30 May 2024
EMA/380155/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cejemly

International non-proprietary name: Sugemalimab

Procedure No. EMEA/H/C/006088/0000

Note

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

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List of abbreviations

1L/2L/3L	first-line/second-line/third-line
ADCC	antibody-dependent cellular mediated cytotoxicity
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
$AUC_{0-\infty}$	area under the serum concentration-time curve extrapolated to infinity
BICR	blinded independent central review
CD4 +	cluster of differentiation
CDC	complement-dependent cytotoxicity
Chemo	chemotherapy
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CL	clearance
C_{max} (CV)	maximum serum concentration
C_{trough}	trough serum concentration
C_{trough},C1	trough serum concentration in Cycle 1
CSCO	Chinese Society of Clinical Oncology
CSR	clinical study report
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
DCO	data cut-off
DCO1	data cut-off 1 = 08 Jun 2020
DCO2	data cut-off 2 = 15 Mar 2021
DCO3	data cut-off 3 = 22 Nov 2021
DoR	duration of response

ECIS	European Cancer Information System
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ENKTL	extranodal natural killer/T-cell lymphoma
E-R	exposure/response
ESCC	oesophageal squamous cell carcinoma
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
GEJ	gastro-oesophageal junction
GC	gastric adenocarcinoma
HCC	hepatocellular carcinoma
HR	hazard ratio
ICI	immune checkpoint inhibitor
IFN-γ	interferon-γ
IgG4	immunoglobulin G4
IL	interleukin
irAE	immune-related adverse event
ITT	intention-to-treat
IV	intravenous
IxRS	interactive voice response system/interactive web response system
MAA	marketing authorisation application
mAb	monoclonal antibody
MAD	mutual acceptance of data
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MTD	maximum tolerated dose
NAb	neutralising antibodies
NCCN	National Comprehensive Cancer Network
NCI	(U.S.) National Cancer Institute
NDA	new drug application
NE	Not estimable or not evaluable

NICE	National Institute for Health and Care Excellence
NMPA	National Medical Products Administration
NOAEL	no observed adverse event level
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand-1
PFS	progression-free survival
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
Q3W	once every 3 weeks
RECIST	response evaluation criteria in solid tumours
RET	rearranged during transfection
ROS1	ROS proto-oncogene 1, receptor tyrosine kinase
RP2D	recommended Phase 2 dose
R/R cHL	relapsed or refractory classical Hodgkin lymphoma
R/R ENKTL	relapsed or refractory extranodal natural killer/T-cell lymphoma
SAE	serious adverse event
SAP	statistical analysis plan
SCS	summary of clinical safety
SD	standard deviation
SOC	standard of care
SOC	system organ class
TEAE	treatment-emergent adverse event
TGI	tumour growth inhibition
TIL	tumour infiltrating leukocyte
TV	tumour volume
UK	United Kingdom

US	United States
Vss	volume of distribution of sugemalimab at steady-state
WCPP	World Cancer Patient Population

1. Background information on the procedure

1.1. Submission of the dossier

The applicant SFL Pharmaceuticals Deutschland GmbH submitted on 4 February 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Cejemly, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: Cejemly 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0194/2022 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance sugemalimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Alar Irs

The application was received by the EMA on	4 February 2023
The procedure started on	23 February 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 May 2023
The CHMP Co-Rapporteur's first Assessment was circulated to all CHMP and PRAC members on	31 May 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	7 June 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 June 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 October 2023
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 1 contract research organisation and 2 clinical investigator sites in China. The outcome of the inspection carried out was issued on:	27 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	20 November 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	14 December 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 May 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Cejemly on	30 May 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	30 May 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed therapeutic indication is: *"Sugemalimab 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 sensitising EGFR, ALK, ROS1 or RET genomic tumour aberrations."*

2.1.2. Epidemiology and risk factors

Lung cancer is the leading cause of cancer mortality worldwide (1.8 million, or 18% of all cancer deaths in 2020), with 2.2 million newly diagnosed cases, or 11.4% of all cancers diagnosed, in 2020. In Europe, 477,534 new lung cancer cases and 384,176 deaths due to lung cancer were estimated to occur in the same year (Globocan 2020).

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related deaths. The risk for lung cancer increases with the number of packs of cigarettes smoked per day and with the number of years spent smoking. Exposed non-smokers also have an increased relative risk of developing lung cancer (NCCN Guidelines v. 3.2022).

2.1.3. Biologic features

Lung cancer is classified into two main types: small cell lung cancer (SCLC) and NSCLC. NSCLC is the predominant subtype, accounting for approximately 85% of all cases. NSCLC can be divided into two major histologic types: non-squamous and squamous cell carcinoma. Non-squamous histology accounts for more than half of all NSCLC, whereas squamous histology accounts for approximately 30% (Brambilla et al, 2014 and Schrump DS et al. NSCLC; Principles and Practice of Oncology. 9th Edition. 2011) in Europe.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

More than half of the patients are diagnosed at an advanced stage of disease, which directly contributes to poor survival, as expressed by an untreated median OS of 4 months and a metastatic 5-year survival rate of <5% (Lindsey A. et al, 2016). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status (PS), and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant metastatic disease, which directly contributes to poor survival prospects.

2.1.5. Management

Over the past decade, there have been considerable advances in the management of NSCLC. Improved understanding of the biology and molecular subtypes of NSCLC has led to development of a number of biomarker-directed therapies for patients with metastatic disease, including drugs targeting EGFR mutations, ALK rearrangements, and other molecular aberrations. These therapies have improved OS for patients with metastatic NSCLC with an oncogenic driver (Arbour and Riely 2019). For patients with metastatic NSCLC with no actionable oncogenic driver, the development of immune checkpoint

inhibitors (ICIs) has transformed the care, providing a survival benefit when administered as monotherapy following disease progression on platinum-based chemotherapy (Borghaei et al 2015, Brahmer et al 2015, Herbst et al 2016, Rittmeyer et al 2017) or when administered with or without chemotherapy in the first-line setting (Borghaei et al 2017, Gandhi et al 2018, Paz-Ares et al 2018, Socinski et al 2018, West et al 2019, Jotte et al 2020, Nishio et al 2021, Paz-Ares et al 2021).

Before ICI therapy became available as the first-line treatment for advanced or metastatic NSCLC, platinum-based doublet therapy was the recommended treatment option in patients with no actionable oncogenic driver and an ECOG performance status of 0 to 2. Pemetrexed use is restricted to non-squamous cell carcinoma in first- (or later-) line of treatment in advanced disease and is preferred to gemcitabine- or docetaxel-based combinations in non-squamous NSCLC (Planchard et al 2018).

The approval of ICIs has now been extended to first-line treatment therapy for NSCLC with no actionable oncogenic driver, either as monotherapy or in combination with chemotherapy (Reck et al 2016, Paz-Ares et al 2018, Mok et al 2019). Pembrolizumab in combination with platinum and pemetrexed has since become a new standard of care for patients with first-line non-squamous NSCLC, irrespective of PD-L1 status (Gandhi et al 2018). ICI monotherapy has been approved for patients with PD-L1 positive expression (≥50%) and, in some countries, the approval was also extended to patients with tumour PD-L1 expression ≥1% (Reck et al 2016, Mok et al 2019, Keytruda USPI 2021, Keytruda SmPC 2021).

Similarly, in the first-line squamous NSCLC setting, pembrolizumab has been approved as first-line treatment therapy for squamous NSCLC, either as monotherapy for the"PD-L1 high"(≥50%) population (and also for the population with PD-L1 ≥1% in the US) (Reck et al 2016) or in combination with chemotherapy irrespective of PD-L1 expression (Paz-Ares et al 2018). More recently, nivolumab/ipilimumab with platinum-doublet chemotherapy has been approved as first-line treatment for NSCLC irrespective of histology, and nivolumab/ipilimumab combination therapy alone was approved in tumours expressing PD-L1 ≥1% in some countries (Opdivo SmPC 2021, Opdivo USPI 2021). Other ICIs approved for treatment in the first-line setting include atezolizumab and cemiplimab as monotherapy for first-line treatment of NSCLC whose tumours have high PD-L1 expression irrespective of histology, and atezolizumab as first-line treatment of metastatic non-squamous NSCLC with no EGFR or ALK genomic tumour aberrations in combination with bevacizumab, paclitaxel, and carboplatin as well as with paclitaxel protein-bound and carboplatin (Tecentriq SmPC 2021, Tecentriq USPI 2021, Libtayo SmPC 2021, Libtayo USPI 2021).
Although there are available products approved in this setting, there is always a need to enrich the treatment armamentarium.

2.2. About the product

Sugemalimab is a fully human immunoglobulin G4 monoclonal antibody. It specifically binds to programmed cell death ligand 1 (PDL1), thus blocking its ligation with PD1. PDL1, when expressed on tumour cells and tumour-infiltrating immune cells, can contribute to the inhibition of an anti-tumour immune response. Binding of PDL1 to the PD1 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 PDL1/PD1 and PDL1/CD80 interactions releases the inhibition of immune responses without inducing antibody dependent cell mediated cytotoxicity (ADCC).

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PD-L1 (Programmed cell death protein 1/death ligand 1) inhibitors, ATC code: L01FF11.

The initially applied and finally agreed indication is: Cejemly 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 sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumour aberrations.

For squamous cell carcinoma:

Sugemalimab 1200 mg (for individuals weighing 115 kg or less) or 1500 mg (for individuals weighing more than 115 kg) is infused intravenously over 60 minutes followed by intravenous infusion of carboplatin and paclitaxel on day 1 for up to 4 cycles every 3 weeks. Thereafter, sugemalimab 1200 mg (for individuals weighing 115 kg or less) or 1500 mg (for individuals weighing more than 115 kg) is administered every 3 weeks for the duration of therapy.

For non-squamous cell carcinoma:

Sugemalimab 1200 mg (for individuals weighing 115 kg or less) or 1500 mg (for individuals weighing more than 115 kg) is infused intravenously over 60 minutes followed by intravenous infusion of carboplatin and pemetrexed on day 1 for up to 4 cycles every 3 weeks. Thereafter, sugemalimab 1200 mg (for individuals weighing 115 kg or less) or 1500 mg (for individuals weighing more than 115 kg) and pemetrexed are administered every 3 weeks for the duration of therapy.

2.3. Type of application and aspects on development

Study CS1001-302 is evaluating the efficacy and safety of sugemalimab 1200 mg IV Q3W combined with platinum-based chemotherapy compared with placebo combined with platinum-based chemotherapy in participants with metastatic NSCLC (ie, histologically confirmed as non-squamous NSCLC or squamous NSCLC).

In addition, 5 studies are supportive of this application with brief summaries presented below:

- CS1001-101: A Phase 1a/b, multicentre, open-label, dose-escalation, and expansion study of sugemalimab in participants with advanced solid tumours or lymphomas
- CS1001-102: A Phase 1, open-label, dose-escalation study of single-agent sugemalimab in participants with advanced solid tumours
- CS1001-201: A Phase 2, single-arm, multicentre study of sugemalimab in participants with relapsed or refractory R/R ENKTL
- CS1001-202: A Phase 2, single-arm, multicentre, study of sugemalimab in participants with R/R cHL
- CS1001-301: A Phase 3, multicentre, randomised, double-blind, placebo-controlled, study of sugemalimab in participants with locally advanced/unresectable (Stage III) NSCLC that has not progressed after prior concurrent/sequential chemoradiotherapy

One study (Study CS1001-102) was conducted in the US to bridge PK data collected in an Asian population.

No scientific advice was given during the development process.

2.4. Quality aspects

2.4.1. Introduction

Sugemalimab, the active substance in Cejemly, is a fully human anti-programmed death-ligand 1 (PD-L1) monoclonal antibody (IgG4 isotype) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

The finished product is presented as concentrate for solution for infusion in a 20 mL single-use vial containing 30 mg/mL of sugemalimab (strength 600 mg).

Sugemalimab is formulated with histidine/histidine hydrochloride, mannitol, sodium chloride, polysorbate 80 (PS80) and water for injections. Prior to administration the product is diluted using 0.9% (w/v) sodium chloride.

2.4.2. Active Substance

2.4.2.1. General information

Sugemalimab is a fully human IgG4 monoclonal antibody composed of two λ (lambda) light chains (LC) and two heavy chains (HC) 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 a mutation at Ser228Pro in the constant region. Based on the primary sequence, sugemalimab has a theoretical molecular weight of 145.8 kDa which includes 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 Fab regions of the heavy and light chains comprise the binding sites with PD-L1. Sugemalimab contains 16 disulfide bonds, including 12 intrachain disulfide bonds and 4 interchain disulfide bonds.

2.4.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Sugemalimab active substance is manufactured by Wuxi Biologics Co. Ltd, 108 Meiliang Rd, Mashan, Binhu district, Wuxi, Jiangsu 214092, China Release and stability testing are also performed at this site. All sites involved in manufacturing and controls of the active substance operate in accordance with EU GMP.

The commercial manufacturing process of sugemalimab active substance encompasses cell culture, harvest and primary capture and purification. Active substance upstream processing begins with the thawing of one vial of the WCB of a CHO-K1 cell line. The cells are propagated through a series of shake flask and cell culture bag stages. The process then proceeds to the production bioreactor stage. After production, the production bioreactor is harvested through a depth filtration step, resulting in the clarified harvest.

Downstream processing includes a series of chromatography, viral inactivation and filtration steps. The sugemalimab active substance is then frozen and stored.

The manufacturing process and process controls are summarised in flow charts and tables. The purpose of each step is clearly stated, and a brief description is provided. Process parameters are listed, including criticality assignment and acceptable ranges. In-process controls (IPCs), including UPB

testing, are provided. Operating sequences and collection of fractions are described for filtration and chromatography steps. Resin materials, buffers, and total number of reuses (where applicable) are provided for the chromatography steps. Filter materials and buffers are provided for the filtration steps. The level of detail regarding the active substance manufacturing process is considered sufficient.

Each WCB give rise to one active substance batch. The scale of the production bioreactor step is given. Information on the scales for the chromatography steps, the filtration steps (virus filtration, intermediate depth filtration, and UF/DF), and the final size of one active substance batch have been provided. The batch numbering system is described.

No reprocessing is claimed. In the event that reprocessing will be required, the applicant will liaise with EMA. This is acceptable.

Active substance transportation is described.

Control of materials

Raw materials

Detailed descriptions of raw materials and consumables such as resins and filters are presented. Qualitative and quantitative compositions are provided for cell culture media.

No components in the commercial manufacturing process for the active substance are directly derived from animal or human sources.

The information regarding raw materials is considered sufficient.

Generation of the cell substrate and cell banks

Sufficiently detailed information has been provided regarding the origin and construction of LC and HC gene constructs and the expression vectors. Sufficient information has also been provided for the origin of the cell substrate.

The cell bank system and manufacturing procedure have been described in sufficient detail. Results from testing of the master cell bank (MCB), WCBs 1 and 2, end-of-production cell bank (EOPCB) have been provided for both characterisation and safety testing according to ICH Q5B and ICH Q5D. Virus testing is in accordance with ICH Q5A. Acceptable tests for sterility, mycoplasma and identity of CHO cells has also been performed. Short descriptions of test methods for cell bank testing have been provided. Information on MCB stability studies and protection from catastrophic events has also been provided. The information is acceptable.

Genetic stability studies demonstrate that the copy numbers of HC and LC were comparable in sugemalimab primary cell bank (PCB), MCB, WCB and EOPCB. DNA sequence analysis was performed on cDNA generated from PCB, MCB, WCB and EOPCB. The sequences were compared to the theoretical sequence. The cDNA sequences were identical to the theoretical sequence, indicating the genetic stability of the cell line.

Control of critical steps and intermediates

Definitions for critical process parameters (CPPs), key process parameters (KPPs), and critical and key performance attributes (CPAs, KPAs) are provided. The definition of CPP is aligned with ICH guidelines. This is endorsed. Further definitions (critical quality attributes (CQAs), acceptable ranges) are available in the manufacturing process development section.

In-process pool hold times and hold conditions are described for each step and are considered validated.

IPCs, performance attributes (process outputs), are presented in a condensed format. Microbial controls are included. Performance attributes are tested against acceptance criteria and the criticality - critical or key - is based on the impact to CQAs and process consistency, respectively.

The limits for microbial controls, including UPB testing ("production bioreactor testing"), are considered acceptable.

No IPCs are included for quality attributes such as size variants, charge variants, or post-translational modifications (PTMs) like N-glycan profile or oxidation during downstream processing. This is considered acceptable.

No intermediates are defined in the sugemalimab active substance manufacturing process in the strict sense, although this is the terminology used by the applicant. The different eluates and filtrates are rather in-process pools.

Process validation and evaluation

An extensive set of studies for process validation is presented, along with descriptions of methods and tools. Consecutive batches for process B were included. Each active substance batch was started from a single WCB vial. The number of batches is appropriately adapted to the production lines/equipment skids for process B. A thorough comparability exercise has been satisfactorily provided, demonstrating comparability between process B and commercial process B'.

The process validation of the active substance manufacturing steps is adequately described and reported. Deviations were acceptably investigated and handled.

For the impurity removal evaluation, samples were withdrawn from three PPQ studies and analysed for purity (size variants and charge variants) and residual host cell DNA, host cell protein (HCP), protein A, antifoam, surfactant, and flocculant. Challenge studies (such as spiking and/or skipping one or more purification steps) were not performed. The validation acceptance criteria were wide but based on the actual results it is agreed that routine purification, as performed during PPQ, demonstrates a sufficient level of clearance of impurities, even though the clearance capacity is not challenged beyond the normal setting.

The risk of extractables and leachables in active substance was evaluated based on an assigned risk level for each single use equipment and submitted. Based on supplier information, the applicant concluded that all components used prior to the UF/DF process would be cleared by the 30 kD UF/DF membrane. Thus, only active substance storage bags and container closure were further evaluated. This is reasonable. It is claimed that all elemental impurities meet the requirement. The organic compounds were also below limits.

Appropriate at-scale in-process hold time studies have been provided.

Small-scale data support the proposed reuse of chromatography resins and UF/DF membranes. The outline and the results are supported. Protocols for concurrent at-scale validation are provided and found acceptable.

Reprocessing is not validated. This is acceptable as no reprocessing is claimed.

In summary, it is agreed that the process validation results support the conclusion that the manufacturing processes (version B) for sugemalimab active substance can be considered validated. Furthermore, it can be noted that comparability has been successfully demonstrated between batches manufactured by process B and process B'.

Overall, process validation is considered satisfactory.

Manufacturing process development

The manufacturing process development of the active substance is adequately described in the dossier.

The comparability studies encompass release tests, characterisation testing, and stability studies at recommended conditions and accelerated conditions. A forced degradation study is presented in the active substance characterisation section. All batches included in the comparability exercises are listed.

The aspects considered and the panel of tests included in the comparability exercise are considered sufficient. Results have now been acceptably presented in tables, plots, chromatograms, electropherograms or spectra.

Process characterisation

An extensive process development programme was submitted. A risk-based approach was presented for identification of CQAs, classification of process parameters, and evaluation of acceptable ranges for process parameters.

The major objection raised during the procedure regarding insufficient justification of the active substance control strategy (identification and justification of CQAs, process parameter criticality and ranges) was satisfactorily addressed by the applicant.

Definitions are provided for most of the applied terminology. CPPs, acceptable ranges (identical to proven acceptable ranges (PARs)), and CQAs are defined in line with ICH Q8 (R2). This is supported. KPPs and KPAs are used for control and evaluation of process performance and operational reliability. The term ”performance attributes” is used for controls usually denoted as IPCs.

A failure mode effect analysis (FMEA) was applied to evaluate which process parameters to include in the process characterisation programme. A second FMEA was conducted after execution of the process characterisation studies to determine the final control strategy and the criticality of process parameters.

Production bioreactor excursion studies are considered adequate.

Characterisation

Sugemalimab is a fully human IgG4 monoclonal anti-PD-L1 antibody expressed in CHO cells. It contains one specific mutation to stabilise the core-hinge region. The proposed mechanism of action include binding to PD-L1 expressed on tumour cells, thereby inhibiting PD-L1 binding to PD-1 on T-cells.

A characterisation study with physicochemical and biological tests of the sugemalimab molecule was presented. Three batches manufactured by process B’ were included in the study. The results indicate that sugemalimab has the covalent structure, post-translational modifications, and other characteristics of a typical human IgG4 antibody derived from CHO cells. Studies of primary, secondary and higher order structure, various physicochemical properties, carbohydrate structure, heterogeneity pattern, and biological functions were included.

A panel of state-of-the-art and some orthogonal tests were applied for many attributes. Characterisation methods and preparations of variants for characterisation studies are sufficiently described. All peaks are defined and relevant chromatograms, electropherograms and spectra with sufficient resolution are provided.

Molecular masses of intact monoclonal antibody, LC and HC, were determined by liquid chromatography mass spectrometry (LC-MS). It is agreed that masses observed are in good correlation with the theoretical values and confirm the primary sequence and carbohydrate structure.

For sequence identification, two enzymatic digests (Lys-C/trypsin and thermolysin) were analysed by LC/MS. Theoretical and observed masses of the fragments are presented and a coverage of 100% is claimed. It is agreed that the results confirm the identity.

The peptide mapping also show oxidation, deamidation, succinimide, pyroglutamate formation at LC N-terminal, C-terminal clipping of lysines, and correct disulfide pairing. Mispairing disulfide bonds were not found.

The extinction coefficient was experimentally determined.

Sugemalimab contains N-linked glycosylation at position Asn298 of each HC. Low levels of high mannose and sialylation are detected. Glycosylation occupancy is approximately 99%.

An extensive evaluation of biological/functional activity is provided, sufficiently supporting the mode of action of sugemalimab. It is agreed that sugemalimab exhibit very low levels of antibody-dependent cellular cytotoxicity (ADCC) (FcγRIIIa binding) and complement-dependent cytotoxicity (CDC) (C1q binding).

For the charge variants, basic and acidic peaks have generally reduced purity compared to the cation exchange high performance liquid chromatography (CEX-HPLC) main peak, with more high molecular weight (HMW) species, pre-peaks, and minor "non-LC-HC". The impurity levels are higher in basic peaks than in acidic peaks. Oxidation is stated to be slightly higher in the basic fraction compared to the main peak, but still within analytical variability. The potency difference also stated to be within the analytical variability.

Active substance product-related and process-related impurities, respectively, are described together with the analytical methods for control. Relevant chromatograms, electropherograms and spectra are provided and most of the peaks are defined. The active substance product-related impurities are HMW species, fragments, disulfide scrambling, isomerisation, oxidation, and aglycosylation. HMWs are present mainly as dimers; species larger than the dimers have not been quantified. The active substance process-related impurities are residual HCP, DNA, protein A, flocculant, cell protective agent and antifoam C. Clearance of residual HCP, residual DNA, and protein A is also discussed in the assessment. Overall, sufficient clearance is considered demonstrated for process-related impurities.

Overall, characterisation of the active substance is considered satisfactory.

2.4.2.3. Specification

Specification

The release and stability specifications for sugemalimab active substance include control of identity, purity and impurities, potency and other general tests.

The proposed list of attributes is considered suitable. The proposed release specification for the active substance is found acceptable, with respect to test methods chosen. The proposed specification limits are based on batch analysis and stability study results. This approach is considered acceptable.

Analytical procedures

Descriptions were provided for all analytical procedures included in the release and shelf-life specifications. Most of the methods described in this part are used for testing of both active substance and finished product.

The non-compendial analytical procedures are described with a sufficient level of detail. Representative chromatograms and electropherograms are provided and a representative dose-response curve is

provided for the potency assay. Compendial procedures have been appropriately verified for their intended use.

The non-compendial procedures applicable to control of both active substance and finished product have been appropriately validated. The validations were performed in accordance with the requirements in ICH Q2(R1).

Reference standards

Information on preparation, qualification, storage and intended use are provided for the reference materials.

A two-tiered reference standard system is applied. The current primary and working reference standards (PRS and WRS) were prepared from the same active substance batch manufactured using the commercial process, the applicant proposes that testing of either is representative to the other. This is considered acceptable.

The preparation, qualification, and re-qualification of reference standards is described in sufficient detail, including specifications and characterisation testing.

PRS and WRS are stored at -70°C ± 10°C. Information of historical reference materials have been provided.

In summary, the reference material system is considered acceptable.

Batch analysis

Batch release results and batch usage overview are provided.

Each batch was tested to the specification in place at the time of manufacture. All limits were met.

Batch results are consistent between process versions A and B. The provided release data from the development (pre-clinical, clinical, and PPQ) batches support a consistent manufacture of the active substance.

Technical drawings of the container closure system are provided. A brief overview is given regarding the active substance container closure material.

It is stated that the container meets the requirements of the EU directive 2002/72/EC (plastic materials in contact foodstuff) (a representative certificate is provided) and specific USP chapters, FDA chapters.

The approach described for assessment of extractables/leachables from the active substance container closure system is found adequate.

With reference to the stability studies in the dossier, the active substance is considered compatible with the container closure system.

The container closure system is considered sufficiently described and found suitable for its intended use.

2.4.2.4. Stability

The subjects covered by the description of the stability studies, stability data and post-approval stability protocol are found appropriate. The chosen analytical methods are adequately stability indicating.

The container closure material is representative to the active substance container closure, except for the volume. This is endorsed.

Stability data for the active substance stored under long-term (-70±10°C), accelerated and stressed conditions were provided.

A commercial shelf life for sugemalimab active substance of 24 months at the recommended long-term storage condition of ≤-70±10^{0}C is proposed, together with predictions of even longer shelf lives as based on statistical evaluation. The figures with trendlines for several years are not considered in the assessment of the stability data.

The applicant concluded that the test results for all active substance batches meet the acceptance criteria and that there are no apparent changes in active substance stored at the long-term storage condition of ≤-70 ±10°C. The applicant also concluded that expected changes were recorded during accelerated and stressed conditions.

The proposed shelf life for the sugemalimab active substance is 24 months when stored at -70 °C ± 10 °C is acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description and composition of the finished product

The finished product is a concentrate for solution for infusion and is a buffered, isotonic, preservative-free solution. It is a clear to opalescent, colourless to slight yellow solution, essentially free from visible particles, with a pH of 5.3 to 5.7.

Each 30 mL vial of finished product contains 600 mg (30 mg/mL) of sugemalimab. Cejemly is supplied as a pack size of two vials to allow administration of a dose of 1200 mg after dilution with a sodium chloride solution (0.9%).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The vial, stopper and seal components are for most parts compliant with appropriate Ph. Eur. monographs for primary containers and closures.

The section on description and composition of the finished product is found acceptable.

Pharmaceutical development

Formulation development

During development, different formulations have been tested for physicochemical and biological stability.

The formulation development section in the dossier describes and justifies the chosen formulation and is sufficiently comprehensive.

Manufacturing process development

The section on manufacturing process development for the finished product has been sufficiently described and justifies the commercial manufacturing process.

The manufacturing process of the finished product includes thawing, pooling of the active substance, sterile filtration of the final formulated bulk, filling and stoppering. The commercial manufacturing process has been characterised through process characterisation studies of each process step and details for these studies are provided in the dossier. A number of relevant CQAs have been identified for the finished product (22 CQAs in total). A risk assessment has thereafter been performed to identify process parameters with potential impact on the CQAs and criticality of the parameters evaluated by a failure mode and effects analysis (FMEA) analysis at various stages to acceptably justify the chosen CQAs, CPPs and control strategy.

Process parameter ranges have been defined and these were later verified upon manufacturing of PPQ runs. Furthermore, process development studies and at-scale runs were performed to define set-points and NORs for the manufacturing process.

It is agreed that the process characterisation studies demonstrate that the finished product manufacturing process is robust and can deliver the required product quality and process consistency when manufacturing is run within the prescribed operating ranges.

Sugemalimab finished product is stored and shipped at 2-8°C. In support of possible temperature excursions during storage or shipment, a thermal cycling study was performed. Acceptable in-use storage conditions are stated below and in the SmPC.

Extractables and leachables

The product-contact surface materials used during manufacturing of finished product were evaluated with respect to potential leachables in relation to the safety concern threshold. Extractable data from the respective vendors of disposables or by extractable studies conducted by the applicant were used for the evaluation. A toxicological assessment was conducted for potential leachables and concluded to pose no risk to patients treated with sugemalimab concentrate for solution for infusion 600 mg/vial (30 mg/mL). This is found acceptable.

Microbiological attributes

The finished product contains no preservatives and is manufactured using an aseptic process including sterilisation by filtration. Sterility and endotoxins are tested as part of product release. Container closure integrity is being monitored by vacuum decay leak testing, a non-destructive testing method and are also tested annually as part of the long-term stability programme. Media fills were executed to demonstrate aseptic processing capability. The information in this section of the dossier is found acceptable.

Compatibility

Compatibility of diluted finished product with IV bags and administration sets of polyethylene, polyolefin and polyvinylchloride contact materials has been demonstrated. Manufacture of the product and process controls

All sites involved in manufacturing and control of the finished product operate in accordance with EU GMP.

Description of manufacturing process, process control and control of critical steps and intermediates

The finished product manufacturing process is summarised in a flow chart and detailed in a written narrative. The manufacturing process consists of active substance thawing, compounding (pooling and mixing), sterile filtration, aseptic filling, stoppering, and capping. The finished product vials are then optically inspected before secondary packaging and stored at 2-8°C.

The CPPs as well as acceptable ranges and NORs have overall been acceptably justified by data presented.

The description of the sections for manufacturing process and process control and control of critical steps and intermediates of the finished product manufacturing process is sufficiently described.

Acceptable ranges are provided for the process parameters and brief process flow diagrams are provided for the manufacturing process of finished product.

The information provided in this section of the dossier is sufficiently detailed.

Process validation

The process validation followed a traditional approach and covered four consecutive production scale batches. The validation was run at set points while the ranges of process parameters were challenged during the manufacturing process development described in the dossier. This approach is found acceptable. The results of IPCs and process characterisation samples met their predefined acceptance criteria and all CPPs were controlled within their predefined ranges. All release results met finished product release specification and all process validation batches demonstrated consistent quality profiles, demonstrating that the finished product can be consistently manufactured within predefined processing parameters.

The presented filter validation comprises membrane compatibility, bacterial retention validation, and bubble point determination. Membrane extractables/leachables were also evaluated. The results demonstrate that the filters are chemically compatible and suitable for use during finished product manufacture.

The aseptic filling has been sufficiently validated with media fills covering the maximum duration of filling. No microbial growth was detected.

Shipping qualification and simulation of transportation studies were performed and support the transportation during commercial distribution.

In conclusion, process validation of the finished product manufacturing process is satisfactory.

2.4.3.2. Product specification

Specification

The specifications for the release and stability of sugemalimab finished product include control of identity, purity and impurities, potency and other general tests.

A comprehensive set of relevant tests is included, covering limits for both release and end-of-shelf life of the various attributes. A justification for each test and acceptance criteria have been provided.

The proposed acceptance criteria for appearance and description (clarity and degree of opalescence, and sub-visible particles), general tests (pH, osmolality and extractable volume), identity, microbiological tests (endotoxin and sterility) and container closure integrity are found acceptable. Overall, the finished product specifications are considered acceptable.

Analytical procedures

Many tests used for release and stability testing of finished product are also used for release and stability testing of active substance. These methods and validation results are presented, discussed, and assessed in the dossier and cover both active substance and finished product. The analytical

procedures were validated in accordance with ICH Q2 and the compendial methods have been verified according to the appropriate Ph. Eur. chapters.

Reference standard

Reference is made to the active substance part. There are no additional reference standards used to test and release the finished product.

Batch analyses

Batch analyses data has been provided for finished product batches used in clinical trials and stability as well as PPQ batches manufactured at full commercial scale. Information on these batches include manufacturing batch number, date, batch size, active substance batch(es) used, manufacturing process of active substance(es) used, formulation and use of the batch. The batch analysis data complies overall with the limits in the proposed finished product release specification in place at the time of manufacture and confirm process and product consistency. In conclusion, the batch data provided demonstrate reproducible manufacturing of sugemalimab finished product.

Characterisation of impurities

Potential process- and product-related impurities are addressed. No new impurities have been identified in the finished product compared to the ones already identified for the active substance. Extractables and leachables are discussed in the dossier (see above).

Elemental impurities

A risk assessment on elemental impurities in line with ICH Q3D has been provided. The applicant's conclusion that the risk of elevated elemental impurity levels is considered negligible and that no routine control of elemental impurities is required is agreed.

Nitrosamine risk assessment

A risk assessment on potential N-nitrosamine contamination has been performed. It is agreed that the risk of formation and entry of N-nitrosamine impurities is negligible in all process steps, in the final formulation and in the primary packaging configuration. No additional specific control is considered necessary.

Container closure system

The primary packaging for sugemalimab finished product is a 20 mL Ph. Eur. Type 1 glass vial sealed with a 20 mm elastomeric stopper and crimped with a 20 mm aluminium-plastic seal cap. All product-contacting materials comply with relevant pharmacopeial requirements.

The container-closure system used for sugemalimab finished product is adequately described. Compatibility of the container closure system with sugemalimab finished product is demonstrated with the stability information and in the development section.

Information is provided in the dossier with respect to sterilisation of the glass vials and rubber stoppers and testing for sterility and bacterial endotoxins. This is found acceptable.

2.4.3.3. Stability of the product

The applicant has provided long (2°C to 8°C), accelerated (25 ± 2°C), stressed and forced degradation studies.

The stability studies are performed in accordance with ICH Q5C and the same container closure system is used for the primary stability batches as well as for the PPQ batches. Furthermore, compatibility for finished product has been demonstrated and concluded.

Photostability testing has been performed according to ICH Q1B and showed that the sugemalimab finished product should be kept in the outer carton to protect from light induced degradation, in line with the wording in section 6.4 in the SmPC.

Compatibility of the finished product with the infusion medium (0.9% sodium chloride solution in a 250 mL infusion bag) has been studied and satisfactorily demonstrated during development and in-use stability studies. In-use stability has been studied to simulate in-use conditions and verify the chemical and physical stability of the finished product as well as to confirm the compatibility with the material of the infusion bags. The study also shows that the use of PES in-line filter is feasible based on the results, and this is at large appropriately reflected in the SmPC.

Considering the totality of the data, the acceptable shelf life for sugemalimab finished product (unopened vial) is 30 months at 2 °C to 8 °C protected from light.

Chemical and physical in-use stability has been demonstrated for up to 24 hours at 2°C to 8°C and for up to 4 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.

2.4.3.4. Adventitious agents

Viral testing of MCB, WCB1 and WCB2, EOPCB has been described in the dossier and virus testing is in accordance with ICH Q5A. Results are as expected for CHO, and only retrovirus-like particles (RVLPs) were observed (intracytoplasmic A-type particles and some C-type particles).

No raw materials of human or animal origin is used in the manufacture except for the CHO cell line. It is stated that foetal bovine serum (FBS) and trypsin were used in early development and during adaptation of the CHO-K1 cells to suspension growth in animal component-free medium. It is further stated that these components were certified to be TSE-free and were tested by the vendor prior to use. Documentation to support that the FBS and trypsin comply with current TSE requirements has been provided.

The studies have been performed with relevant model virus and the results presented indicate efficient reduction of both enveloped and non-enveloped virus. For the two chromatography steps validated, data is presented from experiments with both new and reused resins.

The presented calculation for the potential maximum theoretical quantity of RVLPs per clinical dose demonstrate a sufficient safety margin.

Overall, adventitious agents safety is considered sufficiently assured.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The two major objections identified during the procedure (related to comparability and control strategy) were adequately addressed.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory

consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Cejemly is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the marketing authorisation application for Cejemly is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical programme is focused on the active substance sugemalimab. No new excipient was used in the finished product. The non-clinical development of sugemalimab was based on the regulatory requirements of ICH S6 and ICH S9 guidelines. The pivotal toxicity studies have been conducted in compliance with GLP guidance.

Sugemalimab was tested and compared in nonclinical pharmacology studies against established positive anti-PD-L1 controls. *In vitro* primary pharmacodynamic studies was conducted in engineered PD-1 expressing and PD-L1 expressing cell lines to demonstrate sugemalimab's binding capacity, binding affinity, binding specificity, and species cross-reactivity. In vivo animal studies were conducted to test the dose-dependence of sugemalimab required to significantly reduce tumour volume (TV) and promote tumour growth inhibition (TGI) in humanised tumour mouse models expressing human PD-L1. Secondary pharmacodynamic studies to evaluate possible mechanisms of action of sugemalimab on the immune response included assessments of antibody-dependent effects on cellular cytotoxicity and phagocytosis, as well as immune systemic effects of sugemalimab on CD4+ cell proliferation, CD80 inhibition, and cytokine induction. An evaluation of safety pharmacology endpoints was assessed in conjunction with toxicology studies.

The pharmacokinetic/toxicokinetic (PK/TK) evaluation includes four studies conducted in cynomolgus monkey. These consists of one non-GLP pharmacokinetic single dose of 10, 30 and 90 mg/kg with observations up to 56 days; one non-GLP single-dose of 200 mg/kg TK study with observations up to 28 days; two repeat-dose toxicity GLP studies with doses of 30, 75, and 200 mg/kg administered once weekly for 4 weeks and 26 weeks with 4-week recovery periods. ADA was assessed in all four studies.

The toxicological dossier provides a safety assessment of sugemalimab. The intended clinical formulation is a single use, preservative free, isotonic aqueous solution for intravenous (IV) administration with a concentration of 30mg/mL. The proposed dosing regimen is 1200mg Q3W. The corresponding clinical systemic exposure reported by the applicant is mean C_{max} of 577µg/mL and AUC0-3w of 7304µgxd/mL (stated to represent a typical male Chinese individual of 61.5kg). With regard to the acute and general toxicity tests, the main animal model is cynomolgus macaque (*Macaca fascicularis*). A total of three (3) single dose (1 GLP and 2 non-GLP) studies have been conducted in

order to assess tolerability, exposure, and immunogenicity. Two (2) once-weekly GLP repeat-dose studies of 4- and 26-weeks duration (plus 4w recovery in each study) have also been submitted. A total of five additional studies are included in the toxicological dossier under 'Other toxicity studies'.

No genotoxicity, carcinogenicity, DART or dedicated local tolerance tests were conducted.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In-vitro studies

The applicant has conducted primary pharmacodynamic studies *in vitro* to investigate sugemalimab's binding capacity, binding affinity, binding specificity, and species cross-reactivity. Sugemalimab was tested against positive anti-PD-L1 controls (WBP31BMK6 and WBP31BMK1) in engineered PD-1 expressing and PD-L1 expressing cell lines. WBP31BMK6 was generated by cloning the sequence of the human anti-PD-L1 antibody 2.7A4 as disclosed in the MedImmune patent US 8,7779,108 B2. WBP31BMK1 was generated by cloning the sequence of the human anti-PD-L1 antibody 12A4 as disclosed in the Medarex patent WO 2007/005874 A2.

The binding capacity of sugemalimab was assessed in WBP315.CHO-K1.hPro1.C11, which is a human PD-L1 expressing cell line and human mature dendritic cells (mDC). Compared to negative controls, sugemalimab and reference antibodies (WBP315BMK1 and WBP315BMK6) were bound to WBP315.CHO-K1.hPro1.C11 cell surface, with EC_{50} ranging from 1.08 to 3.09nM. Specifically, the EC50 for sugemalimab was 1.10nM.

The binding capacity of sugemalimab to human, monkey and mouse PD-L1 was investigated and results showed that sugemalimab bound to human and monkey PD-L1 but not to mouse PD-L1. The binding affinity of sugemalimab to WBP315.hPro1.ECD was reported to be high with an affinity constant of 1.38×10^{-9} M.

Competitive blocking effect of sugemalimab against binding of cell surface expressed PD-L1 to PD-1 protein was investigated. Sugemalimab and the two positive controls WBP315BMK1 and WBP315BMK6 were capable of blocking the binding of PD-1 to WBP315.CHO-K1.hPro1.C11 cells, with IC_{50} being 1.93–3.87nM. Specifically, the IC^{50} for sugemalimab was 1.93nM. In a different experiment, competitive blocking of sugemalimab against binding of PD-L1 to CD80 was investigated since interaction of PD-L1 with CD80 may be a mechanism of tumour progression. Both sugemalimab and the positive control (WBP315BMK1) could block the binding of CD80 to PD-L1 at the three concentrations tested (134nM, 67nM and 33.5nM).

Sugemalimab's binding capacity to another ligand, PD-L2 was also investigated. Results showed that sugemalimab bound to PD-L1 protein but not to the PD-L2 protein, in line with the positive controls. Two assays were conducted to investigate epitope binning. The results showed that sugemalimab was in the same or close epitope bin with WBP315BMK1.

In-vivo studies

The applicant has conducted primary pharmacodynamic studies *in vivo* (mice) for efficacy evaluation of sugemalimab. There were two studies (BCG-PS-16033 and 0002-16010) using a similar approach where humanised PD-1 male mice were injected subcutaneously with murine colon carcinoma cells (5×10^5) in the right front flank and subsequently treated with the test article every 2 days for a total of 6 injections at different concentration (3, 10 and 30 mg/kg).

In study BCG-PS-16033, no mortality or obvious clinical signs were found. The mean tumour volume of vehicle control group was 2359 mm^3 at the end of the study (Day 25 after the initial dosing). In 3 mg/kg, 10 mg/kg and 30 mg/kg WBP3155 treated groups, the mean tumour volumes were 949 mm^3, 1416 mm^3 and 1115 mm^3, respectively. The TGI% of WBP3155 at 3 mg/kg, 10 mg/kg and 30 mg/kg dosages were 62.8% (p=0.019), 42.0% (p=0.149) and 55.4% (p=0.039), respectively. It is noted that only 3 mg/kg and 30 mg/kg but not 10 mg/kg reached significance. TGI was observed at all doses, although not in a dose-dependent manner, with significant effects observed at 3 and 30 mg/kg with TGI rates of 62.8% and 55.4% respectively. In the same study, the effect on tumour volume in the treated groups appeared to increase over time compared to vehicle control with the greatest difference at day 25 (study endpoint).

In study 0002-16010, at the timepoint of greatest tumour growth inhibition (day 18 post grouping), the mean tumour volume of vehicle control group was 1798±439 mm^3, while in 1 mg/kg, 3 mg/kg, 10 mg/kg and 30 mg/kg WBP3155 treated groups, the mean tumour volumes were 1215±201 mm^3, 844±162 mm^3, 1061±137 and 1145±177 mm^3, respectively. The tumour growth inhibition TGITV% was 34.1%, 55.8%, 43.1%, and 38.4%, respectively. At the endpoint of this experiment, tumour weight inhibition TGITW% was 23.9%, 45.4%, 34.7% and 16.8%, respectively.

Efficacy evaluation and tumour infiltrating leukocyte (TIL) phenotyping upon sugemalimab monotherapy in the MC38-hPD-L1 murine colon carcinoma model in B-hPD-1/hPD-L1 mice was also assessed (193117-0123). Mice received IP injection of human IgG4 (3 mg/kg, Q2Dx9), sugemalimab (3 mg/kg, Q2Dx9) and sugemalimab (BIWx6). Sugemalimab decreased tumour volume and shifted the immune profile to increase active T cell activity within the tumour microenvironment.

2.5.2.2. Secondary pharmacodynamic studies

In secondary pharmacodynamics *in vitro* studies, sugemalimab's activating effect on immune cell proliferation and cytokine production was tested in human CD4+ T lymphocytes using allogenic and autologous mixed MLR tests.

Effects of sugemalimab on proliferation of CD4+ T lymphocytes and on IFN-γ and IL-2 were tested using mixed lymphocyte reaction (MLR) test. Results indicated that sugemalimab could enhance secretion of IL-2 and IFN-γ and promote proliferation of CD4+ T lymphocytes. The activating effects appeared generally concentration dependent and within the same range as the two positive controls.

When a target cell is bound by a monoclonal antibody, there are mechanisms that can lead to the cell's death: antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). ADCC was tested *in vitro* using target cells (induction of activated human CD4+ T cells) and effector cells (human PBMCs). While PBMC did not kill PD-L1-positive immune cells in the presence of sugemalimab, a small increase in cell lysis can be seen at the two highest doses but this is considered negligible. Sugemalimab's capacity to induce complement-dependent cytotoxicity (CDC) was investigated using activated CD4+ T target cells. Results showed that sugemalimab would not mediate CDC activity, avoiding potential damage to PD-L1 positive lymphocytes.

Antibody-dependent cellular phagocytosis (ADCP) is a mechanism by which macrophages engulf and eliminate the tumour cells targeted with monoclonal antibodies. The applicant has submitted a study entitled Detection of antibody-dependent cellular phagocytosis against raji-PDL1 cells mediated by THP-1 cells. The study is not well described and has several shortcomings. For example, in "2. Materials, reagents, and instruments", atezolizumab, IMM01 and hIgG1-Fc are listed as controls but in "5. Conclusion", hIgG1 and hIgG4 are listed as controls. In the graphs presented, phagocytosis is around 20% even at the lowest concentration of antibodies and in the controls (assumed to be hIgG1 and hIgG4), whether this is background noise or spontaneous phagocytosis is not discussed and puts

the specificity and sensitivity of the assay into question. It is not clear why concentrations of hIgG1 and hIgG4 were different from the other test items. Figure legends are missing, no statistical analysis or p-values were reported, items have missing background information or missing rational for being included in the study, such as IMM01. In the last set of experiment, test items are combined in different combinations. No rational was provided for these combinations. However, this study is considered explorative, and the applicant makes no claim for ADCP activity in SmPC section 5.1.

2.5.2.3. Safety pharmacology programme

For the *in-vivo* assessment, safety pharmacology endpoints (cardiovascular, respiratory, and neural) were included into two repeat-dose toxicity tests (4w and 26w exposures, see the toxicology section below). No adverse outcomes were observed for the safety pharmacological endpoints (NOAEL 200mg/kg, see Toxicological section 3.2.4.). The cardiovascular endpoints were based on electrocardiogram, heart rate and blood pressure measurements. The pulmonary function was investigated via measurements of respiratory rate, tidal volume, and minute volume. Neural/behavioural endpoints used were general attitude/behaviour, gait, posture reactions, spinal nerves, and cranial nerves.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies of sugemalimab with combination chemotherapy were conducted as a part of this development programme. Both chemotherapy and immunotherapy are important options for advanced NSCLC patients, and they have been tested in combination to improve the survival benefits. Moreover, combination of anti-PD-1 or anti-PD-L1 therapy with chemotherapy has been approved in the EU for the first line treatment for metastatic NSCLC without driver mutation. Likewise, sugemalimab was tested in combination with chemotherapy in first line NSCLC patients in this development programme.

2.5.3. Pharmacokinetics

Study DMPK R&D-2015111901-CPK was assessed in this section. This was a non-GLP PK study using a single IV bolus injection of sugemalimab in immunologically naïve male and female cynomolgus monkeys at doses of 10, 30, and 90 mg/kg with observations up to 56 days. Eighteen healthy animals (9/sex) were randomly divided into 3 groups (3/sex/group). Mean pharmacokinetic values are detailed in table below.

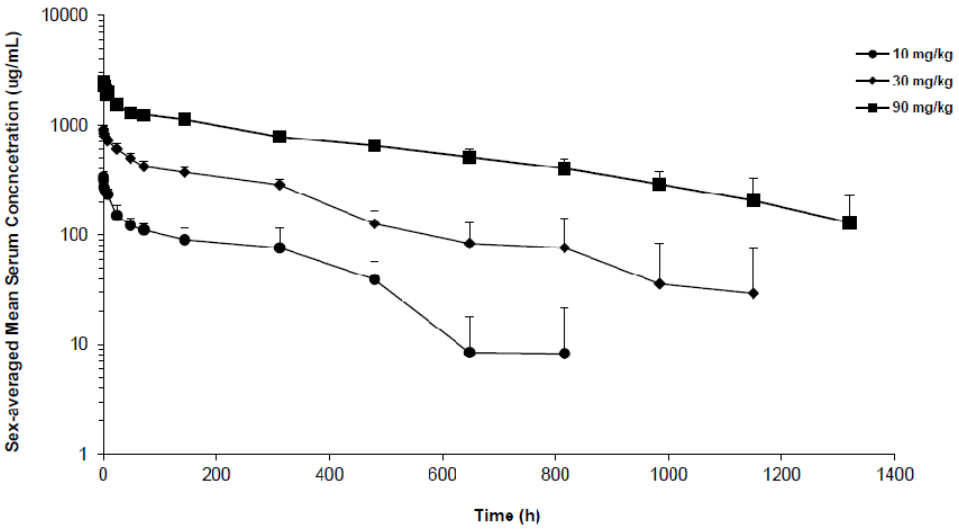
Table 1: Pharmacokinetic parameters

Dose (mg/kg)	Sex	C_0 (µg/mL)	$AUC_{0\text{-last}}$ (h·µg/mL)	$AUC_{0\text{-}\infty}$ (h·µg/mL)	CL (mL/h/kg)	V_{ss} (mL/kg)	$t_{½}$ (h)
10	Male (n = 3)	342 (80.6)	56300 (9420)	56400 (9420)	0.181 (0.0335)	43.2 (7.91)	81.2 (61.4)
	Female (n = 3)	398 (87.8)	32500 (10,500)	33100 (9960)	0.324 (0.109)	54.2 (3.13)	75.8 (4.65)
30	Male (n = 3)	995 (110)	200000 (63200)	219000 (83800)	0.149 (0.0467)	49.4 (11.2)	225 (216)
	Female (n = 3)	896 (70.8)	188000 (23100)	189000 (22900)	0.160 (0.0189)	42.4 (6.88)	148 (67.1)
90	Male (n = 3)	2800 (92.9)	832000 (39500)	957000 (129000)	0.0954 (0.0137)	59.4 (8.75)	445 (136)
	Female (n = 3)	2540 (232)	707000 (108000)	755000 (166000)	0.123 (0.0274)	58.3 (6.42)	259 (185)
Note: Data values are expressed as mean (SD); $t_{1/2}$ is expressed as median (range)							

$AUC_{0\text{-}\infty}$ = area under the serum concentration versus time curve from time 0 to infinity; $AUC_{0\text{-last}}$ = area under the serum concentration versus time curve from time 0 to last observation; C_0 = concentration at time zero/initial concentration; CL = clearance; ELISA = enzyme linked immunosorbent assay; F = female; h = hour; M = male; $t_{1/2}$ = half-life; V_{ss} = volume at steady state

Concentration-time curves indicate that at low dose (10 mg/kg), target-mediated clearance pathways influenced the curve leading to a non-linear PK profile (below figure). This was still partly visible at mid dose (30 mg/kg) but at high dose (90 mg/kg), target appears saturated, and the PK is linear. There was no significant difference in PK between male and female monkeys. TK studies are discussed in the toxicology section.

Figure 1: Sex-averaged mean serum concentration profiles by dose group following a single intravenous injection of sugemalimab



ADA was detected in five animals at low dose, four animals at mid dose, and none in high dose. The presence of ADA at low and mid dose appears to reduce sugemalimab concentrations. ADA presence was observed only in single-dose studies (single dose PK study DMPK R&D-2015111901-CPK and single dose TK study RT-211-0286-TX). No ADA have been detected in both repeat-dose toxicity studies.

2.5.4. Toxicology

The toxicological dossier is based on the active substance (sugemalimab, a IgG4 monoclonal antibody against human PD-L1) being a biopharmaceutical. The main animal model used for the acute and repeat-dose toxicity assessment is the cynomolgus monkey which is reasonable considering the active substance being biopharmaceutical and the results of the tissue cross reactivity (TCR) studies (*Macaca fascicularis*). The intended clinical formulation - intravenous (IV) administration - is used in the toxicological animal studies. A total of three single dose (1 GLP and 2 non-GLP) studies have been conducted to assess tolerability, exposure, and immunogenicity. Two once-weekly GLP repeat-dose studies of 4- and 26-weeks duration (plus 4w recovery in each study) have also been conducted.

The excipients in the clinical formulation are known and not considered a toxicological concern. The proposed dosing regimen is 1200mg Q3W which corresponds to a reported clinical systemic exposure of a mean C_{max} of 577μg/mL and $AUC_{0\text{-}3w}$ of 7304μg•d/mL (stated to represent a typical male Chinese individual of 61.5kg). The formulations used in the toxicity tests have a composition that is identical to the composition of the sugemalimab clinical drug product.

2.5.4.1. Single dose toxicity

The maximum tolerated dose (MTD) of sugemalimab was assessed in acute toxicity study in 4 male and 4 female cynomolgus administered IV single dose from 100, 300 and 1000 mg/kg followed by a 14d post-exposure observational period. No adverse effects were observed. Under the conditions of the study, the MTD was higher than 1000 mg/kg. No TK evaluation was performed.

2.5.4.2. Repeat dose toxicity

Sugemalimab was assessed in two pivotal GLP weekly repeat-dose toxicity tests (4 week and 26 week) in cynomolgus (30, 75 and 200mg/kg IV in both exposure studies). These studies included endpoints for safety pharmacology and local tolerance. There were generally very little changes observed in the toxicity tests - based on standard endpoint assessment for clinical signs, body weight, feeding, gross pathology and histopathology in the single-dose and repeat-dose studies. The exceptions are listed below:

Ophthalmoscopy

There were some sporadic effects reported for the ophthalmoscopy assessments in the repeat-dose toxicity tests. In the 4w test, there was a multifocal retinal depigmentation in one exposed animal at 200mg/kg. In the 26w exposure study, one control female and one middle dose (75mg/kg) female were observed with small and focal cornea opacity in one eye. One high dose (200mg/kg) female manifested medium-size and focal cornea opacity in one eye.

Heart

No cardiac macroscopic effects were detected. In the histopathological assessment, there was slight tendency of increased mononuclear myocardial infiltration (minimal) in the 26w exposure studied. It was detected at 75mg/kg (4/8 animals) and 200mg/kg (4/8 animals) but was also seen in 1/8 control animals. In the recovery, there were 1/4 control animals and 2/4 animals (at 30mg/kg) with minimal mononuclear myocardial infiltration.

Haematological effects

There was a statistically significant reduction (~40% reduction; ANOVA, Dunnett test) in basophilic levels could be seen in males and females at the high dose (200mg/kg) on d180 in the 26w exposure study. No other haematological effects were observed.

Immunological effects

An immunological assessment was included in the 4w and 26w exposure cynomolgus tests. Observations included B and T-cell phenotyping and distribution, cytokine expression, and IgG and complement analysis. No toxicologically relevant sugemalimab-induced changes in these endpoints were detected. The sensitisation potential of sugemalimab was studied in guinea pigs (0.5mL/animal IV induction between d1 and d5, followed by 14d interval before a challenge phase with 1.0ml/animal). There were no indications of adversity (i.e., anaphylactic responses, or more general toxicity such as body weight changes or clinical signs).

Clinical pathology

There was a statistically (ANOVA, Dunnett test) significant increase in globulin levels (+18% to 24% in males, +31% to 34% in females) and a reduction in A/G ratio (-19% to -24% in males, -28% to -31% in females) for 26w exposed males and female cynomolgus (changes evident on d87 and d180 at 200mg/kg). Similar effects were seen in the 4w repeat-dose toxicity test - although only in male animals.

Toxicokinetics (d1, d85 and d176; sampling until 168h post-dose)

The T_{max} ranged from 0.6h to 1.7h, with the T_{max} increasing with dose. The $t_{1/2}$ increased with both time (from d1 to d176) and dose (from d1 to d3). At D3, the average half-lives were 163h to 234.7h (d1), 257.6h to 276.8h (d85), and 300.9h to 366.4h (d176) respectively. There was dose accumulation between d1 and d176 at all doses (2.4x-3.3x C_{max}, 3.3x-4.1x $AUC_{0\text{-}168h}$).

2.5.4.3. Genotoxicity

As sugemalimab is a biopharmaceutical, no genotoxicity tests have been conducted.

2.5.4.4. Carcinogenicity

No carcinogenicity tests have been conducted for sugemalimab.

2.5.4.5. Reproductive and developmental toxicity

No dedicated developmental and reproductive toxicity (DART) tests have been conducted for sugemalimab.

2.5.4.6. Toxicokinetic data

At the high dose of 200 mg/kg (the NOAEL for the repeat-dose cynomolgus toxicity tests), the C_{max} after 26w exposure was 13600 to 15600 µg/mL while the $AUC_{0\text{-}168h}$ was 68800 to 70000 µg•d/mL. There were no consistent sex differences in cynomolgus C_{max} or AUC. In the 4w exposure study, the systemic exposure was being more than dose-proportional (especially for males, both C_{max} and AUC). In the 26w study, the profile was slightly less than dose proportional. Sugemalimab showed dose-accumulation in both the 4w and 26w studies (across 26w, the C_{max} accumulation was 2.4x to 3.3x and the AUC accumulation was 3.3x to 4.1x).

The lowest dose (30mg/kg) in the repeat-dose toxicity tests are most realistic with regard to the clinical exposure (roughly 4x to 5x for C_{max} and AUC). Based on a clinical C_{max} of 577 µg/mL and $AUC_{0\text{-}3w}$ of 7304 µg•d/mL, at the middle dose (75 mg/kg), the animal-to-human exposure margin is 10.9x to 11.6x (C_{max}) and 13.5x to 14.0x (AUC). At 200 mg/kg, the animal-to-human exposure margin (after 26w exposure) was 23.6x to 27x (C_{max}) and 28.3x to 28.8x (AUC) respectively.

It should be noted that the non-clinical AUC was based on 168h (1w) sampling and therefore adjusted to correspond to the clinical AUC (0-3w duration).

With regard to ADA, no antibodies have been detected in the two repeat-dose GLP studies (see also section 2.5.3. [Pharmacokinetics] above).

2.5.4.7. Local tolerance

No dedicated local tolerance studies have been conducted. Based on the repeat-dose toxicity studies in cynomolgus, haemorrhage and/or neutrophil-dominated inflammatory cell infiltration in the vascular/perivascular region were observed at the injection sites in all experimental groups, with no indication of difference between control and exposed animals.

2.5.4.8. Other toxicity studies

In an *in-vitro* study with rabbit red blood cells (RBCs), sugemalimab did not demonstrate any haemolytic or RBC clotting potential. In TCR studies in human, cynomolgus and rat, it was found that sugemalimab demonstrated binding to human placental cells (but not in cynomolgus or rat).

2.5.5. Ecotoxicity/environmental risk assessment

As sugemalimab is a protein, it is assumed to be biodegradable and no Phase I environmental risk assessment is therefore necessary according to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

2.5.6. Discussion on non-clinical aspects

A comprehensive nonclinical programme was conducted to support the MAA of sugemalimab in the proposed clinical dose, route of administration and indication. The non-clinical development was based on the regulatory requirements of ICH S6 and ICH S9 guidelines.

Pharmacology

Overall, the primary *in vitro* pharmacodynamic studies showed adequate activity and specificity for sugemalimab and the results were in line with results from the two reference antibodies used. Furthermore, the effective binding of sugemalimab to a PD-L1 protein expressed in PD-L1 transfected CHO cells has been established. Similarly, sugemalimab effectively bound to naturally expressed PD-L1 on human mDC in a concentration-dependent manner. A cross-species reactivity test indicated that sugemalimab effectively and selectively bound to human and monkey PD-L1 but not to mouse PD-L1. While sugemalimab bound specifically to PD-L1 protein, it did not bind to human expressing PD-L2, another member of the PD-1 ligands. Moreover, sugemalimab competitively blocked binding of PD-L1 to CD80, indicating a possible mechanism of action of sugemalimab to control tumour progression.

Some anti-tumour activity was demonstrated in the *in vivo* pharmacology studies (assessed in humanised PD-1 male mice injected subcutaneously with murine colon carcinoma cells). Although the proposed clinical indication concerns a different type of tumour (NSCLC), this animal disease model is considered acceptable. TGI was observed at all doses, with significant effects observed at the low and high dose group, while the middle group did not reach significance in the first study and anti-tumour activity was seen at day 18 but not at day 21 in the second study ($p>0.05$). The results are not considered robust; however, efficacy has been demonstrated in the clinical studies.

Secondary pharmacodynamic *in vitro* studies showed that sugemalimab could enhance secretion of IL-2 and IFN-γ and promote proliferation of CD4+ T lymphocytes with no ADCC or CDC activity.

Pharmacokinetics/toxicokinetics

The pharmacokinetics of sugemalimab has been adequately evaluated. Data from cynomolgus monkey was used as this is the only pharmacologically relevant species besides human. In general, there was no significant sex-related differences in PK after a single IV injection of sugemalimab at 10, 30, or 90 mg/kg. Serum exposures increased slightly more than dose proportionally with increasing dose from 10 to 30 mg/kg, approaching dose proportionality from 30 to 90 mg/kg. At higher doses, elimination was dominated by nonspecific clearance mechanisms, indicating saturation of target-mediated clearance.

With repeat dosing, there was accumulation of sugemalimab at all dose levels (30, 75, or 200 mg/kg) and no significant sex-related difference in systemic exposure. In the 26-week study, the data

indicated steady state was achieved by Day 85. Accumulation was noted at all dose levels between Day 1 and Day 85; however, it was not observed between Day 85 and Day 176, consistent with achievement of steady state.

ADA presence was observed only in single-dose studies, while no antibodies have been detected in the two repeat-dose toxicology GLP studies.

Toxicology

The proposed NOAEL of 200mg/kg in the 4w exposure study was acceptable (animal-to-human exposure margin of C_{max} ~21x-26x and AUC ~21x-23x). Based on the ophthalmoscopy assessments in the repeat-dose toxicity studies, it cannot be excluded that sugemalimab did cause ocular changes especially at higher doses. Multifocal retinal depigmentation was seen at one high dose (200mg/kg) 4w exposed animal and focal cornea opacity after 26w (one low dose [75 mg/kg] animal and one high dose [200 mg/kg] animal; also, in one control animal). One additional control female animal (in the recovery group) manifested focal cornea opacity in one eye. The C_{max} and AUC-based margins are for 200mg/kg 23.6-28.8x, 75mg/kg 10.9x-14x and 30mg/kg ~4x-5x. This is reflected in section 5.3 of the SmPC.

Clinically, immune-mediated ocular toxicity is a known risk factor for immune checkpoint inhibitors. Immune-mediated ocular adverse reactions (dry eye, conjunctivitis) have been reported in patients receiving sugemalimab in combination with chemotherapy (1.4%). This is reflected in sections 4.2, 4.4, 4.8 of the SmPC.

With regard to the mononuclear myocardial infiltration (minimal) in the 26w+4w repeat-dose toxicity study, this finding is relatively common in macaques, and the severity of the finding was minimal. However, there are clearly more exposed animals with this finding than controls (the main study had 1/8 male + female controls, 4/8 middle dose and 4/8 high dose animals; recovery study had 1/4 controls and 2/4 low-dose animals). Based on somewhat older literature data (Keenan & Vidal, 2006; Vidal et al, 2010, and Chamanza et al, 2010), inflammatory cell infiltrates/foci manifest in cynomolgus at 25.8% to 62.5% background levels which is in the range of animal observations. Myocarditis has been reported in patients receiving sugemalimab (SmPC sections 4.4 and 4.8): additional non-clinical information in SmPC section 5.3 is unlikely to contribute in any meaningful way. It is also noted that "immune-mediated adverse reactions" is listed as an important identified risk in the risk management plan (RMP).

Genotoxicity tests have not been conducted. This is acceptable as sugemalimab is a monoclonal antibody and does not interact with genetic material.

Carcinogenicity studies have not been conducted. This is in accordance with ICH-S6 and ICH-S9.

The absence of dedicated DART studies (e.g., enhanced pre- and postnatal developmental study) is acceptable as it is generally assumed that PD1/PD-L1 binding antibodies possess teratogenic potential and sugemalimab exposure is therefore considered to constitute an embryo-foetal risk factor. Based on literature assessment, the PD-L1/PD-1 signalling pathway plays a role in pregnancy by maintaining maternal immune tolerance to the foetus. In a mouse model of pregnancy, blocking PD-L1 signalling can destroy the immune tolerance to the foetus and increase foetal miscarriages. No foetal malformations associated with blocking PD-L1/PD-1 signalling pathway have been reported in the literature, but immune-related diseases have been observed in PD-1 and PD-L1 gene knockout mice. Based on its mechanism of action, foetal exposure to sugemalimab may increase the risk of developing immune-related disorders or altering normal immune responses. "Reproductive and developmental toxicity" is also listed as an important potential risk in the RMP. Therefore, sugemalimab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Based on a median steady state half-life of 23 days, a 4-month post-treatment contraception period (slightly more than five half-lives) is also not recommended for women of childbearing potential. This is reflected in section 4.6 of the SmPC (but not male patients).

The repeat-dose toxicity studies were considered sufficient for fertility toxicity assessment. With the possible exception of a reduction in relative but not absolute uterine organ weight at 200mg/kg in the main 26w exposure study (no histopathological finings, and not observed after recovery), there were no indications of toxicological effects on the reproductive organs (male and female) in the repeat-dose toxicity studies. This is reflected in the fertility part of section 4.6 of the SmPC. It can be noted that the TCR assessment showed binding to human placental cells (but not cynomolgus).

Sugemalimab is a natural substance (monoclonal antibody), the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, sugemalimab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical dossier submitted for the MAA of Cejemly is considered adequate. Relevant information has been reflected in sections 4.6 and 5.3 of the SmPC.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

In order to provide reassurance that the single pivotal phase III clinical study CS1001-302 was conducted in accordance with GCP requirements, a GCP inspection was triggered. Additional factors supporting the request for inspection were that the clinical study is only conducted in one country and there was no EU inspection history of the sponsor or any of the investigator sites.

The inspectors concluded that the trial and the data reported in the CSR is in accordance with GCP. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2: Clinical pharmacology study package for sugemalimab

Study Number	Study Design	Population	Intravenous Treatment Regimen	N in PopPK
CS1001-101a China (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 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/m^2 IV Day 1; Capecitabine: 1000 mg/m^2/time BID oral Days 1 to 14	29
		Cohort 6: ESCC (1L)	Sugemalimab 1200 mg Q3W + Q3W (up to 6 cycles): Cisplatin: 80 mg/m^2 IV Day 1; 5-FU: 800 mg/m^2/day IV Days 1 to 5	41
		Cohort 7: ESCC (≥ 2L)	Sugemalimab 1200 mg Q3W + Docetaxel 75 mg/m^2, IV Q3W	4
		Cohort 8: Non-sq NSCLC	Sugemalimab 1200 mg Q3W + Q3W (up to 6 cycles): Pemetrexed 500 mg/m^2 IV Day 1; Carboplatin AUC = 5 IV Day 1	21
		Cohort 9: Sq NSCLC	Sugemalimab 1200 mg Q3W + Q3W (up to 6 cycles): Paclitaxel: 175 mg/m^2/day IV Day 1; Carboplatin AUC = 5 IV Day 1	20
		Cohort 11: HCC	Sugemalimab 1200 mg Q3W + Lenvatinib ≥ 60 kg: 8 or 12 mg QD oral; < 60 kg: 4 or 8 mg QD oral	23
		Cohort 12: CRC	Sugemalimab 1800 mg Q3W + regorafenib	13*
CS1001-102 USA (Bridging), (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	Phase 2, single-arm, open-label	R/R ENKTL	Sugemalimab 1200 mg Q3W	80

(10 Nov 2021)				
CS1001-202 China, (19 Feb 2020)	Phase 2, single-arm, open-label	Relapsed or refractory classical Hodgkin lymphoma	Sugemalimab 1200 mg Q3W	80
CS1001-302 China, Ongoing (22 Nov 2021)	Phase 3, randomised, double-blind, placebo-controlled, with chemotherapy	Stage IV NSCLC	Sugemalimab 1200 mg Q3W and platinum-based chemotherapy	320
			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
* PK data available, however not included in popPK				

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Sugemalimab (also referred to as EQ165 or CS1001) is a high-affinity, full-length, fully human IgG4 anti-PD-L1 mAb. It specifically binds to PD-L1, thus blocking its ligation with PD-1. Sugemalimab is produced in CHO cells by fermentation. Sugemalimab is available from 3 manufacturing processes, process A, B and B´, where B´ is the intended commercial substance. Both processes A and B were used in nearly all clinical studies, with the exception of study 101a where only process A and studies 301 and 302 where only process B were used. Process B´ was not included in clinical studies.

Recommended posology:

Sugemalimab 1200 mg is infused intravenously over 60 minutes followed by intravenous (IV) infusion with carboplatin and paclitaxel (squamous cell carcinoma) or carboplatin and pemetrexed (non-squamous cell carcinoma) on day 1 for up to 4 cycles every 3 weeks. Treatment with sugemalimab 1200 mg every 3 weeks continues until disease progression or unacceptable toxicity.

PK is available from 6 clinical studies performed in subjects with different types of solid tumours, lymphoma or haematologic malignancies. PK in the target population is available from both phase 3 studies (301 and 302) and from cohort 8 and 9 of the phase 1 study 101b. All studies were conducted in Asian patients, with the exception of the bridging study 102.

Methods

- *Quantification of sugemalimab (Method 17BASM127)*

Concentrations of free sugemalimab in human serum were determined using a validated ELISA. PD-L1 was used for capture of sugemalimab, and a biotin conjugated anti human IgG4 Fc, streptavidin

peroxidase and TMB were used for detection, where the colorimetric signal was proportional to the sugemalimab concentration.

- *Analysis of sugemalimab immunogenicity*

A standard multi-tiered approach consisting of screening, confirmation, titre, and neutralisation potential was developed to evaluate anti-drug antibodies. Cut-points were determined in healthy subjects using state of the art procedures, and similarly later in study cut-points were determined in cancer patients.

A first-generation assay 17BASM146 had insufficient drug tolerance and was used in study 101a only.

A second-generation assay 19BASM036 was validated and used in all subsequent studies. After acid pre-treatment, ADAs were captured on a sugemalimab-coated plate. After dissociation, the ADAs were transferred to a fresh plate with Ruthenium or biotin labelled sugemalimab solution and neutralisation buffer to form an antibody complex bridge. The samples were added to an MSD-streptavidin plate where the biotin in the complex binds to the streptavidin, allowing unbound material to be washed away. Read buffer was added and the ruthenium ECL signal was measured.

An assay for the investigation of the neutralising potential of ADAs (nAb) was validated, method ICSH 19-118. This method was used for all nAb analyses. ADAs and nAbs in acid treated serum samples were immobilised by binding to a sugemalimab-coated plate. After dissociation and incubation with Sulfo-Tag labelled sugemalimab, nAb were captured on a MSD plate coated with PD-L1 protein. After washing unbound material away, nAbs were indirectly detected by a decrease (inhibition) in response of the Sulfo Tag sugemalimab: PD-L1 complex.

Pharmacokinetic data analysis

Standard non-compartmental analysis was performed in the early studies where rich sampling was applied, and population PK (popPK) was used for all PK data, including analysis of the target population.

Evaluation and Qualification of Models

PopPK analysis

A popPK analysis was performed where the objectives were to develop a popPK model for sugemalimab to describe the serum concentration-data. Specifically, population PK parameters were to be quantified, including typical parameter values and random interindividual and residual variability, as well as identification of covariate effects which describe variability in the PK of sugemalimab.

The pharmacokinetic data used in the population analysis included 7054 PK observations from 1002 patients from six different clinical studies. The covariates available for evaluation are summarised in **Table 3**.

Table 3: Summary of demographics: PopPK analysis dataset

	Age (*years*)	WT (*kg*)	ALB (*g/L*)	ALT (*U/L*)	AST (*U/L*)	CRCL (*mL/min*)	Sex	Race	Disease status	ADA response	Renal function	Hepatic impairment
N	1002	1002	1002	1002	1002	1002	M: 776	White: 20	Lymphoma: 169	No: 890	Normal: 511	Normal: 888
Missing	0	0	0	0	0	0	(77.45%)	(2%)	(16.87%)	(88.82%)	(51%)	(88.62%)
Mean	56.66	62.84	41.56	21.91	24.76	94.52	F: 226	Asian: 978	Other solid tumors: 220	≥ 1 Pos: 112	Mild: 421	Mild: 113
SD	12.07	11.74	5.04	17.4	16.98	28.93	(22.55%)	(97.6%)	(21.96%)	(11.18%)	(42.02%)	(11.28%)
CV %	21.3	18.68	12.12	79.43	68.59	30.61		Other: 4	Stage III NSCLC: 259		Moderate: 70	Moderate: 1
Median	59	61	41.7	17	20	90.88		(0.4%)	(25.85%)		(6.99%)	(0.1%)
Min	18	36	26.1	3	4	33.65			Stage IV NSCLC: 354			
Max	78	124	96	174	194	295.24			(35.33%)			

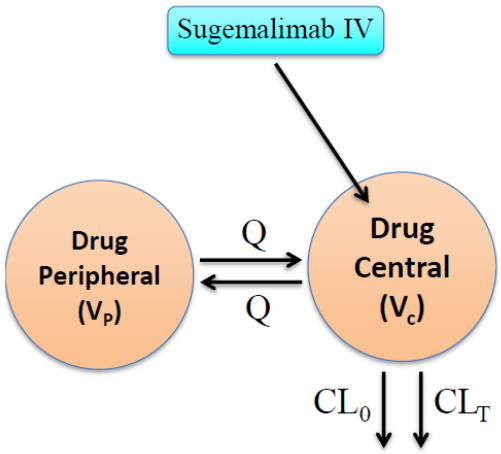
Note: WT = total body weight, ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CRCL = creatinine clearance, ADA = anti-drug antibodies, NSCLC = non-small cell lung cancer. † Renal function was classified using CRCL (Equation 1) as follows: normal (>90 mL/min), mild (60 – <90 mL/min), moderate (30 – <60 mL/min). Hepatic impairment was classified using NCI-OWDG classifications.

The analysis was carried out in NONMEM version 7.4 using the first-order conditional estimation (FOCE) method.

The base model was developed by exploring different structural compartmental models, i.e. 1-n compartment, as well as linear, and parallel linear and non-linear clearance models. Based upon graphical diagnostics, more complex PK models including concentration-dependent clearance (i.e. quasi-steady-state (QSS) approximations of the target-mediated drug disposition (TMDD)) or time-dependent clearance were explored. The base was a two-compartment disposition model with time-dependent elimination. Sugemalimab disposition was modelled in terms of CL, Vc, inter-compartmental clearance (Q) and peripheral volume of distribution (Vp).

The influence of continuous and categorical covariates (Table **3**) were tested for their statistical significance on PK parameters in the model. The final model included body weight, sex, and albumin on CL0 and Vc, sex and time-varying ADA titre on CLT, albumin on Vp, lymphoma disease on Vc and kdes, and NSCLC disease on Vp. A schematic of the final model is shown in Figure 2, with parameter estimates shown in Table 4. A pvcVPC for NSCLC patients stratified by Cycle is shown Figure 3.

Figure 2: Schematic of the final population PK model



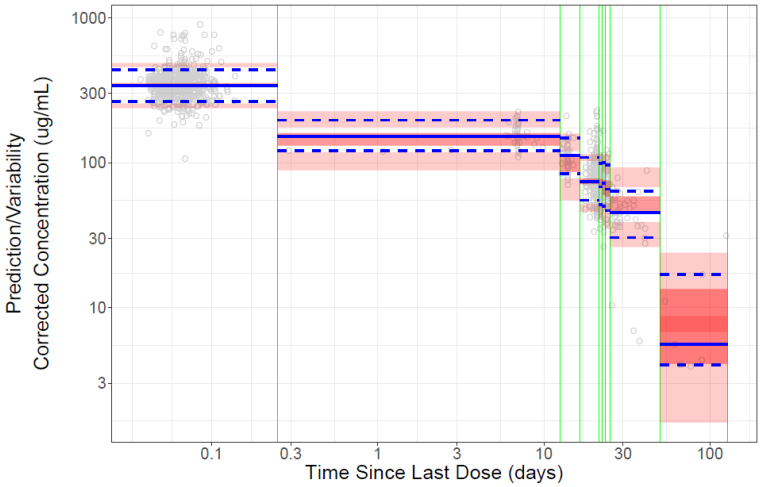
CL_0 = time-independent clearance, CL_T = time-dependent clearance, Q = inter-compartmental clearance, V_c = central volume of distribution, V_p = peripheral volume of distribution, IV = intravenous.

Table 4: Parameter estimates of the final population PK model

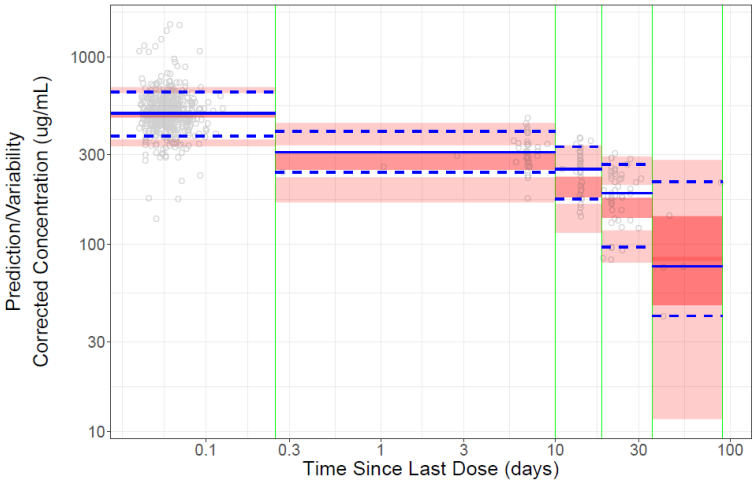
Parameter Name	Estimated Value (%RSE)	95% CI	η-shrinkage (%)
Nonspecific Time-independent Clearance (CL_0, L/day)	0.149 (1.4)	[0.145, 0.153]	
– Effect of Sex on CL_0	0.904 (2.6)	[0.857, 0.947]	
– Effect of Weight on CL_0	0.770 (7.2)	[0.656, 0.878]	
– Effect of Albumin on CL_0	-0.980 (9.0)	[-1.148, -0.808]	
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 on V_c	0.896 (2.1)	[0.860, 0.932]	
Inter-compartmental 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]	16
Between Subject Variability for V_c	18.6 (3.4)	[17.4, 19.8]	20.5
Between Subject Variability for V_p	61.6 (6.5)	[54.0, 69.4]	44.9
Between Subject Variability for CL_T	46.3 (6.5)	[40.0, 51.5]	49.6
Between Subject Variability for k_{des}	104.2 (5.7)	[93.0, 116.6]	39.5
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]	

Figure 3: pvcVPC for the final population PK model for NSCLC patients

pvcVPC for the Final Population PK model: NSCLC – Cycle 1

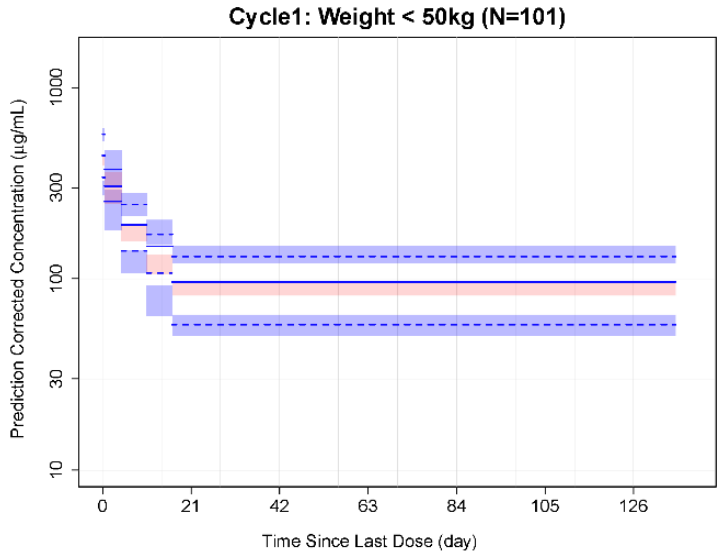


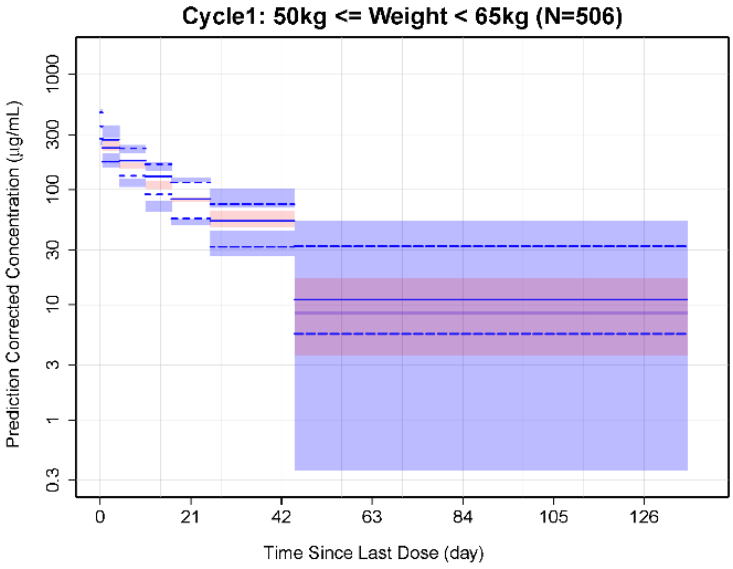
pvcVPC for the Final Population PK model: NSCLC – Cycle 4

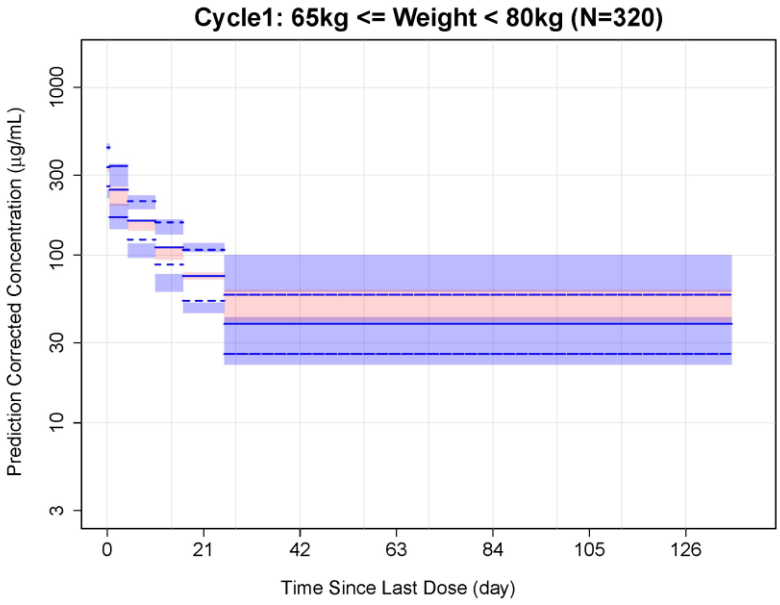


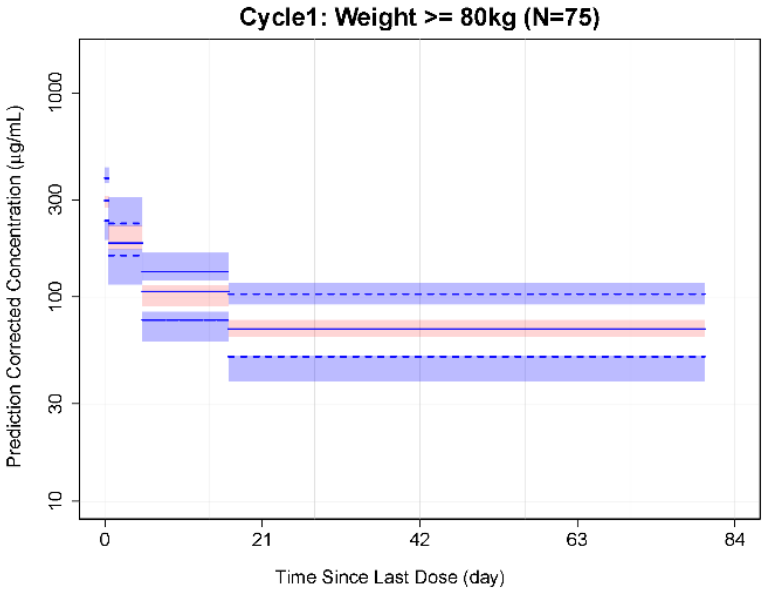
Open circles = individual observed, dashed blue lines = observed 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% prediction interval around the model predicted 10th, 50th, & 90th percentiles, green lines = bin limits. Note: Log-log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

Figure 4: pcVPC for the final population PK model for sugemalimab stratified by body weight during Cycle 1.




Cycle1: 50kg <= Weight < 65kg (N=506)
Prediction Corrected Concentration (µg/mL)
0.3
1
3
10
30
100
300
1000
0
21
42
63
84
105
126
Time Since Last Dose (day)

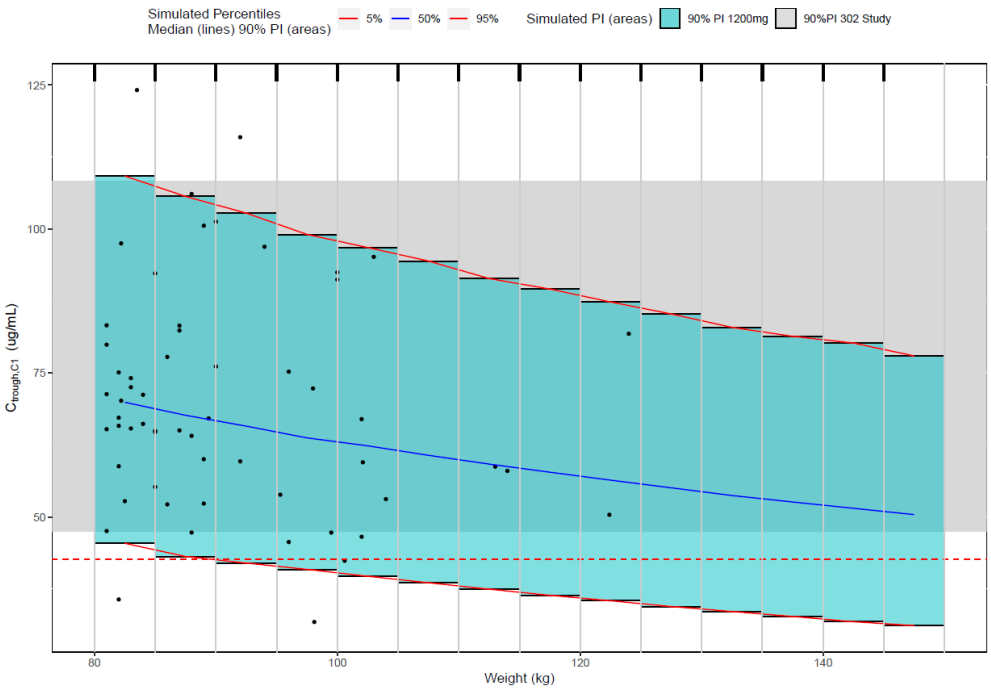




Open circles = prediction-corrected observed data, dashed lines = observed 10th and 90th percentiles of the observed data, solid line = observed median concentration, shaded red areas = simulation-based 95% confidence interval for the median, shaded blue areas = simulation-based 95% confidence intervals for the 10th and 90th percentiles (dashed lines). pcVPC = prediction-corrected visual predictive checks, PK = pharmacokinetic, Kg=kilogram. Note: Log scale is used for the y-axis. These visualisations don't change our conclusions as submitted in the package.

The final population PK model was used to predict sugemalimab exposure metrics vs weight for flat dosing of 1200 mg and are shown in Figure **5** which includes a reference range based on the observed exposure in Study CS1001-302. For the 1200 mg Q3W dose acceptable exposure was maintained up to 115 kg whereas above 115kg, the exposure is lower than the reference range. The simulations for C_{trough} by *dose and body weight strata and for study CS1001-302* are shown in Table **5** and identifies that 1500 mg Q3W in patients >155 kg provides exposures within the reference range. Corresponding simulations were performed for AUC and C_{max} (data not shown).

Figure 5: Simulated exposure (C_{trough},C1) following 1200 mg Q3W for high body weight and reference range from study CS1001-302 with proposed target lower limit (from observed data)



Predicted C_{trough},C1 based on the final population PK model for weight > 80kg population (black circles: individual predictions). The blue and red solid lines are the median and 90% PIs for predicted C_{trough},C1. The blue shaded area encompasses 90% of the simulated patients in each weight stratum (5kg intervals). The grey band encompasses 90% range from Study CS1001-302. The red dotted line represents the 5th percentile of observed C_{trough}, C1 in Study CS1001-302 (42.6 µg/mL).

Table 5: C_{trough},C1 (µg/mL) by dose and body weight strata and for Study CS1001-302 group

Population	Weight (kg)	N	Gmean	Median (5^{th} - 95^{th} Percentile)	% with C_{trough},C1≥ 42.6 µg/mL
From model prediction for Study CS1001-302					
	41-96	320	70.6	71.0(47.4-108.0)	97.8
From simulation patients dosed 1200 mg					
	80-85	1002	70.0	69.8(45.1-109.5)	96.0
	85-90	1002	67.8	67.7(43.3-105.4)	95.6
	90-95	1002	65.7	65.8(42.2-102.4)	94.7
	95-100	1002	63.8	63.9(40.8-99.4)	93.3
	100-105	1002	62.0	62.1(39.7-96.8)	91.9
	105-110	1002	60.3	60.5(38.7-94.5)	90.4
	110-115	1002	58.7	59.3(37.5-92.0)	89.2
	115-120	1002	57.3	57.7(36.3-89.3)	86.8
	120-125	1002	55.8	56.3(35.4-87.6)	84.6
	125-130	1002	54.5	55.0(34.5-85.4)	82.4

Population	Weight (kg)	N	Gmean	Median (5th - 95th Percentile)	% with $C_{trough,C1} \geqslant$ 42.6 µg/mL
	130-135	1002	53.2	53.7(33.6-82.9)	79.9
	135-140	1002	52.0	52.6(32.8-81.9)	77.4
	140-145	1002	50.8	51.5(32.0-79.9)	74.6
	145-150	1002	49.7	50.4(31.2-78.2)	72.0
From simulation patients dosed 1500 mg					
	80-85	1002	87.5	87.3(56.6-136.7)	98.8
	85-90	1002	84.7	84.8(54.2-131.6)	98.4
	90-95	1002	82.2	82.2(52.8-127.9)	98.1
	95-100	1002	79.8	80.0(51.3-124.8)	98.1
	100-105	1002	77.6	77.7(49.8-120.9)	97.8
	105-110	1002	75.5	75.9(48.2-117.8)	97.6
	110-115	1002	73.5	73.9(46.9-114.8)	97.5
	115-120	1002	71.6	72.1(45.8-111.7)	96.7
	120-125	1002	69.8	70.4(44.4-109.0)	96.1
	125-130	1002	68.1	68.9(43.2-106.5)	95.4
	130-135	1002	66.5	67.3(41.9-104.1)	94.4
	135-140	1002	65.0	66.0(41.0-101.9)	93.5
	140-145	1002	63.5	64.4(40.1-99.7)	92.7
	145-150	1002	62.1	63.0(39.2-97.8)	91.3

Gmean is the geometric mean.

Absorption

No absorption study was conducted as sugemalimab is administered by intravenous injection. The median C_{max},ss in patients with NSCLC (stages III/IV)/other solid tumours was predicted to be 591 µg/mL.

PK from patients with different types of cancer is available from the phase Ia/Ia study CS1001-101, with rich PK sampling in part a. Sparse PK data after administration of 1200mg sugemalimab Q3W is available from study 101a part b and phase 2 studies 201 and 202 in lymphoma. All data is included in the popPK analyses and sparse PK data is not further detailed here. Patients in these studies were all Asian and predominantly male.

Both processes materials A and B were used in nearly all clinical studies, with the exception of study 101a where only process A and studies 301 and 302 where only process B were used. A comparison of PK data at cycle 1 was available for 225 patients who received process A material and for 697 patients who received process B material.

Table 6: Comparison of observed PK parameters between processes A and B

PK Parameters	Observed data Geometric Mean and Ratio		90%CI (%)
	Process A/B	Ratio (%)	
$C_{max,C1}$ (µg/mL)	391 / 355	110.03	106.38-113.82

PK Parameters	Observed data Geometric Mean and Ratio		90%CI (%)
	Process A/B	Ratio (%)	
$AUC_{tau,C1}$ (µg•h/mL)	94688 / 89952	105.26	101.49-109.18

Sample size of Observed data: Process material A: 225; Process material B: 697

In study 101a, 29 participants received sugemalimab doses of 3, 10, 20, 40 mg/kg or a fixed dose of 1200 mg administered IV Q3W. Their BW ranged from 41 to 78 kg, with mean 58.9 kg (SD 8.6). PK parameters and concentration/time profiles are shown in Table 7.

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. Therefore, it was noted that the results of t 1/2 , Vss, CL, $AUC_{0-\infty}$ in Cycle 1 calculated by NCA should be treated with caution.

The mean accumulation ratio for each group in Cycle 4 ranged from 1.43 to 2.15 for AUC, and 0.99 to 1.74 for C_{max}. Following multiple IV infusions at the proposed therapeutic dose of 1200 mg Q3W, there was approximately 2-fold accumulation of sugemalimab exposures. Sugemalimab exposures (C_{max} and AUC0-21d) were in a similar range for the weight-based dose of 20 mg/kg and the fixed dose of 1200 mg in Phase 1a.

Sugemalimab was safe and well tolerated in the dose range of 3 mg/kg to 40 mg/kg. There were no DLT events during the study and MTD was not reached. The RP2D was determined to be a fixed dose of 1200 mg Q3W, which was used in nearly all subsequent studies.

Table 7: Summary of sugemalimab pharmacokinetic parameters (NCA) after single- and multiple-dose IV infusion Q3W (Study CS1001-101a)

Parameter (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)	
	n (n*)	Geometric Mean (% Geometric CV)	n (n*)	Geometric Mean (% Geometric CV)	n (n*)	Geometric Mean (% Geometric CV)	n (n*)	Geometric Mean (% Geometric CV)	n (n*)	Geometric Mean (% Geometric CV)
Cycle 1										
AUC_{0-t} (day•μg/mL)	3 (3)	453.67 (10.95)	3 (3)[1]	2099.27 (16.31)	3 (3)	3492.67 (23.82)	3 (3)	9954.30 (12.48)	16 (16)[2]	3813.66 (22.40)
$AUC_{0-\infty}$ (day•μg/mL)	3 (3)	645.19 (19.46)	3 (3)[1]	3195.21 (5.80)	2 (2)[3]	5946.81 (16.16)	3 (3)	17869.92 (37.30)	16 (16)	6802.22 (32.98)
AUC_{0-21d} (day•μg/mL)	3 (3)	453.67 (10.95)	3 (3)[1]	2099.27 (16.31)	3 (3)	3492.67 (23.82)	3 (3)	9954.30 (12.48)	15 (15)	3951.85 (17.67)
C_{max} (μg/mL)	3 (3)	52.82 (15.32)	4 (4)	257.52 (25.25)	3 (3)	349.44 (13.90)	3 (3)	1278.31 (35.34)	16 (16)	422.59 (22.76)
T_{max} (h)[5]	3 (3)	2.05 (1.88, 7.38)	4 (4)	4.55 (1.83, 7.18)	3 (3)	2.92 (2.67, 2.97)	3 (3)	2.17 (2.10, 7.20)	16 (16)	2.06 (1.88, 3.32)
CL (L/day)	3 (3)	0.250 (31.299)	3 (3)[1]	0.200 (12.356)	2 (2)[3]	0.183 (23.120)	3 (3)	0.141 (31.558)	16 (16)	0.176 (32.978)
$t_{1/2}$ (day)[6]	3 (3)	12.19 (3.32)	3 (3)[1]	14.34 (3.59)	2 (2)[3]	15.53 (0.07)	3 (3)	16.12 (5.66)	16 (16)[2]	17.56 (6.24)
V_{ss} (L)	3 (3)	4.27 (10.54)	3 (3)[1]	3.92 (16.01)	2 (2)[3]	4.43 (33.76)	3 (3)	3.29 (26.17)	16 (16)	4.25 (24.18)
Cycle 4										
AUC_{0-t} (day•μg/mL)	1 (1)	1017.55 (-)	1 (1)[1]	3349.00 (-)	3 (3)	5178.05 (30.86)	1 (1)[2]	10665.35 (-)	13 (13)[1,2]	7628.74 (39.54)
AUC_{0-21d} (day•μg/mL)	1 (1)	1017.55 (-)	1 (1)[1]	3349.00 (-)	3 (3)	5178.05 (30.86)	0	-	11 (11)[1]	8548.90 (19.28)
AUC_{0-tau} (day•μg/mL)	1 (1)	1016.78 (-)	1 (1)[1]	3348.56 (-)	3 (3)	4934.00 (39.53)	1 (1)[2]	14272.82 (-)	13 (13)[1,2]	7897.90 (35.57)
C_{max} (μg/mL)	1 (1)	77.61 (-)	2 (2)	285.90 (31.36)	3 (3)	469.78 (14.83)	1 (1)	1187.47 (-)	14 (14)	713.64 (25.77)
C_{min} (μg/mL)	1 (1)	32.70 (-)	2 (2)	38.06 (80.82)	3 (3)	87.56 (99.57)	1 (1)	418.47 (-)	14 (14)	211.79 (65.48)
CL_{ss} (L/day)	1 (1)	0.139 (-)	1 (1)[1]	0.233 (-)	3 (3)	0.224 (47.659)	1 (1)	0.179 (-)	13 (13)[1]	0.152 (35.574)
Accumulation index (AUC)[4]	1 (1)	2.15 (-)	1 (1)[1]	1.43 (-)	3 (3)	1.48 (11.80)	1 (1)[2]	1.58 (-)	13 (13)[1,2]	2.00 (40.34)
Accumulation index (C_{max})	1 (1)	1.30 (-)	1 (1)[1]	0.99 (-)	3 (3)	1.34 (15.99)	1 (1)	1.03 (-)	13 (13)[1]	1.74 (43.87)

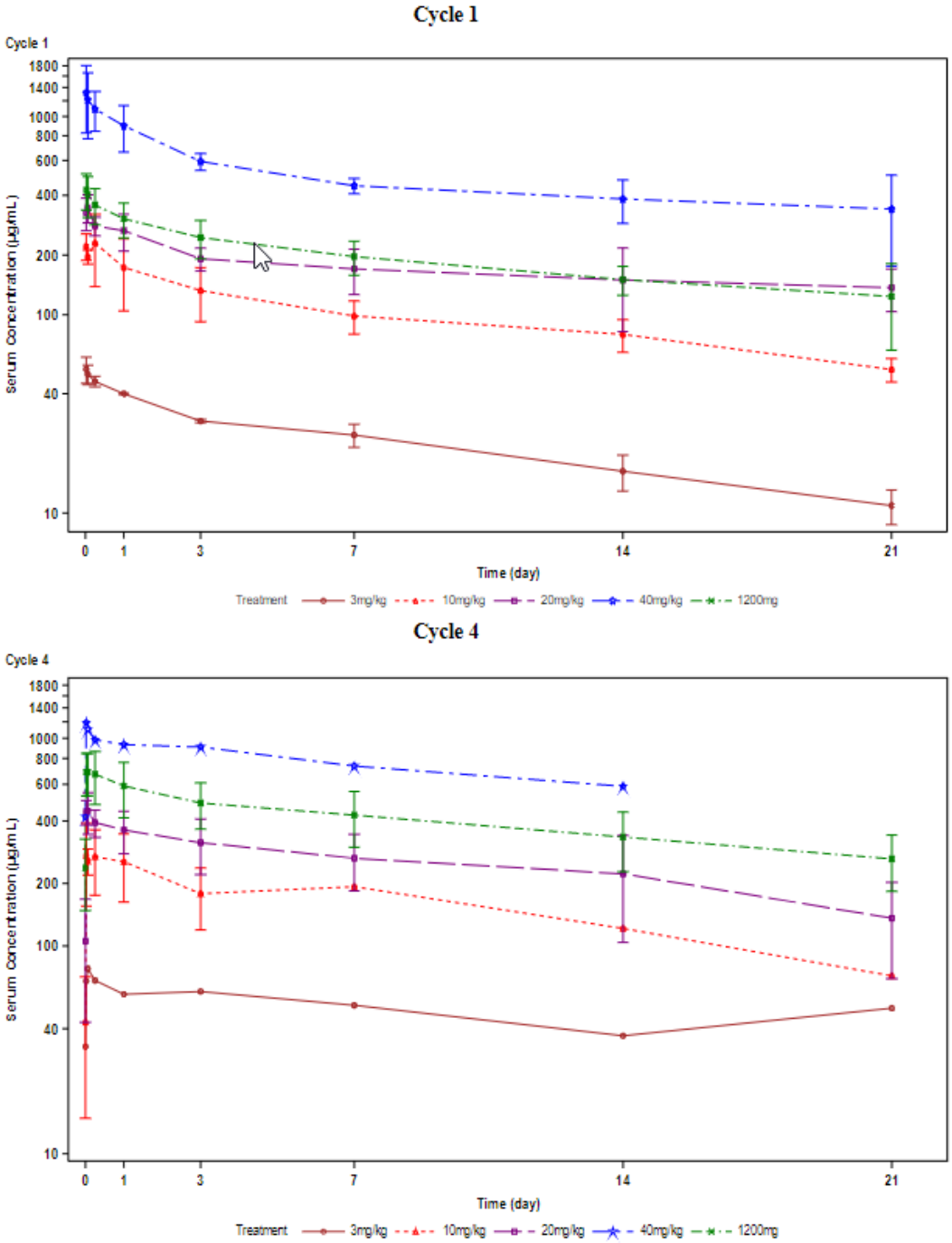
Source: Table 14.4.2a.

The % geometric CV of "-" indicates that the mean geometric CV (CV%) was not calculated due to insufficient number of subjects.

Abbreviations: - = not applicable; n = number of subjects; n* = number of subjects who XXXX, used for the calculation of geometric means; N = number of subjects in the analysis set.

1. Only subject data collected up to 336 h post-dose were included. Subjects 0102001 (Cycle 1) and 0102004 (Cycle 4) in the 10 mg/kg group and Subject 0102013 (Cycle 4) in the 1200 mg fixed dose group were not included in the statistical analysis due to unfinished PK blood sampling;
2. Samples were collected up to 336 h post-dose for Subject 0102008 (Cycle 4) in the 40 mg/kg group, and Subjects 0101010 (Cycle 4), 0101022 (Cycle 4), and 0101023 (Cycle 1) in the 1200 mg fixed dose group;
3. The results of $AUC_{0-\infty}$, $t_{1/2}$, CL, and V_{ss} of Subject 0101011 in the 20 mg/kg group were not included in the statistical analysis results of this table, as detailed in Annex 19: Description of the Calculation of Pharmacokinetic Parameters;
4. Accumulation index AUC = Cycle 4 AUC_{0-21d}/Cycle 1 AUC_{0-21d}, if data were available; otherwise, accumulation index AUC = Cycle 4 AUC_{0-14d}/Cycle 1 AUC_{0-14d};
5. T_{max} was expressed as median (min, max);
6. $t_{1/2}$ was expressed as arithmetic mean (SD).

Figure 6: Serum sugemalimab concentration time plots (arithmetic mean, SD, study 101a)

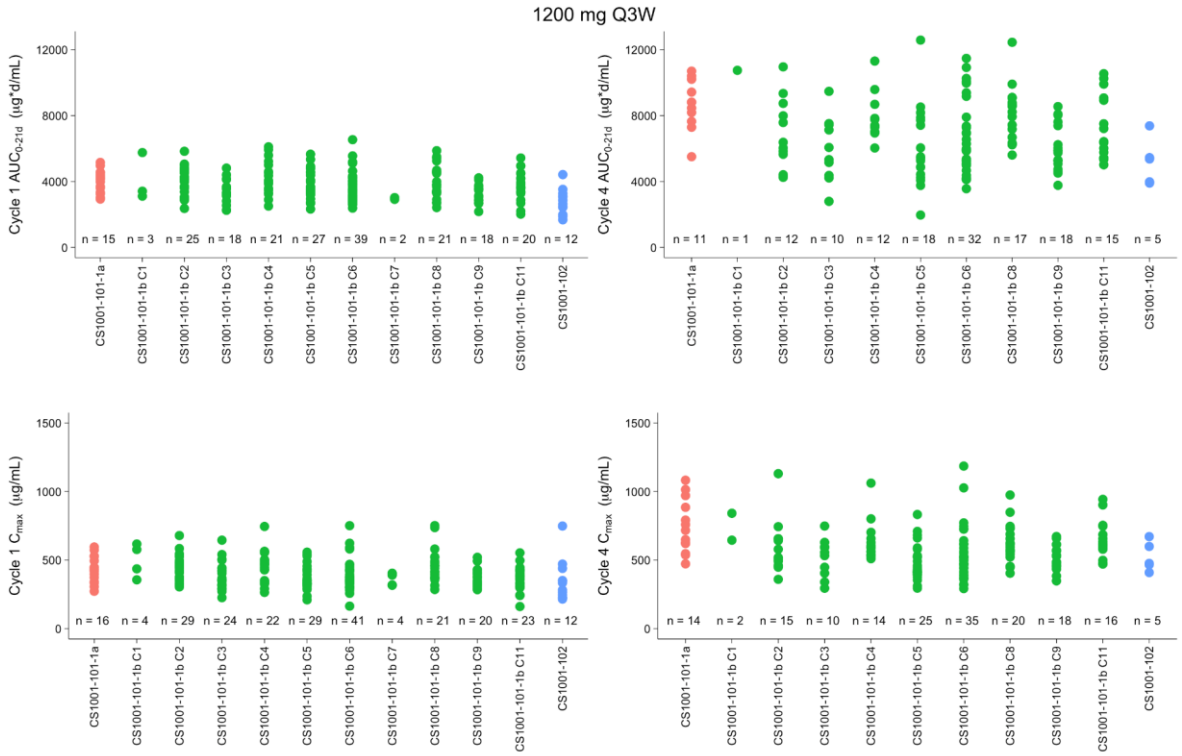


In the dose expansion in study 101 part b (n= 217), all participants were administered a fixed dose of 1200 mg IV Q3W with the exception of cohort 12, where sugemalimab was administered a fixed dose of 1800 mg once every 4 weeks. Cohorts 8 and 9 were non-squamous and squamous NSCLC and included 20 and 21 patients respectively. Patients´ BW ranged from 39 to 104 kg, with mean 60.3 kg (SD 11.3) and median of 59.0 kg. Sugemalimab PK parameters for 1200mg Q3W were similar across the cohorts of different tumour or lymphoma types, which indicate that sugemalimab PK seems unaffected by coadministration with other drugs.

For the first cycle after iv administration of 1800 mg Q4W, the $t_{1/2}$ was 14.0 days, and CL was determined to be 0.228 L/day, C_{max} was 549 µg/mL and AUC_{tau} was 5619 µg•day/mL. At cycle 4, the

mean accumulation ratio (R_{acc}) for AUC during Cycle 4 was 2.13, while the corresponding R_{acc} for C_{max} was 2.22.

Figure 7: 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
Source: Derived from Study CS1001-101a CSR, Study CS1001-101b CSR, and Study CS1001-102 CSR.

Distribution

The central and peripheral volume of distribution for sugemalimab were estimated in the popPK analysis to 3.42 L and 1.84 L in a typical NSCLC patient.

Elimination

The geometric mean CL and terminal half-life across all subjects included in the popPK analysis are shown in the following table:

Table 8: The geometric mean CL and terminal half-life across (PopPK analysis)

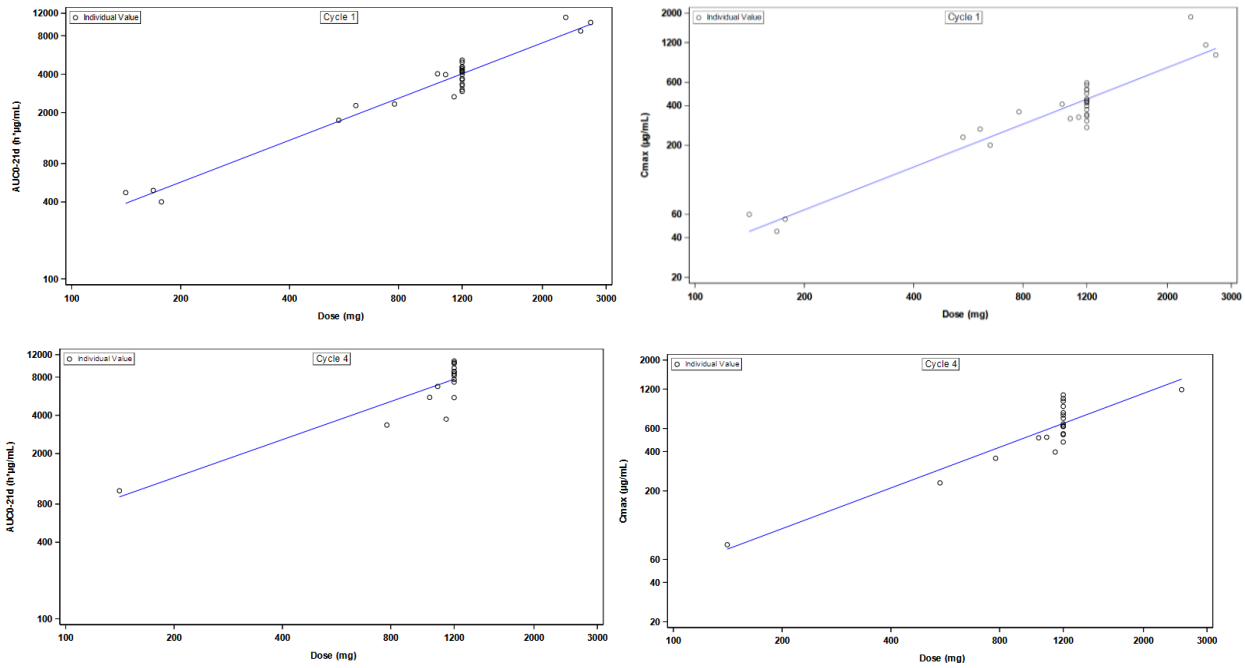
Parameter	n	Geo.Mean	Geo.SD	Geo.CV
CL (Cycle 1) (L/day)	1002	0.211	1.32	28.5
CL (Cycle 4) (L/day)	1002	0.168	1.34	29.5
CL (Cycle 8) (L/day)	1002	0.155	1.32	28.4
Vss (L)	1002	4.88	1.30	27.0
t1/2 (Cycle 1) (days)	1002	17.2	1.29	25.6
t1/2 (Cycle 4) (days)	1002	21.3	1.32	28.7
t1/2 (Cycle 8) (days)	1002	23.0	1.34	29.6

CL = total clearance, Vss = volume of distribution derived as summation of Vc and Vp, t1/2 = elimination t1/2.

Dose proportionality and time dependencies

Sugemalimab systemic exposures (C_{max} and AUC) increased in an approximately dose-proportional manner following single and multiple doses of 3 to 40 mg/kg IV Q3W and a fixed dose of 1200 mg IV Q3W, based on data from study 101a for AUC0-21d and C_{max} at cycle 1 and 4 (below figure).

Figure 8: Dose proportionality assessment for doses from 3 to 40 mg/kg, including 1200 mg (study 101a): AUC0-21d and C_{max} at cycle 1 (top) and cycle 4 (bottom)



The linear regression of the log C_{max} and AUC in Cycle 1 and Cycle 4 had slopes close to 1 with 90% CIs covering 1, showing dose proportionality between 3 mg/kg and 40 mg/kg (including a fixed dose of 1200 mg) (below table).

Table 9: Dose proportionality assessment using linear regression for power model (study 101a)

Parameters	Cycle 1		Cycle 4	
	Slope	90% CI	Slope	90% CI
$AUC_{0\text{-}21d}$	1.09	(1.01, 1.17)	1.00	(0.75, 1.24)
C_{max}	1.08	(0.96, 1.19)	1.03	(0.84, 1.22)

Source: Table 14.4.3a.

Time-dependency in sugemalimab PK was evident in popPK analyses, where CL decreased by 42% from single dose to steady state in a typical patient. The corresponding half-life for the reduction in CL was predicted to be 36.9 days in a typical NSCLC patient. Time-varying ADA titre was a covariate for the time-varying CL component.

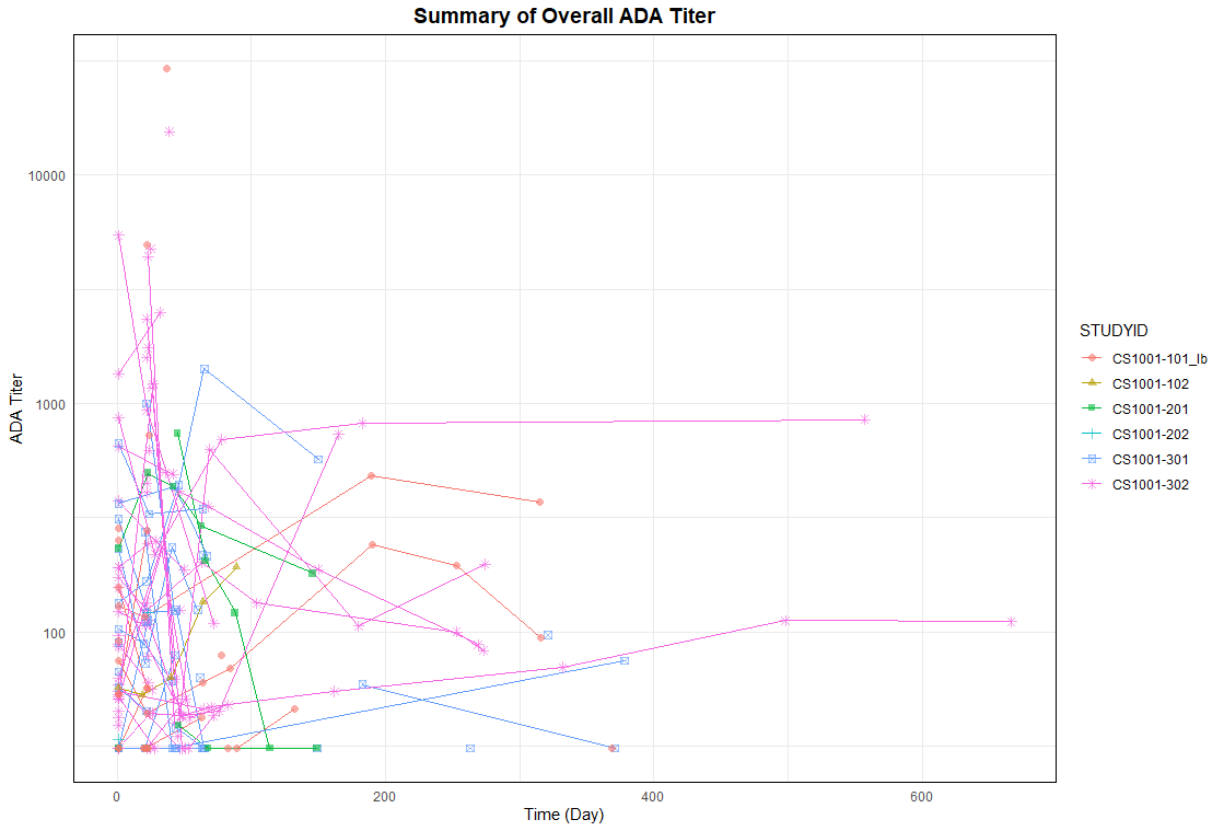
The immunogenicity results per study are summarised in Table 10. Individual titres over time are presented as a spaghetti plot in Figure 9.

Table 10: Summary of immunogenicity results

Study Number	N	Baseline ADA	Post baseline ADA	Treatment induced ADA	ADA incidence	Nab
CS1001-101a	29	2 (6.9%)	NA	NA	6 (20.7%)	NA
CS1001-101b	217	10 (4.6%)	19 (8.8%)	9 (4.1%)	10 (4.6%)	1 (0.5%)
CS1001-102	19	1 (5.3%)	1 (5.3%)	0	1 (5.3%)	NA
CS1001-201	80	2 (2.5%)	4 (5.3%)	3 (3.8%)	3 (3.8%)	1 (1.3%)
CS1001-202	81	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	NA
CS1001-301	255	13 (5.1%)	17 (6.7%)	13 (5.1%)	14 (5.5%)	4 (1.6%)
CS1001-302	309	27 (8.7%)	44 (14.2%)	26 (8.4%)	28 (9.0%)	5 (1.6%)
Overall	990	56 (5.7%)	NA	NA	63 (6.4%)	11 (1.1%)

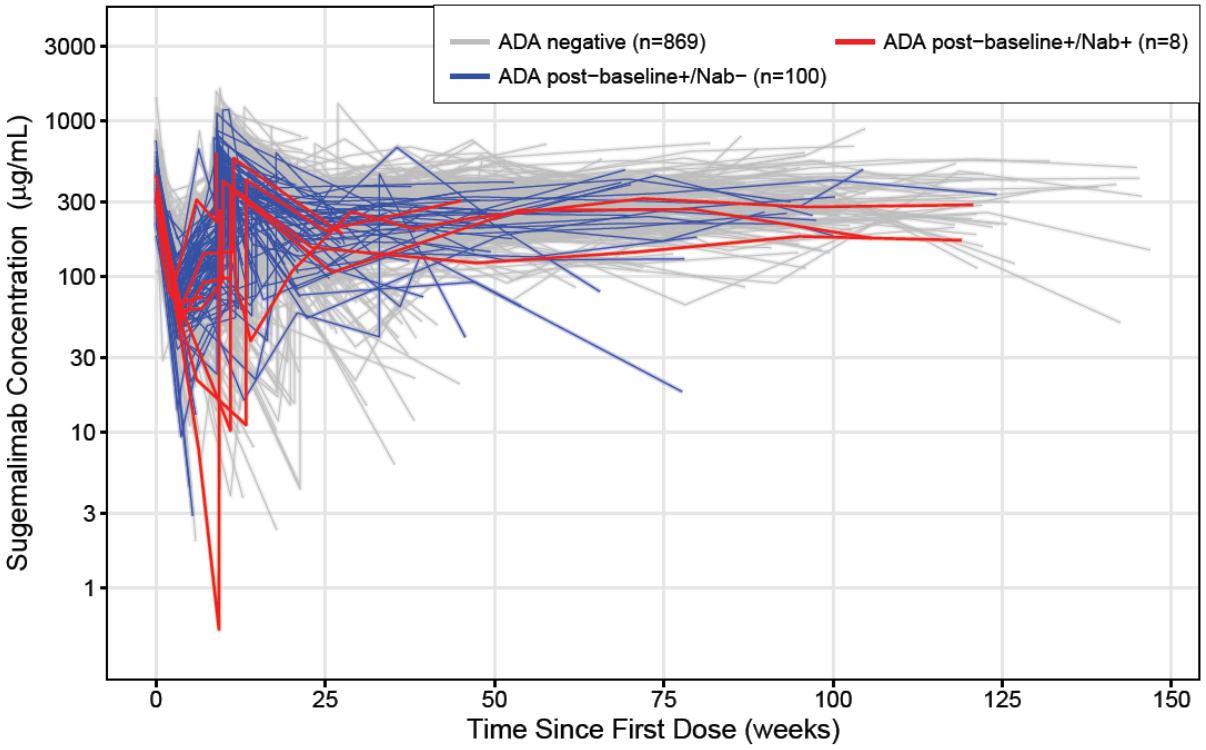
Note: The method for Study CS1001-101a differs and has limited drug tolerance.

Figure 9: Summary of ADA titre across all clinical studies with sugemalimab



The effect of ADA and nAb status on PK is shown for all studies for participants receiving the 1200 mg IV Q3W dose. Across the clinical studies, positive ADA or nAb status did not affect sugemalimab PK, as the distribution of pooled concentration-time profiles of all ADA/nAb-positive participants receiving this dose lay generally within the distribution of negative subjects.

Figure 10: Individual serum concentration-time profiles by ADA and nab 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



Source: PopPK/E-R Analysis Report 270593, Figure 90.

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.

Inter-individual variability (IIV) in PK was determined in the popPK analysis. The IIV in CL after a single dose was estimated to be 28.5% and at steady state, the IIV was estimated to be 28.6%. The IIV in the elimination half-life was 25.6%.

Target population

Sparse PK in the target population is available from both phase 3 studies (301 and 302) and from cohort 8 and 9 of the phase 1 study 101b and is included in the popPK analyses. For immunogenicity, see Table **10**.

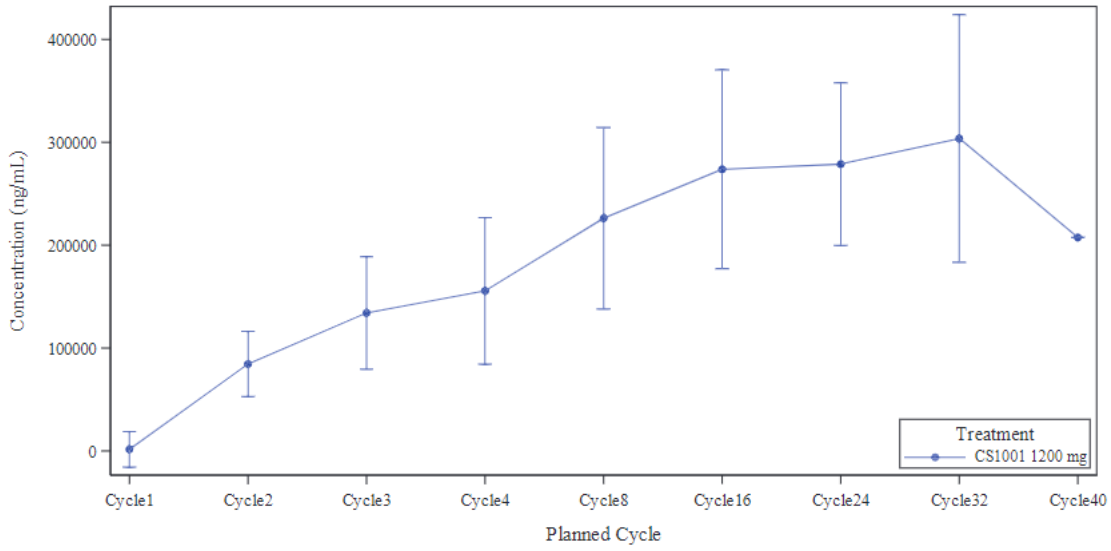
Study CS1001-301: Secondary objectives of study CS1001-301 included assessing the PK profile and immunogenicity of sugemalimab.

As of 8 Mar 2021, a total of 255 participants had received sugemalimab 1200 mg IV Q3W. Patients in the sugemalimab group were predominantly male (92.5%), with a mean age of 61 years and were all of Asian race. Their BW ranged from 42.5 to 98 kg, with mean 63.8 kg (SD 10.07) and median of 62.0 kg.

PK was available for 252 subjects. After multiple doses of sugemalimab at 1200 mg IV Q3W, the geometric mean $C_{trough,C4}$ and $C_{max,C4}$ were 134.4 (CV% 70.75, n = 203) and 546.1 µg/mL (CV% 27.45,

n = 201), respectively. $C_{trough,C2}$ was 78.6 µg/mL (CV% 43.6, n = 235). C_{trough} over time is depicted in Figure 11.

Figure 11: Mean (SD) pre-infusion concentrations of sugemalimab (Study 301)



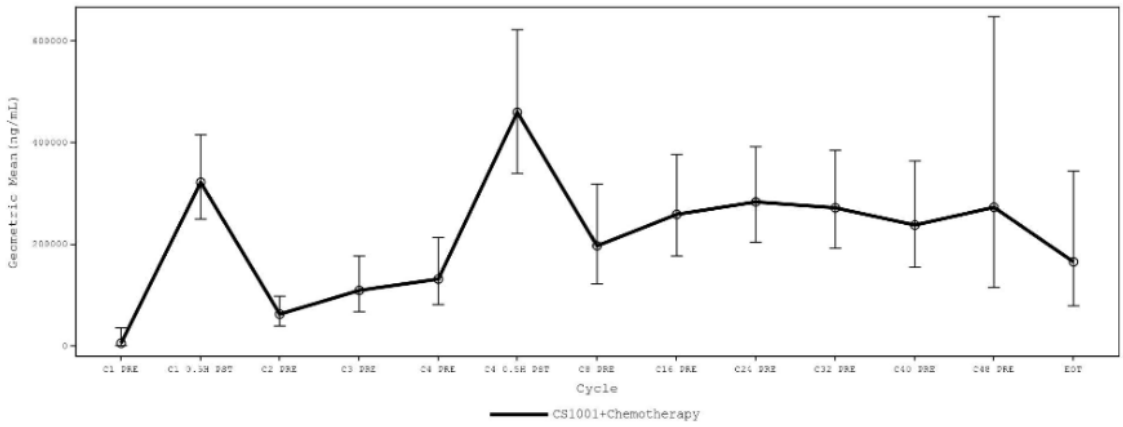
Pivotal study CS1001-302: Description of PK was a secondary objective..

As of 22 Nov 2021, a total of 320 participants had received sugemalimab 1200 mg IV Q3W. Patients in the sugemalimab group were predominantly male (80%), with a mean age of 64 years and were all of Asian race. Their BW ranged from 41 to 96 kg, with mean 62.5 kg (SD 9.7) and median of 61.0 kg.

Sparse blood samples for determination of sugemalimab serum concentrations were collected predose during Cycles 1, 2, 3, 4, and 8, and every 8 cycles thereafter and at the end of infusion during Cycles 1 and 4. An additional sample was taken at the EOT visit. Blood samples for determination of immunogenicity were collected predose during Cycles 1, 2, 3, 4, and 8, and every 8 cycles thereafter. An additional sample was taken at the EOT visit.

PK was available for up to 320 subjects. Sugemalimab geometric mean (CV%) $C_{trough,C4}$ and $C_{max,C4}$ were 131.95 (51.3%) µg/mL and 459.74 (31.0%) µg/mL, respectively. C_{trough} and end of infusion concentrations over time is depicted in Figure 12.

Figure 12: Mean (SD) concentrations of sugemalimab (Study 302)



From a total of 1471 immunogenicity samples (from 309 participants), 96 were ADA positive. The positive samples were attributed to 53 individual patients. ADA titres of up to 15500 were measured. 26 subjects (8.4%) had treatment induced ADA, and the ADA incidence was 9% (28 subjects). Five (1.6%) of 309 patients developed neutralizing anti-sugemalimab antibody.

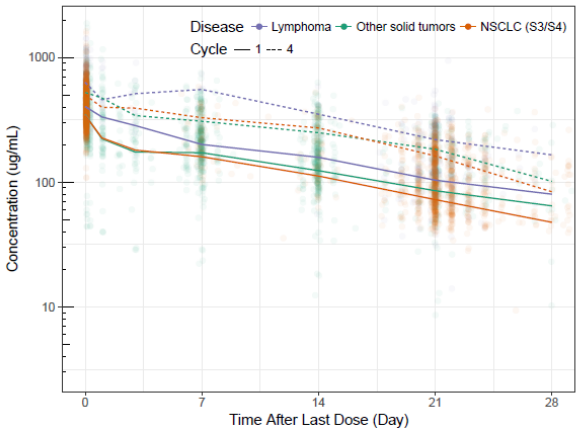
Comparison of PK profiles across disease status

The impact of disease status (i.e. type of cancer) on the sugemalimab PK profile was explored using graphical analysis and was tested as a covariate in the popPK analysis.

In the dataset used to develop the popPK model, 169 patients (17%) had lymphoma, 220 patients (22%) had other solid tumours, 259 patients (26%) had stage III NSCLC and 354 patients (35%) had stage IV NSCLC.

Figure 13 shows median concentration-time profiles of sugemalimab 1200 mg IV by disease and treatment cycle. Patients with lymphoma (purple lines) appeared to have higher sugemalimab exposure on both Cycles 1 & 4 compared to other patient populations (NSCLC and other solid tumours).

Figure 13: Concentration-time profiles by disease and Cycle - 1200 mg fixed dose Q3W.



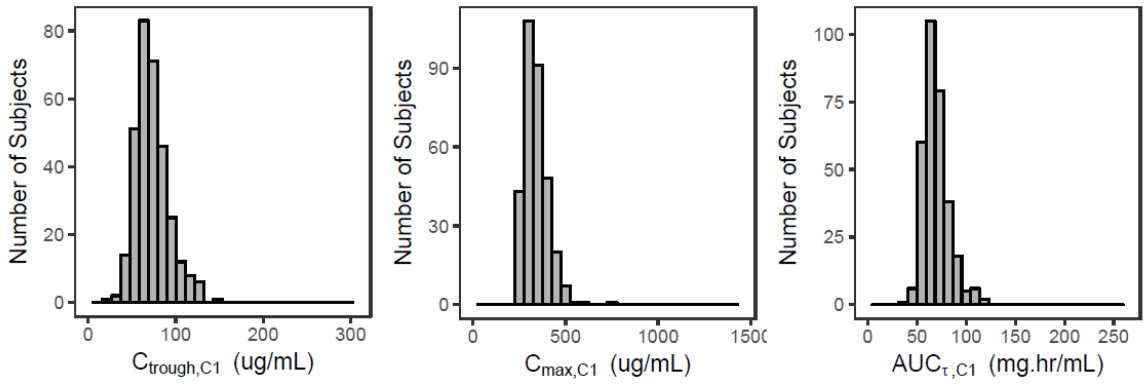
Solid lines show the median with symbols representing the *observed data. The data is shown on a logged Y-axis. Data below the LLOQ (0.2 µg/mL) were excluded.*

Disease status was identified as a significant covariate for sugemalimab PK in the popPK analysis and was included in the final model. Patients with lymphoma disease had 10.4% lower Vc and had a longer

time for the time-varying reduction in clearance (kdes parameter was 95% lower), patients with NSCLC had 221% higher Vp.

Histograms of maximum serum concentration on Cycle 1 (C_{max},C1), $_{trough}$ serum concentration on Cycle 1 (C_{trough},C1), and area under the serum concentration-time curve over the dosing interval on Cycle 1 (AUC_T,C1) are displayed in Figure 3 for subjects in study 302.

Figure 14: Histograms of sugemalimab exposure in study 302



$C_{trough,C1}$ = trough serum concentration on Cycle 1, $C_{max,C1}$ = maximum serum concentration on Cycle 1, $AUC_{\tau,C1}$ = area under the serum concentration-time curve over the dosing interval on Cycle 1.

Special populations

The effect of intrinsic factors on PK is evaluated via population PK analysis (pooling data across trials) and reported in the population PK report. No dedicated formal intrinsic factor PK studies were conducted.

Renal or hepatic function (and/or markers thereof) were not found to be a significant predictor of sugemalimab PK.

Sex was identified as a significant covariate where females were found to have lower Vc (14.2% lower), CL0 (9.6% lower) and CLT (28.7% lower).

Age was explored as a covariate in the covariate analysis during the popPK model development where age was not identified as a statistically significant covariate in the final model (based on $p<0.001$). Table 11 shows how many elderly were included in the studies with PK sampling.

Table 11: Number of elderly patients exposed to sugemalimab in clinical trials

PK Trials	Age 65-74 (Older Patients Number /Total Number)	Age 75-84 (Older Patients Number /Total Number)	Age 85+ (Older Patients Number /Total Number)
CS1001-101 1a	6/29	1/29	0/29
CS1001-101 1b	59/217	1/217	0/217
CS1001-102	8/24	4/24	0/24
CS1001-201	14/80	0/80	0/80
CS1001-202	3/80	0/80	0/80
CS1001-301	67/252	4/252	0/252
CS1001-302	116/320	2/320	0/320
Overall	**546/1002**	**12/1002**	**0/1002**

Study 102 was an ethnic bridging study conducted in the USA, as all other data was generated in Asian subjects. In total, 24 participants with solid tumours were treated as follows: 12 participants at 10 mg/kg IV Q3W and 12 participants at 1200 mg IV Q3W for up to 2 years. The bodyweight mean (range) was 82 kg (53-122 kg) in the 10 mg/kg group and 83 kg (36 to 124 kg) in the 1200 mg group.

PK parameters by group are presented in Table 12.

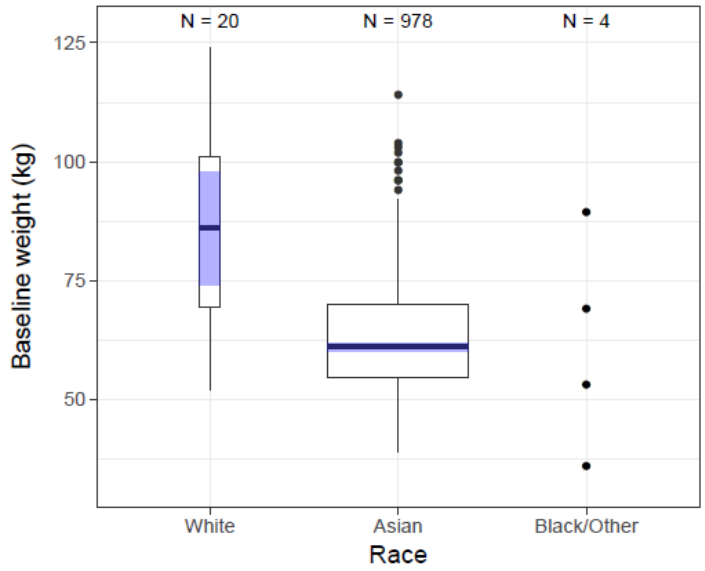
Table 12: Sugemalimab PK parameters at cycles 1 and 4 (Study 102)

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. Source: Clinical Study Report CS1001-102

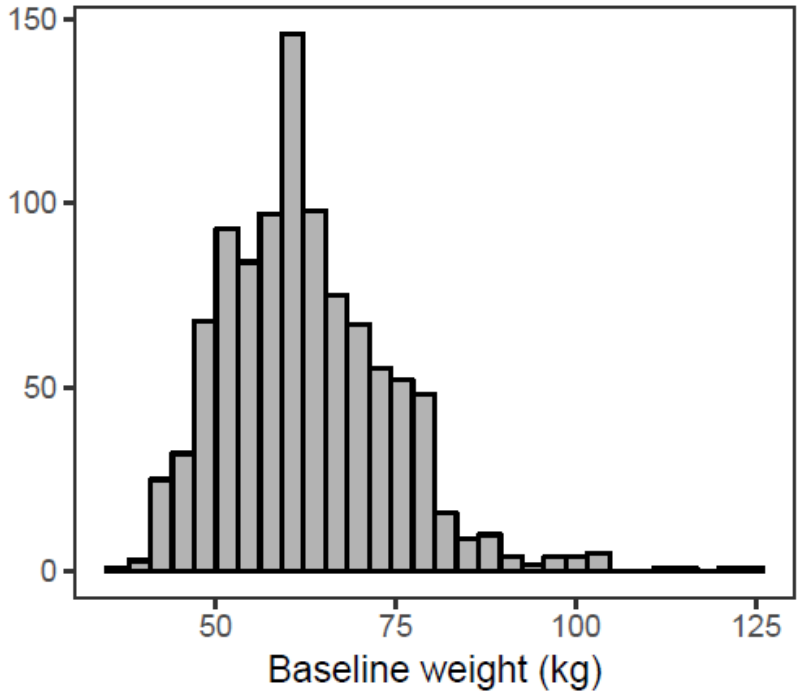
The PK in non-Asian (from study 102) was compared to the Asian population in the popPK analyses. Race was tested as a covariate in the popPK analysis where the majority of the subjects (n=978, 97.6%) were of Asian race. The non-Asian patients consisted of 20 Caucasian subjects and 4 subjects of other races. Race was not identified as a significant covariate in the final popPK model. Weight was generally higher in non-Asian patients compared to Asian patients.

Figure 15: Baseline weight vs race in the PopPK dataset



Weight was tested as a covariate in the popPK analysis where total body weight ranged from 36-124 kg (distribution shown below). For the whole dataset, the 10th and 90th percentiles for BW were 50 and 78 kg.

Figure 16: Weight histogram of patients in the PopPK analysis



The y-axis shows the number of patients in each bar.

Pharmacokinetic interaction studies

No formal drug interaction trials with sugemalimab have been performed.

Exposure relevant for safety

PopPK model predicted exposure at cycle 8 for study CS1001-302 was AUCtau: 163691 hr•µg/mL and C_{max}: 547 µg/mL.

2.6.2.2. Pharmacodynamics

Mechanism of action

The biological activity and function of sugemalimab were characterised in a series of nonclinical studies. The results from the *in vitro* studies demonstrated that sugemalimab bound to human PD-L1, competitively blocked binding of PD-L1 to PD-1 and induced the proliferation of CD4+ T-lymphocytes and the production of IFN-γ and IL-2. Sugemalimab showed no significant ADCC nor CDC on PD-L1 positive immune cells. In *in vivo* efficacy studies, sugemalimab has demonstrated tumour growth inhibition in humanised mouse models.

Primary and Secondary pharmacology

Study CS1001-101

Study CS1001-101a/b was an open-label, dose-finding, and dose expansion study to evaluate the safety, tolerability, PK profile, and preliminary anti-tumour efficacy of sugemalimab in participants with advanced solid tumours or lymphomas. The Phase 1a part of the study is complete and the Phase 1b part of the study is ongoing.

Objectives

Phase 1a (Dose-escalation):

Primary: To evaluate the safety and tolerability of sugemalimab and to determine the MTD and/or RP2D of sugemalimab.

Secondary: To describe the PK profiles of sugemalimab, to evaluate the immunogenicity of sugemalimab, and to preliminarily evaluate the anti-tumour efficacy of sugemalimab.

Phase 1b (Dose expansion):

Primary: To preliminarily evaluate the anti-tumour efficacy of sugemalimab used as a single agent and in combination with other therapies in subjects with various specific tumour types.

Secondary: To further evaluate the safety and tolerability of sugemalimab, to further evaluate the PK profile of sugemalimab, and to assess the immunogenicity of sugemalimab.

Study Design

Phase 1a (Dose-escalation)

In the Phase 1a dose-escalation part of the study, a 3 + 3 dose-escalation design was adopted. Participants received sugemalimab doses of 3, 10, 20, 40 mg/kg and a fixed dose of 1200 mg administered IV Q3W. Blood samples were collected to determine the serum concentration of sugemalimab as well as to assess immunogenicity. During Cycles 1 and 4, intensive PK samples were taken predose and at 0.5, 1.5, and 6 hours post-infusion, and then at 24, 72, 168, and 336 hours. During Cycles 2, 5, 7, 10, 13, 16, and every 8 cycles thereafter, a single predose sample was taken. Samples for immunogenicity were taken predose during Cycles 1, 2, 4, 5, 7, 10, 13, and 16, and then once every 8 cycles.

Phase 1b (Dose Expansion)

In the Phase 1b expansion part of the study, participants are administered a fixed dose of 1200 mg IV Q3W for up to 2 years. Blood samples for determination of sugemalimab serum PK and immunogenicity were collected. During Cycles 1 and 4, samples for PK were taken predose and at 0.5, 168, and 336 hours postdose. During Cycles 2, 5, 7, 10, 13, 16, and then every 8 cycles, predose samples were taken. Predose samples were taken to assess ADA during Cycles 1, 2, 4, 5, 7, 10, 13, and 16, and then every 8 cycles.

In addition, peripheral blood samples were collected before Day 1 administration in Cycles 1, 2, and 4, and the PD-L1 binding (receptor occupancy) in circulating peripheral blood leukocytes was measured by flow cytometry to evaluate the pharmacodynamic characteristics of sugemalimab.

Pharmacodynamic Results

Phase 1a (Dose-escalation)

The selection of a fixed dose of 1200 mg IV infusion Q3W was mainly based on the following:

1. The fixed dose of 1200 mg IV Q3W had acceptable safety and tolerability profiles. No DLT event occurred, and no MTD was obtained. The incidence rates of TEAE and TRAE observed at dose levels of 3 to 40 mg/kg IV Q3W (including the fixed dose of 1200 mg IV Q3W) were comparable, indicating that the occurrence of side effects was not significantly dose dependent at these dose levels.
2. The PK results showed that the exposure of sugemalimab was dose-proportional over the range of 3 to 40 mg/kg IV Q3W (including the fixed dose of 1200 mg IV Q3W). 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.

Based on the aforementioned reasons, sugemalimab showed a wide treatment window and a flat exposure-safety relationship. In addition, considering the convenience of clinical application, the fixed dose of 1200 mg IV Q3W was selected as the recommended dose for subsequent studies.

Phase 1b (Dose Expansion)

Receptor occupancy (RO) data were available from 6 participants in the 1200 mg fixed dose IV Q3W group in this study. At predose on Cycle 2 Day 1, all 5 evaluable patients showed 100% RO. At predose on Cycle 4 Day 1, a 100% RO was consistently observed in all 3 evaluable patients.

Study CS1001-102 (US)

Study CS1001-102 was a Phase 1, open-label, multiple-dose, dose-escalation study to evaluate the safety, tolerability, and RP2D of single agent sugemalimab in participants with advanced solid tumours.

Objectives

Primary: To assess the safety and tolerability of sugemalimab and to determine the RP2D of sugemalimab.
Secondary: To characterise the PK profile of sugemalimab, to evaluate the preliminary anti-tumour activity of sugemalimab, and to assess the immunogenicity of sugemalimab.

Study Design

This study used a 3 + 3 dose-escalation scheme to evaluate 2 dose levels of sugemalimab sequentially: 10 mg/kg IV Q3W and 1200 mg IV Q3W. Both dose levels were determined safe and

tolerable. In total, 24 participants with solid tumours were treated as follows: 12 participants at 10 mg/kg IV Q3W and 12 participants at 1200 mg IV Q3W for up to 2 years.

Serial blood samples for determination of serum PK and immunogenicity were collected throughout the study. During Cycles 1 and 4, intensive samples for PK determination were taken predose and at 0.5, 1.5, and 6 hours post-infusion, and then at 24, 72, 168, and 336 hours. During Cycles 2, 3, 5, 7, 10, 13, 16, and every 8 cycles thereafter, a predose sample was taken. In addition, samples were taken at EOT and at the first safety follow-up visit. Samples for ADA analysis were taken predose at Cycles 1, 2, 3, 4, 5, 7, 10, 13, 16, and every 8 cycles thereafter, as well as at EOT and the first safety follow-up visit. In addition, peripheral blood samples were collected before Day 1 administration in Cycles 1, 2, and 4, and the PD-L1 binding in circulating peripheral blood leukocytes was measured by flow cytometry to evaluate the pharmacodynamic characteristics of sugemalimab.

Pharmacodynamic Results

RO was tested on whole blood samples from 7 evaluable participants in this study (3 in the 10 mg/kg group and 4 in the 1200 mg fixed dose group). All reached 100% RO at the predose of Cycle 2 Day 1. A consistently high level of RO (76% to 100%) was shown in the 3 participants at the predose of Cycle 4 Day 1.

A fixed dose of sugemalimab 1200 mg IV Q3W was selected for further development.

Immunogenicity, Study CS1001-302

Of the 309 immunogenic serum samples in the sugemalimab group, the antidrug antibody-positive case rate of sugemalimab induction was 28 (9.0%) participants. A total of 5 (1.6%) participants developed NAb.

Of the 5 NAb positive participants, 4 had an BOR per Investigator as PR; the remaining participant had an BOR of stable disease with an OS of 10 months. Four participants were alive at the time of interim OS DCO3 with a censored OS ranging from 21.1 to 29.5 months.

Relationship between plasma concentration and effect

Exposure-response analyses were performed for safety- and efficacy-related endpoints. The objectives were to:

• Evaluate the relationship between exposure and the efficacy of sugemalimab when given in combination with chemotherapy in patients with stage IV NSCLC from study CS1001-302, and covariates that may affect the relationship between exposure and efficacy.

• Evaluate the relationship between exposure and the safety of sugemalimab in patients with advanced solid tumours or lymphomas, and covariates that may affect the relationship between exposure and safety.

The efficacy-related endpoints included overall response (OR), progression-free survival (PFS) and overall survival (OS). The relationship between sugemalimab exposure and measures of efficacy was explored in stage IV NSCLC patients based on available data from patients receiving 1200 mg IV Q3W in study CS1001-302. A total of 320 subjects were analysed. Additionally, the 159 subjects in the placebo arm from study CS1001-302 were included in the graphical review of PFS and OS versus exposure quartiles.

Safety-related endpoints included:

- Hepatitis (treatment emergent, immune related)

- Hypothyroidism (treatment emergent, immune related)
- Hyperthyroidism (treatment emergent, immune related)
- Skin adverse reactions (severe, treatment emergent, immune related)
- Skin adverse reactions (excluding severe, treatment emergent, immune related)
- Pneumonitis (treatment emergent, immune related)
- Any ≥ grade 3 treatment emergent sugemalimab related AEs
- Liver enzyme elevation (alanine aminotransferase (ALT) or/and aspartate aminotransferase (AST)>3xULN and total bilirubin (TBIL)≥2xULN)

The relationship between sugemalimab exposure and measures of safety was explored for patients with solid tumours (including stage III and IV NSCLC) and lymphomas from the studies CS1001-101-1a/b, CS1001-102, CS1001-301, CS1001-302 who were treated with sugemalimab. To allow for full characterisation of the exposure-safety relationship, the intravenous doses included ranged from 3 mg/kg - 40 mg/kg Q3W in addition to the proposed clinical dose of 1200 mg Q3W. Each safety endpoint below was dichotomised as experiencing zero or ≥1 occurrence/event. In summary, a total of 842 subjects were included with safety data from four clinical studies (Safety Population).

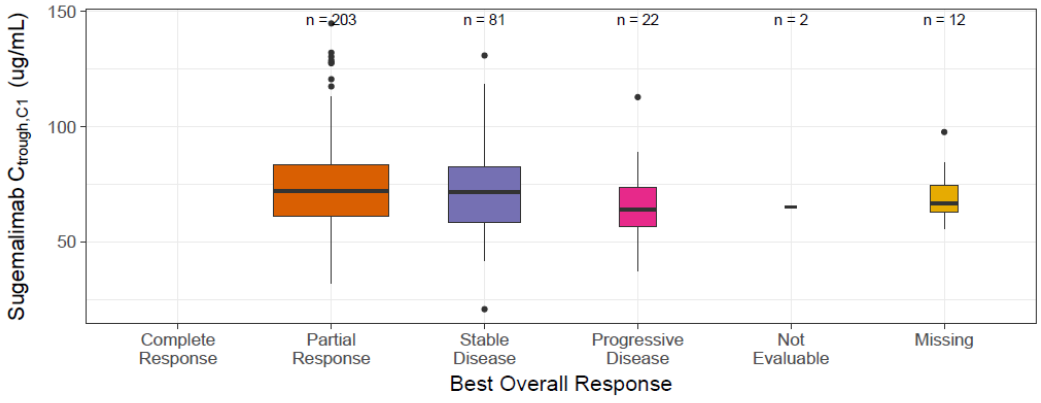
The exposure (individual model predicted concentration-time profile) was generated using maximum a posteriori (MAP) estimates of the PK parameters from the final population PK model and included C_{max}, C_{trough} and AUCτ following a single dose (Cycle 1).

The exposure-response analyses were based on both graphical analysis and model-based approaches.

Efficacy

OR was defined as 'responder' if BOR was CR/PR, and 'non-responder' for other types of BOR i.e. SD, PD, or NE. Boxplots of BOR by, C_{trough},C1 are displayed below.

Figure 17: Boxplots of C_{trough},C1 by best overall response (investigator-assessed)

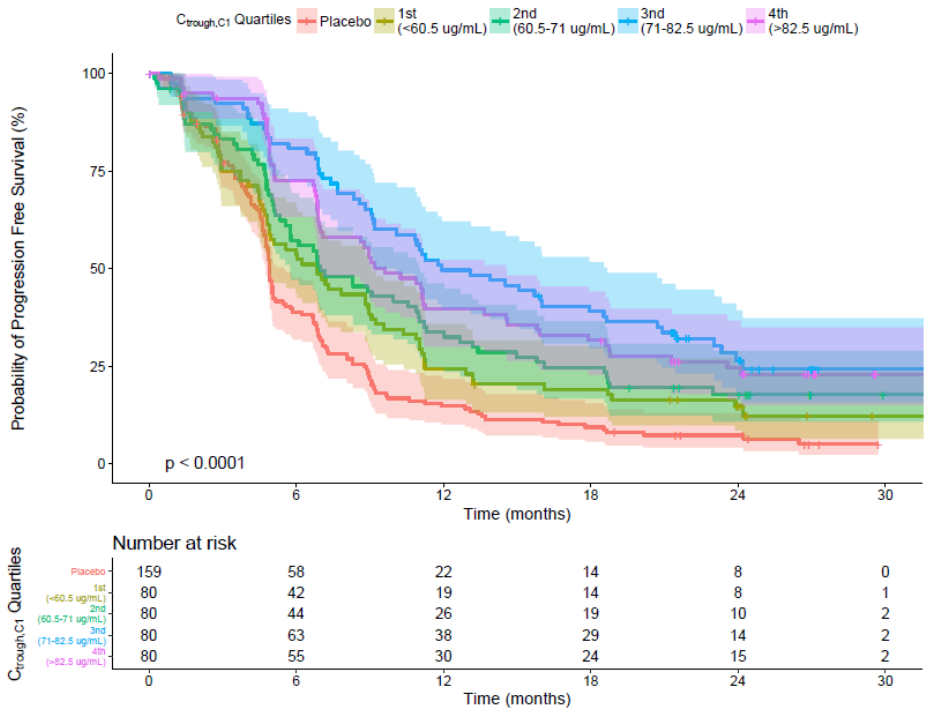


The thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. Box widths are proportional to the square-roots of the number of observations in the groups.

A logistic regression was also performed for OR. The final logistic regression ER model for OR (PR vs SD + PD + NE) showed no significant relationship between sugemalimab exposure (log C_{trough},C1) and the probability of response, with a corresponding p-value of 0.085.

Kaplan-Meier curves of PFS (as assessed by the Investigator) by quartiles of C_{trough},C1 are displayed below.

Figure 18: Progression-free survival by quartiles of C_{trough},C1 (investigator-assessed)

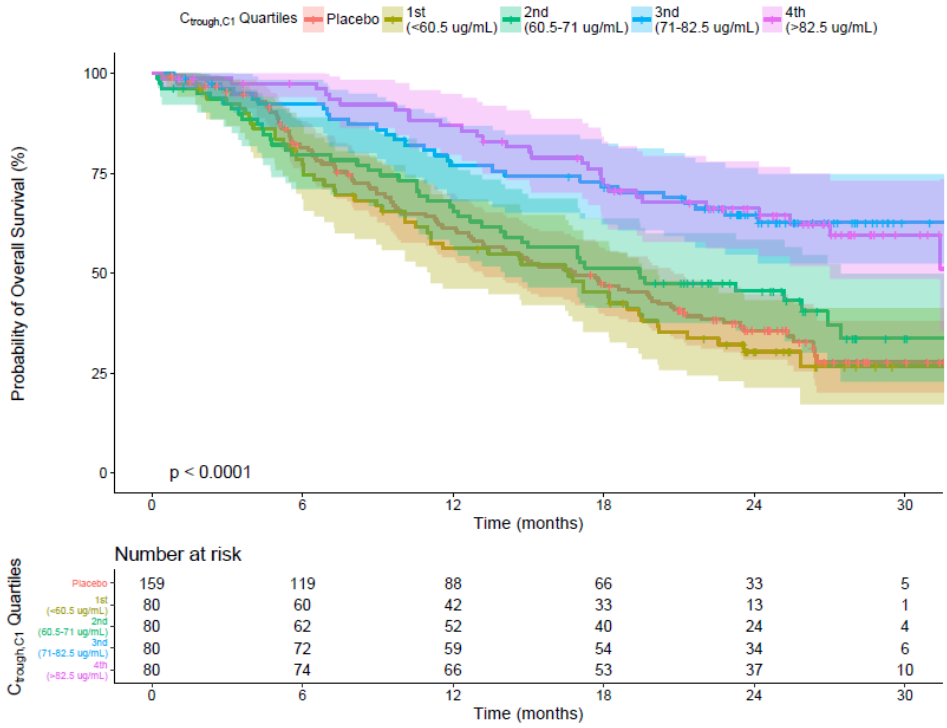


Solid lines represent Kaplan-Meier curves, shaded areas represent 95% CI, and p-value is derived from a log-rank test.

A time-to-event regression analysis was performed for PFS. There was an estimated 9.2% reduction in the hazard of disease progression or death per increase in C_{trough},C1 of 10 µg/mL. The only significant covariate in the final model was baseline PD-L1 expression, where patients with a baseline PD-L1 expression of <1% had an ≈1.46-fold increase in the risk of disease progression.

Kaplan-Meier curves of OS by quartiles of C_{trough},C1 are displayed below .

Figure 19: Overall survival by quartiles of C_{trough},C1



Solid lines represent Kaplan-Meier curves, shaded areas represent 95% CI, and p-value is derived from a log-rank test.

A time-to-event analysis was performed for OS. The model comprised an exponential hazard structure with a linear drug effect. There was an estimated 20.2% reduction in the hazard of death with an increase in C_{trough},C1 of 10 µg/mL. No significant covariates were identified in the final model.

Safety

There was no relationship evident between sugemalimab exposure and an increase probability of safety events for any tested exposure metric (data not shown).

2.6.3. Discussion on clinical pharmacology

Methods

The method for quantification of sugemalimab is adequately validated and showed sufficient selectivity and specificity. The different batches of critical reagents used in the validation and during study sample analysis were adequately qualified.

The reliability of the immunogenicity results from the first-generation ADA assay may be questioned, due to insufficient drug tolerance and poor precision. Thus, immunogenicity may be underestimated in study 101a. As data in the target population is available with another assay, this issue was not pursued.

The second-generation ADA method is fully validated, with sufficient drug and target tolerance for use in the sugemalimab development programme. The different critical reagents were adequately qualified.

The nAb method is fully validated. Drug tolerance was insufficient for the lowest level of positive control (100 ng/mL), thus samples with low nAb levels may be false negative, even at C_{trough} (132 µg/mL at cycle 4 in the pivotal study). As the second-generation ADA method is sufficiently sensitive, the issue is not pursued.

Absorption

No absorption study was conducted as sugemalimab is administered by intravenous injection and is therefore immediately and completely bioavailable.

No study was conducted to compare the PK of sugemalimab process A, B or B´. B´ is the material intended for commercial use, which was not included in clinical studies. Comprehensive analytical comparability studies were required, see Quality section. The absence of in vivo studies between process B and B´ is acceptable as it is supported by in vitro comparability data.

There are differences in the glycosylation pattern between process material A and B that could cause differences in PK. Both processes A and B were used in nearly all clinical studies, with the exception of study 101a where only process A was used and studies 301 and 302 where only process B was used. The applicant clarified that process material information at cycle 1 was available for 994 patients, thereof with PK data for 225 with process A material and 697 with process B material. The observed PK parameters indicate a slightly lower exposure following the administration of process material B compared to A. The 90% CI for C_{max} and AUCtau were within the 80-125% boundaries, thus similarity between process material A and B can be concluded and PK parameters using either process material could be used in the SmPC.

Sampling was insufficient to rely on the elimination rate as calculated by NCA for study 101a. As this data is included in the popPK analyses, this is acceptable.

The applicant presented PK data for cohort 12, receiving 1800 mg sugemalimab Q4W. Clearance was in a similar range as for 1200 mg Q3W and decreased over time.

The visual comparison of PK parameters in study 101b seems to indicate that PK is similar across cancer types, however the popPK analyses, where data from additional studies is included, denotes a higher exposure in lymphoma patients.

The SmPC text on absorption, dose proportionality and accumulation was based on data from study 101a.

Following single- and multiple-doses escalation study of sugemalimab (n=29), sugemalimab exposures (AUC and C_{max}) increased in an approximately dose proportional manner within the dosing range of 3 mg/kg to 40 mg/kg, including a fixed dose of 1200 mg intravenous every 3 weeks. Following multiple intravenous infusions of 1200 mg every 3 weeks (n=16), there was approximately 2-fold accumulation of sugemalimab exposures (see SmPC 5.2).

Distribution

No plasma protein binding or tissue distribution study was performed. This is acceptable.

The distribution of sugemalimab is consistent with reported distribution properties of other IgG1s in human. The volume of distribution of sugemalimab was estimated to be low according to the popPK analysis.

Section 5.2 of the SmPC states that the V_{ss} from popPK analysis was small, with a geometric mean (CV%) V_{ss} of 5.56 L (21%) is based on the volume of distribution from the popPK analysis, which is acceptable.

Elimination

The metabolic pathways of sugemalimab have not been investigated. This is acceptable for an IgG antibody. Commonly the t½ reported for human IgG is around 20 days, though there is a wide range in the reported values.

The proposed text in the SmPC is based on the CL and half-time estimates from the popPK analysis, stating that the geometric mean (CV%) of total clearance (CL) after a single dose was estimated to be 0.235 L/day (24.2%), and at steady state, the geometric mean (CV%) of $t_{1/2}$ was approximately 17.9 days (25.6%) at the end of cycle 1, which is acceptable. Furthermore, the SmPC text regarding elimination describes the time-varying elimination of sugemalimab due to target-mediated drug disposition which is relevant (see below).

Dose proportionality, time dependencies and immunogenicity

Dose proportionality between 3 to 40 mg/kg sugemalimab is agreed.

Sugemalimab showed time-dependent PK, with increased exposure over time. This was described as an empirical component incorporated in the structural popPK model (see target population, below).

Apart from the empirical time-varying CL described above, CL can also vary with time in individual patients by time-varying ADA titre which was a covariate on the time-varying CL component (CL_T), according to the popPK model. Of note, the popPK model predicts that the time-varying CL (CL_T) component approaches the value 0 L/day as time on treatment progresses. As time-varying ADA titre is a covariate on the time-varying CL component, the model will predict that a patient whose ADA titre value increases at a relatively late stage will not achieve a higher clearance. This is considered a limitation of the model since this is not viewed as a mechanistically plausible implementation of ADA titre as a covariate. However, the overall impact of ADA on sugemalimab PK does not appear to be influential, and thus, this issue was not pursued further.

ADA titres were generally higher in study 302 (the prevalence of anti-drug antibodies (ADA) was 17% (53 patients), with 9% (28 patients) as treatment-emergent ADA), and some patients had persistent ADA. It is agreed that the effect of ADA on the PK of sugemalimab leads to exposures within the variability of ADA negative subjects and is thus likely not clinically relevant. This is reflected in section 5.1 of the SmPC.

The inter-individual variability is considered moderate. No intra-individual variability in PK parameters was included in the popPK model, which is considered acceptable.

Target population

Pharmacokinetics of sugemalimab was evaluated in the target population consisting of stage IV NSCLC patients, including analysis using a population pharmacokinetic approach. The objectives outlined for the popPK part are overall relevant.

The popPK was developed on a dataset including 1002 patients, who received sugemalimab doses in the range of 3 to 40 mg/kg and fixed dose of 1200 mg intravenous every 3 weeks, with different disease status, including a total of 7054 observations, from a mixture of studies with rich- and sparse type PK sampling schedules. This is considered an overall solid basis for developing a popPK model to characterise the PK characteristics of sugemalimab.

The available covariates and their distribution appear overall reasonable. The distribution for albumin, which was identified as an influential covariate, covers a wide range of values (26.1-96 g/L). However,

the distribution included a few outlying individuals with very high values (>60 g/L). It is unclear if these outliers had an impact on the estimated coefficients for parameter-covariate relationships including albumin. Since no dose adjustments are deemed necessary based on albumin, the potential influence of these outliers is not considered clinically relevant.

An overall standard battery of graphical and numerical diagnostics was used during the popPK model development, which is acceptable. Parameter uncertainty estimation was performed using sampling importance resampling (SIR), which is considered acceptable. Prediction- and variability-corrected VPCs were generated, which is considered a key diagnostic.

The model development strategy is overall reasonable. Target-mediated drug disposition of sugemalimab was explored as part of the structural model development by investigating time-varying elimination and TMDD using a QSS approximation.

Overall reasonable covariates were explored, including race which is considered important. For investigating influence of ADA, time-varying ADA was explored as a categorical covariate (positive/negative) and as a continuous covariate (titre value) which is acceptable. Several covariates were identified to be significant and hence included in the final model, including sex, weight, albumin, ADA titre and disease state. These covariates are considered overall reasonable and generally in line with the PK behaviour of other checkpoint inhibitors. Of note, albumin was identified as an influential covariate in the model, including a relationship on sugemalimab clearance where higher baseline albumin levels were associated with lower sugemalimab clearance. Higher albumin levels could be indicative of altered (reduced) ability by a patient to break down proteins, and under this hypothesis it could also mean that sugemalimab would also be cleared more slowly in subjects with high albumin levels (as both albumin and sugemalimab are proteins and may be eliminated by similar pathways). Furthermore, albumin level may be correlated with severity of NSCLC disease, with lower baseline albumin for stage IV than stage III disease.

Impact of disease status was explored both graphically and in the covariate analysis of the popPK analysis. Based on the graphical analysis, it appears that exposure was somewhat lower in NSCLC patients than lymphoma patients. Differences in the PK were also identified according to the covariate analysis in the popPK model where lymphoma patients were found to have lower Vc and longer time for reduction in clearance. In addition, NSCLC patients were found to have higher Vp.

Furthermore, body size was included in the model which is a known influential covariate for monoclonal antibodies including checkpoint inhibitors. According to the pvcVPC stratified by body weight during Cycle 1, the model gives an acceptable description of the data (data not shown).

For the pvcVPC stratified by cycle in NSCLC patients there is an under-prediction at Cycle 4 beyond 10 days in the pvcVPC. This model-misspecification is considered a limitation of the final popPK model. Since this misspecification seems specific for late time-points (under-prediction for Cycle 4 but not for Cycle 1), the final popPK model is considered acceptable for making simulations during Cycle 1 to support dose selection.

The simulated exposure (C_{trough},C1) following 1200 mg Q3W for high body weight and reference range from Study CS1001-302 with proposed target lower limit indicate that the exposure is below the target exposure range for a considerable proportion of patients with body weight above 115 kg. As such, an increased dose of 1500 mg Q3W for patients >115 kg was proposed. Simulations which justified the proposed dosing recommendation of 1200 mg Q3W in patients ≤115 kg and 1500 mg Q3W in patients >115 kg were provided. The simulations showed that the expected PK exposure in patients >115 kg better matched the observed exposure in the pivotal Study CS1001-302 when administered 1500 mg Q3W. Increasing the dosage to 1500 mg Q3W is anticipated to effectively mitigate the under-exposure

in C_{trough} and AUC without raising C_{max} by more than 25% and achieve comparable exposures to the patients in the pivotal study CS1001-302 that were dosed with 1200 mg Q3W.

Special populations

Bearing in mind that sugemalimab is a therapeutic protein and is not (directly) subject to renal or hepatic elimination, the lack of a dedicated study is acceptable. The popPK based conclusions are agreed for renal and hepatic impairment.

Regarding renal impairment, a recommendation to administer with caution has been added for severe renal impairment in section 4.2 of the SmPC, and the text in section 5.2 has been aligned with section 4.2 to say that no treatment modification is required in patients with mild or moderate renal impairment.

Regarding hepatic impairment, a recommendation to administer with caution has been added for moderate and severe hepatic impairment in section 4.2 of the SmPC. No treatment recommendation is recommended for patients with mild hepatic impairment as stated in sections 4.2 and 5.2 of the SmPC.

Age was not identified as a statistically significant covariate in the final model (based on $p<0.001$).

Sex was a covariate in the popPK model for sugemalimab (lower clearance and volume for females). The effect of sex on systemic exposure of sugemalimab is not considered clinically meaningful.

Few patients were non-Asians which makes it difficult to firmly conclude whether there is an effect or not of race on the PK characteristics of sugemalimab. However, there was no observed PK difference in sugemalimab between Asian and non-Asian participants and sugemalimab is a monoclonal antibody and is not subject to metabolism or active secretion processes which is known to differ according to race. For a patient of similar bodyweight, sugemalimab PK is thus likely insensitive to race/ethnicity.

Of note, the body weight of the Asian patients studied in this procedure is expected to be lower than in the general EU population. This may explain why non-Asian patients appeared to have lower exposure than Asian patients.

Body size is a known influential covariate for monoclonal antibodies including checkpoint inhibitors. Hence, body weight was explored as a covariate, using a power model (see discussion in the target population section).

Pharmacokinetic interaction studies

The lack of pharmacokinetic interaction studies is acceptable. Since sugemalimab is cleared from the circulation through catabolism, no metabolic interactions with other medicinal products are expected. This is adequately reflected in section 4.5 of the SmPC.

Pharmacokinetics-pharmacodynamics

Overall, reasonable objectives and data selection has been performed for the exposure-response analysis. For efficacy, only patients from the target population (stage IV NSCLC patients) are selected which is acceptable. However, this means that nearly all efficacy data are from the 1200 mg Q3W regimen which is a big limitation which should be taken into consideration when interpreting the exposure-efficacy analyses.

For efficacy endpoints, overall relevant endpoints were included. This included a dichotomous categorical endpoint, OR, and two TTE endpoints, PFS and OS. Based on the results for PFS, there was a potential exposure-response trend seen in the data and according to the model-based analysis. For

OR and OS, no clear exposure-response trends were seen. Considering that only a single dose-level was included, overall the results do not indicate any strong exposure-response relationship.

For the ER analyses of safety endpoints, overall relevant endpoints were included where exposure-response analyses were performed using graphical and model-based approaches. Neither approach (graphical and model-based) identified any meaningful exposure-response relationship. In contrast to the exposure-response analysis of efficacy endpoints, more than a single dose level was included for safety endpoints. The dose range covered 3 mg/kg to 40 mg/kg. However, there were very few subjects in the 3 and 40 mg/kg dose arms (n=3 each) and most subjects were treated with 1200 mg sugemalimab Q3W. In addition, there were 16 patients treated with 10 mg/kg. Overall, this is not considered an optimal dataset for identifying exposure-response in safety endpoints and no firm conclusions can be drawn. The data should be interpreted with caution.

Efficacy simulations were performed to support dose selection in the non-Asian population. The efficacy simulations were stratified by populations with different body weight including Asian, non-Asian and extreme body weight populations. Overall, the simulations were conducted in a reasonable manner. However, the exposure-response analyses for efficacy had overall low impact and are not considered sufficiently robust to give substantial support for the dosing recommendations for non-Asian patients.

The ER analyses for efficacy and safety are considered to have low impact for the overall benefit-risk assessment in the current procedure and hence, the outlined limitations of the ER analyses will not be pursued further.

2.6.4. Conclusions on clinical pharmacology

The PK of sugemalimab is generally well-described. The clinical pharmacology part of the dossier is overall acceptable.

2.6.5. Clinical efficacy

The primary demonstration for the efficacy of sugemalimab in the treatment of adults with metastatic NSCLC comes from the pivotal, Phase 3, randomised, double-blind, placebo-controlled study, CS1001-302. Supportive evidence for sugemalimab efficacy comes from the Phase 3, randomised, double-blind, placebo-controlled study in participants with locally advanced, unresectable (Stage III) NSCLC, CS1001-301.

Table 14: Overview of clinical efficacy studies for sugemalimab in the treatment of metastatic NSCLC

	Study CS1001-302 (pivotal)	Study CS1001-301 (supportive)
Study design	Phase 3, multicentre, randomised, and double-blind sugemalimab administration in combination with chemotherapy	Phase 3, randomised, double blind, placebo controlled, monotherapy
Description	First-line metastatic (Stage IV) NSCLC/ITT	Stage III NSCLC/ ITT
Study objectives/ population	Primary Objective: To compare efficacy between sugemalimab in combination with platinum-based chemotherapy and placebo in combination with platinum-based chemotherapy	Primary Objective: To compare the efficacy of sugemalimab and placebo
Sugemalimab dose regimen	Sugemalimab 1,200 mg intravenous infusion/ Q3W	Sugemalimab dose 1,200 mg intravenous infusion
No of patients (N)	479 enrolled	381 enrolled
Gender M/F, Median Age	M 80%/F 20%, Median age 63	M 92%/F 8%, Median age 61
Start date	13 December 2018	26 October 2018
Completion date	Ongoing	Ongoing
Primary endpoint(s)	PFS (per RECIST v1.1), assessed by investigator	PFS (per RECIST v1.1), assessed by BICR
Countries	China (35 centres)	China (50 centres)

2.6.5.1. Dose response studies

Refer to section 2.6.2.2

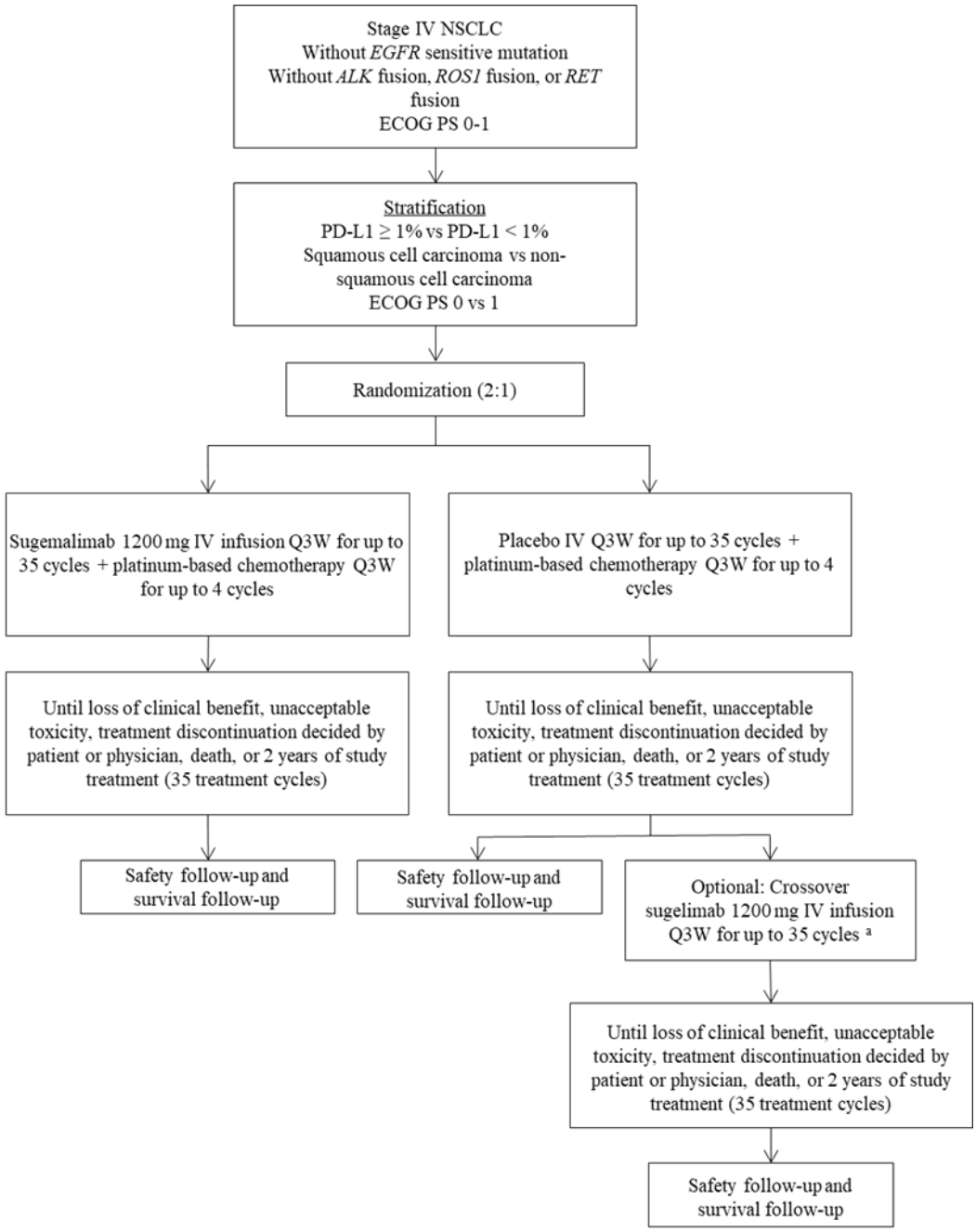
2.6.5.2. Main study

Study CS-1001-302 (GEMSTONE-302): a multicentre, randomised, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of sugemalimab combined with platinum-based chemotherapy versus placebo in combination with chemotherapy in first-line, treatment-naïve participants with metastatic NSCLC.

The study was conducted exclusively in China and has completed enrolment.

The study included 3 phases: screening (up to 28 days prior to the first dose), treatment (until PD, unacceptable toxicity, loss of clinical benefit, participant withdrawal of informed consent, death, other causes specified in the protocol, or 2 years of sugemalimab treatment), and follow-up (including safety follow-up and survival follow-up).

Figure 20: Study design for study CS1001-302



Methods

- **Study Participants**

The study was conducted in China. A total of 35 centres screened and randomised patients.

Main Inclusion Criteria

1. 18-75 years of age (18 and 75 included) on the day of signing ICF.
2. Histologically or cytologically confirmed stage IV non-small cell lung cancer (staged according to the 8th International Association for the Study of Lung Cancer (IASLC) classification; squamous cell or non-squamous cell histology). Without known EGFR sensitive mutation, ALK fusion, ROS1

fusion or RET fusion. Testing of actionable mutations were done locally according to routine clinical practice.

3. Patients did not receive systemic treatment for advanced/metastatic NSCLC. Patients who received chemotherapy and/or radiotherapy as neoadjuvant/adjuvant therapy were eligible if the therapy was completed at least 6 months before being diagnosed as stage IV NSCLC.
4. ECOG PS of 0-1.
5. Patients were required to have adequate organ function as assessed in the following laboratory tests (patients must not have received any blood transfusion, apheresis component infusion, erythropoietin, granulocyte colony stimulating factor or other medical supportive treatment within 14 days prior to the experimental drug administration):
   - ANC ≥1.5 × 109/L
   - Platelets ≥100 × 109/L
   - Haemoglobin ≥9 g/dL or ≥5.6 mmol/L
   - Serum creatinine clearance ≥50 mL/min (according to Cockcroft-Gault equation)
   - Total bilirubin ≤1.5 × ULN
   - AST and ALT ≤2.5 × ULN; ≤5 × ULN for patients with hepatic metastasis
   - INR, PT or aPTT ≤1.5 × ULN
   - TSH ≤ULN (if TSH is outside normal range, free T3 and free T4 levels must be within normal range)

Main Exclusion Criteria

1. Patients with active or untreated central nervous system (CNS) metastasis and/or carcinomatous meningitis were excluded with the following exceptions:
   - Patients with previously treated brain metastasis may participate provided the brain metastasis was clinically stable with radiological evidence for at least 4 weeks, the patient had no new or enlarged brain metastasis (confirmed before the first dose of study medication), and the patient was off corticosteroids 3 days prior to dosing with study medication.
   - Patients with asymptomatic brain metastasis (i.e., no progressive central nervous system symptoms caused by metastasis, no requirements for corticosteroids, and no lesion > 1.5 cm) may have participated but required regular imaging of the brain as a site of disease.
2. Patients with active autoimmune disease or prior history of autoimmune disease that may relapse (such as systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, autoimmune thyroid conditions, vasculitis, etc.) or at risk of having these conditions (for example having received organ transplantation or immune suppressant treatment). Patients with the following conditions were allowed to be screened: Type I diabetes mellitus, hypothyroidism or hyperthyroidism that were managed without immunosuppressant treatment, and a dermatological condition that doesn't require systemic treatment (such as leukoderma, psoriasis or alopecia), or diseases not expected to relapse without any external triggering factors.

3. Currently under systemic corticosteroid treatment (equivalent to > 10 mg/day prednisone) or any other form of immune suppressing treatment within 14 days prior to the first dose of sugemalimab.
4. Any prior treatment of antibody/drug that targets T-cell coregulatory proteins (immune checkpoints, including PD-1, PD-L1, CTLA4, TIM3, LAG3, etc.).

Patients with major cardiovascular disease (for example heart failure of New York Heart Association (NYHA) Grade 2 or above, unstable angina, unstable arrhythmia); acute myocardial infarction, unstable angina, stroke, or transient ischemic attack within 6 months before first dose of study treatment; severe arrhythmia that necessitates medication ;patients who had a live-virus vaccine administration within 28 days of the study treatment start; HIV infection**,** hepatitis B or hepatitis C infection; a history of interstitial lung disease or idiopathic pulmonary fibrosis.

- **Treatments**

Eligible participants were randomised 2:1 to receive either 1,200 mg sugemalimab in combination with platinum-based chemotherapy or placebo in combination with platinum-based chemotherapy Q3W. This comparator was based on the CSCO guidelines for SOC treatment and administration at the time of protocol development and study initiation in 2018.

Both treatment groups received induction treatment consisting of carboplatin in combination with pemetrexed (for non-squamous histology) or paclitaxel (for squamous histology) for up to 4 cycles with additional maintenance treatment with sugemalimab/placebo in combination with pemetrexed for participants with non-squamous cell histology and sugemalimab/placebo monotherapy for participants with squamous histology. Each cycle consisted of 21 days (3 weeks).

The maximum duration for the treatment of sugemalimab or placebo was up to 35 cycles (approximately 2 years) or until PD, unacceptable toxicity, loss of clinical benefit, withdrawal of informed consent, death, or other reasons stipulated in the protocol. The follow-up phase included safety and survival follow-up.

Dose modification of sugemalimab or placebo:

Dose modification was not permitted for either sugemalimab or placebo. In case of any treatment-related adverse event, sugemalimab should be withheld or discontinued. The withholding of sugemalimab or placebo should not exceed 12 weeks.

Dose modification of chemotherapy:

Dose modification of chemotherapy was permitted and followed local clinical practice and the package inserts of medications. The investigator could reduce the dose according to the severity of AE occurred after chemotherapy monotherapy or combination therapy, when necessary.

- **Objectives**

Table 13: Study objectives

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

- **Outcomes/endpoints**

Assessment schedule

Screening and double-blind phase: All patients received chest/abdomen/pelvis enhanced CT or MRI scanning (chest CT must be performed if others were examined with MRI). Scanning without contrast was acceptable if the patient had a hypersensitivity to contrast. Chest X-ray or ultrasound should not be used to measure tumour lesions. The following radiology assessment method should be consistent with that used at baseline for tumour lesions. The same radiology equipment was preferred in the following tumour evaluation visits. The 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 (1) progression of disease (PD), (2) lost to follow-up, (3) death, or (4) end of study, whichever occurred first. PFS, ORR and DoR assessed by the investigator were based on radiological findings according to RECIST v1.1.

Cross-over phase: The radiological assessment finding that confirmed PD could be used as the baseline tumour assessment of the cross-over phase if all of the following criteria were met: the patient received the first sugemalimab monotherapy within 1 month after the radiological assessment; the patient didn't take any anti-neoplastic treatment after radiological assessment and prior to the first sugemalimab monotherapy.

Radiological tumour assessment was carried out every 9 weeks thereafter until (1) PD, (2) lost to follow-up, (3) death, and (4) end of study, whichever occurred first. ORR, DoR and PFS were assessed by the investigators according to RECIST v1.1 and OS were determined.

BICR committee reviewed all randomised patients' radiological tumour data according to RECIST v1.1. Refer to BICR Charter for roles, responsibilities and protocols of BICR.

Primary Efficacy Endpoint

The primary endpoint was PFS assessed by the investigator according to RECIST v1.1. PFS was defined as the time from the date of randomisation to disease progression or death whichever occurred first. Patients without an event (no disease progression or death) were censored at the date of "last tumour assessment". Patients without post-baseline tumour assessment were censored at the date of randomisation.

The EMA censoring rules (Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man) were applied, i.e. not censoring patients with unallowed anti-neoplastic treatment nor missing two or more consecutive tumour assessments.

Secondary Efficacy Endpoints

Double-blind phase:

- Overall survival (OS): the time from the randomisation date to all-cause death date.
- Progression-free survival (PFS, assessed by BICR according to RECIST v1.1).
- PFS in patients with PD-L1 ≥1% (assessed by the investigator according to RECIST v1.1).
- Objective response rate (ORR, assessed by the investigator according to RECIST v1.1): the number and percentage of patients who achieved objective tumour response (CR [complete response] or PR [partial response]).
- Duration of response (DoR, assessed by the investigator according to RECIST v1.1): the time between the date of the earliest qualifying response and the date of progressive disease or all-cause death, whichever occurred first.

Cross-over phase: Efficacy in the cross-over phase was analysed in patients who crossed over from the placebo group and received at least 1 dose of sugemalimab. Baseline tumour assessment for the cross-over phase was defined as the last tumour assessment prior to sugemalimab administration. Efficacy was assessed by the investigator per RECIST v1.1. The efficacy endpoints in the cross-over phase included:

- OS: the time from the first sugemalimab administration in the cross-over phase till all-cause death.
- ORR, assessed by the investigator according to RECIST v1.1: the number and percentage of patients who achieved objective tumour response (CR or PR). Patients with measurable lesion were considered as responders if the first CR or PR was confirmed in ≥4 weeks.
- DoR: As defined above.
- PFS (assessed by the investigator according to RECIST v1.1): the time from the first sugemalimab dose date in the cross-over phase till progressive disease or death, whichever occurred first.
- **Sample size**

Initially, this study had two co-primary endpoints, PFS in subjects with PD-L1 ≥ 1% and PFS in all subjects. The planned total sample size was 480 subjects (2:1) including 288 in the PD-L1 ≥ 1% subgroup. The hypotheses made were that of a hazard ratio for PFS of 0.60 in subjects with PD-L1 ≥ 1% and 0.70 in all subjects. Median PFS in the control group was assumed to be 6 months. The overall

significance level was set to 0.05 (2-sided). The study was event-driven, and the final analysis was to be performed after approximately 360 PFS events had been observed (all subjects) implying 89% power.

For OS, the number of events was estimated assuming a HR of 0.72, a median OS in the control group of 12 months, a two-sided significance level of 0.05 and power 80%. The OS final analysis was planned to occur when approximately 360 events had been observed.

Within a protocol amendment (CSP version 2, 07 April 2020), PFS in subjects with PD-L1 ≥ 1% became a secondary endpoint. The rationale for one primary endpoint alone, PFS in all subjects, was stated to be emerging external data (identified by the applicant) for products in the same class (e.g., pembrolizumab) that combined with chemotherapy in first-line NSCLC patients showed benefits in a PD-L1 expression level-independent manner.

The original sample size estimation was revised but the total sample size did not change. At the time of this CSP amendment, patient enrolment was still ongoing (last patient was randomised 15 May 2020).

Initially, one interim analysis had been planned for each co-primary endpoint, respectively. Within amendment CSP version 2 (07 April 2020) the interim analysis of PFS in subjects with PD-L1 ≥ 1% was removed and only one interim analysis of PFS (all subjects) remained, planned to be performed after 252 PFS events (70% of the number targeted events) or when last subject had been randomised, whichever occurred later. The type I error was to be controlled using a Lan-DeMets method with an approximate O'Brien-Fleming boundary.

The OS final analysis was to be performed when approximately 360 events had been observed. One interim analysis was planned when 252 OS events had been observed (70% data information) or the last subject had been randomised, whichever occurred later. The type I error was to be controlled using Lan-DeMets method with an approximate Pocock boundary.

An independent data monitoring committee (iDMC) was to monitor the data for the interim PFS analysis and make recommendations to sponsor according to the pre-defined boundaries.

- **Randomisation and Blinding (masking)**

Randomisation was performed 2:1 using a stratified block randomisation and an Interactive Voice/Web Response System (IVRS/IWRS).

This was a double-blind study with treatment assignments to be blinded to patients, investigators/study staff, and the Sponsor's study team members.

Unblinding of treatment assignment for an individual patient could occur in emergent medical situations or for other safety reasons. Unblinding of an individual patient had to occur after radiologically confirmed progressive disease (assessed by the investigator) whereafter the subject could receive open-label sugemalimab monotherapy provided pre-defined criteria had been met. The possibility to receive open-label sugemalimab monotherapy applied to both treatment arms; the necessity to unblind treatment assignment will have been explained by that the criteria differed depending on whether the subject had progressed while on sugemalimab or placebo.

All radiologic images (except for those taken during cross-over phase) were to be sent to a central radiology laboratory for blinded independent central review (BICR).

- **Statistical methods**

The original statistical analysis plan (SAP) (version 1.0, version date: 05 June 2020) was amended once. The final version of SAP is version 1.1 (version date: 22 April 2021). Both versions have been submitted and both refer to the study protocol version 2.0 (April 7, 2020). The key changes in version

1.1 were added details of the statistical method for describing on-study or follow-up anticancer therapy and adding a new subgroup category for the subgroup analysis by PD-L1 expression level, i.e., PD-L1 ≥50%; 50%> PD-L1 ≥1% based on central lab tested PD-L1 expression value.

At the time of change in primary endpoints (from two to one, CSP version 2.0, 7 Apr 2020) the SAP was not yet final. This change also affected the protocol-defined statistical considerations and analysis. The change in primary endpoints simplified both the originally interim analysis plan and the multiple testing procedure.

PFS analysis (primary endpoint)

The primary efficacy analysis set was the intent-to-treat (ITT) including all randomised subjects.

The pre-specified and primary analysis method was a **Cox regression** model with treatment group and the stratification variables used at randomisation, i.e., ECOG PS, PD-L1 expression value, and histology type (according to IVRS/IWRS). Estimate of the hazard ratio (HR) and corresponding 95% confidence interval (CI) has been presented. Testing of treatment group difference was performed based on a stratified **log-rank test** and the stratification factors used at randomisation. The **Kaplan Meier** method was used to estimate median PFS, PFS at different timepoints and corresponding 95% CIs (by Brookmeyer Crowley method). A Kaplan Meier plot was provided.

Pre-planned PFS **sensitivity analyses** included an unstratified analysis, and the following analyses respectively, to assess impact of non-allowed anti-cancer therapy and missed tumour assessments:

- Subjects who had used unallowed anti-neoplastic treatment before PFS were to be censored on the last tumour assessment day before the use of unallowed treatment. Subjects without any tumour assessment after the baseline were to be censored at the date of randomisation.
- Subjects who had missed 2 or more consecutive tumour assessments before PFS event were to be censored before the last tumour assessment date prior to the PFS event. Subjects without any tumour assessment after the baseline were to be censored at the date of randomisation.

In addition, analyses investigating potential impact on PFS (investigator-assessed) and PFS assessed by BICR of the **COVID-19** epidemic has been performed (prespecified in the SAP).

Secondary endpoint analyses

In the analysis of **OS**, subjects alive were to be censored at the last known date alive. Subjects without any data after baseline were to be censored at the date of randomisation. The statistical analysis method for OS was the same as that for the primary efficacy endpoint.

The same methods as used for the primary endpoint were also used for the analysis of **PFS** (assessed by the investigator) and PFS (assessed by BICR) among subjects with **PD-L1 ≥ 1%**.

The analysis of **ORR** (CR+PR) was based on a Cochran-Mantel-Haenszel test stratified by the randomisation stratifications factors (ECOG performance status, histology type and PD-L1 according to IVRS/IWRS). ORR for each treatment group and the difference between groups have been provided with 95% CIs estimated using the Clopper Pearson method. The analysis of ORR required that subjects included in the ITT set also had measurable disease at baseline: no subject was excluded in the analysis of ORR.

Multiple testing procedure

The testing strategy to control overall type I error was a **sequential testing procedure** that implied that when the PFS null hypothesis had been rejected the following secondary endpoints were to be analysed in the following order using a significance level of 0.05:

1) OS

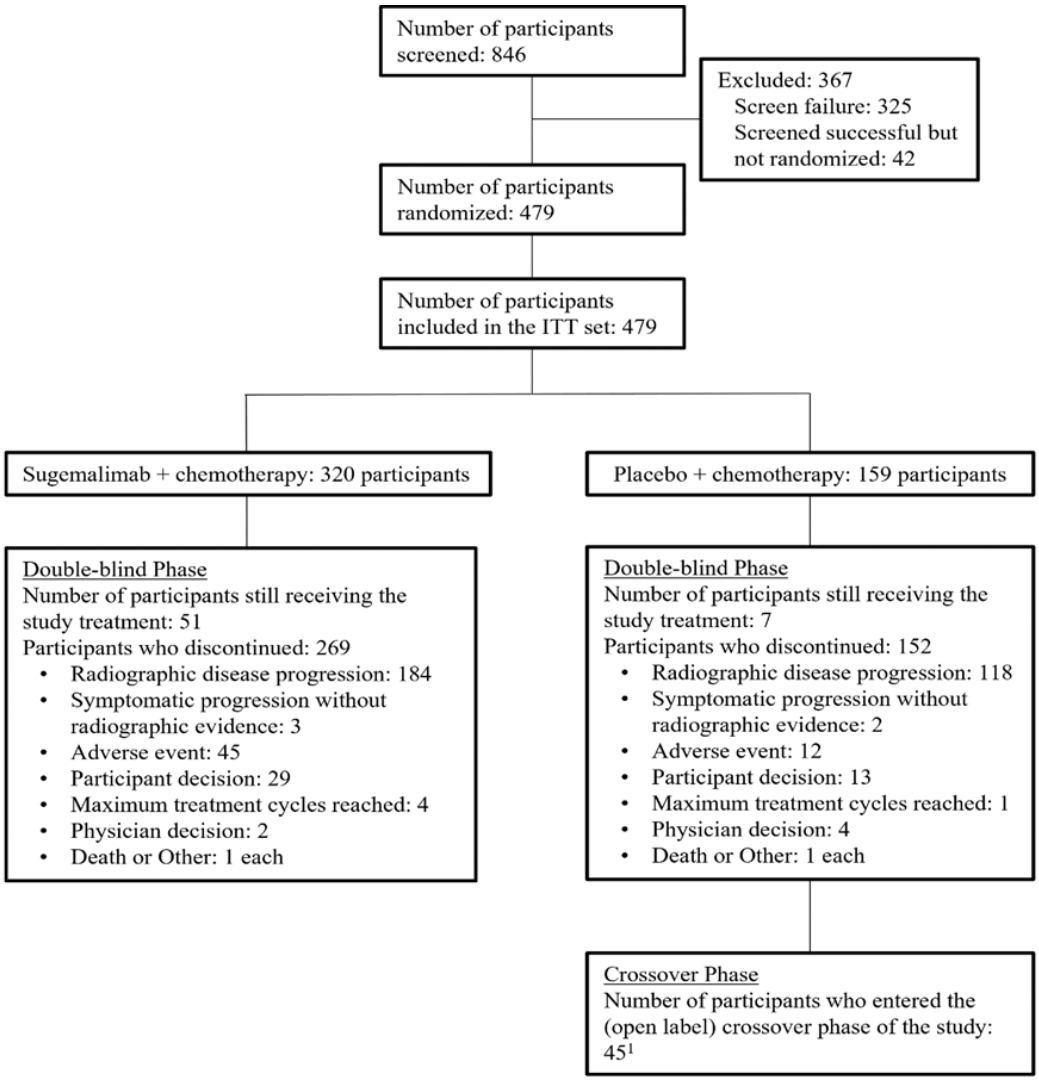
2) PD-L1 ≥ 1% PFS (as assessed by the investigators according to RECIST v1.1)

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

Results

- **Participant flow**

Figure 21: Participant disposition – Study CS1001-302 (OS interim analysis DCO3 – 22 Nov 2021)



[1] Only participants originally randomised to the placebo group and crossed over to receive open-label sugemalimab were included.

42 patients were successfully screened but were not enrolled as they either had squamous cell carcinoma and/or PD-L1 expression level <1%, and enrolment into their respective groups was already completed.

Table 14: Reasons for study discontinuation

	sugemalimab+ Chemotherapy	Placebo+ Chemotherapy	Total
Treated[a]	320(100.0%)	159(100.0%)	479(100.0%)
Discontinued Study	174(54.4%)	113(71.1%)	287(59.9%)
Death	156(48.8%)	97(61.0%)	253(52.8%)
Lost to Follow-up	6(1.9%)	6(3.8%)	12(2.5%)
Withdrawal by Patient	12(3.8%)	10(6.3%)	22(4.6%)
Study Terminated by Sponsor	0	0	0
Other	0	0	0

Percentage is based on the randomised patients.
[a] Patient who take any dose of sugemalimab/Placebo or Carboplatin, Pemetrexed, or Paclitaxel is deemed as treated patients.

Double-blind Phase

As of the data cut-off date (22 November 2021), the median follow-up time (range) in the sugemalimab group and the placebo group was 25.4 months and 24.9 months, respectively.

Cross-over Phase:

As of the data cut-off date (22 November 2021), there were 102 patients who had radiographic disease progression during the double-blind phase voluntarily entered the cross-over phase to receive open-label sugemalimab monotherapy.

Of them, a total of 63 patients received sugemalimab monotherapy 1200 mg, IV infusion, and 45 patients, from the placebo group of the double-blind phase, satisfied the protocol-defined cross-over requirements and were included in the safety analysis set for cross-over phase and a total of 4 (8.9%) patients remained on treatment with sugemalimab at the time of data cut-off.

During the cross-over phase, the primary reason for the discontinuation of sugemalimab treatment was radiographic disease progression (32, 71.1%), 4 (8.9%) patients discontinued due to patient's decision.

Out of the 45 protocol-defined cross-over patients, the number of patients who discontinued study was 26 (57.8%), which was solely due to death.

- **Recruitment**

Between 13 Dec 2018 and 15 May 2020, 479 participants were randomly assigned to sugemalimab in combination with chemotherapy or placebo in combination with chemotherapy. The majority of the 35 sites randomised approximately 10-20 patients, but this ranged from 3 to 74 patients (one site randomising by far the highest number).

- **Conduct of the study**

DCO1	data cut-off 1 = 08 Jun 2020
DCO2	data cut-off 2 = 15 Mar 2021
DCO3	data cut-off 3 = 22 Nov 2021

As of 22 November 2021, the original protocol (dated 02 August 2018) has been revised three times. All amendments had been implemented before the reported data cut-off date for the PFS interim analysis.

4.7% of patients in the sugemalimab arm and 4.4% of patients in the placebo arm had at least one important protocol deviation.

Part of the study was performed during the COVID-19 epidemic/pandemic. The COVID-19 start date was set as January 22, 2020. There was no amendment to the protocol describing measures and actions planned to mitigate potential impact of the epidemic. This have been described in separate documents. The number of subjects per treatment arm with at least one Covid-19 related protocol deviation was similar comparing the sugemalimab (131/320; 40.9%) and placebo (59/159; 37.1%) treatment arm. Further, also the deviation category pattern was similar, the most common category of protocol deviation in both arms being deviations to the visit schedule.

Table 15: Summary of important protocol deviations – ITT 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%)

Table 16: Occurrence of COVID-19 related protocol deviations in Study CS1001-302

	Sugemalimab+ Chemotherapy (N=320)	**Placebo+ Chemotherapy (N=159)**
Number of Patients with at Least One Covid-19 Related Protocol Deviation	**131 (40.9%)**	**59 (37.1%)**
Overall Total Number of Covid-19 Related Protocol Deviations	**273**	**107**
Protocol Deviation Category		
Concomitant Medication Criteria	3 (0.9%)	1 (0.6%)
Efficacy Criteria	37 (11.6%)	20 (12.6%)
IP Compliance	6 (1.9%)	3 (1.9%)
Laboratory Assessment Criteria	20 (6.3%)	10 (6.3%)
Study Procedures Criteria	23 (7.2%)	13 (8.2%)
Visit Schedule Criteria	106 (33.1%)	44 (27.7%)

- **Baseline data**

Table 17: Demographics and baseline characteristics – ITT analysis set – Study CS1001-302

Demographic or Baseline Characteristic	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)
Body Weight at Baseline (kg)			
Mean (SD)	62.488 (9.7117)	64.131 (8.8530)	63.033 (9.4578)
Median	61.0	64.0	62.0
Min - Max	41.0 - 96.0	44.0 - 88.0	41.0 - 96.0
ECOG PS 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)
PD-L1 (from Central Lab), n (%)			
⩾ 1%	196 (61.3)	95 (59.7)	291 (60.8)
< 1%	124 (38.8)	64 (40.3)	188 (39.2)

Table 18: Baseline disease characteristics - ITT analysis set – Study CS1001-302

Baseline Characteristic	Sugemalimab + Chemotherapy N = 320	Placebo + Chemotherapy N = 159	Total N=479
Time From Initial Diagnosis (Years)[a]			
Mean (SD)	0.318 (0.9997)	0.434 (1.1909)	0.357 (1.0671)
Median	0.079	0.079	0.079
Min - Max	0.02 - 9.67	0.02 - 9.61	0.02 - 9.67
Histological Type, n (%)			
Squamous cell carcinoma	129 (40.3)	63 (39.6)	192(40.1%)
Non-squamous cell carcinoma	191 (59.7)	96 (60.4)	287(59.9%)
Cancer Stage at Screening, n (%)[b]			
IV	320 (100.0)	159 (100.0)	479(100.0%)
Baseline Liver Metastases, n (%)			
Yes	39 (12.2)	18 (11.3)	57(11.9%)
No	281 (87.8)	141 (88.7)	422(88.1%)
Baseline Brain Metastases, n (%)			
Yes	50 (15.6)	17 (10.7)	67(14.0%)
No	270 (84.4)	140 (88.1)	410(85.6%)

Table 19: Baseline biomarker in patients with non-squamous cell carcinoma

	sugemalimab+ Chemotherapy N=320	Placebo+ Chemotherapy N=159	Total N=479
Non-Squamous Cell Carcinoma	191	96	287
EGFR Mutation Status			
Negative	190(99.5%)	95(99.0%)	285(99.3%)
Positive	1(0.5%)	0	1(0.3%)
Unknown	0	1(1.0%)	1(0.3%)
ALK Rearrangement Status			
Negative	155(81.2%)	78(81.3%)	233(81.2%)
Positive	0	0	0
Unknown	36(18.8%)	18(18.8%)	54(18.8%)
ROS1 Translocation Status Negative	147(77.0%)	73(76.0%)	220(76.7%)
Positive	0	0	0
Unknown	44(23.0%)	23(24.0%)	67(23.3%)
RET Mutation Status Negative	96(50.3%)	50(52.1%)	146(50.9%)
Positive	0	0	0
Unknown	95(49.7%)	46(47.9%)	141(49.1%)
PD-L1 (from Central Lab) >=1%	115(60.2%)	56(58.3%)	171(59.6%)
<1%	76(39.8%)	40(41.7%)	116(40.4%)

Table 20: Baseline biomarker in patients with squamous cell carcinoma

	sugemalimab+ Chemotherapy N=320	Placebo+ Chemotherapy N=159	Total N=479
Squamous Cell Carcinoma	129	63	192
EGFR Mutation Status			
Negative	27(20.9%)	16(25.4%)	43(22.4%)
Positive	0	0	0
Unknown	102(79.1%)	47(74.6%)	149(77.6%)
ALK Rearrangement Status			
Negative	28(21.7%)	18(28.6%)	46(24.0%)
Positive	0	0	0
Unknown	101(78.3%)	45(71.4%)	146(76.0%)
ROS1 Translocation Status			
Negative	25(19.4%)	14(22.2%)	39(20.3%)
Positive	0	0	0
Unknown	104(80.6%)	49(77.8%)	153(79.7%)
RET Mutation Status Negative	15(11.6%)	10(15.9%)	25(13.0%)
Positive	0	0	0
Unknown	114(88.4%)	53(84.1%)	167(87.0%)
PD-L1 (from Central Lab)			
>=1%	81(62.8%)	39(61.9%)	120(62.5%)
<1%	48(37.2%)	24(38.1%)	72(37.5%)

Table 21: Baseline biomarker in the ITT population

	sugemalimab+ Chemotherapy N=320	Placebo+ Chemotherapy N=159	Total N=479
All	320	159	479
EGFR Mutation Status			
Negative	217(67.8%)	111(69.8%)	328(68.5%)
Positive	1(0.3%)	0	1(0.2%)
Unknown	102(31.9%)	48(30.2%)	150(31.3%)
ALK Rearrangement Status			
Negative	183(57.2%)	96(60.4%)	279(58.2%)
Positive	0	0	0
Unknown	137(42.8%)	63(39.6%)	200(41.8%)
ROS1 Translocation Status			
Negative	172(53.8%)	87(54.7%)	259(54.1%)
Positive	0	0	0
Unknown	148(46.3%)	72(45.3%)	220(45.9%)
RET Mutation Status			
Negative	111(34.7%)	60(37.7%)	171(35.7%)
Positive	0	0	0
Unknown	209(65.3%)	99(62.3%)	308(64.3%)
PD-L1 (from Central Lab)			
>=1%	196(61.3%)	95(59.7%)	291(60.8%)
<1%	124(38.8%)	64(40.3%)	188(39.2%)

Patients with known EGFR sensitive mutation, ALK fusion, ROS1 fusion or RET fusion were excluded from the study.

- **Numbers analysed**

Table 22: Intent-to-treat analysis set

	CS1001+Chemotherapy N=320	Placebo+Chemotherapy N=159	Total N=479
Intent-to-Treated Analysis Set [a]	320	159	479
Safety Analysis Set [b]	320	159	479

[a] All patients who were randomized into the study.
[b] All patients who were randomized and received at least one dose of the study drugs.

Table 23: Safety analysis set – cross over

	CS1001
Efficacy Analysis Set - Cross Over [a]	45
Evaluable Analysis Set [b]	45
Safety Analysis Set - Cross Over [c]	45

[a] All patients who entered cross over phase, were diagnosed as PD by investigator and didn't take any CS1001 during double-blind phase and received at least one dose of CS1001 during cross over phase.
[b] Evaluable analysis set is defined as efficacy analysis set excluding treatment-ongoing patients who have not reached the time for their first post-baseline tumor assessment.
[c] All patients who entered cross over phase, didn't take any CS1001 during double-blind phase and received at least one dose of CS1001 during cross over phase.

All randomised patients were included in the ITT.

- **Outcomes and estimation**

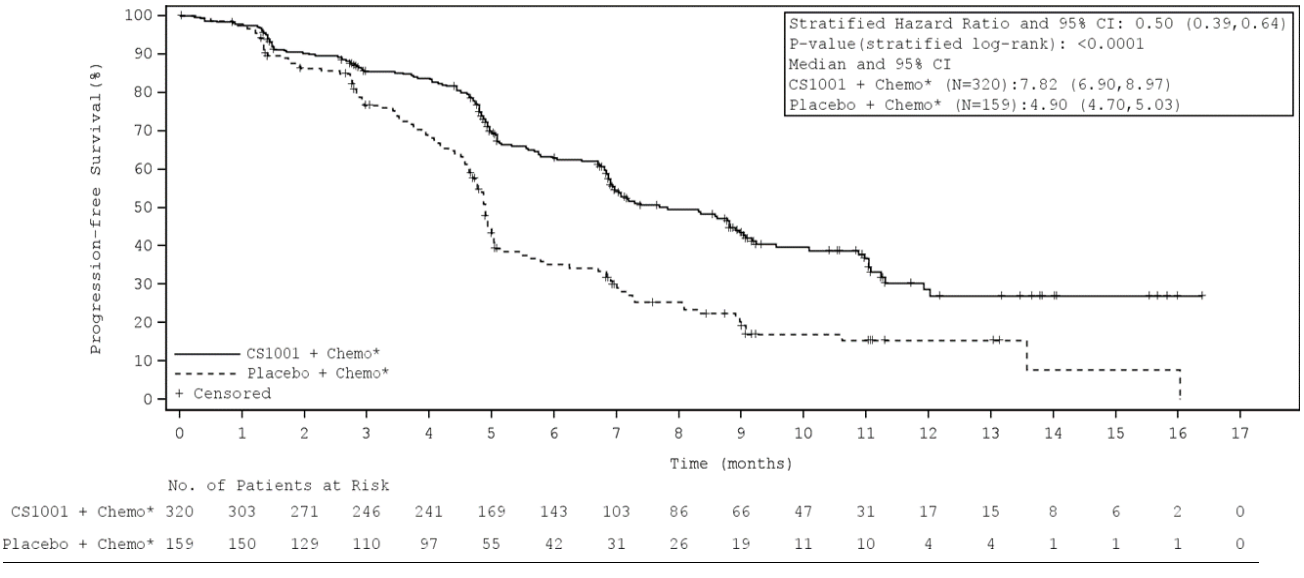
Primary endpoint:

PFS Assessed by Investigator

Interim PFS Analysis – (DCO1 - 08 Jun 2020)

At the prespecified PFS interim analysis with a median follow-up of 8.67 months and 8.34 months for the sugemalimab group and placebo group, respectively, the study met the primary endpoint with a statistically significant improvement in investigator-assessed PFS. The positive PFS interim results crossed the actual boundary of 0.0188 from the O'Brien Fleming alpha spending function, and the IDMC recommended unblinding of the study to the sponsor. The study was still blinded for participants and investigator for additional follow-up of PFS and OS.

Figure 22: Kaplan-Meier Curve for Investigator-Assessed Progression-free Survival - ITT Analysis Set – Study CS1001-302 (PFS Interim Analysis DCO1 - 08 Jun 2020)



Final PFS Analysis – (DCO2 - 15 Mar 2021)

At the prespecified PFS final analysis with a median follow-up of 17.81 months and 17.51 months for the sugemalimab group and placebo group, respectively, the magnitude of improvement in investigator-assessed PFS was maintained.

Table 24: Summary of investigator-assessed progression-free survival - ITT analysis set – Study CS1001-302 (PFS final analysis DCO2 - 15 Mar 2021)

	Sugemalimab + Chemotherapy	Placebo + Chemotherapy
	N = 320	N = 159
Participants with Event, n (%)	223 (69.7)	135 (84.9)
Death	33 (10.3)	10 (6.3)
Progressive disease	190 (59.4)	125 (78.6)
Censored Participants, n (%)	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% percentile[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 (2-sided log-rank test)	< 0.0001	
HR	0.48	
95% CI	(0.39, 0.60)	
Unstratified Analysis		
P value (2-sided log-rank test)	< 0.0001	
HR	0.50	
95% CI	(0.40, 0.62)	
Progression-free Survival Rate[c]		
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%)	
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%)	

Figure 23: Kaplan-Meier Curve for Investigator-Assessed Progression-free Survival - ITT Analysis Set – Study CS1001-302 (PFS Final Analysis DCO2 - 15 Mar 2021)

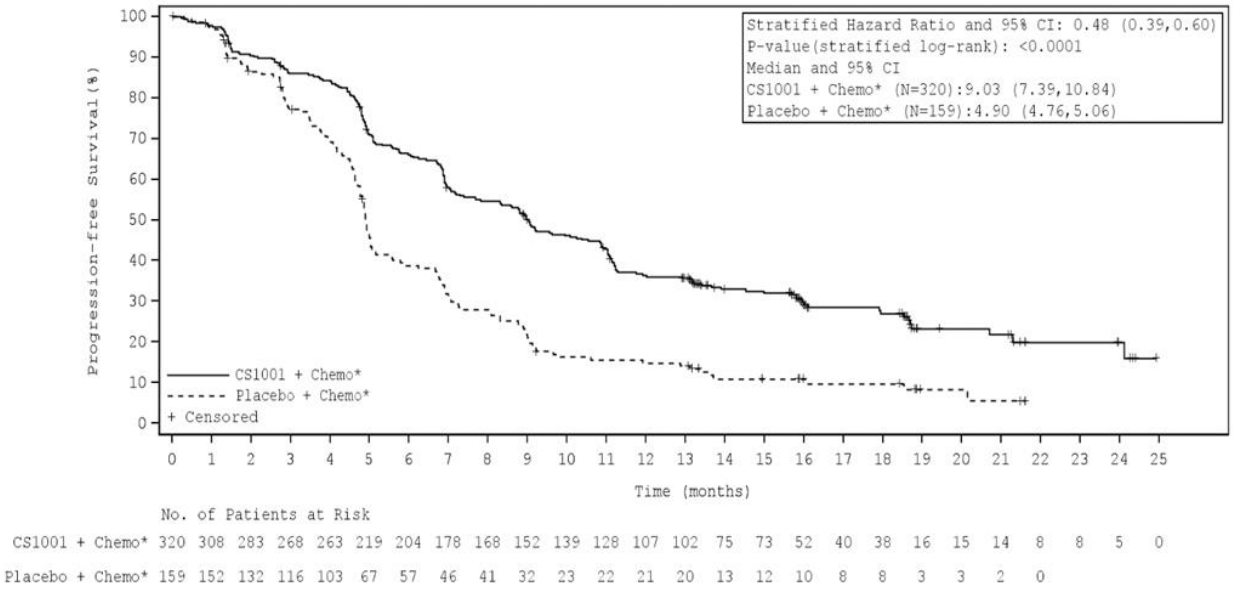


Table 25: Reasons for PFS censoring in Study CS1001-302 (data cut-off date 15 Mar 2021)

	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%)**
Withdrawal by patients	9 (2.8%)	6 (3.8%)
No evaluable post-baseline tumour assessment	1 (0.3%)	1 (0.6%)
Lost to follow-up	0	1 (0.6%)
Alive and not progressed	87 (27.2%)	16 (10.1%)

Secondary endpoints

Overall survival

The protocol-prespecified event-driven OS interim analysis was performed after 252 OS events had occurred, with a median follow-up of 25.43 and 24.94 months for the sugemalimab and placebo group, respectively.

Table 26: Summary of overall survival - ITT analysis set – Study CS1001-302 (OS interim analysis DCO3 - 22 Nov 2021)

	Sugemalimab + Chemotherapy N = 320	Placebo + Chemotherapy N = 159
Participants with Event, n(%)	156 (48.8%)	97 (61.0%)
Censored Participants	164 (51.3%)	62 (39.0%)
Overall Survival (Months)		
Median[a]	25.43	16.85
95% CI[a]	(20.14, -)	(12.81, 20.67)
25% and 75% percentile[a]	10.84, -	7.79, -

	Sugemalimab + Chemotherapy N = 320	Placebo + Chemotherapy N = 159
Range	0.2 to 34.8 +	0.3 to 32.3 +
Stratified Analysis[b]		
P value (2-sided log-rank test)	0.0008	
HR	0.65	
95% CI	(0.50, 0.84)	
Unstratified Analysis		
P value (2-sided log-rank test)	0.0009	
HR	0.65	
95% CI	(0.51, 0.84)	
Overall Survival Rate[c]		
12 months	71.6%	61.4%
95% CI	(66.3%, 76.3%)	(53.0%, 68.7%)
Difference	10.2%	
95% CI	(0.9%, 19.6%)	
24 months	51.7%	35.6%
95% CI	(45.9%, 57.3%)	(27.7%, 43.6%)
Difference	16.1%	
95% CI	(6.3%, 26.0%)	

Figure 24: Kaplan-Meier Plot of Interim Overall Survival Analysis - ITT Analysis Set – Study CS1001-302 (OS Interim Analysis DCO3 - 22 Nov 2021)

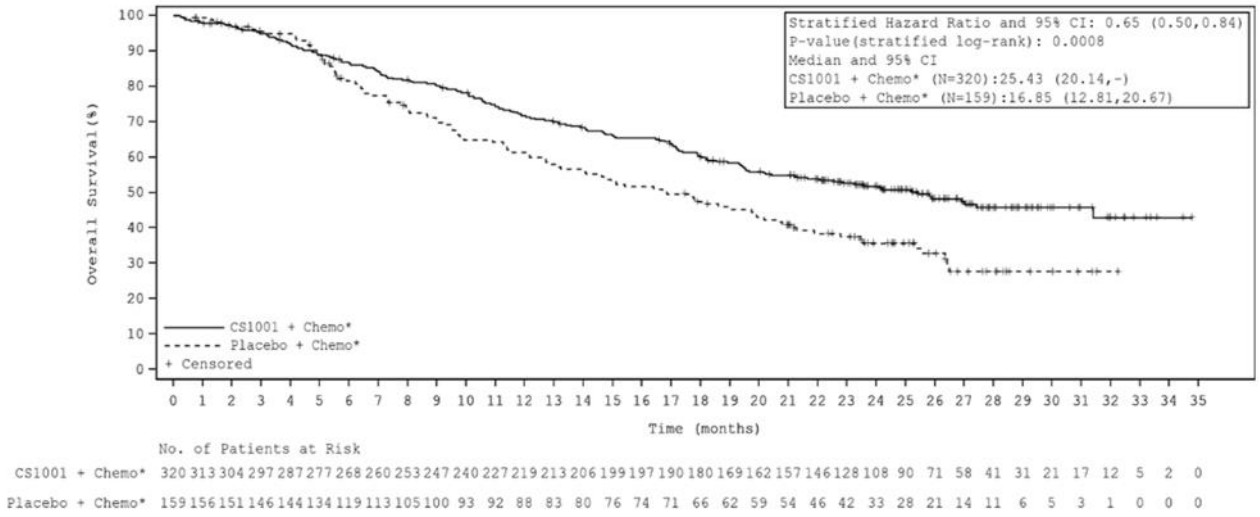


Table 27: Reasons for OS censoring in Study CS1001-302 (data cut-off date 22 Nov 2021)

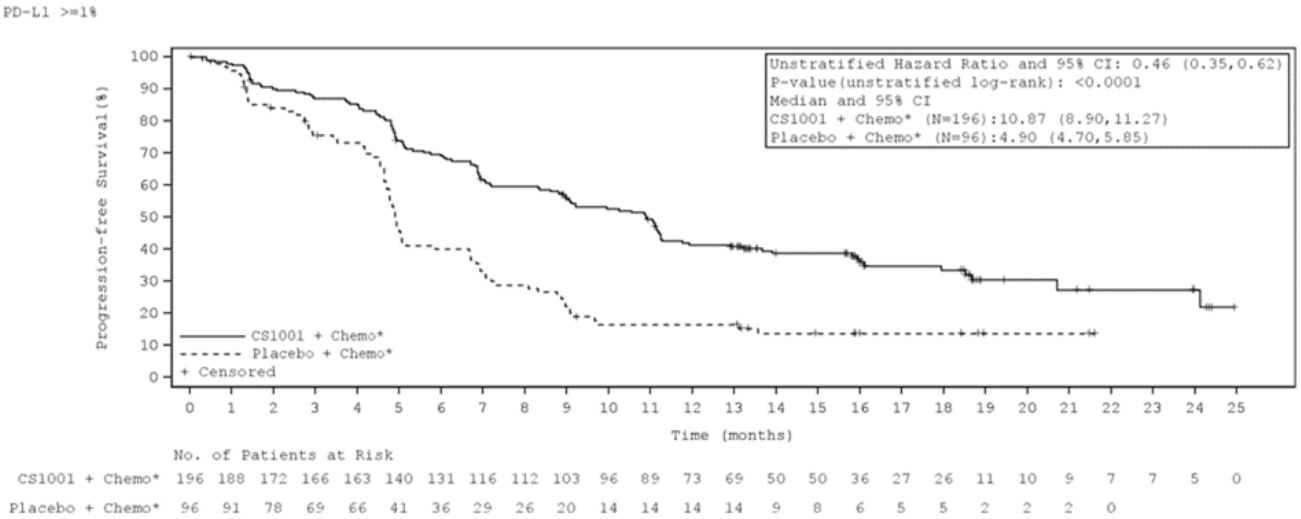
	Sugemalimab + Chemotherapy (N=320)	Placebo + Chemotherapy (N=159)
Patients with Event	**156 (48.8%)**	**97 (61.0%)**
Patients Censored	**164 (51.3%)**	**62 (39.0%)**
Withdrawal by patient	12 (3.8%)	10 (6.3%)
Lost to follow-up	6 (1.9%)	6 (3.8%)
Alive	146 (45.6%)	46 (28.9%)

PFS Assessed by Investigator in Participants with PD-L1 Expression ≥ 1%

The statistical testing for investigator assessed PFS per RECIST v1.1 for participants with PD L1 ≥ 1% was conducted based on the interim OS data cut-off date of 22 Nov 2021, after the OS endpoint reached statistical significance at the interim OS analysis.

Treatment with sugemalimab in combination with chemotherapy showed a statistically significant improvement in investigator-assessed PFS for participants with PD-L1 ≥ 1% compared with those treated with placebo in combination with chemotherapy. In participants with PD-L1 expression ≥ 1%, investigator assessed median PFS was 10.9 months (95% CI: 8.90, 11.27) with sugemalimab versus 4.90 months (95% CI: 4.70, 5.85) with placebo (unstratified HR 0.46 [95% CI 0.35, 0.62], TP < 0.0001).

Figure 25: Kaplan-Meier Plot of Progression-free Survival of Patients with PD-L1≥1% or PD-L1<1% Assessed by Investigator, ITT Analysis Set, PFS Final Analysis



ORR Assessed by Investigator

Table 28: Overall response assessed by investigator – participants with measurable disease at baseline – ITT analysis set – Study CS1001-302 (DCO3-22 Nov 2021)

	Sugemalimab + Chemotherapy N = 320	Placebo + Chemotherapy N = 159
Objective Response Rate (CR + PR), n (%)	203 (63.4)	64 (40.3)
95% CI[a]	(57.9%, 68.7%)	(32.6%, 48.3%)
Differences in Objective Response Rates[b]	23.2%	
95% CI	(13.9%, 32.5%)	
P value (CMH)	< 0.0001	
Best Overall Response[c]		
CR	0	0
95% CI[a]	(0.0%, 1.1%)	(0.0%, 2.3%)
PR, n (%)	203 (63.4)	64 (40.3)
95% CI[a]	(57.9%, 68.7%)	(32.6%, 48.3%)
SD, n (%)	81 (25.3)	73 (45.9)
95% CI[a]	(20.6%, 30.4%)	(38.0%, 54.0%)
PD, n (%)	22 (6.9)	15 (9.4)
95% CI[a]	(4.4%, 10.2%)	(5.4%, 15.1%)
NE, n (%)	2 (0.6)	1 (0.6)
NA, n (%)	12 (3.8)	6 (3.8)

DCO3 date: 22 Nov 2021

Duration of response

The DoR analysis was performed on participants who achieved an objective response (CR + PR).

Table 29: Summary for DoR assessed by investigator – participants with tumour evaluated as CR or PR – ITT analysis set Study CS1001-302 (DCO3 – 22 Nov 2021)

	Sugemalimab + Chemotherapy N = 203	Placebo + Chemotherapy N = 64
Participants with Responses (CR + PR), n (%)	203 (100.0)	64 (100.0)
Number of Participants with Events, n (%)	144 (70.9)	56 (87.5)
PD, n (%)	133 (65.5)	53 (82.8)
Death, n (%)	11 (5.4)	3 (4.7)
Number of Censored Participants, n (%)	59 (29.1)	8 (12.5)
DoR (Months)		
Median[a]	9.92	4.44
95% CI[a]	(8.57, 13.24)	(3.52, 6.08)
25% and 75% Percentile[a]	4.93, 31.51	3.48, 7.82
Range	0.7 to 31.5	0.0 + to 26.0 +

- **Ancillary analyses**

Subgroup analyses

Presented subgroup results of PFS and OS showed an overall consistent treatment effect. HR for PFS for patients with PD-L1<1% was 0.56 (0.40, 0.77).

Figure 26: Forest Plot of HR for PFS Assessed by Investigator in CS1001-302 – Subgroup Analysis (PFS Final Analysis DCO2 - 15 Mar 2021)

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	8.97	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	8.94	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)

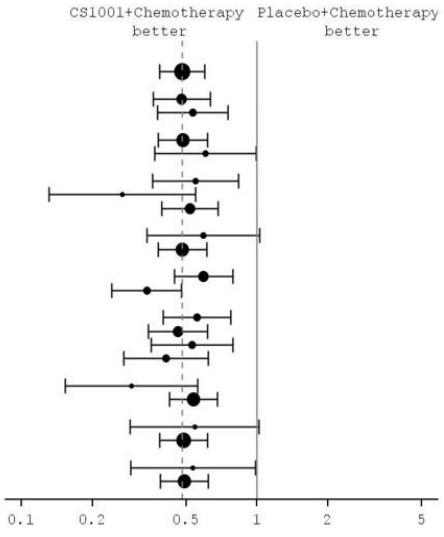
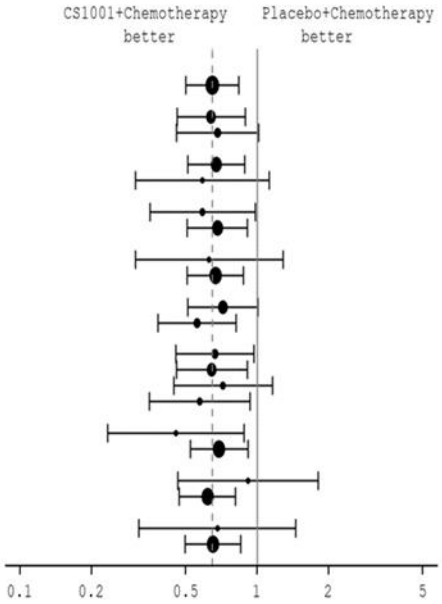


Figure 27: Forest Plot of Interim Overall Survival Hazard Ratio by Subgroup in Study CS1001-302 (OS Interim Analysis DCO3 - 22 Nov 2021)

Baseline Risk Factor	CS1001+ Chemotherapy (N=320) Event/n	Median	Placebo+ Chemotherapy (N=159) Event/n	Median	Hazard Ratio(95% CI)
All Patients	156/320	25.43	97/159	16.85	0.65 (0.50, 0.84)
Age(yrs)					
<65 years	98/202	25.43	55/91	16.69	0.64 (0.46, 0.89)
>= 65 years	58/118	23.59	42/68	16.85	0.68 (0.46, 1.01)
Sex					
Male	133/254	22.83	82/129	15.41	0.67 (0.51, 0.89)
Female	23/66	-	15/30	23.46	0.59 (0.31, 1.13)
Smoking Status					
Never	38/88	-	24/40	16.85	0.59 (0.35, 0.98)
Current or Former	118/232	24.18	73/119	16.69	0.68 (0.51, 0.91)
ECOG					
0	21/59	-	12/25	23.56	0.63 (0.31, 1.28)
1	135/261	23.26	85/134	15.41	0.67 (0.51, 0.87)
Histology Type					
NSQ	86/191	26.91	54/96	19.81	0.72 (0.51, 1.01)
SQ	70/129	23.26	43/63	12.16	0.56 (0.38, 0.82)
PD-L1					
<1%	70/124	19.38	43/64	14.75	0.66 (0.45, 0.97)
>=1%	86/196	27.01	54/95	18.96	0.64 (0.46, 0.91)
>=1% and <50%	46/92	23.26	27/48	17.68	0.72 (0.44, 1.16)
>=50%	40/104	-	27/47	19.75	0.57 (0.35, 0.93)
Brain Metastases					
Yes	25/50	22.08	14/17	8.97	0.45 (0.23, 0.88)
No	131/270	25.43	81/140	17.81	0.69 (0.52, 0.91)
Liver Metastases					
Yes	27/39	16.59	12/18	11.96	0.91 (0.46, 1.80)
No	129/281	27.43	85/141	17.77	0.62 (0.47, 0.81)
Prior Cancer Therapy					
Yes	15/34	25.89	12/24	16.69	0.68 (0.32, 1.45)
No	141/286	25.20	85/135	17.68	0.65 (0.50, 0.85)



- **Summary of main efficacy results**

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30: Summary of efficacy for trial CS1001-302

Title: A Multi-Center, Randomised, Double-Blind, Phase III Study of Platinum-Based Chemotherapy With or Without sugemalimab in Stage IV Non-Small Cell Lung Cancer Subjects		
Study identifier	CS1001-302, GEMSTONE-302	
Design	Phase III, blinded, randomised, two treatment arms, cross-over, multi-centre	
	Duration of main phase:	Approximately 3 years First patient randomised: 28 Dec 2018 Last patient randomised: 20 May 2020 Data cutoff date: 22 Nov 2021
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority	

Title: A Multi-Center, Randomised, Double-Blind, Phase III Study of Platinum-Based Chemotherapy With or Without sugemalimab in Stage IV Non-Small Cell Lung Cancer Subjects			
Study identifier	CS1001-302, GEMSTONE-302		
Treatments groups	sugemalimab+ chemotherapy		1,200 mg sugemalimab in combination with platinum-based chemotherapy Q3W Induction: 4 cycles Maintenance up to 35 cycles (approximately 2 years) <u>Squamous</u> Induction: 1,200 mg sugemalimab in combination with paclitaxel Q3W for 4 cycles Maintenance: 1,200 mg sugemalimab Q3W for up to 35 cycles <u>Non-squamous</u> Induction: 1,200 mg sugemalimab in combination with pemetrexed Q3W for 4 cycles Maintenance: 1,200 mg sugemalimab in combination with pemetrexed Q3W for up to 35 cycles N=320
	Placebo+ chemotherapy		Placebo in combination with platinum-based chemotherapy Q3W Induction: 4 cycles Maintenance up to 35 cycles <u>Squamous</u> Induction: placebo in combination with paclitaxel Q3W for 4 cycles Maintenance: placebo Q3W for up to 35 cycles <u>Non-squamous</u> Induction: placebo in combination with pemetrexed Q3W for 4 cycles Maintenance: placebo in combination with pemetrexed Q3W for up to 35 cycles N=159
Endpoints and definitions	Primary endpoint	Progression free survival (PFS) ITT	PFS assessed by investigators according to RECIST v1.1 in the ITT population Interim and final
	Secondary endpoint	Overall survival (OS) ITT	OS Interim and final
	Secondary endpoint	Overall response rate (ORR)	ORR assessed by investigators according to RECIST v1.1
Database lock	22 November 2021		

<u>Results and Analysis</u>

Analysis description	**Primary Analysis**		
Analysis population and time point description	Final PFS Analysis 15 March 2021, ITT		
Descriptive statistics and estimate variability	Treatment group	sugemalimab+ chemotherapy	placebo+chemotherapy
	Number of subjects	n=320	n=159
	PFS, patients with event (%)	223 (69.7%)	135 (84.9%)

Title: A Multi-Center, Randomised, Double-Blind, Phase III Study of Platinum-Based Chemotherapy With or Without sugemalimab in Stage IV Non-Small Cell Lung Cancer Subjects			
Study identifier	CS1001-302, GEMSTONE-302		
	Median PFS, months (95% CI)	9.03 (7.4-10.8)	4.9 (4.8-5.1)
Effect estimate per comparison	PFS ITT	Comparison groups	sugemalimab+chemotherapy vs placebo+chemotherapy
		Hazard ratio (HR)	0.48
		95% CI	0.39, 0.60
		P-value	<0.0001
Analysis description	**Secondary analysis** Prespecified analysis of OS 22 Nov 2021, ITT		
Descriptive statistics and estimate variability	Treatment group	sugemalimab+ chemotherapy	placebo+chemotherapy
	Number of subjects	320	159
	OS, patients with event (%)	156 (48.8%)	97 (61.0%)
	Median OS, months (95% CI)	25.4 (20.1-NE)	16.9 (12.8-20.7)
	ORR, % (95% CI)	63.4 (57.9-68.7)	40.3 (32.6-48.3)
Effect estimate per comparison	OS ITT	Comparison groups	sugemalimab vs placebo
		Hazard ratio (HR)	0.65
		95% CI	0.51, 0.84
		P-value	0.0008

2.6.5.3. Clinical studies in special populations

Table 31: Exposure to sugemalimab 1200 mg by age

	Age 65-74 (Older Patients Number /Total Number)[1]	Age 75-84 (Older Patients Number /Total Number)[1]	Age 85+ (Older Patients Number /total Number)[1]
Controlled Trials[2]	207/620	6/620	0/620
Non-Controlled trials[3]	83/406	4/406	0/406

1. Patients dosed with sugemalimab 1200 mg
2. Studies CS1001-301 and CS1001-302
3. Studies CS1001-101, CS1001-102, CS1001-201, and CS1001-202

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Apart from testing for EGFR mutational status in participants with non-squamous NSCLC, testing for genomic tumour aberrations/oncogenic drivers was not mandatory for enrolment. All patients who had signed informed consent agreed to provide 5 sections of formalin-fixed tumour tissue samples from non-radiated sites collected at or after the diagnosis of stage IV NSCLC for PD-L1 assay, if approved by the Ethics Committee. PD-L1 expression were detected by VENTANA PD-L1 (SP263) immunohistochemical method in central laboratory on a BenchMark autostainer assay (Roche Tissue Diagnostics, Oro Valley, AZ, USA) according to the manufacturer's instructions. VENTANA PD-L1 (SP263) is a fully validated in vitro diagnostic (IVD) assay intended for the qualitative detection of PD-L1 in formalin-fixed, paraffin-embedded (FFPE) tissue specimens of non-small cell lung cancer (NSCLC) and urothelial carcinoma (UC). VENTANA PD-L1 (SP263) is also certified by a CE mark for intended use area based on a method comparison study. The proportion of tumour cells with PD-L1 membrane staining at any intensity above background staining was evaluated.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

N/A.

2.6.5.6. Supportive study - Study CS1001-301

Study design

Study CS1001-301 is a multicentre, randomised, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of sugemalimab monotherapy versus placebo. The study is evaluating sugemalimab as consolidation therapy in participants with locally advanced/unresectable (Stage III) NSCLC whose disease had not progressed after prior concurrent or sequential chemoradiotherapy. Participants with known EGFR mutation, ALK fusion, or ROS1 fusion were excluded.

Eligible participants were randomised to receive either intravenously sugemalimab 1,200 mg Q3W or matching placebo. The primary endpoint was PFS as assessed by BICR in the ITT population.

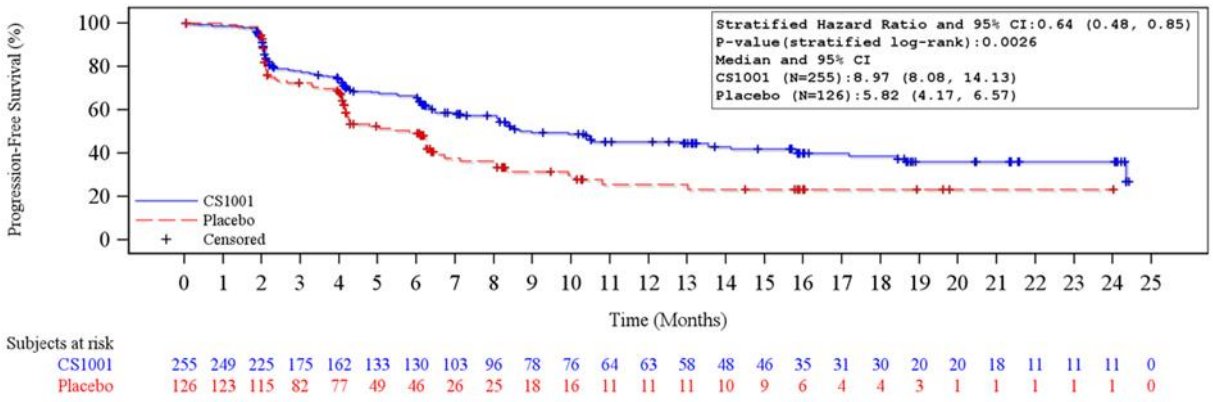
Results

A total of 381 participants were randomised to sugemalimab (N = 255) and placebo (N = 126). As of the DCO date 08 Mar 2021, 110 (43.1%) participants in the sugemalimab group and 44 (34.9%) participants in the placebo group remain on treatment.

All participants were Asian. Per protocol eligibility criteria, all participants were diagnosed with Stage III NSCLC.

PFS was significantly longer with sugemalimab than with placebo (median: 8.97 months [95% CI: 8.08, 14.13] vs 5.82 months [95% CI 4.17, 6.57]; stratified analysis HR: 0.64; 95% CI: 0.48, 0.85; P = 0.0026). Data for the OS-related analysis were not mature.

Figure 28: Kaplan Meier Curve of PFS Assessed by BICR -ITT Analysis Set – Study CS1001-301 (8 Mar 2021 DCO)



2.6.6. Discussion on clinical efficacy

GCP

In order to provide reassurance that the single pivotal phase III clinical study CS1001-302 was conducted in accordance with GCP requirements, a GCP inspection was triggered. Additional factors supporting the request for inspection were: the clinical study is conducted only in one country and there was no EU inspection history of the sponsor or any of the investigator sites.

The inspectors concluded that the trial and the data reported in the CSR is in accordance with GCP.

Design and conduct of clinical studies

The pivotal study supporting the sought indication is the ongoing Study CS1001-302, a Phase 3 randomised, double-blind trial of sugemalimab combined with chemotherapy versus placebo in combination with chemotherapy in first-line, metastatic NSCLC.

The comparator was based on the CSCO guidelines for SOC treatment and administration at the time of protocol development and study initiation in 2018. Both treatment groups received induction treatment consisting of carboplatin in combination with pemetrexed (for non-squamous histology) or paclitaxel (for squamous histology) for up to 4 cycles, with additional maintenance treatment with sugemalimab/placebo in combination with pemetrexed for participants with non-squamous cell histology and sugemalimab/placebo monotherapy for participants with squamous histology. The chemotherapy-backbone in the pivotal study (CS1001-302) is in line with the ESMO guidelines and is accepted. Moreover, while the standard of care in the EU presently includes a PD1/PD-L1 targeting agent, a comparison versus placebo as add on to chemotherapy isolates drug effects through superiority. While this design does not provide a relative effect estimate to the established standard of care, it does produce robust evidence of efficacy, similar to what has been accepted for previous approvals of this class of medicines, avoiding the potential pit-falls of non-inferiority comparisons.

The primary endpoint was PFS, which is an appropriate endpoint in this setting. The analysis of PFS used the EMA censoring rules. Secondary endpoints were OS, PFS by BICR, PFS in PD-L1≥1% (investigator), ORR (investigator) and DoR. The OS analysis might be confounded by cross-over (see discussion further below).

At randomisation, subjects were stratified based on PD-L1 status (≥1% vs <1%), histology (squamous vs non-squamous) and ECOG (0 vs 1). The stratification factors are endorsed. In the CSP no specific details have been found on how masking of randomised treatments was to be ensured. According to the CSR, sugemalimab was provided as a solution for infusion (600 mg/20 mL/vial): the placebo provided was sugemalimab corresponding placebo which is taken to imply that sugemalimab and sugemalimab placebo were identical in appearance. After radiologically confirmed progressive disease (assessed by the investigator) treatment assignment was unblinded for that patient. This is not optimal and may have implied a risk of unintentional unblinding of the treatment assignment at a site among those who had not (yet) progressed. However, the many strata may have made it more difficult to guess depending also on number of subjects randomised at the site. The majority of sites randomised approximately 10-20 patients, but this ranged from 3 to 74 patients (one site randomising by far the highest number).

Statistical/methodological considerations

Overall, the SAP appears appropriate. The primary efficacy analysis was based on the ITT set and included all randomised subjects. For the analysis of the primary (PFS) and most important secondary (OS) time-to-event endpoint, conventional methods have been used. The primary endpoint primary analysis relied on assessments by the investigators. In addition, analyses were pre-specified to be based on PFS-events as assessed by a blinded independent central review committee (BICR). Interim analyses (PFS and OS) were planned before the start of the study as described in the original version of the CSP. A multiple testing procedure for secondary endpoints was also in place before the study was initiated.

The SAP (first version 5 June 2020) can be considered to have been authored somewhat late, approximately 17 months after randomisation of the first patient (December 2018), but importantly, was final before the performance of the PFS interim analysis (data cut-off date of 8 June 2020). A second version of the SAP (v 1.1, 22 Apr 2021) was dated after the final PFS analysis (based on a data

cut-off 15 March 2021). Both versions have been provided, and key changes (version 1.1) can be accepted despite their late origin. The assessment of the interim and final analysis of PFS is facilitated by the fact that both were performed under the same SAP version.

Within CSP version 2.0 (7 Apr 2020) the originally planned co-primary endpoints, PFS in subjects with a PD-L1 expression ≥1%, and PFS in all subjects, were changed, which also simplified the interim analysis plan and the multiple testing procedure. At the time, the SAP was not yet final. Regarding the lack of transparency if only the SAP was to be considered, the statistical analysis plan was sufficiently well described in the CSP and the changes made can be followed.

The applicant justified the change in primary endpoints referring to emerging external data which appear legitimate. The change implied that the former co-primary endpoint (PFS in the subgroup of subjects with a PD-L1 expression ≥1%) became a secondary endpoint and was included in the multiple testing procedure (MTP). No concern has been raised with the outcomes at hand.

The only other analysis that seemingly was performed based on the PFS interim data cut-off was PFS by BICR. PFS by BICR was not included in the MTP and is considered supportive. This analysis was repeated at the final PFS analysis, and it is reasonable that it was performed based on the same data cut-offs as PFS as assessed by the investigator. Concordance analyses between investigator tumour assessment and BICR tumour assessment have been presented for both interim PFS, final PFS and updated PFS analysis.

Part of the study was performed during the COVID-19 epidemic/pandemic. The number of subjects per treatment arm with at least one Covid-19 related protocol deviation was similar comparing the sugemalimab (131/320; 40.9%) and placebo (59/159; 37.1%) treatment arm. Further, also the deviation category pattern was similar, the most common category of protocol deviation in both arms being deviations to the visit schedule.

Distribution of frequency and type of major protocol deviations is balanced between the arms of randomisation and therefore they are not considered to impact final study results.

Besides the interim analysis outcome (data cut-off date 08 June 2020), the outcomes from the final PFS analysis (data cut-off 15 March 2021) as well as an updated PFS analysis have been reported, the latter performed based on the data cut-off for the pre-specified OS interim analysis (data cut-off 22 November 2021).

The primary/final analyses of secondary efficacy endpoints were performed after the OS interim analysis had demonstrated a statistically significant difference between treatment arms.

Recruitment and conduct of the study

The study was conducted exclusively in China. A total of 846 patients were screened and 479 patients were randomised with a 2:1 ratio to sugemalimab in combination with chemotherapy group (n=320) and placebo in combination with chemotherapy group (n=159 patients). All randomised patients received treatment.

Efficacy data and additional analyses

Overall distribution of baseline characteristics is generally well balanced between the two treatment arms. Patients were exclusively of Asian origin. The median age of included patients was 63 years. 61% of patients were younger than 65 years. This is a relatively high fraction of patients considering that the average age of a patient getting diagnosed with NSCLC is around 70.

Comparing baseline characteristics of study CS1001-302 with literature data, several other points differ from real life EU patients (i.e. ca. 45% female, 10% never smoker, 70% non-squamous, Simeone et al. 2019). In study CS1001-302, 20% were female, 27% were never smokers, 60% were non-

squamous. However, with a PD-L1-inhibitor, there is no biologic rational for expecting different treatment results due to the mentioned differences in baseline characteristics. The median weight of included patients was 62 kg.

Patients were included regardless of PD-L1 expression. Participants with known EGFR mutation, ALK fusion, ROS1 fusion, or RET fusion were excluded. The testing for actionable mutations was done locally according to routine clinical practice. The exclusion of patients with known driver mutations is reflected in the indication wording and this is endorsed.

External validity

It is notable that the pivotal study was conducted exclusively in China; that the median age was a mere 63 years; that 80% of patients were male; and that the median weight was 62 kg. Reviewing this through the lens of the ICH E5 document on ethnic factors in the acceptability of foreign clinical data, the following was noted: In order to provide reassurance that the single pivotal phase III clinical study CS1001-302 was conducted in accordance with GCP requirements, a GCP inspection was triggered. Additional factors supporting the request for inspection were that the clinical study was only conducted in one country and there was no EU inspection history of the sponsor or any of the investigator sites. The inspectors concluded that the trial and the data reported in the CSR are GCP compliant.

With respect to similarity of disease, it is known that e.g., EGFR mutations are more common in East Asian population. Having tested for this, however, data on the treatment of NSCLC from East Asia have previously been considered extrapolable to an EU setting. However, PK analyses identified body weight as a clinically significant predictor for sugemalimab PK. Since the European population are expected to have significantly higher body weight than the in study CS1001-302, 1500 mg Q3W is recommended in patients >115 kg (see Section 2.6.3 discussion on clinical pharmacology).

While the actual study population differs from the composition of patients with NSCLC in EU, with regards to relatively low age, the high proportion of males, and perhaps also the high proportion of smokers, this is not considered to impact the external validity of results, which are within the range that might be anticipated based on prior experience of this drug class.

Therefore, the pharmacodynamic results are accepted as externally valid. However, due to the considerably lower body weight distribution in the pivotal study, and the unavailability of an acceptable exposure-response model informed by randomised dose comparison, a higher dosing regimen of 1500 mg Q3W in patients >115 kg is recommended (see section 2.6.3 discussion on clinical pharmacology).

Results

A statistically significant and clinically meaningful improvement in **PFS** assessed by investigator per RECIST v1.1 was shown for sugemalimab in combination with chemotherapy at the interim analysis. With a total of 268 PFS events (56% of the total population), the stratified HR was 0.50 (95% CI: 0.39, 0.64], P < 0.0001). The median PFS was 7.8 months (95% CI: 6.90, 8.97) versus 4.9 months (95% CI: 4.70, 5.03) in the sugemalimab group and placebo group (Δ PFS gain 2.9 months).

In the final analysis of PFS, the stratified HR was 0.48 (95% CI: 0.39, 0.60; P < 0.0001). The median PFS in the sugemalimab group was 9.0 versus 4.9 months in the placebo group.

Pre-planned PFS sensitivity analyses included an unstratified analysis, and analyses respectively, to assess impact of non-allowed anti-cancer therapy and missed tumour assessments. The analysis to assess impact of COVID-19 implied that subjects experiencing >3 weeks delay of chemotherapy administration or >9 weeks delay of sugemalimab/placebo administration were to be censored before the last tumour assessment date prior to COVID-19. The analysis implied that 5 and 2 subjects in the

sugemalimab arm and placebo arm respectively with an event (in the primary analysis) instead were censored.

As has been shown, the impact on the final PFS analysis outcome was minor, irrespective of analysis.

The sugemalimab arm showed a statistically significant improvement in **OS** compared with the placebo arm. With a total of 253 OS events (53% of the total population) the stratified HR was 0.65 (95% CI: 0.50-0.84, P = 0.0008). The median OS in the sugemalimab group was 25.4 months compared with 16.9 months in the placebo group (Δ OS gain 8.5 months). After the double-blind phase, 45 patients crossed over from the placebo arm to the sugemalimab arm and this might have confounded OS analysis. However this is not expected to have a clinically relevant impact.

The PFS and OS results were supported by **ORR**. In the sugemalimab arm, 63.4% (203) patients achieved PR and in the placebo arm 40.3% (64) patients achieved PR. No patient, in either arm, achieved CR. The difference in ORR was 23.2 percentage points, P value < 0.0001.

Presented subgroup results of PFS and OS showed a treatment effect that was consistent across PD-L1 expression strata. With respect to histology, efficacy was convincing in both squamous and non-squamous disease.

2.6.7. Conclusions on the clinical efficacy

Sugemalimab in combination with standard chemotherapy for either non-squamous or squamous cell histology demonstrated efficacy in patients with metastatic NSCLC in 1st line treatment in the ITT population with regards to the primary endpoint of PFS and the secondary endpoints of OS and ORR in the context of study CS1001-302.

2.6.8. Clinical safety

The integrated safety analysis include data from the pivotal study CS1001-302, a sugemalimab combination therapy safety pool and a sugemalimab monotherapy safety pool.

All participants in the safety pool received at least one dose of sugemalimab 1200 mg IV Q3W.

The integrated safety analysis main components:

- Study CS1001-302; DCO 22 Nov. 2021 (DCO 15 May 2023 for AESI) (n=320)
- Sugemalimab chemotherapy combination – CS1001-101b; DCO 16 Aug 2021 (cohort 8+9 NSCLC; n=41, cohort 5 GAC/GEJAC, ESCC; n=74) and CS1001-302; DCO 22 Nov. 2021 (n=320); total n=435
- Sugemalimab monotherapy – CS1001-101a/b; DCO 16 Aug 2021 (advanced solid tumours and lymphoma; n=95), CS1001-102; DCO 8 Feb 2021 (advanced solid tumours; n=12), CS1001-201; DCO 10 Nov 2020 (R/R ENKTL; n=80), CS1001-202; DCO 19 Feb 2020 (R/R cHL; n=81), CS1001-301; DCO 8 Mar 2021 (Stage III NSCLC; n=255), and CS1001-302, DCO 22 Nov 2021 (crossover phase, n=45); total n=568

2.6.8.1. Patient exposure

Table 32: Patient exposure

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with exposure duration >6 months safety data	Patients with exposure duration >12 months safety data	Patients with exposure duration >21 months safety data
Placebo-controlled[1]	860[3]	620	620	349	181	85
Active - controlled	NA	NA	NA	NA	NA	NA
Open studies[2]	431	431	406	189	92	42
Post marketing	NA	1,439.3[4]	UNK	UNK	UNK	UNK
Compassionate use	NA	NA	NA	NA	NA	NA

Abbreviations: NA=Not applicable; UNK=Unknown

1) Placebo-controlled trials: Studies CS1001-301 and CS1001-302 (including patients dosed with sugemalimab in the cross-over period)
2) Open studies: Studies CS1001-101, CS1001-102, CS1001-201, and CS1001-202
3) Number of patients randomised
4) Post-marketing patient exposure was estimated as 1439.3 patient/years by 30 Jun 2023. This estimation was based on the fixed dose of 1200 mg, once every 3 weeks, 52 weeks one year, for each patient

Study CS1001-302

In Study CS1001-302, 320 participants 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. The mean number of treatment cycles was 14.9 and 8.5 for sugemalimab and placebo respectively.

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 of chemotherapy initially. Median number of cycles of pemetrexed was 8.0 in the sugemalimab group and 6.0 in the placebo group for patients with non-squamous histology.

Integrated safety pool

In 435 participants who received at least one dose of sugemalimab 1200 mg in combination with chemotherapy, the median (range) duration and cycle of sugemalimab treatment were 7.20 (0.2 to 34.7) months and 10.0 (1 to 49) cycles. In the sugemalimab chemotherapy combination safety pool 59.5% received sugemalimab for ≥ 6 months, 32.6% ≥ 12 months and 20.2% beyond 21 months.

In the sugemalimab chemotherapy safety pool several different chemotherapy regiments were used, mostly with limited number of cycles given (maximum 6 cycles). Median number of cycles given ranged from 1.5 to 8 and between 5-6 for the chemotherapy that was given as set number of cycles.

In 568 participants who received at least one dose of sugemalimab 1200 mg monotherapy, the median (range) duration and cycle of sugemalimab treatment were 5.59 (0.1 to 37.4) months and 8.0 (1 to 54) cycles. In the sugemalimab monotherapy safety pool 47.0% received sugemalimab for ≥ 6 months, 22.2% ≥ 12 months and 3.7% beyond 21 months.

45 patients from the placebo + chemotherapy treatment arm of CS1001-302 crossed over following confirmed radiographic disease progression to receive open-label sugemalimab monotherapy. The median number of cycles sugemalimab monotherapy received was 6.0 for this subpopulation.

The treatment duration in the sugemalimab combination safety pool was similar to the duration in the primary safety study. This is however expected since the vast majority of patients in the total combination pool is derived from the pivotal study. The exposure in the non-NSCLC sugemalimab combination safety pool was shorter compared to the pivotal study.

2.6.8.2. Adverse events

Study CS1001-302

Table 33: Overview of treatment-emergent adverse events, Study CS1001-302 double-blind phase (safety analysis set)

	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)

	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)
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	**114 (35.6)**	**26 (16.4)**

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

Treatment Emergent Adverse Events

Table 34: Most commonly reported treatment-emergent adverse events (at least 10% of participants in either treatment group by preferred term) by system organ class and preferred term, study CS-302 double-blind phase (safety analysis set)

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)

System Organ Class Preferred Term	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)
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

Table 35: Overview of treatment-emergent adverse events, sugemalimab safety pool (safety analysis set)

	Sugemalimab + Chemotherapy					
	NSCLC					
TEAE category	**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 Monotherapy (N=568) n (%)**
Number of Patients with						
Any TEAE	**319 (99.7)**	**41 (100.0)**	**360 (99.7)**	**74 (100.0)**	**434 (99.8)**	**541 (95.2)**
Any TEAE of Grade 3-5	207 (64.7)	35 (85.4)	242 (67.0)	60 (81.1)	302 (69.4)	181 (31.9)
Any Serious TEAE	110 (34.4)	21 (51.2)	131 (36.3)	40 (54.1)	171 (39.3)	144 (25.4)
Any TEAE Leading to Infusion Interruption	8 (2.5)	0	8 (2.2)	1 (1.4)	9 (2.1)	5 (0.9)

	Sugemalimab + Chemotherapy					
	NSCLC					
TEAE category	**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 Monotherapy (N=568) n (%)**
Any TEAE Leading to Treatment Cycle Delayed	144 (45.0)	22 (53.7)	166 (46.0)	35 (47.3)	201 (46.2)	141 (24.8)
Any TEAE Leading to Treatment Discontinuation	62 (19.4)	18 (43.9)	80 (22.2)	30 (40.5)	110 (25.3)	61 (10.7)
Any TEAE Leading to Death	20 (6.3)	4 (9.8)	24 (6.6)	5 (6.8)	29 (6.7)	19 (3.3)
Any Treatment-Related AE(TRAE)	**317 (99.1)**	**41 (100.0)**	**358 (99.2)**	**73 (98.6)**	**431 (99.1)**	**435 (76.6)**
Any TRAE of Grade 3-5	185 (57.8)	32 (78.0)	217 (60.1)	54 (73.0)	271 (62.3)	72 (12.7)
Any Serious TRAE	78 (24.4)	13 (31.7)	91 (25.2)	25 (33.8)	116 (26.7)	63 (11.1)
Any TRAE Leading to Infusion Interruption	7 (2.2)	0	7 (1.9)	1 (1.4)	8 (1.8)	5 (0.9)
Any TRAE Leading to Treatment Cycle Delayed	129 (40.3)	19 (46.3)	148 (41.0)	33 (44.6)	181 (41.6)	84 (14.8)
Any TRAE Leading to Treatment Discontinuation	51 (15.9)	16 (39.0)	67 (18.6)	23 (31.1)	90 (20.7)	42 (7.4)
Any TRAE Leading to Death	11 (3.4)	1 (2.4)	12 (3.3)	1 (1.4)	13 (3.0)	7 (1.2)
Any Sugemalimab-Related TEAE	**264 (82.5)**	**40 (97.6)**	**304 (84.2)**	**67 (90.5)**	**371 (85.3)**	**435 (76.6)**
Any Sugemalimab-Related TEAE of Grade 3-5	95 (29.7)	17 (41.5)	112 (31.0)	32 (43.2)	144 (33.1)	72 (12.7)
Any Sugemalimab-Related Serious TEAE	53 (16.6)	11 (26.8)	64 (17.7)	16 (21.6)	80 (18.4)	63 (11.1)
Any Sugemalimab-Related TEAE Leading to Any Treatment Infusion Interruption	1 (0.3)	0	1 (0.3)	1 (1.4)	2 (0.5)	5 (0.9)
Any Sugemalimab-Related TEAE Leading to Any Treatment Cycle Delayed	82 (25.6)	17 (41.5)	99 (27.4)	20 (27.0)	119 (27.4)	84 (14.8)
Any Sugemalimab-Related TEAE Leading to Any Treatment Discontinuation	38 (11.9)	12 (29.3)	50 (13.9)	18 (24.3)	68 (15.6)	42 (7.4)
Any Sugemalimab-Related TEAE Leading to Death	7 (2.2)	1 (2.4)	8 (2.2)	1 (1.4)	9 (2.1)	7 (1.2)
Any Infusion-Related Reaction TEAE	**12 (3.8)**	**2 (4.9)**	**14 (3.9)**	**5 (6.8)**	**19 (4.4)**	**19 (3.3)**

	Sugemalimab + Chemotherapy					
	NSCLC					
TEAE category	**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 Monotherapy (N=568) n (%)**
Any Sugemalimab Infusion-Related Reaction TEAE	6 (1.9)	2 (4.9)	8 (2.2)	3 (4.1)	11 (2.5)	19 (3.3)
Investigator Assessed irAE[a]	**114 (35.6)**	**21 (51.2)**	**135 (37.4)**	**47 (63.5)**	**182 (41.8)**	**238 (41.9)**

[a] Immune-related AEs by Sponsor assessment are provided in the individual CSRs.
MedDRA version 24.1.
AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; TEAE = treatment-emergent adverse event

Table 36: Most Commonly Reported Treatment-Emergent Adverse Events (at Least 10% of Participants Overall by Preferred Term) by System Organ Class and Preferred Term, Sugemalimab Safety Pool (Safety Analysis Set)

	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 Monotherapy (N=568) n (%)**
Number of patients with at least one TEAE	**319 (99.7)**	**41 (100.0)**	**360 (99.7)**	**74 (100.0)**	**434 (99.8)**	**541 (95.2)**
Investigations	**281 (87.8)**	**36 (87.8)**	**317 (87.8)**	**66 (89.2)**	**383 (88.0)**	**378 (66.5)**
Neutrophil count decreased	185 (57.8)	24 (58.5)	209 (57.9)	40 (54.1)	249 (57.2)	51 (9.0)
White blood cell count decreased	180 (56.3)	23 (56.1)	203 (56.2)	45 (60.8)	248 (57.0)	65 (11.4)
Platelet count decreased	108 (33.8)	17 (41.5)	125 (34.6)	35 (47.3)	160 (36.8)	43 (7.6)
Aspartate aminotransferase increased	114 (35.6)	16 (39.0)	130 (36.0)	18 (24.3)	148 (34.0)	120 (21.1)
Alanine aminotransferase increased	112 (35.0)	14 (34.1)	126 (34.9)	13 (17.6)	139 (32.0)	117 (20.6)
Weight increased	76 (23.8)	5 (12.2)	81 (22.4)	3 (4.1)	84 (19.3)	40 (7.0)
Gamma-glutamyltransferase increased	48 (15.0)	12 (29.3)	60 (16.6)	9 (12.2)	69 (15.9)	38 (6.7)
Weight decreased	39 (12.2)	6 (14.6)	45 (12.5)	15 (20.3)	60 (13.8)	35 (6.2)
Lymphocyte count decreased	22 (6.9)	13 (31.7)	35 (9.7)	10 (13.5)	45 (10.3)	29 (5.1)
Blood bilirubin increased	28 (8.8)	6 (14.6)	34 (9.4)	8 (10.8)	42 (9.7)	59 (10.4)
Blood and lymphatic system disorders	**261 (81.6)**	**38 (92.7)**	**299 (82.8)**	**63 (85.1)**	**362 (83.2)**	**158 (27.8)**

	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 Monotherapy (N=568) n (%)
Anaemia	245 (76.6)	33 (80.5)	278 (77.0)	59 (79.7)	337 (77.5)	130 (22.9)
Leukopenia	33 (10.3)	8 (19.5)	41 (11.4)	7 (9.5)	48 (11.0)	12 (2.1)
Metabolism and nutrition disorders	**211 (65.9)**	**29 (70.7)**	**240 (66.5)**	**53 (71.6)**	**293 (67.4)**	**216 (38.0)**
Decreased appetite	92 (28.8)	15 (36.6)	107 (29.6)	36 (48.6)	143 (32.9)	33 (5.8)
Hypoalbuminaemia	59 (18.4)	13 (31.7)	72 (19.9)	15 (20.3)	87 (20.0)	46 (8.1)
Hyponatraemia	46 (14.4)	10 (24.4)	56 (15.5)	17 (23.0)	73 (16.8)	40 (7.0)
Hyperglycaemia	45 (14.1)	12 (29.3)	57 (15.8)	14 (18.9)	71 (16.3)	53 (9.3)
Hypokalaemia	44 (13.8)	4 (9.8)	48 (13.3)	20 (27.0)	68 (15.6)	41 (7.2)
Hypercholesterolaemia	38 (11.9)	9 (22.0)	47 (13.0)	10 (13.5)	57 (13.1)	33 (5.8)
Hypertriglyceridaemia	26 (8.1)	18 (43.9)	44 (12.2)	10 (13.5)	54 (12.4)	33 (5.8)
Gastrointestinal disorders	**185 (57.8)**	**27 (65.9)**	**212 (58.7)**	**59 (79.7)**	**271 (62.3)**	**169 (29.8)**
Nausea	77 (24.1)	18 (43.9)	95 (26.3)	34 (45.9)	129 (29.7)	28 (4.9)
Constipation	75 (23.4)	10 (24.4)	85 (23.5)	24 (32.4)	109 (25.1)	37 (6.5)
Vomiting	44 (13.8)	9 (22.0)	53 (14.7)	25 (33.8)	78 (17.9)	26 (4.6)
Diarrhoea	32 (10.0)	9 (22.0)	41 (11.4)	16 (21.6)	57 (13.1)	28 (4.9)
General disorders and administration site conditions	**182 (56.9)**	**25 (61.0)**	**207 (57.3)**	**48 (64.9)**	**255 (58.6)**	**170 (29.9)**
Pyrexia	55 (17.2)	8 (19.5)	63 (17.5)	17 (23.0)	80 (18.4)	87 (15.3)
Asthenia	56 (17.5)	9 (22.0)	65 (18.0)	13 (17.6)	78 (17.9)	14 (2.5)
Fatigue	42 (13.1)	6 (14.6)	48 (13.3)	10 (13.5)	58 (13.3)	16 (2.8)
Skin and subcutaneous tissue disorders	**134 (41.9)**	**17 (41.5)**	**151 (41.8)**	**29 (39.2)**	**180 (41.4)**	**109 (19.2)**
Rash	59 (18.4)	8 (19.5)	67 (18.6)	17 (23.0)	84 (19.3)	46 (8.1)
Alopecia	62 (19.4)	5 (12.2)	67 (18.6)	2 (2.7)	69 (15.9)	2 (0.4)
Respiratory, thoracic and mediastinal disorders	**109 (34.1)**	**21 (51.2)**	**130 (36.0)**	**23 (31.1)**	**153 (35.2)**	**195 (34.3)**
Cough	31 (9.7)	12 (29.3)	43 (11.9)	3 (4.1)	46 (10.6)	74 (13.0)
Infections and infestations	**111 (34.7)**	**16 (39.0)**	**127 (35.2)**	**24 (32.4)**	**151 (34.7)**	**175 (30.8)**
Pneumonia	43 (13.4)	5 (12.2)	48 (13.3)	5 (6.8)	53 (12.2)	59 (10.4)
Upper respiratory tract infection	34 (10.6)	6 (14.6)	40 (11.1)	7 (9.5)	47 (10.8)	60 (10.6)
Musculoskeletal and connective tissue disorders	117 (36.6)	16 (39.0)	133 (36.8)	18 (24.3)	151 (34.7)	93 (16.4)
Arthralgia	43 (13.4)	3 (7.3)	46 (12.7)	7 (9.5)	53 (12.2)	27 (4.8)
Nervous system disorders	94 (29.4)	23 (56.1)	117 (32.4)	24 (32.4)	141 (32.4)	51 (9.0)

	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 Monotherapy (N=568) n (%)
Hypoaesthesia	31 (9.7)	10 (24.4)	41 (11.4)	8 (10.8)	49 (11.3)	9 (1.6)
Renal and urinary disorders	54 (16.9)	9 (22.0)	63 (17.5)	25 (33.8)	88 (20.2)	84 (14.8)
Proteinuria	28 (8.8)	6 (14.6)	34 (9.4)	20 (27.0)	54 (12.4)	54 (9.5)
Cardiac disorders	47 (14.7)	9 (22.0)	56 (15.5)	12 (16.2)	68 (15.6)	42 (7.4)
Endocrine disorders	45 (14.1)	7 (17.1)	52 (14.4)	12 (16.2)	64 (14.7)	122 (21.5)
Hypothyroidism	35 (10.9)	3 (7.3)	38 (10.5)	7 (9.5)	45 (10.3)	89 (15.7)
Psychiatric disorders	41 (12.8)	9 (22.0)	50 (13.9)	9 (12.2)	59 (13.6)	30 (5.3)
Vascular disorders	31 (9.7)	7 (17.1)	38 (10.5)	10 (13.5)	48 (11.0)	38 (6.7)
Injury, poisoning and procedural complications	16 (5.0)	2 (4.9)	18 (5.0)	3 (4.1)	21 (4.8)	78 (13.7)

The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 24.1.
MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; PT = preferred term; SOC = system organ class

Treatment Emergent Adverse Events by Severity

Table 37: Grade 3 to 5 treatment-emergent adverse events (cut-off of at least 2 patients per preferred term) by system organ class and preferred term, study CS1001-302 double-blind phase (safety analysis set)

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%)**
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%)
Gamma-glutamyltransferase increased	9(2.8%)	3(1.9%)
Lymphocyte count decreased	9(2.8%)	3(1.9%)
Weight increased	6(1.9%)	1(0.6%)
Blood alkaline phosphatase increased	4(1.3%)	0
Alanine aminotransferase increased	3(0.9%)	4(2.5%)
Amylase increased	3(0.9%)	0
Blood bilirubin increased	3(0.9%)	0
Lipase increased	3(0.9%)	0
Aspartate aminotransferase increased	2(0.6%)	3(1.9%)
Transaminases increased	2(0.6%)	0
Weight decreased	0	2(1.3%)
Blood and lymphatic system disorders	**72(22.5%)**	**30(18.9%)**
Anaemia	48(15.0%)	18(11.3%)
Neutropenia	12(3.8%)	7(4.4%)
Febrile neutropenia	7(2.2%)	1(0.6%)
Leukopenia	6(1.9%)	2(1.3%)
Myelosuppression	6(1.9%)	3(1.9%)
Metabolism and nutrition disorders	**33(10.3%)**	**11(6.9%)**
Hyponatraemia	11(3.4%)	1(0.6%)
Hypertriglyceridaemia	7(2.2%)	1(0.6%)
Hypokalaemia	6(1.9%)	2(1.3%)
Hyperglycaemia	4(1.3%)	3(1.9%)
Diabetes mellitus	3(0.9%)	0
Hypochloraemia	3(0.9%)	0
Hypophosphataemia	3(0.9%)	0
Infections and infestations	**25(7.8%)**	**10(6.3%)**
Pneumonia	16(5.0%)	9(5.7%)
Upper respiratory tract infection	3(0.9%)	0
Urinary tract infection	3(0.9%)	0
Bronchitis	2(0.6%)	1(0.6%)
Septic shock	2(0.6%)	0
General disorders and administration site conditions	**15(4.7%)**	**11(6.9%)**
Death	7(2.2%)	3(1.9%)
Fatigue	3(0.9%)	1(0.6%)
Asthenia	2(0.6%)	3(1.9%)
Malaise	2(0.6%)	2(1.3%)
Gastrointestinal disorders	**14(4.4%)**	**6(3.8%)**
Vomiting	5(1.6%)	2(1.3%)
Diarrhoea	3(0.9%)	0
Abdominal pain	2(0.6%)	0
Stomatitis	2(0.6%)	0
Nausea	1(0.3%)	3(1.9%)
Hepatobiliary disorders	**10(3.1%)**	**2(1.3%)**
Hepatic function abnormal	7(2.2%)	2(1.3%)
Respiratory, thoracic and mediastinal disorders	**10(3.1%)**	**3(1.9%)**

MedDRA System Organ Class MedDRA Preferred Term	Sugemalimab+ Chemotherapy N=320	Placebo+ Chemotherapy N=159
Immune-mediated lung disease	3(0.9%)	0
Respiratory failure	3(0.9%)	0
Cardiac disorders	**8(2.5%)**	**2(1.3%)**
Cardiac failure	4(1.3%)	1(0.6%)
Nervous system disorders	**6(1.9%)**	**2(1.3%)**
Cerebral infarction	4(1.3%)	0
Skin and subcutaneous tissue disorders	**6(1.9%)**	**0**
Rash	3(0.9%)	0
Vascular disorders	**5(1.6%)**	**1(0.6%)**
Hypertension	4(1.3%)	0
Renal and urinary disorders	**4(1.3%)**	**1(0.6%)**
Renal failure	2(0.6%)	0
Injury, poisoning and procedural complications	**2(0.6%)**	**0**
Vascular access complication	2(0.6%)	0

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.

Table 38: Grade 3 to 5 treatment-emergent adverse events (at least 5% of participants overall by preferred term) by system organ class and preferred term, sugemalimab safety pool (safety analysis set)

	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 Monotherapy (N=568) n (%)**
Number of patients with at least one TEAE of grade 3-5	**207 (64.7)**	**35 (85.4)**	**242 (67.0)**	**60 (81.1)**	**302 (69.4)**	**181 (31.9)**
Investigations	**140 (43.8)**	**22 (53.7)**	**162 (44.9)**	**42 (56.8)**	**204 (46.9)**	**55 (9.7)**
Neutrophil count decreased	104 (32.5)	18 (43.9)	122 (33.8)	19 (25.7)	141 (32.4)	8 (1.4)
White blood cell count decreased	46 (14.4)	7 (17.1)	53 (14.7)	10 (13.5)	63 (14.5)	6 (1.1)
Platelet count decreased	34 (10.6)	4 (9.8)	38 (10.5)	13 (17.6)	51 (11.7)	5 (0.9)
Blood and lymphatic system disorders	**72 (22.5)**	**15 (36.6)**	**87 (24.1)**	**21 (28.4)**	**108 (24.8)**	**24 (4.2)**
Anaemia	48 (15.0)	10 (24.4)	58 (16.1)	18 (24.3)	76 (17.5)	18 (3.2)
Metabolism and nutrition disorders	**33 (10.3)**	**8 (19.5)**	**41 (11.4)**	**18 (24.3)**	**59 (13.6)**	**37 (6.5)**
Infections and infestations	**25 (7.8)**	**5 (12.2)**	**30 (8.3)**	**5 (6.8)**	**35 (8.0)**	**44 (7.7)**
Gastrointestinal disorders	**14 (4.4)**	**2 (4.9)**	**16 (4.4)**	**13 (17.6)**	**29 (6.7)**	**17 (3.0)**
General disorders and administration site conditions	**15 (4.7)**	**1 (2.4)**	**16 (4.4)**	**7 (9.5)**	**23 (5.3)**	**12 (2.1)**

The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 24.1.

MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; PT = preferred term; SOC = system organ class

Adverse Events of Special Interest (AESI)

Immune-related AEs are considered AESIs in the sugemalimab clinical studies.

Table 39: Overall summary of immune-related adverse events according to investigator assessment in the study CS1001-302 (safety analysis set, DCO 15 May 2023)

	Sugemalimab + Chemotherapy (N=320)	Placebo + Chemotherapy (N=159)
Number of Patients with at Least One Event	**117(36.6%)**	**27(17.0%)**
Number of Patients with at Least One		
Grade 3-5 Event	24(7.5%)	4(2.5%)
Serious Event	22(6.9%)	3(1.9%)
Event Leading to Drug Permanently Discontinued	13(4.1%)	1(0.6%)
Event Leading to Drug Interruption	30(9.4%)	4(2.5%)
Event Leading to Death	1(0.3%)	0(0.0%)
Event Treated with Systemic Corticosteroid	31(9.7%)	3(1.9%)
Event Treated with High Dose Systemic Corticosteroid	21(6.6%)	3(1.9%)

Table 40: Immune-related adverse events from investigator assessment by category, study CS1001-302 double-blind phase DCO of 15-May-2023 (safety analysis set)

Category	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)
Number of Participants With at Least One Event	**117 (36.6)**	**27 (17.0)**
Hypothyroidism	41 (12.8)	5 (3.1)
Hyperthyroidism	31 (9.7)	3 (1.9)
Hepatitis	29 (9.1)	8 (5.0)
Skin adverse reaction (excluding severe)	26 (8.1)	9 (5.7)
Colitis	8 (2.5)	2 (1.3)
Pneumonitis	8 (2.5)	2 (1.3)
Myocarditis	7 (2.2)	0
Diabetes mellitus	6 (1.9)	2 (1.3)
Severe skin adverse reactions	6 (1.9)	0
Myositis	6 (1.9)	3 (1.9)
Nephritis (including renal failure)	5 (1.6)	1 (0.6)
Arthritis	3 (0.9)	1 (0.6)
Thrombocytopenia	2 (0.6)	2 (1.3)
Thyroiditis	2 (0.6)	1 (0.6)
Upper gastrointestinal disorders	2 (0.6)	0
Ocular toxicities	1 (0.3)	0
Pancytopenia/bicytopenia	1 (0.3)	0
Pancreatitis	1 (0.3)	0
Adrenal insufficiency	0	1 (0.6)

Table 41: Overall summary of immune-related adverse events from investigator assessment, sugemalimab safety pool (safety analysis set)

	Sugemalimab + Chemotherapy				
	302 NSCLC (N=320)	NSCLC Total (N=361)	Other Indications (N=74)	Total (N=435)	Monotherapy (N=568)
Number of Participants With at Least One Event	**114 (35.6%)**	**135 (37.4%)**	**47 (63.5)**	**182 (41.8)**	**238 (41.9)**
Number of Patients with at Least One					
Grade 3-5 Event	22 (6.9%)	24 (6.6%)	8 (10.8%)	32 (7.4%)	30 (5.3%)
Serious Event	21 (6.6%)	24 (6.6%)	8 (10.8%)	32 (7.4%)	41 (7.2%)
Event Leading to Suge Treatment Discontinued	11 (3.4%)	16 (4.4%)	6 (8.1%)	22 (5.1%)	27 (4.8%)
Event Leading to Suge Interrupted (cycle delayed/ infusion interruption)	28 (8.8%)	32 (8.9%)	4 (5.4%)	36 (8.3%)	50 (8.8%)
Event Leading to Death	1 (0.3%)	1 (0.3%)	0	1 (0.2%)	3 (0.5%)

Event Treated with Systemic Corticosteroid	28 (8.8%)	28 (7.8%)	0	28 (6.4%)	47 (8.3%)
Event Treated with High Dose Systemic Corticosteroid	19 (5.9%)	19 (5.3%)	0	19 (4.4)	41 (7.2%)

IrAEs were reported in 182 (41.8%) participants in the sugemalimab in combination with chemotherapy group. The most frequently reported irAE categories in the sugemalimab chemotherapy pool were immune-related hypothyroidism (62 [14.3%] participants), immune-related skin adverse reactions (excluding severe) (46 [10.6%] participants), immune-related hepatitis (42 [9.7%] participants), and immune-related hyperthyroidism (41 [9.4%] participants.

In the sugemalimab monotherapy pool, irAEs were reported in 238 (41.9%) participants. the most frequently reported irAE categories in the sugemalimab monotherapy pool were immune-related hypothyroidism (95 [16.7%] participants), immune-related hyperthyroidism (64 [11.3%] participants), immune-related pneumonitis (53 [9.3%] participants), immune-related skin adverse reactions (excluding severe) (52 [9.2%] participants), and immune-related hepatitis (46 [8.1%] participants).

Infusion-related reaction Adverse Events

In Study CS1001-302, infusion-related reaction TEAEs were reported in 12 (3.8%) participants in the sugemalimab + chemotherapy arm and 8 (5.0%) participants in the placebo + chemotherapy arm. Except for anaphylactic reaction and infusion-related reaction in 3 (0.9%) participants each in the sugemalimab + chemotherapy arm and pruritus in 2 (1.3%) participants in the placebo + chemotherapy arm, all other infusion-related reaction TEAEs by PT were single-case occurrences.

The majority of the infusion related reactions were of grade 1 or 2. In the sugemalimab + chemotherapy arm one patient each hade grade 3 rash maculo-papular and anaphylactic reaction and in the placebo + chemotherapy arm one patient had blood pressure increased of grade 3. None of the events were classified as serious or led to discontinuation of treatment.

Methodology for determination of ADRs

Source Data

The following data was assessed for sugemalimab ADR identification:

- Main data: TEAEs observed in sugemalimab chemotherapy combination safety pool (N=435)
- Supplementary data: TEAEs observed in sugemalimab monotherapy safety pool (N=568)

Methodology for ADR identification

Medico-scientific judgment guided by Bradford-Hill criteria was applied for the assessment and identification of the ADRs with below considerations.

- The frequency of TEAE and TRAE, and the proportion of the TRAE/TEAE.
- The comparison of the TEAE frequency between treatment group and placebo group.
- Temporal relationship between event onset and treatment exposure.
- Dose-response association.
- Association with the known mechanisms of action.
- De-challenge and re-challenge result.

- Coherence with existing medical knowledge and available experimental evidence from clinical and pre-clinical studies.
- Analogy with reactions that can be observed for medicinal products with similar chemical structures and/or mechanisms of action.

All TEAEs meeting the following criteria were selected for individual medical review. Preferred Terms (PTs) that logically describe the same safety event were reviewed together.

- TEAEs observed in sugemalimab chemotherapy combination safety pool
    - TEAEs observed in>2 patients
    - TEAEs observed in ≤ 2 patients, which pertained to immune-related class effect and/or fell into European Medicines Agency (EMA) Designated Medical event (DME) category
- TEAEs observed in sugemalimab monotherapy safety pool
    - TEAEs which pertained to immune-related class effect and/or fell into European Medicines Agency (EMA) Designated Medical event (DME) category, but not observed in sugemalimab chemotherapy combination safety pool

If the available evidence was sufficient to support reasonable possibility of a causal relationship with sugemalimab, the TEAE was included as an ADR.

Grouping of the identified ADRs

For the identified ADRs from sugemalimab chemotherapy combination safety pool that represented the same or a similar medical concept were grouped as appropriate. The grouped PT was marked and the note was added under ADR table accordingly for interpretation.

Frequency of identified ADRs

The frequency of the identified ADRs from sugemalimab chemotherapy combination safety pool was calculated by PTs/grouped PTs based on TEAE.

The new methodology for adjudication of ADRs has been presented and understood.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious Adverse Events

Table 42: Serious treatment-emergent adverse events (at least 2% of participants in either treatment group by preferred term) by system organ class and preferred term, study CS1001-302 double-blind phase (safety analysis set)

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)

System Organ Class Preferred Term	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)
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)

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

Table 43: Serious treatment-emergent adverse events (at least 2% of participants overall by preferred term) by system organ class and preferred term, sugemalimab safety pool (safety analysis set)

	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 Monotherapy (N=568) n (%)
Number of patients with at least one serious TEAE	**110 (34.4)**	**21 (51.2)**	**131 (36.3)**	**40 (54.1)**	**171 (39.3)**	**144 (25.4)**
Investigations	**19 (5.9)**	**9 (22.0)**	**28 (7.8)**	**10 (13.5)**	**38 (8.7)**	**8 (1.4)**
Platelet count decreased	10 (3.1)	4 (9.8)	14 (3.9)	3 (4.1)	17 (3.9)	1 (0.2)
Neutrophil count decreased	6 (1.9)	3 (7.3)	9 (2.5)	2 (2.7)	11 (2.5)	0
Infections and infestations	**27 (8.4)**	**2 (4.9)**	**29 (8.0)**	**4 (5.4)**	**33 (7.6)**	**51 (9.0)**
Pneumonia	18 (5.6)	1 (2.4)	19 (5.3)	2 (2.7)	21 (4.8)	34 (6.0)
Blood and lymphatic system disorders	**21 (6.6)**	**5 (12.2)**	**26 (7.2)**	**5 (6.8)**	**31 (7.1)**	**6 (1.1)**
Anaemia	11 (3.4)	1 (2.4)	12 (3.3)	4 (5.4)	16 (3.7)	3 (0.5)
Respiratory, thoracic and mediastinal disorders	**15 (4.7)**	**3 (7.3)**	**18 (5.0)**	**6 (8.1)**	**24 (5.5)**	**40 (7.0)**
Immune-mediated lung disease	4 (1.3)	0	4 (1.1)	0	4 (0.9)	15 (2.6)
Pneumonitis	1 (0.3)	0	1 (0.3)	2 (2.7)	3 (0.7)	12 (2.1)
General disorders and administration site conditions	**13 (4.1)**	**2 (4.9)**	**15 (4.2)**	**8 (10.8)**	**23 (5.3)**	**9 (1.6)**
Death	7 (2.2)	0	7 (1.9)	3 (4.1)	10 (2.3)	5 (0.9)
Gastrointestinal disorders	**8 (2.5)**	**3 (7.3)**	**11 (3.0)**	**7 (9.5)**	**18 (4.1)**	**14 (2.5)**
Metabolism and nutrition disorders	**7 (2.2)**	**1 (2.4)**	**8 (2.2)**	**5 (6.8)**	**13 (3.0)**	**5 (0.9)**
Nervous system disorders	**7 (2.2)**	**3 (7.3)**	**10 (2.8)**	**3 (4.1)**	**13 (3.0)**	**2 (0.4)**

	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 Monotherapy (N=568) n (%)
Hepatobiliary disorders	**8 (2.5)**	**2 (4.9)**	**10 (2.8)**	**1 (1.4)**	**11 (2.5)**	**9 (1.6)**
Cardiac disorders	**8 (2.5)**	**0**	**8 (2.2)**	**1 (1.4)**	**9 (2.1)**	**6 (1.1)**
Injury, poisoning and procedural complications	**0**	**1 (2.4)**	**1 (0.3)**	**2 (2.7)**	**3 (0.7)**	**17 (3.0)**

The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 24.1.
MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; PT = preferred term; SOC = system organ class

Deaths

Table 44: Summary of deaths, study CS1001-302 (safety analysis set)

	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)

This summary included all participants who died during the double-blind phase and crossover phase as of the data cutoff date of 22 Nov 2021.
CSR = clinical study report

Among the 26 deaths in the sugemalimab group designated to other, 8 occurred without prior detection of disease progression. In the placebo group 2/9 deaths occurred without prior detection of disease progression. Hence, the majority of deaths occurred after detection of disease progression.

Table 45: Treatment-emergent adverse events leading to death by system organ class and preferred term, study CS1001-302 double-blind phase (safety analysis set)

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

System Organ Class Preferred Term	Sugemalimab + Chemotherapy (N = 320) n (%)	Placebo + Chemotherapy (N = 159) n (%)
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)

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

Table 46: Summary of deaths, sugemalimab combination therapy pool (safety analysis set)

	Sugemalimab + Chemotherapy			Sugemalimab + Targeted Therapy (N = 23) n (%)	Total (N = 458) n (%)
	NSCLC (N = 361) n (%)	Non-NSCLC (N = 74) n (%)	Total (N = 435) n (%)		
Number of Participant Deaths	**178 (49.3)**	**44 (59.5)**	**222 (51.0)**	**13 (56.5)**	**235 (51.3)**
Primary Cause of Death					
Disease progression	133 (36.8)	28 (37.8)	161 (37.0)	8 (34.8)	169 (36.9)
Adverse event	17 (4.7)	2 (2.7)	19 (4.4)	2 (8.7)	21 (4.6)
Other	28 (7.8)	14 (18.9)	42 (9.7)	3 (13.0)	45 (9.8)

This summary included all participants who died as of the data cutoff date for each study.
NSCLC = non-small cell lung cancer

Table 47: Summary of deaths, sugemalimab monotherapy pool (safety analysis set)

	CS1001-101a/b (N = 95) n (%)	CS1001-102 (N = 12) n (%)	CS1001-201 (N = 80) n (%)	CS1001-202 (N = 81) n (%)	CS1001-301 (N = 255) n (%)	CS1001-302 Crossover (N = 45) n (%)	Total (N = 568) n (%)
Number of Participant Deaths	59 (62.1)	7 (58.3)	28 (35.0)	6 (7.4)	33 (12.9)	26 (57.8)	159 (28.0)
Primary Cause of Death							
Disease progression	49 (51.6)	6 (50.0)	18 (22.5)	2 (2.5)	22 (8.6)	22 (48.9)	119 (21.0)
Adverse event	0	1 (8.3)	5 (6.3)	0	9 (3.5)	1 (2.2)	16 (2.8)
Other	9 (9.5)	0	5 (6.3)	4 (4.9)	2 (0.8)	3 (6.7)	23 (4.0)
Unknown	1 (1.1)	0	0	0	0	0	1 (0.2)

This summary included all participants who died as of the data cutoff date for each study.

Table 48: Treatment-emergent adverse events leading to death by system organ class and preferred term, sugemalimab safety pool (safety analysis set)

	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 Monotherapy (N=568) n (%)**
Number of patients with at least one TEAE leading to death	**20 (6.3)**	**4 (9.8)**	**24 (6.6)**	**5 (6.8)**	**29 (6.7)**	**19 (3.3)**
General disorders and administration site conditions	**7 (2.2)**	**0**	**7 (1.9)**	**4 (5.4)**	**11 (2.5)**	**5 (0.9)**
Death	7 (2.2)	0	7 (1.9)	3 (4.1)	10 (2.3)	5 (0.9)
Multiple organ dysfunction syndrome	0	0	0	1 (1.4)	1 (0.2)	0
Nervous system disorders	**4 (1.3)**	**2 (4.9)**	**6 (1.7)**	**1 (1.4)**	**7 (1.6)**	**0**
Cerebral infarction	3 (0.9)	0	3 (0.8)	1 (1.4)	4 (0.9)	0
Cerebral haemorrhage	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0
Cerebrovascular disorder	0	1 (2.4)	1 (0.3)	0	1 (0.2)	0
Haemorrhage intracranial	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0
Infections and infestations	**5 (1.6)**	**0**	**5 (1.4)**	**0**	**5 (1.1)**	**5 (0.9)**
Pneumonia	3 (0.9)	0	3 (0.8)	0	3 (0.7)	4 (0.7)
Septic shock	2 (0.6)	0	2 (0.6)	0	2 (0.5)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**3 (0.9)**	**2 (4.9)**	**5 (1.4)**	**0**	**5 (1.1)**	**5 (0.9)**
Haemoptysis	0	2 (4.9)	2 (0.6)	0	2 (0.5)	2 (0.4)
Respiratory failure	2 (0.6)	0	2 (0.6)	0	2 (0.5)	0
Immune-mediated lung disease	1 (0.3)	0	1 (0.3)	0	1 (0.2)	2 (0.4)
Interstitial lung disease	0	0	0	0	0	1 (0.2)

	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 Monotherapy (N=568) n (%)
Blood and lymphatic system disorders	**1 (0.3)**	**0**	**1 (0.3)**	**0**	**1 (0.2)**	**0**
Myelosuppression	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0
Cardiac disorders	**1 (0.3)**	**0**	**1 (0.3)**	**0**	**1 (0.2)**	**1 (0.2)**
Cardiac failure	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Atrial flutter	0	0	0	0	0	1 (0.2)
Gastrointestinal disorders	**1 (0.3)**	**0**	**1 (0.3)**	**0**	**1 (0.2)**	**1 (0.2)**
Abdominal pain	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0
Upper gastrointestinal haemorrhage	0	0	0	0	0	1 (0.2)
Hepatobiliary disorders	**0**	**0**	**0**	**0**	**0**	**1 (0.2)**
Acute hepatic failure	0	0	0	0	0	1 (0.2)
Immune system disorders	**0**	**0**	**0**	**0**	**0**	**1 (0.2)**
Haemophagocytic lymphohistiocytosis	0	0	0	0	0	1 (0.2)
Renal and urinary disorders	**0**	**0**	**0**	**0**	**0**	**1 (0.2)**
Acute kidney injury	0	0	0	0	0	1 (0.2)

The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 24.1.
MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; PT = preferred term; SOC = system organ class

2.6.8.4. Laboratory findings

Liver Chemistry Parameters

Overall, in study CS1001-302, the frequency of elevated liver function test was similar for both the sugemalimab + chemotherapy and the placebo + chemotherapy arm. A higher frequency in the sugemalimab + chemotherapy compared to the placebo + chemotherapy arm was noted for alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3 × ULN and total bilirubin ≥1.5 × ULN, 6 (1.9%) and 1 (0.6%) patient. 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.

In the sugemalimab chemotherapy combination safety pool, 8 (1.8%) participants in the sugemalimab in combination with chemotherapy group had ALT or AST > 3 × ULN and total bilirubin ≥ 2 × ULN. Of these, 2 participants with non-NSCLC in the sugemalimab in combination with chemotherapy group had ALT and/or AST > 3 × ULN, total bilirubin ≥ 2 × ULN, and ALP < 2 × ULN.

In the sugemalimab monotherapy safety pool, 18 (3.2%) participants had ALT or AST > 3 × ULN and total bilirubin ≥ 2 × ULN. Of these, 4 (0.7%) participants had ALT or AST > 3 × ULN, total bilirubin ≥ 2 × ULN, and ALP < 2 × ULN.

Haematology

In study CS1001-302, the frequency of haematology abnormalities was similar between the sugemalimab + chemotherapy arm and the placebo + chemotherapy arm. The highest frequency of grade 3-4 was for low neutrophils with a frequency of 34.1% for the sugemalimab + chemotherapy arm and 37.7% for the placebo + chemotherapy arm.

In the sugemalimab chemotherapy combination safety pool the most commonly reported haematology parameter with shifts from Grade 0 to 2 at baseline to Grade 3 or 4 worst postbaseline were low neutrophils (155 [36.2%] participants), low leucocytes (76 [17.7%] participants), low haemoglobin (76 [17.7%] participants), low platelets (57 [13.4%] participants) and low neutrophils (43 [10.1%] participants); the other shifts in clinical chemistry parameters were reported in < 5% of participants.

In the sugemalimab monotherapy safety pool the most commonly reported haematology parameter with shifts from Grade 0 to 2 at baseline to Grade 3 or 4 worst postbaseline were low lymphocytes (54 [9.7%] participants) and low haemoglobin (29 [5.2%] participants); all other shifts in clinical chemistry parameters were reported in < 5% of participants.

Biochemistry

In study CS1001-302, the changes in serum chemistry were similar between the treatment and the control arm.

In the sugemalimab chemotherapy combination safety pool the most commonly reported clinical chemistry parameters with shifts from Grade 0 to 2 at baseline to Grade 3 or 4 worst postbaseline were low sodium (27 [6.3%] participants); all other shifts in clinical chemistry parameters were reported in < 5% of participants.

In the sugemalimab monotherapy safety pool the most commonly reported clinical chemistry parameter with shifts from Grade 0 to 2 at baseline to Grade 3 or 4 worst postbaseline were high gamma-glutamyltransferase (15 [11.0%] participants) and low sodium (30 [5.4%] participants); all other shifts in clinical chemistry parameters were reported in < 5% of participants.

2.6.8.5. Safety in special populations

Study CS1001-302

Intrinsic factors

Consistent results for overview safety parameters for gender, weight quartiles, tumour histology and PD-L1 status (data not shown).

In the sugemalimab + chemotherapy arm 118 (36.9%) of patients were ≥ 65 years old and for the placebo + chemotherapy arm there were 68 (42.8%). There is a trend towards higher frequency of overview safety parameters for older patients, this is however also mirrored in the placebo + chemotherapy arm.

Extrinsic factors

Extrinsic factors were not analysed.

Integrated safety pool

For the sugemalimab chemotherapy combination safety pool no consistent trend for differences regarding overview safety parameters can be identified for gender, age (<65 >65), weight, ECOG (0 vs. 1-2), histology, PD-L1 expression (data not shown).

For the sugemalimab monotherapy safety pool no consistent trend for differences regarding overview safety parameters can be identified for gender, age (<65 ≥ 65), weight, ECOG (0 vs. 1-2), histology (only based on Study CS1001-301) and PD-L1 expression (data not shown).

Extrinsic factors

Extrinsic factors were not analysed.

Table 49: Adverse events by age group

MedDRA Terms	Age <65 (N=293)	Age 65-74 (N=182)	Age 75+ (N=4)
Total AEs	**291 (99.3%)**	**181 (99.5%)**	**4 (100.0%)**
Serious AEs – Total	**85 (29.0%)**	**72 (39.6%)**	**2 (50.0%)**
- Fatal	15 (5.1%)	14 (7.7%)	0
- Hospitalisation/prolong existing hospitalisation	73 (24.9%)	65 (35.7%)	2 (50.0%)
- Life-threatening	8 (2.7%)	5 (2.7%)	0
- Disability/incapacity	0	0	0
- Other (medically significant)	2 (0.7%)	2 (1.1%)	0
AE leading to drop-out	33 (11.3%)	24 (13.2%)	0
Psychiatric disorders (SOC)	36 (12.3%)	23 (12.6%)	1 (25.0%)
Nervous system disorders (SOC)	71 (24.2%)	53 (29.1%)	1 (25.0%)
Accidents and injuries (SMQ[1])	7 (2.4%)	4 (2.2%)	0
Cardiac disorders (SOC)	31 (10.6%)	33 (18.1%)	0
Vascular disorders (SOC)	26 (8.9%)	17 (9.3%)	0
Cerebrovascular disorders (SMQ[1])	10 (3.4%)	5 (2.7%)	0
Infections and infestations (SOC)	87 (29.7%)	64 (35.2%)	3 (75.0%)
Anticholinergic syndrome (PT)	0	0	0
Quality of life decreased[2](PT)	0	0	0
Sum of postural hypotension (LLT), falls (PT), black outs (LLT), syncope (PT), dizziness (PT), ataxia (PT), and fractures (HLGT)	15 (5.1%)	11 (6.0%)	0

1) For the SMQs, the "broad" search includes both the "narrow" terms and the additional "broad" terms.
2) Patient reported quality of life was not assessed in Study CS1001-302.

There are too few patients over 75 years of age to draw any specific conclusions for this group.

The frequency of serious adverse events was higher for patients 65-74 years old compared to patients under 65. The specific terms increasing is hospitalisation/prolong existing hospitalisation (24.9% vs. 35.7% for <65 and 65-74 respectively), SOC cardiac disorders (10.6% vs. 18.1% for <65 and 65-74 respectively).

2.6.8.6. Immunological events

In the sugemalimab + chemotherapy group 53 (17.2%) samples were ADA positive. Of these, 28 (9.1%) were treatment emergent and 25 (8.1%) were non-treatment emergent. 5 (1.6%) samples were NAb positive and 48 (15.5%) samples were NAb negative.

Overall, the frequency reported for overview AEs parameters are similar between the ADA negative and ADA positive population. It is noticed that the frequency of TEAEs grade ≥3 (61.3% vs. 73.6%) and serious TEAEs (30.1% vs. 43.4%) are higher in the ADA positive population.

In the sugemalimab chemotherapy combination safety pool the frequency of ADA positive samples was 16.3%.

Table 50: Adverse events according to ADA status in patients (sugemalimab chemotherapy safety pool)

Adverse Event Category Preferred Term	Total (N = 418) ADA Negative (N = 350) n (%)	 ADA Positive[1] (N = 68) n (%)
Any TEAE	349 (99.7)	68 (100.0)
Most frequently reported TEAEs		
Anaemia	277 (84.9)	53 (77.9)
Neutrophil count decreased	208 (59.4)	38 (55.9)
White blood cell count decreased	208 (59.4)	36 (52.9)
Any TEAE of Grade 3 to 5	235 (67.1)	52 (76.5)
Any serious TEAE	123 (35.1)	34 (50.0)
Any TEAE leading to death	18 (5.1)	5 (7.4)
Any TEAE leading to sugemalimab treatment discontinuation	52 (14.9)	8 (11.8)
Any sugemalimab-related TEAE	298 (85.1)	60 (88.2)
Any sugemalimab-related serious TEAE	57 (16.3)	16 (23.5)
Any irAE by Investigator assessment	150 (42.9)	26 (38.2)
Most Frequently Reported irAE Categories by Investigator Assessment		
Immune-related hypothyroidism	51 (14.6)	10 (14.7)
Immune-related skin adverse reaction (excluding severe)	36 (10.3)	9 (13.2)
Immune-related hyperthyroidism	32 (9.1)	9 (13.2)
Immune-related hepatitis	31 (8.9)	8 (11.8)

1. ADA positive was defined as at least one baseline or post-baseline positive ADA test.

Overall, the frequency reported for overview AEs parameters are similar between the ADA positive and ADA negative population. It is noticed that the frequency of TEAEs ≥3 (67.0% vs. 74.3%) and serious TEAEs (35.1% vs. 49.3%) are higher in the ADA positive population.

In the sugemalimab monotherapy safety pool the ADA status showed 38 (7.7%) ADA positive samples. Overall, the frequency reported for overview AEs parameters are similar between the ADA positive and ADA negative population.

The higher frequency of grade TEAEs grade ≥3 and serious TEAEs in the ADA positive population is noted. The sample sizes are small, and this could be related to chance findings.

The presence of neutralising antibody (NAb) was tested in all available pre-dose samples at each cycle in the Studies CS1001-101, CS1001-201, CS1001-301 and CS1001-302 populations.

Table 51: Status of neutralising antibodies

	Sugemalimab + Chemotherapy				
	302 NSCLC (N=320)	NSCLC Total (N=361)	Other Indications (Non-NSCLC) (N=74)	Total (N=435)	Monotherapy (N=430[1])
Number of Patients with NAb Positive, n (%)	5(1.6%)	5(1.4%)	1(1.4%)	6(1.4%)	5(1.2%)

1. No NAb data are available for patients in Study CS1001-102, Study CS1001-202 and patients dosed with sugemalimab in the Study CS1001-302 cross-over period

2.6.8.7. Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted with sugemalimab. This is considered acceptable.

2.6.8.8. Discontinuation due to adverse events

Adverse Events Leading to Dose Modification

Study CS1001-302

No dose modifications were permitted for sugemalimab or placebo in CS1001-302. However, next dose could be delayed. Dose modifications for chemotherapy followed local clinical practice and the product information for each medication.

For discontinuation due to adverse event, see separate heading.

123 (38.4%) patients in the sugemalimab group experienced treatment cycle delays due to TEAEs vs. 50 (31.4%) patients in placebo group. The majority of the patients experienced 1 cycle delay 80/320 (25.0%) in the sugemalimab group and 39/159 (24.5%) in the placebo arm. More patients in the sugemalimab group had 2 cycles delayed, 30/320 (9.4%) compared to 6/159 (3.8%) in the placebo group. The majority of delays were 1-21 days, 96/320 (30.0%) for the sugemalimab group and 47/159 (29.6%) for the placebo group. Number of patients with TEAEs leading to dose modifications for chemotherapy was similar across the arms in CS1001-302, 47/320 (14.7%) for the sugemalimab group and 30/159 (18.9%) for the placebo group.

The most frequent TEAEs SOC (>5%) leading to dose modification was investigations (28/320; 8.8% for sugemalimab group and 23/159; 14.5% for placebo group). The most frequent TEAEs PT(≥5%) leading to dose modifications included platelet count decreased (15/320; 4.7% for sugemalimab group and 8/159; 5.0% for placebo group) and neutrophil count decreased (14/320; 4.4% for sugemalimab group and 16/159; 10.1% for placebo group).

Integrated safety pool

178/435 (40.9%) patients in the sugemalimab chemotherapy safety pool experienced treatment cycle delays due to TEAEs. The majority of the patients experienced 1 cycle delay 111/435 (25.5%) and 41/435 (9.4%) patients in the combined sugemalimab chemotherapy safety pool have 2 cycles delayed. The duration of cycle delay was 1-21 days for 145 (33.3%) patients and 22-42 days for 24 (5.5%) patients.

The most common SOC (>5%) included Blood and lymphatic system disorders (61/435; 14.0%), Infections and infestations (26/435; 6.0%) and Investigations (99/435; 22.8%). The most common

PTs (>5%) included Anaemia (45/435; 10.3%) and neutrophil (36/435; 8.3%), platelet (35/435; 8.0%) and white blood cell (30/435; 6.9%) count decreased.

For the monotherapy safety pool 115/568 (20.2%) of patients experienced cycle delays due to TEAE, 92/568 (16.2%) experienced 1 and 16/568 (2.8%) experienced 2. For 66 (11.6%) the delay was 1-21 days and for 28 (4.9%) it was 22-42 days. The most common SOC (>5%) was Infections and infestations (30/568; 5.3%) and Respiratory, thoracic and mediastina disorders (35/568; 6.2%). No PT was reported for >5% of the patients.

Discontinuation due to adverse events

Study CS1001-302

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 majority of the events were reported in < 1% of participants by PT in both treatment groups. 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.

The incidence of TEAEs leading to discontinuation of any study drug was numerically higher in the sugemalimab group compared with the placebo group (62 [19.4%] vs 18 [11.3%] participants). The majority of the events were reported in < 1% of participants by PT in both treatment groups. The most frequently reported (≥ 1% of participants) TEAEs leading discontinuation of any study drug by PT were pneumonia (6 [1.9%] and 4 [2.5%] participants, respectively), anaemia (6 [1.9%] and 3 [1.9%] participants, respectively) and death (4 [1.3%] and 2 [1.3%] participants, respectively).

Integrated safety pool

For the sugemalimab chemotherapy combination safety pool 25.3% of patients had at least one TEAE leading to any treatment discontinuation. The most frequent reported PTs were anaemia (4.1%) and platelet count decreased (1.6%). The frequency of other reported TP was below 1%.

In the sugemalimab monotherapy pool, TEAEs leading to permanent discontinuation of sugemalimab treatment were reported in 61 (10.7%) participants. The most frequently reported TEAEs leading to discontinuation of treatment by PT were immune-mediated lung disease (11 [1.9%] participants) and pneumonia and pneumonitis (6 [1.1%] participants each); the remaining TEAEs leading to permanent discontinuation of treatment by PT occurred in < 1% of participants each.

2.6.8.9. Post marketing experience

To date, sugemalimab has only been authorised for marketing in China. Sugemalimab in combination with chemotherapy for metastatic NSCLC was approved in December 2021 and as monotherapy for stage III NSCLC in June 2022.

2.6.9. Discussion on clinical safety

The presented amount of safety data is considered acceptable to describe the toxicity profile of sugemalimab in the intended indication.

Pivotal study CS1001-302

Exposure: In study CS1001-302 the median number of treatment cycles was 10.0 vs. 6.0 for the sugemalimab + chemotherapy and placebo + chemotherapy treatment arm respectively. The mean number of treatment cycles was 14.9 and 8.5 respectively. The proportion of patients completing the protocol maximum treatment cycles for initial chemotherapy was similar between the treatment arms at 80.3 % for sugemalimab + chemotherapy and 78.0% for placebo + chemotherapy respectively. No dose reduction for sugemalimab was allowed but next dose could be withheld.

TEAEs: The most common TEAEs were anaemia (sugemalimab + chemotherapy vs. placebo + chemotherapy; 245, 76.6% vs 113, 71.1%), neutrophil count decreased (186, 58.1% vs 94, 59.1%), and white blood cell count decreased (180, 56.3% vs 94, 59.1%).

Hypothyroidism, as expected by the mechanism of action, was more common in the sugemalimab + chemotherapy arm at 10.9% compared to 1.9% in the placebo + chemotherapy arm.

By severity: Grade 3 to 5 TEAEs were reported in 207 (64.7%) participants in the sugemalimab + chemotherapy arm and 99 (62.3%) participants in the placebo + chemotherapy arm. The most common TEAEs grade ≥3 were neutrophils decreased (sugemalimab + chemotherapy vs. placebo + chemotherapy; 32.5% vs. 33.3%), anaemia (15.0% vs. 11.3%), white blood count decreased (14.4% vs. 17.0%), platelet count decreased (10.6% vs. 10.1%). The reported grade 3 to 5 TEAEs with a frequency over 2% is reflective of the expected safety profile of the chemotherapy backbone.

SAEs: The frequency of serious treatment emergent adverse events was similar between the sugemalimab + chemotherapy and placebo + chemotherapy treatment arms with 34.4% (110 events) and 30.8% (49 events) respectively. The most frequently reported serious TEAE by PT was pneumonia, which occurred in 18 (5.6%) participants in the sugemalimab + chemotherapy treatment arm and 12 (7.5%) participants in the placebo + chemotherapy treatment arm. All other serious TEAEs by PT were reported with ≤ 5% incidence in both treatment groups.

Deaths: There were 156 (48.8%) deaths recorded in the sugemalimab + chemotherapy treatment arm during the study period and 97 (61%) in the placebo + chemotherapy arm. The majority of events was attributed to the disease under study, 117 (36.6%) events for sugemalimab + chemotherapy and 81 (50.9%) for placebo + chemotherapy. The summary of death overview attribute 13 (4.1%) deaths to adverse events as primary cause for the sugemalimab + chemotherapy arm and 7 (4.4%) for the placebo + chemotherapy arm. The number of deaths attributed to "other" was 26 (8.1%) for sugemalimab + chemotherapy and 9 (5.7%) for the placebo + chemotherapy arm. Among the 26 deaths in the sugemalimab group designated to other, 8 occurred without prior detection of disease progression. In the placebo group 2/9 deaths occurred without prior detection of disease progression. Hence, the majority of deaths occurred after detection of disease progression. The number of deaths attributed to "other" is considered high but is explained by unconventional handling of death reporting during the study. Deaths have automatically been assigned to AE, unexplained or other based of predefined criteria not including reviewing the actual cause of death. The handling of deaths in the trial hampers the detailed assessment of causality. The presently reported treatment emergent adverse events leading to death is overall compatible with the safety profile of PD1/PD-L1 inhibitors in combination with chemotherapy in Study CS1001-302.

Adverse events of special interest - Immune-related AEs:

The incidence of Investigator-assessed irAEs was higher in the sugemalimab + chemotherapy arm compared with the placebo + chemotherapy arm (117 [36.6%] vs 27 [17.0%] participants).

The most frequently reported Investigator-assessed irAE categories in the sugemalimab + chemotherapy arm and placebo + chemotherapy arm were hypothyroidism (41 [12.8%] and

5 [3.1%] participants, respectively), hyperthyroidism (31 [9.7%] and 3 [1.9%] participants, respectively), hepatitis (29 [9.1%] and 8 [5.0%] participants, respectively), and skin adverse reaction (excluding severe) (26 [8.1%] and 9 [5.7%] participants, respectively); all other irAE categories were reported in < 3% of participants in each treatment group.

Integrated safety pool

The safety profile in the sugemalimab chemotherapy combination safety pool is driven by the profile presented in the pivotal study as the vast majority of patients in this pool is from the pivotal study.

Exposure:

The median number of cycles was 10.0 and mean number of cycles 14.8 for the total sugemalimab + chemotherapy safety pool. In the sugemalimab chemotherapy combination safety pool 59.5% received sugemalimab for ≥ 6 months, 32.6% ≥ 12 months and 20.2% beyond 21 months.

The median number of treatment cycles in the sugemalimab monotherapy safety pool was 8.0 with a mean number of cycles of 10.9. In the sugemalimab monotherapy safety pool 47.0% received sugemalimab for ≥ 6 months, 22.2% ≥ 12 months and 3.7% beyond 21 months.

TEAEs: The most frequently reported TEAEs (≥ 30% of participants) by PT in the sugemalimab chemotherapy combination safety pool were anaemia (337 [77.5%] participants), white blood cell count decreased 248 [57.0%] participants), neutrophil count decreased (249 [57.2%] participants), platelet count decreased (160 [36.8%] participants), aspartate aminotransferase increased (148 [34.0%] participants), decreased appetite (143 [32.9%] participants), and alanine aminotransferase increased (139 [32.0%] participants).

The most frequently reported TEAEs (≥ 20% of participants) by PT in the sugemalimab monotherapy safety pool were anaemia (130 [22.9%] participants), aspartate aminotransferase increased (120 [21.1%] participants), and alanine aminotransferase increased (117 [20.6%] participants).

By severity: In the sugemalimab chemotherapy combination safety pool 69.4% were reported to have any TEAE of grade 3-5. The most common Grade 3-5 TEAEs was neutrophil count decreased (32.4%), anaemia (17.5%) and white blood cell count decreased (14.5%).

In the sugemalimab monotherapy safety pool 31.9% were reported to have any TEAE of grade 3-5. The most common Grade 3-5 TEAEs was pneumonia (4.9%) and anaemia (3.2%).

SAEs: In the sugemalimab chemotherapy combination safety pool 39.3% experienced any treatment-emergent SAE. The most frequently reported serious TEAE by PT was pneumonia, which occurred in 19 (5.3%) participants with NSCLC in the sugemalimab in combination with chemotherapy group. The remaining serious TEAEs by PT occurred in < 4% of participants each.

In the sugemalimab monotherapy safety pool 11.1% experienced any treatment-emergent SAE. the most frequently reported serious TEAE by PT was pneumonia (34 [6.0%] participants); the remaining serious TEAEs by PT occurred in < 3% of participants each.

Deaths: In the sugemalimab chemotherapy combination safety pool there were 161 (37.0%) deaths attributed to disease progression as primary cause. For 19 (4.4%) were the primary cause of death adverse event and 42 (9.7) events are reported under "other".

Treatment-emergent AEs leading to death were reported in 29 (6.7%) participants with in the sugemalimab in combination with chemotherapy safety pool, which included 20 participants in the double-blind phase of Study CS1001-302 (Table **45**). The reported TEAEs leading to death assigned to more than one patient in the sugemalimab chemotherapy combination safety pool was death 10

(2.3%), cerebral infarction 4 (0.9%), pneumonia 3 (0.7%), septic shock 2 (0.5%), haemoptysis 2 (0.5%) and respiratory failure 2 (0.5%).

In the sugemalimab monotherapy safety pool where there 119 (21%) deaths attributed to disease progression as primary cause. For 16 (2.8%) the primary cause of death was listed as adverse event, for 23 (4.0%) it was reported under "other" and for 1 (0.2%) reported as unknown.

Treatment-emergent AEs leading to death were reported in 19 (3.3%) participants with in the sugemalimab in combination with chemotherapy safety pool.

The reported TEAEs leading to death assigned to more than one patient in the sugemalimab monotherapy safety pool was death 5 (0.9%), pneumonia 4 (0.7%), haemoptysis 2 (0.4%), immune-mediated lung disease 2 (0.4%) and respiratory failure 2 (0.5%).

For the summary of deaths in the sugemalimab combination therapy pool and for the sugemalimab monotherapy safety pool the frequency of primary cause of death as "other" is continuously high.

Adverse events of special interest

Immune-related AEs:

IrAEs were reported in 182 (41.8%) participants in the sugemalimab chemotherapy combination safety pool. The most frequently reported irAE categories in the sugemalimab chemotherapy pool were immune-related hypothyroidism (62 [14.3%] participants), immune-related skin adverse reactions (excluding severe) (46 [10.6%] participants), immune-related hepatitis (42 [9.7%] participants), and immune-related hyperthyroidism (41 [9.4%] participants.

In the sugemalimab monotherapy pool, irAEs were reported in 238 (41.9%) participants. The most frequently reported irAE categories in the sugemalimab monotherapy pool were immune-related hypothyroidism (95 [16.7%] participants), immune-related hyperthyroidism (64 [11.3%] participants), immune-related pneumonitis (53 [9.3%] participants), immune-related skin adverse reactions (excluding severe) (52 [9.2%] participants), and immune-related hepatitis (46 [8.1%] participants).

Immune-related adverse reactions have been identified as an important risk in the RMP and a patient card will be provided to patients in order to mitigate those risks. They are also included in section 4.4 of the SmPC in order to warn healthcare professionals and provide recommendations on how to mitigate them when applicable.

2.6.10. Conclusions on the clinical safety

Safety data for sugemalimab for the treatment of NSCLC generally reflect the known toxicity profile of checkpoint inhibitors in combination with chemotherapy.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 52: List of safety concerns

Important identified risks	Immune-mediated adverse reactions
Important potential risks	Reproductive and developmental toxicity
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 53: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immune-mediated adverse reactions	**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 card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None proposed.* **Additional pharmacovigilance activities**: *None proposed.*
Reproductive and developmental toxicity	**Routine risk minimisation measures:** *SmPC Section 4.6* *PL Section 2* *Restricted medical prescription.* **Additional risk minimisation measures:** *None proposed.*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None proposed.* **Additional pharmacovigilance activities**: *None proposed.*

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 20 Dec 2021. The new EURD list entry will therefore use the 20 Dec 2021 to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Cejemly (sugemalimab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication for sugemalimab is for the "combination with platinum-based chemotherapy for the first-line treatment of adults with metastatic non-small-cell lung cancer (NSCLC), with no sensitising EGFR mutations, or ALK, ROS1, or RET genomic tumour aberrations."

3.1.2. Available therapies and unmet medical need

For patients with metastatic NSCLC lacking an actionable oncogenic driver and PD-L1 positive, ESMO Clinical Guidelines recommend treatment with PD-1/PD-L1 immune checkpoint inhibitors, nivolumab, pembrolizumab, or atezolizumab in combination with platinum-based chemotherapy doublet (ESMO, 2022). Of those, pembrolizumab, is considered standard first-line treatment for patients with advanced or metastatic NSCLC and PD-L1 expression ≥ 50%. Although there are available products approved in this setting, there is always a need to enrich the treatment armamentarium.

3.1.3. Main clinical studies

The pivotal study CS1001-302 is a multicentre, randomised, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of sugemalimab combined with platinum-based chemotherapy (n=320) versus placebo in combination with chemotherapy (n=159). Patients were treatment-naïve participants with metastatic NSCLC, histologically or cytologically confirmed as non-squamous or squamous. Participants with known EGFR mutations, ALK fusions, ROS1 fusions, or RET fusions, or previous systemic treatment for metastatic disease were excluded.

The study was conducted exclusively in China.

3.2. Favourable effects

The sugemalimab arm showed a statistically significant improvement in PFS and OS compared with the placebo arm.

In the interim analysis of **PFS**, the stratified HR was 0.50 (95% CI: 0.39, 0.64; P<0.0001). The median PFS in the sugemalimab group was 7.82 versus 4.90 months in the placebo group.

In the final analysis of **PFS**, the stratified HR was 0.48 (95% CI: 0.39, 0.60; P<0.0001). The median PFS in the sugemalimab group was 9.0 versus 4.9 months in the placebo group.

For **OS**, the stratified HR was 0.65 (95% CI: 0.50-0.84, P=0.0008). The median OS in the sugemalimab group was 25.4 months compared with 16.9 months in the placebo group.

The PFS and OS results were supported by **ORR**. In the sugemalimab arm, 63.4% patients achieved PR and in the placebo arm 40.3% patients achieved PR (P<0.0001). No patient, in either arm, achieved CR.

Presented subgroup results of PFS and OS showed an overall consistent treatment effect, including meaningful treatment effects regardless of PD-L1 expression status, or squamous/non-squamous histology.

3.3. Uncertainties and limitations about favourable effects

The study population differs from the composition of patients with NSCLC in EU, with regards to relatively low age, the high proportion of males, and perhaps also the high proportion of smokers. However, this is not expected to impact the external validity of results, which are within the range that might be anticipated based on prior experience of this class of medicines.

3.4. Unfavourable effects

Study CS1001-302

The median number of treatment cycles was 10.0 vs. 6.0 for the sugemalimab + chemotherapy and placebo + chemotherapy treatment arm respectively. 80.3 % for sugemalimab + chemotherapy and 78.0% for placebo + chemotherapy completed the initial chemotherapy treatment cycles.

The most common TEAEs were anaemia (sugemalimab + chemotherapy vs. placebo + chemotherapy; 245, 76.6% vs 113, 71.1%), neutrophil count decreased (186, 58.1% vs 94, 59.1%), and white blood cell count decreased (180, 56.3% vs 94, 59.1%).

Grade 3 to 5 TEAEs were reported in 207 (64.7%) participants in the sugemalimab + chemotherapy arm and 99 (62.3%) participants in the placebo + chemotherapy arm.

The most common TEAEs grade ≥3 were neutrophils decreased (sugemalimab + chemotherapy vs. placebo + chemotherapy; 32.5% vs. 33.3%), anaemia (15.0% vs. 11.3%), white blood count decreased (14.4% vs. 17.0%), platelet count decreased (10.6% vs. 10.1%).

The frequency of serious treatment emergent adverse events was similar between the sugemalimab + chemotherapy and placebo + chemotherapy treatment arms with 34.4% (110 events) and 30.8% (49 events) respectively.

The most frequently reported serious TEAE by PT was pneumonia, which occurred in 18 (5.6%) participants in the sugemalimab + chemotherapy treatment arm and 12 (7.5%) participants in the placebo + chemotherapy treatment arm.

There were 156 (48.8%) deaths recorded in the sugemalimab + chemotherapy treatment arm during the study period and 97 (61%) in the placebo + chemotherapy arm. The majority of events was attributed to the disease under study, 117 (36.6%) events for sugemalimab + chemotherapy and 81 (50.9%) for placebo + chemotherapy.

The summary of death overview attribute 13 (4.1%) deaths to adverse events as primary cause for the sugemalimab + chemotherapy arm and 7 (4.4%) for the placebo + chemotherapy arm. The number of deaths attributed to "other" was 26 (8.1%) for sugemalimab + chemotherapy and 9 (5.7%) for the placebo + chemotherapy arm.

The incidence of Investigator-assessed irAEs was higher in the sugemalimab + chemotherapy arm compared with the placebo + chemotherapy arm (117 [36.6%] vs 27 [17.0%] participants).

The most frequently reported Investigator-assessed irAE categories in the sugemalimab + chemotherapy arm and placebo + chemotherapy arm were hypothyroidism (41 [12.8%] and 5 [3.1%] participants, respectively), hyperthyroidism (31 [9.7%] and 3 [1.9%] participants, respectively), hepatitis (29 [9.1%] and 8 [5.0%] participants, respectively), and skin adverse reaction (excluding severe) (26 [8.1%] and 9 [5.7%] participants, respectively).

Findings from the integrated safety pool are in line with those from the pivotal study.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Effects Table for sugemalimab in combination with chemotherapy for the treatment of metastatic NSCLC (Study CS1001-302)

PFS data cut-off: 08 June 2020

OS and safety data cut-off: 22 November 2021

AESI data cut-off: 15 May 2023

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS, median	Time from the date of randomisation to first tumour progression or death	months	7.8	4.9	Presented subgroup results of PFS and OS showed an overall consistent treatment effect.	CSR
		HR, 95% CI	0.50 (0.39, 0.64)			
OS, median	Time from randomisation until death	months	25.4	16.9		
		HR, 95% CI	0.65 (0.51, 0.84)			
ORR		%	63.4	40.3		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Summary	Grade 3-5 TEAEs	%	64.7	62.3		
	SAE	%	34.4	30.8		
	Death due to AE	%	6.3	5.7		
	Discontinuations of any drug due to TEAEs	%	19.4	11.3		
	AESI – irAE	%	36.6	17.0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A clinically meaningful benefit in PFS and OS of sugemalimab in combination with chemotherapy compared to placebo in combination with chemotherapy was demonstrated in patients with metastatic NSCLC.

The safety profile of sugemalimab in combination with chemotherapy reflects the added toxicities of the single components and is overall similar to what has been observed for other anti-PD-1/PD-L1 chemotherapy combinations in similar settings.

The pivotal study was conducted exclusively in China. With respect to similarity of disease, it is known that e.g., EGFR mutations are more common in the East Asian population. Having tested for this, however, data on the treatment of NSCLC from East Asia have previously been considered extrapolable to an EU setting, as supported by the dedicated PK study conducted by the applicant in the US, CS1001-102 or in the popPK analysis where there were no observed PK differences between Asian and non-Asian participants and the E-R simulations which indicated no effect of race on efficacy outcomes. With regards to the class of anti-PD-1/PD-L1 targeting agents, available data do not indicate that ethnic factors would be key determinants of response, as supported by a literature review of ICI mAbs, including pembrolizumab, atezolizumab, and nivolumab by Lee et al. that concluded that Asian participants with squamous and non-squamous NCSLC demonstrated comparable outcomes to Caucasian participants in terms of response rates and survival benefits (Lee, 2020). Furthermore, other currently authorised products in the EU of the same class such as atezolizumab, pembrolizumab or nivolumab, do not require a modification in dose or dose regimen, which could further support that ethnic factors would not be key determinants of response.

While the actual study population differs from the composition of patients with NSCLC in EU, with regards to relatively low age, the high proportion of males, and perhaps also the high proportion of smokers, this is not considered to impact the external validity of results, which are within the range that might be anticipated based on prior experience of this class of medicines.

Moreover, while the standard of care in EU presently includes a PD1/PD-L1 targeting agent, a comparison versus placebo as add on to chemotherapy isolates drug effects through superiority. While

this design does not provide a relative effect estimate to the established standard of care, it does produce robust evidence of efficacy, similar to what has been accepted for previous approvals of this class of medicines.

3.7.2. Balance of benefits and risks

In view of the relevant improvement in PFS and OS, the benefit of treatment with sugemalimab in combination with chemotherapy in metastatic NSCLC outweighs its associated risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Cejemly is positive.

4. Recommendations

Outcome

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

Cejemly 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 sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumour aberrations.

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

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Cejemly is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Cejemly have access to/are provided with the patient card.

The patient card shall contain the following key elements:

- Description of the main signs and symptoms of the irARs and the importance of notifying their treating physician immediately when symptoms occur.
- Reminder to carry the patient card at all times.
- Contact details of the Cejemly prescriber.

New Active Substance Status

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