (1.6)	1 (2.4)	6 (1.7)	1 (1.4)	7 (1.6)	0	7 (1.5)
Hepatic function abnormal	3 (0.9)	0	3 (0.8)	1 (1.4)	4 (0.9)	0	4 (0.9)
Hepatitis	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Immune-mediated hepatic disorder	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Immune-mediated hepatitis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Infections and infestations	8 (2.5)	2 (4.9)	10 (2.8)	0	10 (2.3)	0	10 (2.2)
Pneumonia	6 (1.9)	1 (2.4)	7 (1.9)	0	7 (1.6)	0	7 (1.5)
Septic shock	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Conjunctivitis	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Injury, poisoning and procedural complications	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Femur fracture	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Investigations	4 (1.3)	0	4 (1.1)	1 (1.4)	5 (1.1)	4 (17.4)	9 (2.0)
Bilirubin conjugated increased	0	0	0	0	0	2 (8.7)	2 (0.4)
Blood bilirubin increased	0	0	0	0	0	2 (8.7)	2 (0.4)
Platelet count decreased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (4.3)	2 (0.4)
Blood creatinine increased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Creatinine renal clearance decreased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Gamma-glutamyltransferase increased	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Myocardial necrosis marker increased	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Metabolism and nutrition disorders	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Hyponatraemia	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.9)	0	3 (0.8)	0	3 (0.7)	0	3 (0.7)
Gastrointestinal stromal tumour	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Malignant peritoneal neoplasm	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Oesophageal carcinoma	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Nervous system disorders	3 (0.9)	1 (2.4)	4 (1.1)	0	4 (0.9)	0	4 (0.9)
Cerebral infarction	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)

Haemorrhage intracranial	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Immune-mediated encephalitis	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Peripheral motor neuropathy	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Renal and urinary disorders	3 (0.9)	0	3 (0.8)	0	3 (0.7)	0	3 (0.7)
Nephritis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Renal failure	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Renal impairment	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	7 (2.2)	2 (4.9)	9 (2.5)	4 (5.4)	13 (3.0)	0	13 (2.8)
Immune-mediated lung disease	3 (0.9)	0	3 (0.8)	0	3 (0.7)	0	3 (0.7)
Interstitial lung disease	1 (0.3)	1 (2.4)	2 (0.6)	1 (1.4)	3 (0.7)	0	3 (0.7)
Pneumonitis	0	0	0	2 (2.7)	2 (0.5)	0	2 (0.4)
Respiratory failure	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Haemoptysis	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Pulmonary embolism	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Tracheal stenosis	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)
Skin and subcutaneous tissue disorders	1 (0.3)	1 (2.4)	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Immune-mediated dermatitis	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Rash	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Vascular disorders	2 (0.6)	1 (2.4)	3 (0.8)	1 (1.4)	4 (0.9)	0	4 (0.9)
Venous thrombosis limb	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0	2 (0.4)
Superior vena cava syndrome	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Venous thrombosis	0	0	0	1 (1.4)	1 (0.2)	0	1 (0.2)

Note:
MedDRA version 24.1.
TEAE: Treatment-emergent adverse event.
A patient with multiple conditions within a category (SOC or PT) is counted only once within that category.
The percentages are calculated based on the number of safety analysis set.
Data cut-off date for Study 101-1a: 16AUG2021; 101-1b: 16AUG2021; 102: 08FEB2021; 201: 10NOV2021; 202: 19FEB2020; 301: 08MAR2021; 302: 22NOV2021.

Table CS21: TEAEs Leading to Treatment Discontinuation by System Organ Class and Preferred Term Monotherapy

System Organ Class Preferred Term	101a/b (N=95) n (%)	102 (N=12) n (%)	201 (N=80) n (%)	202 (N=81) n (%)	301 (N=255) n (%)	302 Crossover (N=45) n (%)	Total (N=568) n (%)
Number of patients with at least one TEAE leading to treatment discontinuation	11 (11.6)	3 (25.0)	10 (12.5)	6 (7.4)	29 (11.4)	2 (4.4)	61 (10.7)
Blood and lymphatic system disorders	2 (2.1)	0	0	0	0	0	2 (0.4)
Anaemia	1 (1.1)	0	0	0	0	0	1 (0.2)
Pancytopenia	1 (1.1)	0	0	0	0	0	1 (0.2)
Cardiac disorders	0	0	0	1 (1.2)	1 (0.4)	0	2 (0.4)
Atrial flutter	0	0	0	0	1 (0.4)	0	1 (0.2)
Cardiac failure	0	0	0	0	1 (0.4)	0	1 (0.2)
Myocarditis	0	0	0	1 (1.2)	0	0	1 (0.2)
Endocrine disorders	0	0	0	1 (1.2)	0	0	1 (0.2)
Hypothyroidism	0	0	0	1 (1.2)	0	0	1 (0.2)
Gastrointestinal disorders	0	0	1 (1.3)	0	0	0	1 (0.2)
Intestinal obstruction	0	0	1 (1.3)	0	0	0	1 (0.2)
General disorders and administration site conditions	0	1 (8.3)	1 (1.3)	1 (1.2)	1 (0.4)	0	4 (0.7)
Death	0	0	0	0	1 (0.4)	0	1 (0.2)
Pain	0	0	0	1 (1.2)	0	0	1 (0.2)
Performance status decreased	0	1 (8.3)	0	0	0	0	1 (0.2)
Pyrexia	0	0	1 (1.3)	0	0	0	1 (0.2)
Hepatobiliary disorders	3 (3.2)	0	1 (1.3)	0	0	0	4 (0.7)
Hepatic function abnormal	3 (3.2)	0	1 (1.3)	0	0	0	4 (0.7)
Immune system disorders	0	0	2 (2.5)	1 (1.2)	0	0	3 (0.5)
Haemophagocytic lymphohistiocytosis	0	0	2 (2.5)	0	0	0	2 (0.4)
Anti-neutrophil cytoplasmic antibody positive vasculitis	0	0	0	1 (1.2)	0	0	1 (0.2)

Infections and infestations	1 (1.1)	0	1 (1.3)	1 (1.2)	4 (1.6)	1 (2.2)	8 (1.4)
Pneumonia	0	0	0	1 (1.2)	4 (1.6)	1 (2.2)	6 (1.1)
Pulmonary tuberculosis	1 (1.1)	0	0	0	0	0	1 (0.2)
Septic shock	0	0	1 (1.3)	0	0	0	1 (0.2)
Injury, poisoning and procedural complications	0	0	0	0	2 (0.8)	0	2 (0.4)
Radiation pneumonitis	0	0	0	0	2 (0.8)	0	2 (0.4)
Investigations	2 (2.1)	1 (8.3)	2 (2.5)	0	1 (0.4)	0	6 (1.1)
Blood bilirubin increased	1 (1.1)	1 (8.3)	2 (2.5)	0	0	0	4 (0.7)
Aspartate aminotransferase increased	1 (1.1)	1 (8.3)	0	0	0	0	2 (0.4)
Blood creatine phosphokinase increased	0	0	0	0	1 (0.4)	0	1 (0.2)
Metabolism and nutrition disorders	1 (1.1)	0	0	0	0	0	1 (0.2)
Electrolyte imbalance	1 (1.1)	0	0	0	0	0	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (1.1)	0	0	0	1 (0.4)	0	2 (0.4)
Immune-mediated myositis	1 (1.1)	0	0	0	1 (0.4)	0	2 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.1)	0	0	0	0	0	1 (0.2)
Endometrial cancer	1 (1.1)	0	0	0	0	0	1 (0.2)
Nervous system disorders	0	0	1 (1.3)	0	0	0	1 (0.2)
Facial nerve disorder	0	0	1 (1.3)	0	0	0	1 (0.2)
Renal and urinary disorders	0	1 (8.3)	1 (1.3)	0	0	0	2 (0.4)
Acute kidney injury	0	1 (8.3)	0	0	0	0	1 (0.2)
Nephritic syndrome	0	0	1 (1.3)	0	0	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (1.2)	20 (7.8)	1 (2.2)	22 (3.9)
Immune-mediated lung disease	0	0	0	0	10 (3.9)	1 (2.2)	11 (1.9)
Pneumonitis	0	0	0	0	6 (2.4)	0	6 (1.1)
Interstitial lung disease	0	0	0	1 (1.2)	2 (0.8)	0	3 (0.5)
Haemoptysis	0	0	0	0	2 (0.8)	0	2 (0.4)
Skin and subcutaneous tissue disorders	0	0	0	0	1 (0.4)	0	1 (0.2)
Rash	0	0	0	0	1 (0.4)	0	1 (0.2)

Note:
MedDRA version 24.1.
TEAE: Treatment-emergent adverse event.
A patient with multiple conditions within a category (SOC or PT) is counted only once within that category.
The percentages are calculated based on the number of safety analysis set.
Data cut-off date for Study 101-1a: 16AUG2021; 101-1b: 16AUG2021; 102: 08FEB2021; 201: 10NOV2021; 202: 19FEB2020; 301: 08MAR2021; 302: 22NOV2021.

A higher percentage of patients discontinued treatment in the sugemalimab arm (14.1%) than the placebo arm (7.5%).
A wide range of AEs resulted in treatment discontinuation of sugemalimab. These were mainly within the system organ class of infections/infestations (2.5%), respiratory disorders (2.2%) and hepatobiliary disorders (1.6%) in Study CS1001-301.
Adverse events leading to discontinuation of sugemalimab as monotherapy (pooled data from various studies) followed a similar trend; the most commonly affected system organ class: respiratory disorders (3.9%), infections/infestations (1.4%), investigations (1.1%, mostly liver enzyme abnormalities).

Safety of sugemalimab in non-Asian patients (Study CS1001-102)

Table CS22: Study Drug Exposure in CS1001-102

	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Number of cycles			
n	12	12	24
Mean (SD)	3.8 (4.61)	6.8 (8.62)	5.3 (6.93)
Median	3.0	3.0	3.0
Min, Max	1, 18	1, 29	1, 29
Cumulative actual dose administered (mg)			
n	12	12	24
Mean (SD)	2791.5 (2839.50)	8200.0 (10346.01)	5495.8 (7917.07)
Median	1999.5	3600.0	2517.5
Min, Max	767, 11340	1200, 34800	767, 34800
Duration of treatment (weeks)			
n	12	12	24
Mean (SD)	11.14 (14.087)	20.52 (26.033)	15.83 (21.023)
Median	8.93	9.00	9.00
Min, Max	1.0, 54.0	3.0, 87.0	1.0, 87.0

Abbreviation: SAS = Safety Analysis Set; SD = Standard Deviation.

Duration of treatment was defined as minimum of (treatment end date – treatment start date +21, study discontinue date treatment start date +1).

Table CS23: Overall Summary of Treatment-Emergent Adverse Events in CS1001-102

	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Number of patients with at least one TEAE	12 (100.0%)	12 (100.0%)	24 (100.0%)
Number of patients with at least one			
Treatment-related TEAE	10 (83.3%)	8 (66.7%)	18 (75.0%)
Serious TEAE	3 (25.0%)	6 (50.0%)	9 (37.5%)
Treatment-related serious TEAE	0	1 (8.3%)	1 (4.2%)
Grade 3-5 TEAE	5 (41.7%)	9 (75.0%)	14 (58.3%)
Treatment-related Grade 3-5 TEAE	1 (8.3%)	1 (8.3%)	2 (8.3%)
TEAE leading to death	1 (8.3%)	1 (8.3%)	2 (8.3%)
Immune-related TEAE	0	0	0
Infusion-related reaction	0	0	0
TEAE leading to drug interruption	0	2 (16.7%)	2 (8.3%)
TEAE leading to drug permanently discontinued	1 (8.3%)	3 (25.0%)	4 (16.7%)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities; NCI-CTCAE = National Cancer Institute Common Toxicity Criteria for Adverse Events; SAS = Safety Analysis Set; TEAE = Treatment-Emergent Adverse Event.

NCI-CTCAE version 4.03.

MedDRA version 23.1.

TEAE was defined as any AE that occurred or worsened on or after the initiation of study drug.

Table CS24: Treatment-Related Treatment-Emergent Adverse Events

MedDRA System Organ Class MedDRA Preferred Term	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Number of patients with at least one event	10 (83.3%)	8 (66.7%)	18 (75.0%)
General disorders and administration site conditions	**7 (58.3%)**	**2 (16.7%)**	**9 (37.5%)**
Fatigue	6 (50.0%)	2 (16.7%)	8 (33.3%)
Pyrexia	2 (16.7%)	0	2 (8.3%)
Chills	1 (8.3%)	0	1 (4.2%)
Influenza like illness	1 (8.3%)	0	1 (4.2%)
Investigations	**4 (33.3%)**	**2 (16.7%)**	**6 (25.0%)**
Blood alkaline phosphatase increased	3 (25.0%)	2 (16.7%)	5 (20.8%)
Aspartate aminotransferase increased	2 (16.7%)	0	2 (8.3%)
Blood bilirubin increased	1 (8.3%)	0	1 (4.2%)
Platelet count decreased	1 (8.3%)	0	1 (4.2%)
Gastrointestinal disorders	**2 (16.7%)**	**2 (16.7%)**	**4 (16.7%)**
Nausea	2 (16.7%)	0	2 (8.3%)
Constipation	0	1 (8.3%)	1 (4.2%)
Dysphagia	0	1 (8.3%)	1 (4.2%)
Gastrooesophageal reflux disease	1 (8.3%)	0	1 (4.2%)
Vomiting	1 (8.3%)	0	1 (4.2%)
Renal and urinary disorders	**1 (8.3%)**	**2 (16.7%)**	**3 (12.5%)**
Proteinuria	1 (8.3%)	1 (8.3%)	2 (8.3%)
Acute kidney injury	0	1 (8.3%)	1 (4.2%)
Blood and lymphatic system disorders	**1 (8.3%)**	**1 (8.3%)**	**2 (8.3%)**
Anaemia	1 (8.3%)	0	1 (4.2%)
Lymphadenopathy	0	1 (8.3%)	1 (4.2%)
Metabolism and nutrition disorders	**2 (16.7%)**	**0**	**2 (8.3%)**
Decreased appetite	2 (16.7%)	0	2 (8.3%)
Musculoskeletal and connective tissue disorders	**1 (8.3%)**	**1 (8.3%)**	**2 (8.3%)**
Myalgia	0	1 (8.3%)	1 (4.2%)
Neck pain	1 (8.3%)	0	1 (4.2%)
Endocrine disorders	**0**	**1 (8.3%)**	**1 (4.2%)**
Hypothyroidism	0	1 (8.3%)	1 (4.2%)
Respiratory, thoracic and mediastinal disorders	**0**	**1 (8.3%)**	**1 (4.2%)**
Dyspnoea	0	1 (8.3%)	1 (4.2%)
Skin and subcutaneous tissue disorders	**1 (8.3%)**	**0**	**1 (4.2%)**
Pruritus	1 (8.3%)	0	1 (4.2%)
Vascular disorders	**0**	**1 (8.3%)**	**1 (4.2%)**
Hot flush	0	1 (8.3%)	1 (4.2%)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities; SAS = Safety Analysis Set.
MedDRA version 23.1.
Treatment-emergent adverse event (TEAE) was defined as any AE that occurred or worsened on or after the initiation of study drug.
For frequency counts by preferred term, multiple occurrences of the same condition in an individual were counted only once.
Source: Table t_ae_rel_SA

Table CS25: Grade 3/4/5 Treatment-Related Treatment-Emergent Adverse Events

MedDRA System Organ Class MedDRA Preferred Term	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Number of patients with at least one event	1 (8.3%)	1 (8.3%)	2 (8.3%)
Blood and lymphatic system disorders	**1 (8.3%)**	**0**	**1 (4.2%)**
Anaemia	1 (8.3%)	0	1 (4.2%)
Renal and urinary disorders	**0**	**1 (8.3%)**	**1 (4.2%)**
Acute kidney injury	0	1 (8.3%)	1 (4.2%)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities; NCI-CTCAE = National Cancer Institute Common Toxicity Criteria for Adverse Events; SAS = Safety Analysis Set.
NCI-CTCAE version 4.03.
MedDRA version 23.1.
Treatment-Emergent adverse event (TEAE) was defined as any AE that occurred or worsened on or after the initiation of study drug.
For frequency counts by system organ class or preferred term, multiple occurrences of the same condition in an individual were counted only once.
Source: Table t_ae_ctc_2cat_rel_SA

Table CS26: Serious Treatment-Emergent Adverse Events

MedDRA System Organ Class MedDRA Preferred Term	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Number of patients with at least one event	3 (25.0%)	6 (50.0%)	9 (37.5%)
Gastrointestinal disorders	**1 (8.3%)**	**3 (25.0%)**	**4 (16.7%)**
Small intestinal obstruction	1 (8.3%)	1 (8.3%)	2 (8.3%)
Abdominal pain	0	1 (8.3%)	1 (4.2%)
Ascites	0	1 (8.3%)	1 (4.2%)
Small intestinal perforation	0	1 (8.3%)	1 (4.2%)
Infections and infestations	**2 (16.7%)**	**2 (16.7%)**	**4 (16.7%)**
Pneumonia	2 (16.7%)	0	2 (8.3%)
Bacteraemia	0	1 (8.3%)	1 (4.2%)
Sepsis	0	1 (8.3%)	1 (4.2%)
Metabolism and nutrition disorders	**0**	**1 (8.3%)**	**1 (4.2%)**
Hypercalcaemia	0	1 (8.3%)	1 (4.2%)
Hypokalaemia	0	1 (8.3%)	1 (4.2%)
Product issues	**0**	**1 (8.3%)**	**1 (4.2%)**
Device dislocation	0	1 (8.3%)	1 (4.2%)
Renal and urinary disorders	**0**	**1 (8.3%)**	**1 (4.2%)**
Acute kidney injury	0	1 (8.3%)	1 (4.2%)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities; SAS = Safety Analysis Set.
MedDRA version 23.1.
Treatment-emergent adverse event (TEAE) was defined as any AE that occurred or worsened on or after the initiation of study drug.
For frequency counts by preferred term, multiple occurrences of the same condition in an individual were counted only once.

Table CS27: Treatment-Emergent Adverse Events Leading to Death

MedDRA System Organ Class MedDRA Preferred Term	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Number of patients with at least one event	1 (8.3%)	1 (8.3%)	2 (8.3%)
Infections and infestations	**1 (8.3%)**	**0**	**1 (4.2%)**
Pneumonia	1 (8.3%)	0	1 (4.2%)
Renal and urinary disorders	**0**	**1 (8.3%)**	**1 (4.2%)**
Acute kidney injury	0	1 (8.3%)	1 (4.2%)

Table CS28: Treatment-Emergent Adverse Events Leading to Drug Permanently Discontinued

MedDRA System Organ Class MedDRA Preferred Term	CS1001 10 mg/kg (N=12)	CS1001 1200 mg (N=12)	Total (N=24)
Number of patients with at least one event	1 (8.3%)	3 (25.0%)	4 (16.7%)
General disorders and administration site conditions	**1 (8.3%)**	**1 (8.3%)**	**2 (8.3%)**
Performance status decreased	1 (8.3%)	1 (8.3%)	2 (8.3%)
Investigations	**0**	**1 (8.3%)**	**1 (4.2%)**
Aspartate aminotransferase increased	0	1 (8.3%)	1 (4.2%)
Blood bilirubin increased	0	1 (8.3%)	1 (4.2%)
Renal and urinary disorders	**0**	**1 (8.3%)**	**1 (4.2%)**
Acute kidney injury	0	1 (8.3%)	1 (4.2%)

Neither immune-related TEAEs nor infusion-related reactions were reported during the study.

Twenty-four non-Asian patients were exposed to single agent sugemalimab in Study CS1001-102 (the Phase 1 study intended for ethnic bridging). 12 patients received a dose of 10 mg/kg, and the other 12 had a fixed dose of 1200 mg, once every 3 weeks. The median number of cycles received by both dose groups was 3 (about 9 weeks).

The common side effects observed in this study were fatigue, increased ALP, pyrexia, increased AST, nausea, decreased appetite and proteinuria.
There were no immune-related adverse events or infusion-related reactions reported during the study.

Four patients permanently discontinued due to abnormal liver function, acute kidney injury and deterioration in performance status.

The median duration of exposure was too short and the number of non-Asian patients was too small in this study to make any meaningful comparison with data from the pivotal study. However, it is acknowledged that the toxicity profile is likely to be similar between Asians and non-Asians.

Post marketing experience/Risk management
Sugemalimab is authorised for marketing in China. No new safety concerns have been identified in the post-marketing period in China (up to 30 June 2023).

Overall conclusions on clinical safety
The safety database of sugemalimab in combination with platinum-based chemotherapy for NSCLC is largely made up of 320 patients in the sugemalimab arm of Study CS1001-302.This combination is tolerable in Asians. 14.1% of patients (n=45) in Study CS1001-302 permanently discontinued treatment, with the most common reasons being pneumonia, immune-related lung disease and liver function abnormality.

The combination of sugemalimab + chemotherapy has not been studied in non-Asians. Sugemlaimab as monotherapy was given to 24 non-Asian patients in Study CS1001-102, of whom 12 received the proposed fixed dose of 1200 mg. Among these 12 patients, 2 permanently discontinued treatment due to acute kidney injury and liver function abnormality.

Whilst it is not possible to make any meaningful comparison between these studies, the general toxicity profile is anticipated to be similar between Asians and non-Asians, as for other checkpoint inhibitors.

IV.6 Risk Management Plan (RMP)
The company has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional risk minimisation measures and additional pharmacovigilance activities have been proposed:

Summary of important risks

Important identified risk: immune-related adverse reactions	
Evidence for linking the risk to the medicine	Immune-related adverse reactions may occur during immunotherapy or following its discontinuation and may involve any tissues and organs. Different symptoms or signs may present depending on the organ involved. Immune-related adverse reactions can be mild, moderate, or severe in severity, ranging from asymptomatic to life-threatening or leading to death. Some serious immune-related adverse reactions may have a relatively large impact on the quality of life of patients, but most immune-related adverse reactions resolve after active intervention and treatment, with no significant impact on quality of life expected in the future. Other anti-programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) products have confirmed the occurrence of
Important identified risk: immune-related adverse reactions	
	immune-related adverse reactions, which have been listed as important identified or potential risks in these products.
Risk factors and risk groups	Specific risk factors or risk groups have not been identified.
Risk minimisation measures	**Routine risk minimisation measures** *SmPC Section 4.2* *SmPC Section 4.4* *SmPC Section 4.5* *SmPC Section 4.8* *PL Section 2* *PL Section 4* *Restricted medical prescription.* **Additional risk minimisation measures** Patient alert card.

Important potential risk: Reproductive and developmental toxicity	
Evidence for linking the risk to the medicine	Reproductive and developmental toxicity studies have not been conducted with sugemalimab but based on the mechanism of action of PD-1/PD-L1, it may be inferred that sugemalimab has the potential to cause reproductive and developmental toxicity. Reproductive and developmental toxicity has also been listed as an important potential risk for other anti PD-1/PD-L1 products.
Risk factors and risk groups	Exposure during pregnancy.
Risk minimisation measures	**Routine risk minimisation measures** *SmPC Section 4.6* *PL Section 2* *Restricted medical prescription.* **Additional risk minimisation measures:** *None proposed.*
Missing information: Use in patients ≥ 75 years old	
Risk minimisation measures	**Routine risk minimisation measures** *SmPC Section 4.2* *Restricted medical prescription.* **Additional risk minimisation measures:** *None proposed.*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Integrated safety analysis based on post-marketing data

This is acceptable.

IV.7 Discussion on the clinical aspects

The pivotal study of sugemalimab met its primary endpoint and demonstrated manageable toxicities. Sugemalimab has similar efficacy and safety to other anti-PD-L1 antibodies used to treat lung cancer.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product in the treatment of adults with metastatic non-small-cell lung cancer (NSCLC) with no sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumour aberrations.

For products authorised with conditions
Eqjubi has been authorised with the condition to provide additional measures to minimise the risk. The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	Due date
Prior to launch of sugemalimab, the Marketing Authorisation Holder (MAH) must agree the content and the format of the UK Patient Alert Card and its UK distribution plan with the MHRA. The Patient Alert Card is to address the safety concern of immune-related adverse reactions and it should be in line with the key elements described in the RMP.	03/10/2029

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**