19 September 2024
EMA/465512/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hetronifly

International non-proprietary name: serplulimab

Procedure No. EMEA/H/C/006170/0000

Note

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

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List of abbreviations

AC	Affinity Chromatography
ACL	Automatic chemiluminescent immunoassay
ADA	Anti-drug antibody
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AEX	Anion Exchange Chromatography
AEXAnion	Exchange Chromatography
AI	Accumulation index
ALT	Alanine transaminase
AQL	Acceptance Quality Limit
AS	Active substance
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
AUC0-inf	Area under the concentration-time curve from time 0 to infinity
AUC0-tau	Area under the concentration-time curve from time 0 to the end of dosing interval
AUCss	Area under the concentration-time curve at steady state
BLQ	Below quantifiable limit
BMI	Body mass index
Cavg1	Model-predicted average concentration after the first cycle of treatment
CCIT	Container Closure Integrity Test
CD	Circular Dichroism
CDC	Complement Dependent Cytotoxicity
CDR	Complementarity Determining Region
CE-SDS	Capillary Electrophoresis -Sodium Dodecyl Sulfate
CEX	Cation Exchange Chromatography
CEXCation	Exchange Chromatography
CFU	Colony Forming Unit
cGMP	current Good Manufacturing Practices
CHO	Chinese Hamster Ovary

CI	Confidence interval
CIP	Clean in Place
cIPC	Critical In-process Control
CL	Clearance
CL0	Baseline clearance
CLss	Clearance at steady state
Cm	Centimeter
Cmax	Maximum concentration
Cmax,ss	Maximum concentration at steady state
Cmax1	Model-predicted maximum concentration after the first cycle of treatment
Cmin	Minimum concentration
Cmin,ss	Minimum concentration at steady state
Cmin1	Model-predicted minimum concentration after the first cycle of treatment
CNS	Central nervous system
COA	Certificate of Analysis
COC	Certificate of Compliance
COI	Certificate of Irradiation
COQ	Certificate of Qualification
COR	Certificate of Release
CPP	Critical Process Parameter
CPV	Continued Process Verification
CQA	Critical Quality Attribute
CR	Complete response
CS	Clinically significant
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough concentration
CV	Column Volume
DAP	Data analysis plan
DDI	Drug-drug interaction
DLS	Dynamic Light Scattering
DNA	Deoxyribonucleic Acid

DO	Dissolved Oxygen
DOR	Duration of response
DP	Drug Product
DS	Drug Substance
DSC	Differential Scanning Calorimetry
E&L	Extractable and Leachable
EC50	Effective concentration at 50% of maximal activity
ECG	Electrocardiogram
ECL	Electrochemiluminescence immunoassay
ECOG	Eastern Cooperative Oncology Group
EFA	Effective Filtration Area
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
EOPB	End of Production Cell Bank
EP	European Pharmacopeia
E-R	Exposure-response
ERA	Environmental risk assessment
ESCC	Esophageal Squamous Cell Carcinoma
ESMO	European Society for Medical Oncology
ES-SCLC	Extensive stage small cell lung cancer
EU	Endotoxin Unit
exp(Tmax)	Ratio of clearance at the maximum change to clearance at baseline
Fab	Fragment antigen binding
Fc	Fragment Crystallizable
Fc	Fragment crystallizable
FcRn	The Neonatal Fc Receptor
FcγR	Fc Gamma Receptor
FDA	Food and Drug Administration
FIH	First in human
FIO	For Information Only
FLR	Fluorescence Spectrum
FP	Finished product
FTIR	Fourier Transform Infrared Spectroscopy

g/L	gram/liter
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPP	General Process Parameter
h	hour
HC	Heavy Chain
HCP	Host Cell Protein
HLX10	Serplulimab
HMW	High Molecular Weight
HPLC	High Performance Liquid Chromatography
(h)PBMC	(Human) Peripheral blood mononuclear cell
HR	Hazard ratio
IC50	Mean half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonization
iCPD	Immune confirmed progressive disease
IgG	Imunoglobulin G
IL	Interleukin
IND	Investigational New Drug
IPC	In-process Control
irAE	Immune-related adverse event
iRECIST	Modified RECIST 1.1 for immune-based therapeutics
IRR	Infusion-related reaction
IRRC	Independent Radiology Review Committee
ISO	International Organization for Standardization
ITSM	Immunoreceptor tyrosine-based switch motif
ITT	Intent-to-treat Set
iUPD	immune confirmed progressive disease
IV	Intravenous
Kd	Dissociation constant, affinity
kDa	Kilodalton
KLH	Keyhole limpet haemocyanin
KM	Kaplan-Meier

KPP	Key Process Parameter
L	Liter
LC	Light Chain
LDH	Lactate dehydrogenase
LMH	Liter per Square Meter per Hour
LLOQ	Lower limit of quantification
LRV	Log Reduction Value
m2	Square Meter
mAb	Monoclonal Antibody
MAD	Mutual Acceptance of Data
MALS	Multi-Angle Light Scattering
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minutes
mL	Milliliter
mmol	Millimole
MoA	Mechanism of Action
MRI	Magnetic resonance imaging
MS	Mass Spectrometry
MSD ELC	Meso Scale Discovery Electrochemiluminescence
MSI	Microsatellite instability
MSI-H	Metastatic microsatellite instability-high
MTD	Maximum tolerated dose
MuLV	Murine Leukemia Virus
MVM	Minute Virus of Mice
MW	Molecular Weight
N/A	Not Applicable
NA	Not available
NAb	Neutralizing antibody
NANA	N-Acetyl-Neuraminic Acid
NCCN	National Comprehensive Cancer Network
NCS	Non-clinically significant

NDA	New drug application
NGHC	Non-glycosylated Heavy Chain
NGNA	N-Glycoly-Neuraminic Acid
NMPA	National Medical Products Administration
NMT	Not More Than
NSCLC	Non-small cell lung cancer
OCB	Original Cell Bank
O-RABS	Open Restrict Access Barrier System
ORR	Objective response rate
OS	Overall survival
P	Passage
P1.0	Process 1.0
P1.1	Process 1.1
P1.2	Process 1.2
P1.3	Process 1.3
P2.0	Process 2.0
P3.0	Process 3.0
PAR	Proven Acceptable Range
PBMCs	Peripheral Blood mononuclear cell
pcVPC	Prediction-corrected visual predictive check
PD	Pharmacodynamics
PD	Progressive disease
PD-1	Programmed Cell Death-1
PD-L1	Programmed Cell Death Ligand-1
PFS	Progression-free survival
PFS2	Time to second/subsequent objective tumour progression on next-line treatment or death from any cause
Ph. Eur.	European Pharmacopoeia
PHA-L	Phytohemagglutinin-L
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetics
PPQ	Process Performance Qualification
PPS	Per Protocol Set
PR	Partial response

PRV	Pseudorabies Virus
PS	Performance status
PT	Preferred term
PTM	Post-translational Modification
PUPSIT	Pre-Use Post Sterilization Integrity Test
PVDF	Polyvinylidene Fluoride
PVDF	Polyvinylidene Fluoride
Q2/3/4/6W	Once every 2/3/4/6 weeks
QTc	QT interval corrected for heart rate
QTPP	Quality Target Product Profile
Rac(AUCss)	Accumulation ratio of steady state area under the concentration-time curve
Rac(Cmax)	Accumulation ratio of maximum concentration
RECIST	Response Evaluation Criteria in Solid Tumors
Reo-3	Reovirus Type 3
RO	Receptor occupancy
RP2D/3D	Recommended Phase II/III dose
rpm	Revolutions Per Minute
RSE	Residual standard error
SAE	Serious adverse event
SCLC	Small Cell Lung Cancer
SCLC	Small cell lung cancer
SD	Standard deviation
SEC	Size Exclusion Chromatography
SF	Shake Flask
SIP	Sanitize in Place
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SPR	Surface plasmon resonance
SS	Safety set
SUS	Single Use System
t1/2	Half-life
T3	Triiodothyronine
T4	Thyroxine

TC50	Time when half-maximum change in clearance is achieved
TCR	Tissue cross-reactivity
TEAE	Treatment-emergent adverse event
TFF	Tangential Flow Filtration
TGI (%)	Tumour growth inhibition (rate)
TK	Toxicokinetic
TDAR	T cell-dependent antibody response
Tmax	Time to maximum concentration
TMP	Transmembrane Pressure
TNF	Tumour necrosis factor
TNM	Tumour/Node/Metastasis
TPS	Tumour proportion score
TTC	Threshold of toxicological concern
UF/DF	Ultrafiltration/Diafiltration
UPB	Unprocessed Bulk
US	United States
USP	United States Pharmacopoeia
VALG	Veterans Administration Lung Study Group
Vc	Volume of distribution in central compartment
VCD	Viable Cell Density
Vp	Volume of distribution in peripheral compartment
Vss	Steady-state volume of distribution
WBC	White blood cell
WCB	Working Cell Bank
WFI	Water for Injections
λ	Sigmoid factor of time-varying clearance

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Henlius Europe GmbH submitted on 2 March 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Hetronifly, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2022.

Hetronifly, was designated as an orphan medicinal product EU/3/22/2731 on 9 December 2022 in the following condition: treatment of small cell lung cancer.

The applicant applied for the following indication:

Hetronifly in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Hetronifly (serplulimab) as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Hetronifly.

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

The application submitted is 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(s) P/0471/2020 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.

1.4.2. New active substance status

The applicant requested the active substance serplulimab 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.

1.5. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14/11/2019	EMEA/H/SA/4295/2/2019/II	Pierre Demolis Serena Marchetti
28/05/2020	EMEA/H/SA/4295/2/FU/1/2020/II	Serena Marchetti Kolbeinn Gudmundsson
19/05/2022	EMA/SA/0000082390	Silvijus Abramavicius Flora Musuamba Tshinanu

The protocol assistance pertained to the following clinical aspects:

- Design of the proposed phase 3 study HLX10-005-SCLC301 and more specifically: primary endpoint, background chemotherapy, dose and dosing scheme, the patient selection criteria, the stratification factors, primary and secondary endpoints, study duration, sample size and statistical considerations; number of representative EU patients in the clinical trial

1.6. Steps taken for the assessment of the product

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

Rapporteur: Eva Skovlund Co-Rapporteur: Aaron Sosa Mejia

The application was received by the EMA on	2 March 2023
The procedure started on	23 March 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 June 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	27 June 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 July 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 October 2023
The following GMP, GCP and GLP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– GCP inspections at two clinical investigator sites, one in China (between 08/04/2024 to 12/04/2024) and one Georgia (between 12/02/2024 to 16/02/2024) and of the sponsor site in China	8 – 12 April 2024 12 – 16 February 2024

(between 15/04/2024 to 22/04/2024). The outcome of the inspections carried out was issued on 02/07/2024.	15 – 22 April 2024
– A GMP inspections at ''Shanghai Henlius Biologics Co., Ltd. Building No.1, No. 182, Wenjun Road, Songjiang, Shanghai, Public Republic of China'' was performed between 14-18 August 2023. The outcome of the inspection was issued on 14/08/2023. – A GMP inspection at ''Shanghai Henlius Biopharmaceutical Co., Ltd. Building D. 1289 Yishan Road. Shanghai. China'' was performed on 14th August 2023. The outcome of the inspection was issued on 14/08/2023.	14 – 18 August 2023
– GLP inspection was carried out at a Facility in China between 16/11/2023 to 18/11/2023. The GLP inspection report was available on 25/01/2024.	16 – 18 November 2023
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	21 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 and to be sent to the applicant on	14 December 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 August 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	09 September 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 Hetronifly on	19 September 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	19 September 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed therapeutic indication is as follows: "Hetronifly in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive stage-small cell lung cancer (ES-SCLC)".

SCLC may be divided into limited stage and extensive stage disease, based on a staging system, either Veterans Administration Lung Study Group (VALG) or the Tumour/Node/Metastasis (TNM) classification of UICC, 8th edition. The VALG has been widely applied to stage patients due to its simplicity and clinical utility. On the other hand, TNM classification depends on pathological staging and is more complicated. TNM classification does not often alter clinical management due to the predominance of advanced stage at presentation. Additionally, TNM classification is less powerful in prognostication for SCLC compared to non-small cell lung cancer (NSCLC) and is most useful to identify patients who are beneficial to surgery. Surgery is a treatment option in highly selected limited-stage SCLC patients only.

2.1.2. Epidemiology

Lung cancer is the leading cause of cancer mortality worldwide, responsible for almost one in five deaths in 2020. Small-cell lung cancer represents about 15% of all lung cancers (Wéber et al 2023). Most cases of SCLC present as extensive-stage (~70%), while the remaining (~30%) present with limited disease. In first line treatment of extensive-stage SCLC, median OS was 8.8 months in a retrospective chart review started from 2015 in France, Italy, and UK (Blackhall et al 2023), prior to introduction of novel treatment options in the form of immunotherapies.

Of risk factors, SCLC is strongly associated with smoking, up to 9 in 10 cases are caused by smoking (Wéber et al 2023). Men and women remain in different phases of the smoking epidemic: In male populations rates are predominantly stable or in decreasing rates while rates among female populations are increasing (Miranda-Filho et al 2018).

2.1.3. Aetiology and pathogenesis

SCLC is a neuroendocrine tumour which is distinct from most types of NSCLC by rapid doubling time and growth and early development of metastases. Diagnosis of SCLC is based upon light microscopy of a sample, either cytological or histological specimen. Additionally, standard immunohistochemical markers for lung origin and/or neuroendocrine features are useful for diagnosis. No molecular markers are recommended for treatment selection in SCLC. In particular, the use of PD-L1 immunohistochemistry as a predictive survival biomarker does not appear to be related to response of immunochemotherapy (Liu et al 2021).

2.1.4. Clinical presentation, diagnosis and prognosis

The clinical presentation of SCLC is often related to symptoms that arise from the central airways, with cough, dyspnoea, weight loss and frailty. Typically, the tumour infiltrates the submucosa and gradually narrows the bronchial lumen through extrinsic or endobronchial expansion. Post-obstructive

pneumonia and hemoptysis are less common than with NSCLC due to its growth pattern. Approximately 70% of SCLC patients present with metastatic disease, with a tendency to spread to liver, adrenals, bone, bone marrow and brain (Ko J et al 2021).

Although SCLC is responsive to chemotherapy and radiotherapy, it relapses within months despite treatment. The median survival range from the time of diagnosis for ES-SCLC is 8 to 13 months, while limited stage disease is approximately 7 months longer. Less than 5 percent of patients with ES disease survive 2 years. Long-term survival data for patients with ES disease treated with a combination of chemotherapy and immunotherapy are awaited (Puglisi et al 2010).

2.1.5. Management

In general, surgery is the only therapeutic treatment in SCLC, but it is no option in ES-SCLC. The aim of other therapy is to prolong survival. Standard of care since the 1990s has been platinum-based chemotherapy regimen including two agents, either cisplatin or carboplatin in combination with etoposide. Cisplatin and carboplatin are found to be comparable in efficacy outcomes in ES-SCLC. The use of maintenance chemotherapy or multiple-drug regimens have not been shown to offer benefits compared to a two-drug combination. The combination of carboplatin and etoposide may have a more profitable toxicity profile than a cisplatin and etoposide-based regimen. Carboplatin-etoposide poses a less risk of nephrotoxicity, neuropathy and ototoxicity, while cisplatin-etoposide has less risk for hematologic toxicity and interstitial pneumonitis (Jiang et al 2021).

Atezolizumab and durvalumab are humanised monoclonal PD-L1 antibodies that have improved survival in combination with a platinum agent and etoposide during induction and continued as maintenance. Comparisons across trials suggest equivalent efficacy and toxicity in combination with chemotherapy in induction phase. Immunotherapy as maintenance, however, has not demonstrated benefits in patients treated with chemotherapy only (Zhang et al 2023).

The 2021 ESMO guideline recommendations for SCLC include cisplatin or carboplatin in combination with etoposide in ES-SCLC, in addition to atezolizumab and durvalumab as induction and maintenance. Further, in patients with response to treatment consolidation thoracic radiation is a treatment option. In patients with contraindication to immunotherapy, prophylactic cranial irradiation is a treatment option (ESMO Clinical Practice Guidelines 2021).

2.2. About the product

Mechanism of action:

Serplulimab is a humanised monoclonal antibody which binds to the PD-1 receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Serplulimab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Claimed and final approved indication:

Serplulimab in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive stage-small cell lung cancer (ES-SCLC).

Posology:

The recommended dose of serplulimab is 4.5 mg/kg every 3 weeks should be administered intravenously until disease progression or unacceptable toxicity.

Dose escalation or reduction of Hetronifly is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability. Dose withholding for up to 12 weeks for tolerability is acceptable.

Serplulimab should be withheld or discontinued to manage adverse reactions as described in the table below.

Table 1. Recommended treatment modifications for serplulimab

Immune-related adverse reactions	**Severity**	**Treatment modification#**
Immune-related lung disease	Grade 2	Withhold until adverse reactions recover or improve to Grade 1
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold until adverse reactions recover or improve to Grade 1
	Grade 4 or recurrent Grade 3	Permanently discontinue
Hepatitis	Grade 2 with AST or ALT > 3 to 5 times ULN, or total bilirubin > 1.5 to 3 times ULN	Withhold until adverse reactions recover or improve to Grade 1
	Grade 3 or 4 with AST or ALT > 5 times ULN, or total bilirubin > 3 times ULN	Permanently discontinue
Nephritis and renal dysfunction	Grade 2 elevation of serum creatinine	Withhold until adverse reactions recover or improve to Grade 1
	Grade 3 or 4 elevation of serum creatinine	Permanently discontinue
Endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, Grade 2 or 3 hyperthyroidism, Grade 2 or 3 hypophysitis, Grade 2 adrenal insufficiency, Grade 3 hyperglycaemia or type 1 diabetes mellitus	Withhold until symptoms resolve and management with corticosteroids is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 hyperglycaemia	Permanently discontinue
Skin adverse reactions	Grade 3	Withhold until adverse reactions recover or improve to Grade 1
	Grade 4 Stevens Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue
Other immune-related adverse reactions	Grade 3 or 4 elevation of serum amylase or lipase Grade 2 or 3 pancreatitis Grade 2 myocarditis* Grade 2 or 3 other immune-mediated adverse reactions occurred for the first time	Withhold until adverse reactions recover or improve to Grade 1

Immune-related adverse reactions	Severity	Treatment modification[#]
	Grade 3 decreased platelet count (thrombocytopenia) or white blood cell count	
	Grade 4 pancreatitis or recurrent pancreatitis of any grade Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 4 other immune-related adverse reactions occurred for the first time Grade 4 or recurrent Grade 3 decreased platelet count (thrombocytopenia) or white blood cell count	Permanently discontinue
Infusion-related reactions	Grade 2	Reduce infusion rate to half rate or interrupt. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0).
ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.
[#]: Serplulimab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones.
*: The safety of retreatment with serplulimab in patients who experienced immune-related myocarditis is not clear.

Method of administration

Hetronifly is for intravenous use. The initial infusion rate should be set up to 100 ml per hour. If the first infusion is well tolerated, all subsequent infusions may be shortened to 30 minutes (± 10 minutes).

When administered in combination with chemotherapy, Hetronifly should be given first followed by chemotherapy on the same day. Use separate infusion bags for each infusion.

Hetronifly must not be administered as an intravenous push or bolus injection.

The total dose of Hetronifly required should be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection.

2.3. Type of application and aspects on development

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as solution for infusion containing 10 mg/mL of serplulimab as active substance. The active substance and finished product are also described as HLX10 AS and HLX10 FP in this report.

Other ingredients are: Citric acid monohydrate, sodium citrate, sodium chloride, mannitol, polysorbate 80 and water for injections.

The product is available in 10 mL Type I clear glass vial with chlorobutyl rubber stopper and aluminium-plastic combination caps containing 100 mg of serplulimab.

2.4.2. Active substance

2.4.2.1. General information

The active substance, serplulimab, is a humanised recombinant IgG4 monoclonal antibody that targets programmed cell death 1 (PD-1) and blocks its interaction with the ligands PD-L1 and PD-L2. Serplulimab is secreted as a disulfide-linked glycosylated tetramer consisting of two identical 443 amino acids in heavy chains (HC) and two identical 214 amino acids in *kappa* light chains (LC). Each heavy chain contains an N-glycosylation site located at asparagine 293 (N293). A serine to proline S224P mutation has been introduced to prevent Fab-arm exchange.

2.4.2.2. Manufacture, process controls and characterisation

The active substance is manufactured at Shanghai Henlius Biopharmaceuticals Co., Ltd. (Building D) Block 1, No. 1289 Yishan Road, Xuhui District, Shanghai, China. Satisfactory compliance with GMP has been demonstrated.

Serplulimab is expressed by CHO cells in a fed batch process. The working cell bank (WCB) is scaled-up in shake flasks and seed bioreactors and seeded in a 2000 L fed batch production bioreactor. The bioreactor culture is harvested, clarified, viral inactivated and purified. Purification of the active substance (HLX10) involves Protein A Affinity Chromatography (AC), Cation Exchange Chromatography (CEX), and Anion Exchange Chromatography (AEX). An Ultrafiltration/Diafiltration (UF/DF) unit operation is used for protein concentration and buffer exchange. The excipients mannitol and polysorbate 80 are added, and then the formulated active substance solution is 0.2 μm filtered and dispensed into irradiated disposable bags and stored at 2-8 °C for long-term storage.

The active substance manufacturing process has been thoroughly detailed, with in-process controls specified for each step and their acceptance criteria well justified. The provided process parameters and in-process controls, along with other control measures, align with the process description and are sufficient to ensure the quality and safety of the serplulimab active substance as well as to monitor process consistency.

A master cell bank (MCB) and working cell bank (WCB) have been established and characterisation test reports for the cell banks are provided. No materials of human or animal origin are used in the manufacturing process.

Process validation

The process validation of the HLX10 active substance (AS) manufacturing process was performed on three consecutive AS commercial scale (2000 L) manufactured as process performance qualification (PPQ) batches.

Results of process parameters for each unit operation conform to the pre-defined acceptance criteria. All the process parameters including critical process parameters (CPPs) meet the acceptable range, and all the in-process controls (IPCs) meet the process validation acceptance criteria. The extended test results on PPQ batches are provided for low pH viral inactivation and filtration, CEX and AEX steps.

All the results for process-related impurities and product-related impurities conform to the acceptance criteria.

Hold time studies are performed using scaled down models and intermediates from commercial batches to support the hold-time of intermediates. Reprocessing in designated approach is considered acceptable.

In conclusion, the active substance manufacturing process has been validated adequately.

Manufacturing process development

Five AS processes in different stages are described. The batches produced according to each process are listed, and the process changes are adequately described.

Comparability between the 2000 L-scale process and the earlier clinical stage process has been performed. Acceptance criteria have been established. The process changes occurring during the development have been assessed for impact to product quality, and the active substance manufactured at the commercial manufacturing site has been demonstrated to be comparable to the material used for clinical trials.

Process characterisation

The process characterisation study of each unit operation was mainly carried out with multivariate studies (e.g. Design of experiment (DoE)) and univariate (e.g., one factor at a time) as appropriate to establish parameter-attribute relationships, using qualified scale-down models. Therefore, we determine CPPs and KPPs, and identify robust normal operating ranges (NORs) and proved acceptable ranges (PARs).

Characterisation

Structure, physicochemical characteristics and biological properties of serplulimab manufactured by the PPQ process were elucidated by release tests and extended characterisation assays. The analytical results are consistent with the proposed structure. Forced degradation studies were conducted.

The serplulimab active substance has been sufficiently characterised by various orthogonal methods. The results reveal that the active substance has the expected structure of a humanized IgG4-type antibody. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities.

The biological activity of serplulimab was characterised to demonstrate the mechanism of action (MoA) of serplulimab *in vitro*.

Binding to Fc receptors was assessed by both SPR and ELISA, and results showed that serplulimab did not bind to FcyRIIIa and had little binding to C1q. Finally, the cell-based assays were conducted to determine the absence of Fc-mediated effector functions (i.e. ADCC and CDC), as expected for IgG4 construct. Serplulimab has been shown to retain binding to FcRn in SPR assay.

Impurities

Residual HCP, Protein A, and DNA are shown to be present at low levels in the batches tested. Clearance study results and safety risk assessment for process-related impurities conclude with low risk.

2.4.2.3. Specification

Specification

The active substance release and shelf-life specifications include control of identity, purity and impurities, potency and other general tests. The specification acceptance criteria are considered acceptable.

Analytical procedures

The analytical procedures have been described in adequate detail.

Validation of analytical procedures

Analytical procedures of tests included in the specification have been adequately validated.

Batch analyses

An overview of all batches and batch release data has been provided.

Justification of specification

An overview with all batch data used for setting the specification limits show the clinical experience variation and the appropriate limits.

Reference Standards or Materials

Four reference materials are established. Appropriate reference material characterisation has been performed. The listed requalification requirements and the listed characterisation tests for new working reference material are considered acceptable.

Container Closure System

HLX10 AS is stored in selected storage bag. The applicant states that processing conditions meet the "Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMA/410/01 Rev. 3). A TSE certificate for the storage bag has been provided. Extractable and leachables studies have been performed using representative bag. The results indicate that the container closure system of AS are suitable for use for long-term storage.

2.4.2.4. Stability

Stability

The proposed shelf-life of HLX10 AS is 12 months, stored at 5±3 °C protected from light. The long term stability data provided for the three PPQ batches at the intended storage temperature of 5±3 °C for 12 months, conform to the acceptance criteria. The proposed stability program is in general found acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The product is a sterile, preservative-free, non-pyrogenic, clear to slightly opalescent, colourless to slightly yellow solution for injection with a concentration of 10 mg/mL. Each vial is filtered and filled with 10 mL HLX10 AS. The product should be stored at 2-8 °C and protected from light.

The finished product (FP) contains Citric acid monohydrate, sodium citrate, sodium chloride, mannitol, polysorbate 80 and water for injections as excipients, which meet the requirements of the European Pharmacopoeia.

Pharmaceutical development

The AS and FP have the same formulation and no additional excipients are added during the manufacturing of FP. Formulation studies for the FP were performed. The experimental setup and the results are included.

Manufacturing process development

The HLX10 FP manufacturing process has been developed and optimized through several process stages.

A comparability exercise of HLX10 FP batches produced using the later stages of process development is presented. All presented results met the comparability acceptance criteria.

A process characterisation (PC) study is presented in the manufacturing process development section. The study is mainly based on the quality target product profile and the impact on process parameters on critical quality attributes (CQAs). Potential critical process parameters (pCPP) were identified according to their influence on CQAs. Parameters with high or moderate risk priority were defined as pCPPs. Process parameters with low risk were defined as non-CPP after subject matter expert (SME) determination. The HLX10 FP process parameter categorization is adequately described. All identified CQAs and critical process parameters are presented.

2.4.3.2. Manufacture of the product and process controls

The FP is manufactured at Shanghai Henlius Biopharmaceuticals Co., Ltd. (Building D) Block 1, No. 1289 Yishan Road, Xuhui District, Shanghai, China. The EU release testing and QP release locations are also described in the dossier. Satisfactory compliance with GMP has been demonstrated.

Overview of the FP manufacturing process and controls

The FP manufacturing process, including sterile filtration, filling, etc., is a standard antibody manufacturing process. The core manufacturing steps include HLX10 AS mixing, sterile filtration, filling, stoppering, capping, visual inspection, labelling and packaging. The process is described in sufficient detail.

FP manufacturing process steps are controlled by non-critical and critical process parameters (non-CPPs and CPPs), and in process controls (IPCs). The FP process controls are adequately described. The proposed CPPs, process monitoring parameters and IPCs are deemed sufficient to control the FP manufacturing process. Process time at room temperature is also controlled.

Process validation

Finished product PPQ was performed on three consecutive batches of FP commercial scale production. For each unit operation of the FP process, all the results of CPPs, non-CPPs, IPCs and enhanced monitoring controls are presented. All pre-defined acceptance criteria were met. The FP process was found to be properly validated and the commercial process of FP is qualified.

Operation duration and hold-time qualification studies were conducted on the commercial batches and the overall manufacturing time is set and controlled.

The aseptic process simulation (media fill simulation) is adequately presented. The filter validation is presented to demonstrate the filter performance and validity.

2.4.3.3. Product specification

Specification

The acceptable release and shelf-life specifications of HLX10 FP include control of identity, purity and impurities, potency and other general tests.

Analytical procedures and reference standards

The analytical methods used for release testing are described and validated, and compendial methods are verified. The validation results demonstrate that the methods are suitable for their intended use in release and stability testing of FP.

The applicant intends to transfer all analytical methods for testing of the FP to the companies in the EU. Detailed information of these companies can be found in the dossier.

Batch analysis

An overview of all FP batches and full release testing data were provided. All results were compliant with the specifications.

Characterisation of impurities

HLX10 FP is produced from AS by sterile filtration and aseptic filling. Thus, all impurities of HLX10 FP were derived from AS, and there were no new impurities generated during the manufacturing of FP.

A summary of the risk assessment for elemental impurities in accordance with ICH Q3D is included in the dossier. No risk for presence of nitrosamine impurities has been identified as per the nitrosamine risk evaluation report.

Container closure

The container closure system of HLX10 FP is adequately presented. The system consists of 10 ml Type I clear glass vial with chlorobutyl rubber stopper and aluminium-plastic combination caps.

The container closure system is adequately tested in terms of microbial contamination as well as extractables and leachables. The results of the container closure integrity test (CCIT) indicate that the container closure system of HLX10 FP can ensure sterility of the product. The container closure components are suitable for use for long-term storage.

2.4.3.4. Stability of the product

The stability protocol is in accordance with ICH guidelines and is acceptable. The proposed storage condition for FP is 5±3 °C (protected from light), and the proposed shelf life is 36 months, which is endorsed. 36 months of stability data are available for three FP batches manufactured using the proposed FP commercial process, stored at 5±3°C protected from light.

After approval, the applicant commits to conduct stability studies on at least one batch of FP each year under long-term (5±3°C) condition, unless there is no production that year. The annual stability protocol is presented.

The shelf life is 36 months when stored at 5±3°C and protected from light.

From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C. This 24

hour hold may include up to 6 hours at room temperature (≤ 25ºC). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

2.4.3.5. Adventitious agents

The information provided on adventitious agents is considered mainly adequate and the general strategy of viral safety of the manufacturing process follows the requirements of ICH Q5A. The virus test results for MCB, WCB and limit of *in vitro* cell age (LIVCA) are provided demonstrating that no adventitious agents were detected except from retroviral particles Type A and type C. The viral clearance study was conducted to evaluate the virus removal/inactivation capability of commercial process. The study was carried out using scale down models. Four model viruses including Murine Leukaemia Virus (MuLV), Pseudorabies Virus (PRV), Reovirus Type 3 (Reo-3) and Minute Virus of Mice (MVM) were used in this study. The log reduction factors demonstrate effective viral reduction for all model viruses.

TSE risk statements from the manufacturer have been provided for the raw material and consumables. The manufacturer confirms that the processing conditions comply with the "Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMA/410/01 Rev. 3).

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

A major objection regarding confirmation of GMP compliance for the manufacturing sites in China has been resolved.

Active substance and finished product specifications are considered appropriate, and the acceptance limits are acceptable.

The manufacturing process of FP comprises sterile filtration and filling, etc.

The comparability exercise performed on active substance and finished product batches covers the manufacturing history and is considered adequate.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of the tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Hetronifly 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.

No further Recommendations for future quality development have been made.

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

2.5. Non-clinical aspects

2.5.1. Introduction

Serplulimab is a humanised monoclonal IgG4 antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. By binding to PD-1 and inhibition of ligand binding, serplulimab potentiates T-cell responses (CD4+ T cell proliferation, T cell activation and cytokine release), including anti-tumour responses.

The nonclinical data comprises *in vitro* and *in vivo* pharmacodynamics studies, and pharmacokinetics (PK) and toxicity studies in cynomolgus monkeys, in line with ICH S9 and ICH S6(R1).

Serplulimab from two drug substance manufacturing processes has been used during the non-clinical development (see section 'Quality aspects'). Process 3.0 was used for the long-term repeat-dose toxicity study, while process 1.0 was used for all other nonclinical studies, including pharmacology.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The biological activity of serplulimab was demonstrated in a series of *in vitro* pharmacology studies. Serplulimab inhibited PD-1/PD-L1 (IC_{50} = 406.5 ng/mL) and PD-1/PD-L2 (IC_{50} = 445.8 ng/mL) interactions. Co-culturing monocyte-derived dendritic cells from one donor with CD4+ T cells from a different donor in the presence of serplulimab or its isotype control antibody showed that PD-1 blockade with serplulimab systematically resulted in a titratable enhancement of T cell proliferation, starting at a concentration of 0.06 µg/mL. Serplulimab treatment also dose-dependently increased IL-2 secretion, a hallmark of T-cell proliferation. The cellular functional properties of serplulimab were found comparable to those of other authorised anti-PD1 (results not shown).Receptor occupancy was measured *in vitro* by flow cytometry of peripheral blood CD3+ T cells after pre-incubating human whole blood samples from 6 healthy donors with various doses of serplulimab. Target occupancy of serplulimab on CD3+ T cells from all subjects increased in a concentration dependent manner. The mean concentration of all blood samples required to achieve 50% receptor occupancy was 0.47 ± 0.48 µg/mL (SD). This is in line with the IC_{50} values for binding to PD-L1 and PD-L2. Greater than 70% receptor occupancy was reached at 2 µg/mL of serplulimab in all donor blood samples except one (results not shown).

Complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) activities were evaluated *in vitro* in assays using cells from healthy donors. Serplulimab did not mediate CDC activity at concentrations up to 50 µg/mL, and is considered to be without ADCC activity (results not shown).

Serplulimab binds to human and cynomolgus monkey PD-1 with Kd values of 1.68 and 4.78 nM, respectively, indicating that the affinity of serplulimab to human PD-1 is 3-fold higher than for cynomolgus monkey PD-1. Cynomolgus monkey was the selected species for toxicity testing. Flow cytometry analyses confirmed the ability of serplulimab to bind PD-1 expressing immune cells as shown by binding ability of serplulimab to PHA-L activated human T cells. The EC_{50} of serplulimab was 64.4 ng/mL and comparable to that of other authorised anti-PD1 (results not shown).

In vivo anti-tumour activity was assessed in tumour-bearing mouse models using cell lines from human colorectal cancer, NSCLC and breast carcinoma. In the presence of human PBMCs, repeated systemic administration of serplulimab at 30 mg/kg/twice per week resulted in 53- 60% tumour

growth inhibition (TGI) in tumour-bearing mice inoculated with human colon cancer or human non-small cell lung cancer cells. No significant effect was seen without hPBMCs, suggesting that serplulimab exerts its anti-tumour effect through the action of immune cells in the hPBMCs (results not shown).

Serplulimab exhibited similar TGI as other authorised anti-PD1 in a humanised mouse model inoculated with human breast carcinoma cells. In a syngeneic human PD-1 knock-in mouse model implanted with huPD1-L1 transfected murine colon cancer cells, serplulimab achieved complete tumour eradication, while other authorised anti-PD1 inhibited tumour growth but not tumour regression (results not shown).

The anti-tumour effect of serplulimab in combination with HLX04, a mAb similar to bevacizumab targeting VEGF, were evaluated in FaDu, NCI-H292 or HT-29 cell line xenograft tumour models. While the addition of serplulimab did not increase the antitumour effect of HLX04 in the FaDu model, beneficial effects were seen with the addition of serplulimab in the two other models (results not shown).

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were conducted.

2.5.2.3. Safety pharmacology programme

Selected safety pharmacology endpoints were evaluated as part of the 13-week toxicology study conducted in cynomolgus monkeys. No serplulimab-related safety pharmacology findings on central nervous system (CNS), cardiovascular, or respiratory functions were noted in the 13-week toxicology study (results not shown).

Selected parameters (ECG, blood pressure and body temperature) were also monitored in the 31-week study, without findings (results not shown).

2.5.2.4. Pharmacodynamic drug interactions

No specific studies for drug interactions were conducted.

2.5.3. Pharmacokinetics

The pharmacokinetic (PK) and toxicokinetic (TK) properties of serplulimab were characterised in cynomolgus monkeys, since serplulimab binds specifically to human and monkey PD-1 but not to either mouse or rat PD-1.

PK studies were conducted with single dose intravenous infusions at 3, 10 and 30 mg/kg in monkeys (P16-106-YD). TK data and ADA data were also collected as part of the 4-week (P16-106-TS), two 13-week (P16-106-CD, P23-S272-RD) and a 31-week (P19-S162-RD) repeat-dose toxicology and toxicokinetic studies of serplulimab.

Method validation

An enzyme-linked immunosorbent assay (ELISA) method and an electrochemiluminescence method (MSD ELC) were originally developed and validated for quantification of serplulimab or anti-serplulimab antibodies in toxicology studies conducted in cynomolgus monkeys (study Nos P16-106-MT and P16-106-2MT). These validations were, however not found GLP-compliant following the study-triggered GLP inspections.

Two additional method validation studies to support bioanalysis/toxicokinetics of serplulimab and anti-serplulimab antibodies (study Nos P23-S272-PKV and P23-S272-ADAV) in the new pivotal 13-week repeat-dose toxicity study (P23-S272-RD) were performed by the applicant and submitted during the evaluation of the application to support the MAA.

An ELISA method was developed for the quantification of serplulimab in cynomolgus monkey serum. The ELISA method was validated with regard to selectivity, specificity, calibration curve (0.9 to 54.0 µg/mL), precision, accuracy, dilution linearity, hook effect, haemolytic effect and the parallelism of the method, as well as the stability of serplulimab (study No P23-S272-PKV).

A chemiluminescent immunoassay method for analysis of anti-serplulimab antibody in cynomolgus monkey serum was developed and validated. Anti-serplulimab antibodies were shown to be stable in monkey serum after five freeze/thaw cycles. Other parameters including selectivity and hook effect also met the predefined criteria for the validation (study No P23-S272-RD).

Pharmacokinetics

The pharmacokinetic profile of serplulimab was investigated in a single dose PK study by IV infusion to cynomolgus monkeys at3, 10 and 30 mg/kg. PK data following repeated dosing at 5, 50 and 100 mg/kg were collected in a 4-week dose range finding study, and in the 13 and 31-week toxicity studies.

Serplulimab exhibited linear pharmacokinetic profile following **single** IV dosing from 3 to 30 mg/kg in cynomolgus monkeys, without significant sex-related differences. Serplulimab had relatively small volume of distribution (38.05 to 53.52 mL/kg) and long elimination half-life (137.97 to 256.99 hours), as expected for an IgG4 monoclonal antibody.

Following repeated weekly dosing there was a slight accumulation, with accumulation index (AI) ranging from 1 to 5 in ADA negative animals (results not shown). There was a tendency to sex-related differences in exposure (C_{max} and AUC_{last}, but not AUC_{inf}) at some time points. Anti-drug antibodies (ADAs) were detected at low titres in most animals following repeated dosing. Overall, when the ADA negative animals were analysed separately, a linear, dose-proportional drug exposure was observed. High ADA titres increased serplulimab clearance, but the animals still had measurable serum concentrations throughout the studies, indicating adequate exposure of the animals.

Further, data from the 13-week repeat-dose toxicity study have demonstrated sustained receptor occupancy (RO) at end of dosing in animals considered as ADA positive (results not shown), indicating that serplulimab maintains its activity in ADA-positive animals throughout the study.

Distribution, metabolism and excretion

Studies on distribution, metabolism and excretion have not been conducted. Antibodies are degraded into peptides and amino acids by proteases. Furthermore, serplulimab is also thought to be degraded through receptor-mediated drug disposition in PD-1-expressing T cells after internalisation and subsequently degradation by lysosomes.

2.5.4. Toxicology

A limited toxicology dossier has been provided, comprising a dose-range finding 4-week study and 13- and 31-week repeat dose toxicity studies in cynomolgus monkeys, two tissue-cross-reactivity studies with human tissue and a haemolysis effect study. Except for the 4-week study, all other studies are claimed performed according to GLP standards. Due to GLP-compliance issues, a new GLP-compliant 13-week repeat-dose toxicity study (study No P23-S272-RD) was performed by the applicant. Method validation studies to support bioanalysis/toxicokinetics of serplulimab and anti-serplulimab antibodies

(study Nos P23-S272-ADAV and P23-S272-PKV) in the new pivotal 13-week repeat-dose toxicity study were also conducted.

2.5.4.1. Single dose toxicity

No single dose toxicity studies were performed.

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity studies were conducted with IV serplulimab at 5, 50 and 100 mg/kg/week. In general, serplulimab was well tolerated at doses up to 50 mg/kg/week. Effects on the immune system, such as ADA were detected at long-term dosing, an increased cytokine (IL-4, IL-6, and interferon γ), as well as increases in CD8+ T cells (results not shown). The effects were mostly mild and not reflected in clinical observations and are considered related to the MOA.

Two deaths were reported (one high-dose female in the 13-week study and one mid-dose female in the 31-week study) (results not shown), likely due to treatment-related anaphylactic reactions. Moderate spinal cord gliosis and neuropil degeneration were noted at histopathological examination of the female from the 13-week study. In the initial 13-week study, one high-dose female was euthanised in moribund condition at D55 due to weight loss and diarrhoea, possibly related to an ongoing amoebae infection. An immune-related adverse effect of serplulimab cannot be ruled out, exacerbating or causing the infection.

In the initial 13-week repeat-dose study, loose stool/soft stool were noted in all treatment groups from doses of 5 mg/kg but with higher incidence and longer duration in females of the 100 mg/kg group. Similar incidences of loose stools and soft stools were noted in the high dose group in the 31-week repeat-dose toxicity study, however with incidences comparable to that of the control group (results not shown).

Marked treatment-related decreases in CD3+ and CD4+ lymphocyte count of approximately 50% in the majority of male individuals compared to their pre-dose level were noted in the 100 mg/kg group in the 13-week repeat-dose toxicity study. Similar findings were not seen in females (results not shown).

In the 31-week repeat-dose toxicity study, findings included non-reversable perivascular mononuclear inflammation in the choroid plexus in the brain with a dose-dependent higher frequency in the 100 mg/kg group (5/8 compared to 1/8 in the lower dose groups). The NOAEL was determined to 50 mg/kg (results not shown).

An additional 13-week repeat-dose study (P23-S272-RD) was performed by the applicant and submitted during the MAA procedure. Immune-related effects were noted as formation of ADAs, but exposure levels were still considered sufficiently in excess of the clinically relevant exposure. No apparent treatment-related findings were noted in any other immune-related parameters, including CD3+ and CD4+ T lymphocytes for which a reduction was seen in high-dose males in the initial 13-week study (results not shown).

Compared to the previous studies, observations of loose stool/soft stool appeared to be more transient with no clear dose- or time-dependent pattern and with the highest incidence observed in the placebo group. Rectal prolapse was observed in a male animal (#2362752) in the 100 mg/kg/week groups. As no correlation with loose/soft stool was noted, it appears to be unrelated to serplulimab treatment (results not shown).

Injection site findings of skin erythema correlated with histopathological findings of mechanical injury and appeared to be procedure related. The histopathology report showed no clear dose-dependent evidence of perivascular mononuclear cuffing in the brain or choroid plexus, as previously seen in the 31-week repeat-dose toxicity study. However, minimal mononuclear cell infiltrations were seen in one female in the 15 mg/kg/week group, one male in the 50 mg/kg/week group and one female in the 100 mg/kg/week group. No noteworthy serplulimab-related safety findings were seen on cardiovascular or respiratory functions.

In conclusion no adverse findings were observed in this additional 13-week repeat-dose toxicity study across any of the examined parameters, and overall, serplulimab was well tolerated. NOAEL was determined to the highest dose, 100 mg/kg/week.

2.5.4.3. Genotoxicity

In accordance with ICH S6 (R1) and ICH S9 guideline no information has been submitted on the genotoxic potential of serplulimab.

2.5.4.4. Carcinogenicity

In accordance with ICH S6 (R1) and ICH S9 guideline no information has been submitted on the carcinogenic potential of serplulimab.

2.5.4.5. Reproductive and developmental toxicity

In line with the ICH S9 guideline, no dedicated studies investigating the effect of serplulimab on fertility and early embryonic development, or pre- and postnatal toxicology were performed.

2.5.4.6. Toxicokinetic data

Toxicokinetic data is addressed in section 2.5.3 'Pharmacokinetics'.

Upon request by the CHMP, an interspecies comparison table was presented based on exposure levels in 13- and 31-week repeat-dose toxicity studies at NOAEL (50 mg/kg), exposure levels in the new 13-week RD toxicity study (P23-S272-RD, NOAEL 100 mg/kg) and patients from two clinical trials. The data indicate exposure margins of more than 21- and 36-fold for Cmax and AUC respectively (data not shown).

2.5.4.7. Other toxicity studies

Immunotoxicity

Immune related effects were noted in the 4-week and the 13-week repeat dose toxicity study. Increased IL-4, IL-6, and interferon γ in addition to an increase in CD8+ T cell was noted and is pharmacological related to the mode of action. In the 13-week and the 31-week studies single cases of anaphylactic reactions were noted, related to ADA-formation. The repeated administration of serplulimab in cynomolgus monkeys had no significant effects on the TDAR after KLH injection (results not shown).

Tissue cross reactivity (TCR)

The TCR study in human tissue showed binding of serplulimab-biotin in lymph node, lung, ileum, stomach, spleen, fallopian tube, colon, and thymus. Staining was noted in lymphocytes from the stomach, jejunum, colon, spleen, thymus, and mesenteric lymph node in cynomolgus monkey tissue.

Generally, the tissue cross-reactivity study showed comparable staining in human and Cynomolgus monkey tissue, restricted to lymphocyte membranes (results not shown).

Haemolysis

At 10 mg/mL, serplulimab had no haemolytic or aggregation effect in haemolysis tests using human RBCs under the study conditions (results not shown).

Local tolerance

Evaluation of the local tolerance was assessed as part of the initial 13-week repeat-dose toxicity study, claimed without any findings.

2.5.5. Ecotoxicity/environmental risk assessment

The applicant has submitted an acceptable ERA concluding that due to its nature, serplulimab is unlikely to result in a significant risk to the environment. Serplulimab is a protein composed of natural amino acids, and proteins are expected to biodegrade in the environment and not pose a significant risk. Therefore, serplulimab is exempt from preparation of an ERA as per 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

Serplulimab from two drug substance processes have been used during the non-clinical development. Process 3.0 was used for the long-term repeat-dose toxicity study, while process 1.0 was used for all other nonclinical studies, including pharmacology. Based on the comparability exercise on drug substance, the lack of pharmacology studies with process 3.0 material is considered acceptable.

Primary pharmacodynamic studies

Based on the results from a non-clinical *in vitro* study (Study InVitro-HLX10-005), the applicant claims that serplulimab does not mediate ADCC at concentrations up to 100 µg/mL. In both ADCC assays there was a big variability in lysis levels for all test substances (serplulimab, other authorised anti-PD1 and positive control) at all test concentrations, with no clear difference between positive control and serplulimab at clinically relevant test concentrations. Based on the presented data, it appears that the positive control had comparable ADCC potential with serplulimab at most test concentrations. Furthermore, in one of the two assays it appears that the serplulimab lysis level increases at concentrations above 10 µg/mL. In addition, it is unclear how cytotoxicity was defined in order to reach lysis levels above 100%. Taken together, the validity of the assay is questioned, and a final conclusion regarding ADCC cannot be reached based on these data. In module 3.2.S of the application dossier, however, negative result from another ADCC assay is presented, based on a reporter gene-based bioassay with Jurkat effector cells (Jurkat CD16a/ NFAT cells) and target cells (PD-1 Jurkat T cells). Thus, serplulimab can be considered without ADCC activity, in line with what is expected for an IgG4.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies have been executed, which is acknowledged and in accordance with relevant guideline (ICH S6 (R1)).

Safety Pharmacology

The omission of stand-alone safety pharmacology studies for serplulimab is accepted and in line with ICH S6(R1). Safety pharmacology parameters were assessed as part of the GLP-compliant 13-week repeat dose toxicity study without findings of concern.

The death of one female dosed at 100 mg/kg in the initial 13-week repeat-dose study was ascribed as treatment-related anaphylactic reactions by the applicant. However, in the 31-week repeat-dose toxicity study, infiltrates of mononuclear cells were present around blood vessels of brain choroid plexus in 1/8 (minimal), 1/7 (minimal), and 5/8 (4 minimal, 1 slight) animals at 5, 50 and 100 mg/kg at the end of dosing period. At end of the recovery period, minimal mononuclear cell infiltrates in choroid plexus of the brain were observed in 2/4 and 2/4 animals at 50 and 100 mg/kg. In the new 13-week toxicity study (P23-S272-RD), minimal mononuclear cell infiltrations were seen in one female in the 15 mg/kg/week group, one male in the 50 mg/kg/week group and one female in the 100 mg/kg/week group. Since the findings are more sporadic and not clearly dose-dependent, they are not a determining factor for setting the NOAEL. Hence, based on these results, the potential association between serplulimab and spinal cord gliosis, along with neuropil degeneration in the mentioned female animal, could not be determined. The findings in the 31-week repeat-dose toxicity study are likely related to 'immune-mediated encephalitis', which is substantiated by the findings from the new 13-week repeat-dose study and is considered adequately reflected in the SmPC section 4.8.

Pharmacodynamic drug interaction

Serplulimab is to be used in combination with carboplatin and etoposide. No non-clinical PD data have been provided in support of this combination, but no interaction is expected at receptor level based on their mechanism of action.

Pharmacokinetics

Validation reports have been provided for an ELISA method to determine serplulimab in monkey plasma, and an MSD ECL method for ADA measurements, methods applied in the initial 13-week and the 31-week toxicity studies. These validations were conducted, and were originally claimed to be in compliance with GLP by the applicant. Based on the outcome of the GLP inspection, however, these methods are not considered GLP-compliant. Anticipating a negative outcome from the study-specific GLP inspection, method validation studies to support bioanalysis/toxicokinetics of serplulimab and ADA (study Nos P23-S272-ADAV and P23-S272-PKV) in the new pivotal 13-week repeat-dose toxicity study were conducted. Both validation methods are considered GLP-compliant and fit for purpose.

The PK/TK and ADA analyses supporting the initial 13- and 31-week studies were all conducted , and are not considered GLP-compliant. The TK and ADA data from the additional 13-week study is, however, considered GLP-compliant.

ADAs were detected at low titres in most animals following repeated dosing. High ADA titres increased the serplulimab clearance, but the animals still had measurable serum concentrations throughout the studies, indicating adequate exposure of the animals.

No information on potential neutralising ADAs has been provided. As indicated in ICH S6(R1), characterisation of neutralising potential is warranted when ADAs are detected and there is no PD marker to demonstrate sustained activity in the *in vivo* toxicology studies. Receptor occupancy data may be considered as a PD marker for activity. While not analysed in the 31-week study, data from the

13-week study have demonstrated sustained RO at end of dosing in animals considered as ADA positive. Thus, the lack of further characterising of the ADA neutralising potential is considered acceptable.

Toxicology

Based on the high similarity in PD-1 binding affinity and pattern of tissue cross reactivity findings between human and cynomolgus monkey, it is agreed that the cynomolgus monkey provides a suitable model for repeat-dose toxicity evaluation of serplulimab with respect to predicting potential adverse clinical reactions in humans.

Study-specific GLP inspections were initiated for the initial 13-week repeat-dose toxicity study (P16-106-CD), two method validation studies (P16-106-MT and P16-106-2MT), TK- and ADA-parts of the 31-week repeat dose toxicity study (P19-S162-RD), and two tissue cross reactivity studies (O16-106-1ZJ and O16-106-2ZJ). Due to critical non-compliance, none of the studies are considered GLP-compliant.

Anticipating a negative outcome, the applicant opted to conduct a new 13-week repeat dose toxicity study in monkeys (P23-S272-RD). Method validation studies to support bioanalysis/toxicokinetics of serplulimab and anti-serplulimab antibodies (study Nos P23-S272-ADAV and P23-S272-PKV) in the new pivotal 13-week repeat-dose toxicity study were also conducted. These studies were conducted under a GLP audit program and in general appear GLP compliant. In view of the planned patient population, and in line with ICH S9, a GLP-compliant 3-month repeat-dose toxicity study is considered sufficient. No adverse findings were observed across any of the examined parameters in the new 13-week study, and overall, serplulimab was well tolerated at doses up to 100 mg/kg/week. Study differences were however observed in the dose formulations between the groups. However, it was agreed with the applicant that the discrepancies in formulations were not expected to affect the outcome of the toxicity assessment or the comparison between the different doses of serplulimab in the newly conducted pivotal 13-week repeat-dose toxicity.

In the initial 13-week study T-cell receptor occupancy (RO) was analysed in blood samples from recovery group male monkeys collected at day 85, 105 and 134, showing significant RO in all animals at end of dosing (study day 85). All but one high-dose animal was found ADA positive at D85, defined as ADA positive in both screening and confirmatory assays. This suggests that serplulimab maintains its activity in ADA-positive animals throughout dosing, and that potential neutralising ADAs is of no major concern.

Loose stools and/or soft stools were observed in all groups in the 13-week and 31-week studies. Compared to these previous studies, observations of loose stool/soft stool appeared to be more transient with no clear dose- or time-dependent pattern in the new 13-week toxicity study. In the clinical setting, diarrhoea has been reported as a common adverse reaction ($\geq$ 5% occurrence). Also, enteritis and immune-related colitis have been reported but with a less common frequency. These GI findings are sufficiently described in the SmPC with an increased focus on monitoring potential aggravations in patients. Hence, the non-clinical findings of loose/soft stool are therefore also considered sufficiently covered by the clinical information presented in the SmPC.

Marked treatment-related decreases in CD3+ and CD4+ lymphocyte count of approximately 50% in the majority of male individuals compared to their pre-dose level were noted in the 100 mg/kg group in the initial 13-week repeat-dose toxicity study. No potential mechanism(s) or factors contributing to the reduction have been identified. No significant gender differences were seen in drug exposure. Similar reduction in CD3+ and CD4+ T cells were not observed in the new 13-week repeat-dose toxicity study (P23-S272-RD). CD3+ and CD4+ T-cell counts were not measured in the clinical setup for serplulimab, but diverging results were seen in clinical studies with other anti-PD-1 antibodies.

Hence, a potential clinical relevance of these findings in serplulimab-dosed animals cannot be excluded.

In the 31-week repeat dose toxicity study few clinical findings were noted and poor consistency was seen to findings in the initial 13-week study but was more in line with the new 13-week repeat dose toxicity study with only a few serplulimab-related toxicity findings. Minimal to slight mononuclear cell infiltrate around blood vessels of brain choroid plexus and minimal mononuclear cell infiltrate around blood vessels and within the interstitium of the epididymides were noted and the findings were only partly reversible. A concern was raised regarding the non-reversable perivascular mononuclear inflammation in the choroid plexus as a dose-dependent higher frequency were noted in the 100 mg/kg group (5/8 compared to 1/8 in the lower dose groups). Furthermore, the findings correlated with histopathological findings of moderate spinal cord gliosis and neuropil degeneration in the brain in a female monkey dying in the 13-week repeat-dose study. The NOAEL was lowered by the applicant to 50 mg/kg as the findings in the brain observed at the 100 mg/kg dose were considered adverse.

The findings of mononuclear cell infiltrate around blood vessels of brain choroid plexus could be related to immune-mediated encephalitis. In the new 13-week repeat-dose studies, sporadic non-dose dependent findings of minimal mononuclear cell infiltrations in three animals could substantiate the ability of serplulimab to induce immune-mediated encephalitis. It is generally accepted that immune checkpoint inhibitors such as anti-PD-1 monoclonal antibodies have immune mediated adverse events leading to imbalances in immune tolerance, including the regulation of neuroinflammation. Serplulimab related findings of immune-mediated encephalitis have also been seen with a low incidence in the clinical setting (two cases) and is considered sufficiently addressed in the SmPC (section 4.8 Undesirable effects). However, a potential association between serplulimab and spinal cord gliosis, along with neuropil degeneration in one female animal in the 13-week repeat-dose study, remains uncertain.

In the new 13-week and the 31-week repeat dose toxicity study, injection site findings of skin erythema correlated with histopathological findings of mechanical injury (haemorrhage, necrosis, fibrosis and mild inflammation) in all groups including placebo. These findings appeared to be procedure-related rather than an effect of serplulimab treatment.

In the initial 13-week study and the 31-week study, the NOAEL was determined to 50 mg/kg/week. In the new 13-week study, however, NOAEL was determined to 100 mg/kg/week. Following correction for differences in dosing interval between monkeys (7 days) and humans (14 days), this corresponds to exposure multiples 55-fold and 64-fold clinical exposure at Cmax and AUC, respectively, at serplulimab doses of 3 mg/kg.

Table 2. Drug exposure in nonclinical and clinical studies and safety margin

Drug exposure at NOAEL	**C_{max} (μg/mL)**	**$AUC_{0-\tau}$ (h·mg/mL)**	**Safety margin - C_{max}**	**Safety margin- $AUC_{0-\tau}$**
At 50 mg/kg/week, Day 85, 13-week toxicity study (P16-106-CD)	4176.15	466.03	27.36*, 34.80#	/*, 40.37#
At 50 mg/kg/week, Day 176, 31-week toxicity study (P19-S162-RD)	3341.16	416.78	21.89*, 27.84#	/*, 36.10#
At 100 mg/kg/week, Day 85, 13-week toxicity study (P23-S272-RD)	6695	741	43.86*, 55.79#	/*, 64.18#
4.5 mg/kg Q3W, cycle 8, HLX10-005-SCLC301 trial	152.63	/	NA	NA
3.0 mg/kg Q2W, cycle 3, HLX10-001 trial	120.0	23.09	NA	NA

Note: *: safety margin=mean C_{max} or AUC_{0-t} in animals at 50 or 100 mg/kg/C_{max} or AUC_{0-t} in patients treated with 4.5 mg/kg Serplulimab at cycle 8 in HLX10-005-SCLC301 trial .
#: safety margin=mean C_{max} or AUC_{0-t} in animals at 50 or 100 mg/kg/C_{max} or AUC_{0-t} in patients treated with 3.0 mg/kg Serplulimab at cycle 3 in HLX10-001 trial .
/: no data; NA: not applicable.

Based on the outcome of the study-triggered GLP-inspection, the two formerly submitted tissue cross-reactivity studies (study Nos O16-106-1ZJ and O16-106-2ZJ) are non-GLP compliant. The applicant was asked to comment on the impact on the quality of the tissue cross-reactivity studies. It was agreed with the applicant that tissue cross-reactivity studies are more important in supporting first-in-human clinical trials than late-stage clinical development, but the lack of quality and integrity of these studies are not considered good practice according to existing guidance. However, as the impact of lack of tissue cross-reactivity data on clinical safety evaluation and risk/benefit assessment is limited at this point in time, the issue was not be further pursued.

Reproductive and developmental toxicity

Reproductive toxicity studies have not been performed. Instead, the applicant has submitted a review of the physiological functions of PD-1/PD-L pathway and presented a weight of evidence (WoE) based assessment of reproduction and embryo-foetal development toxicity, in line with ICH S6(R1).

The PD-1/PD-L1 pathway is involved in maintaining tolerance to the foetus throughout pregnancy. Based on the mechanism of action and WoE, the risk of serplulimab to the reproduction and embryo-foetal development can be predicted. The potential risks of using serplulimab during pregnancy include increased rates of miscarriage and stillbirth. Exposure of foetuses to serplulimab can increase the risk of immune-mediated disorders. These concerns are adequately reflected in SmPC section 4.6.

Tissue cross reactivity

Based on the outcome of the study-triggered GLP-inspection, the two tissue cross-reactivity studies (study Nos O16-106-1ZJ and O16-106-2ZJ) are deemed non-GLP compliant. Hence, these studies can neither be considered reliable nor acceptable from a regulatory point of view. However, as the impact of lack of tissue cross-reactivity data on clinical safety evaluation and risk/benefit assessment is limited at time of MAA, this is not further pursued.

Genotoxicity and carcinogenicity

No studies have been performed to assess the genotoxic or carcinogenic potential of serplulimab.

Environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, serplulimab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the pharmacology, pharmacokinetic and toxicity studies provided indicate that serplulimab is a specific PD-1 inhibitor with high affinity for both human and cynomolgus monkey PD-1. Biological activity has been confirmed *in vitro*, and in tumour models *in vivo*. In general, serplulimab was tolerated in monkeys following repeated dosing for up to 31 weeks, with individual adverse findings partly considered related to ADA formation and anaphylactic reactions.

A major objection (MO) was initially raised during the evaluation procedure concerning the GLP status of the site where toxicity studies were conducted. Study specific GLP-inspections were therefore triggered. The final inspection report identified critical non-compliance in all inspected studies.

Considering the applied indication and the adequacy of the new GLP-compliant pivotal 13-week repeat-dose toxicity study (P23-S272-RD), no grounds exist for maintaining the MO. Approval may be considered acceptable from a non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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**

Serplulimab has been administered to human subjects in eight clinical cancer studies, of which two have been submitted within the current application, see table below.

Table 3. Clinical studies of serplulimab included in the MAA dossier

Study	**ASTRUM-005 (Pivotal study)**	**HLX10-001 (FIH)**
No. of centers/ locations	103 sites in 6 countries	5 sites in Taiwan
Design	Randomized, Double-Blind, Multicenter, Phase III Study	First-in-human, Phase I, prospective, open-label, dose-escalation study
Study posology	4.5 mg/kg IV, each cycle every 3 weeks (21 days)	0.3, 1, 3, 10 mg/kg biweekly, until disease progression
Study Objective	Evaluate efficacy of chemotherapy in combination with HLX10 versus placebo in ES-SCLC	Evaluate safety, max. tolerated dose, PK, PD, immunogenicity and antitumor activity
Subjects by arm	Treatment +chemotherapy arm: 389 Placebo + chemotherapy arm: 196	Dose-finding cohort: 29 Dose expansion cohort: ≤40
Duration	Sep-2019 to jun-2022	Feb-2018 to Aug 2022
Gender M/F, age	82% male. Mean age 61.1 years	Mean age 60 years
Diagnosis	Extended stage small cell lung cancer	Advanced or metastatic solid tumor cancers
Primary endpoint	Overall survival	Numbers and percentage of AEs

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Pharmacokinetic data for the current application are based on eight clinical studies (Table 4) in cancer patients with serplulimab administered over the dose range of 0.3-10 mg/kg every 2nd week (Q2W), 4.5 mg Q3W and flat doses of 200 mg Q2W, 300 mg Q3W and 400 mg Q4W. Further details on study design and cutoff dates for safety data are provided in (Table 34, in the Clinical safety section). The main PK evaluation was based on a population-based PK approach combining results from these studies. Detailed PK data are presented from two studies: The first-in-human (FIH) study HLX10-001 provided rich PK data from a broader range of weight-based and flat doses administered to patients

with various cancers, while study ASTRUM-005 supports the marketing authorisation application (MAA) of serplulimab in ES-SCLC patients with the 4.5 mg/kg Q3W dosing regimen. PK samples were sparsely collected in the pivotal study. No dedicated ADME, organ impairment or drug-drug interaction (DDI) studies were performed. No dose adjustments in special populations have been proposed by the applicant.

Table 4. Description of clinical studies included in the popPK dataset

Study ID	Dosing regimen	PK sampling	ADA sampling	Subject number	Data cutoff: PK, ADA and dosing
HLX10-001	0.3 mg/kg Q2W, 1 mg/kg Q2W, 3 mg/kg Q2W, 10 mg/kg Q2W, 200 mg Q2W, 300 mg Q3W	Cycle 1 and Cycle 3: pre-dose, at the end of infusion (with 30 minutes allowable), and at 2, 6, 24, 48, 96, and 168 hours after first infusion; pre-dose and at the end of second infusions (with 30 minutes allowable). Cycle 2, Cycle4 to Cycle 6: pre-dose and after the first infusion or up to 24 weeks (whichever came first). the 28-day follow-up visit.	Cycle 1: pre-dose before the first and second infusion. Cycle 2 to Cycle 6: pre-dose before the first infusion. the 28-day follow-up visit.	52	2021-07-05
HLX10-004-NSCLC303	4.5mg/kg Q3W	Cycle 1: pre-dose (within 7days), at the end of HLX10 infusion (within 2 hours). Cycle 8: pre-dose (within 3days), at the end of HLX10 infusion (within 2 hours). Cycle 2, Cycle 4, Cycle 6 and every 4 Cycle after Cycle 8: pre-dose (within 3days); EOT visit and safety follow-up.	Cycle 1: pre-dose (within 7days). Cycle 2, Cycle 4, Cycle 6, Cycle 8 and every 4 Cycle thereafter: pre-dose (within 3days); EOT visit and safety follow-up.	412	2021-03-30
HLX10-008-HCC201	3mg/kg Q2W	Cycle 1: pre-dose (within 7days), at the end of HLX10 infusion (within 2 hours), and at the end of HLX04 infusion (within 2 hours); Cycle 8: pre-dose (within 3days), at the end of HLX10 infusion (within 2 hours), and at the end of HLX04 infusion (within 2 hours); Cycle 2, Cycle 4, Cycle 6 and every 4 Cycle after Cycle 8: pre-dose (within 3days) ; EOT visit and safety follow-up.	Cycle 1: pre-dose (within 7days); Cycle 2, Cycle 4, Cycle 6, Cycle 8 and every 4 Cycle thereafter: pre-dose (within 3days).	123	2021-03-10
HLX10-010-MSI201	3mg/kg Q2W	Cycle 1 and Cycle 8: pre-dose (within 24 hours), at the end of HLX10 infusion (within 2 hours); Cycle 2, Cycle 4, Cycle 6 and every 4 Cycle after Cycle 8: pre-dose (within 24 hours) ; EOT visit and Day30 (±7 days) after the final dose at the time of safety follow-up.	Cycle 1, Cycle 2, Cycle 4, Cycle 6, Cycle 8 and every 4 Cycle after Cycle 8: pre-dose (within 24 hours) ; EOT visit and safety follow-up.	108	2021-07-10
HLX10-011-CC201	4.5mg/kg Q3W	Cycle 1 and Cycle 8: pre-dose (within 24 hours) before HLX10 infusion, at the end of HLX10 infusion (within 0.5 hours); Cycle 2, Cycle 4, Cycle 6 and every 4 Cycle after Cycle 8: pre-dose (within 24 hours) ; EOT visit and safety follow-up.	Cycle 1, Cycle 2, Cycle 4, Cycle 6, Cycle 8 and every 4 Cycle after Cycle 8: pre-dose (within 24 hours) before HLX10 infusion.	21	2021-02-19

HLX10HLX04-001	1 mg/kg Q2W, 3 mg/kg Q2W, 10 mg/kg Q2W	Cycle 1 and Cycle 4: pre-dose (within 30 minutes) before HLX10 infusion, at the end of HLX10 infusion (within 5 minutes), 2(±15 minutes), 8(±30 minutes), 24(±60 minutes), 48(±60 minutes), 96(±120 minutes), 168(±120 minutes), 336(±120 minutes, before Day15 infusion) hours postdose of HLX10 infusion; Cycle 2, Cycle 3 and Cycle 6: pre-dose (within 30 minutes) before HLX10 infusion, at the end of HLX10 infusion (within 5 minutes); EOT visit and Day 28 after the last infusion of HLX10 and HLX04.	Cycle 1: pre-dose (within 30 minutes) before HLX10 infusion, Day15 pre-dose (within 30 minutes) before HLX10 infusion; Cycle 3, Cycle 6 and every 3 Cycle after Cycle 6: pre-dose (within 30 minutes) before HLX10 infusion; EOT visit and Day 28 after the last infusion of HLX10 and HLX04.	26	2020-11-30
HLX10HLX07-001	3 mg/kg Q2W	Cycle 1 and Cycle 3: Day1 pre-dose (within 1 hour) before HLX10 infusion, at the end of HLX10 infusion but before HLX07 infusion (within 30 minutes after HLX10 infusion), at the end of HLX07 infusion (within 30 minutes), 2(±15 minutes), 24(±2 hours), 72(±6 hours), 168(±6 hours) post dose of HLX07 infusion, Day15 pre-dose (within 1 hour) before HLX10 infusion, at the end of HLX07 infusion (within 30 minutes); Cycle 2, Cycle 4 and Cycle 6: Day1 pre-dose (within 1 hour) before HLX10 infusion, at the end of HLX07 infusion (within 30 minutes); EOT visit and follow-up visit1 .	Cycle 1: Day1 and Day 15 pre-dose (within 1 hour) before HLX10 infusion Even Cycle(2,4,6,.etc): Day1 pre-dose (within 1 hour) before HLX10 infusion; EOT visit and follow-up visit1.	13	2021-03-31
HLX10-005-SCLC301 (ASTRUM-005)	4.5mg/kg, Q3W	Cycle 1: Day1 pre-dose (within 7 days) before HLX10 infusion, at the end of HLX10 infusion (within 2 hours); Cycle 8: Day1 pre-dose (within 3 days) before HLX10 infusion, at the end of HLX10 infusion (within 2 hours); Cycle 2, Cycle 4, Cycle 6 and every 4 cycles after Cycle 8: pre-dose (within 3 days) before HLX10 infusion; EOT visit and safety follow-up.	Cycle 1: Day1 pre-dose (within 7 days) before HLX10 infusion; Cycle 2, Cycle 4, Cycle 6, Cycle 8 and every 4 cycles thereafter: pre-dose (within 3 days) before HLX10 infusion.	389	2021-06-30

Bioanalytical methods

Bioanalytical methods used to assess PK and immunogenicity of serplulimab in the current MAA comprised ELISA, automatic chemiluminescent (ACL) and electrochemiluminescence (ECL) assays. Immunogenicity assessment of serplulimab ADAs in serum was evaluated with a 3-tier approach composed of screening, confirmation, and titre determination. ELISA and ECL were employed to detect neutralising antibodies (NAb) against serplulimab.

Cross-validation of ADA methods across studies has not been performed, with potential implications for comparability of immunogenicity results across studies.

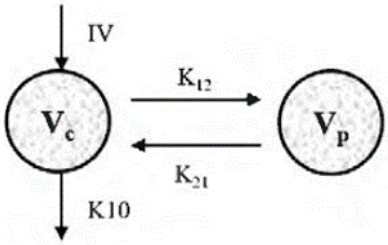
PopPK model

Plasma concentration-time data from eight clinical studies (Table 4) were analysed with nonlinear mixed-effects modelling (NONMEM vs.7.5.0, FOCE-INTER). The popPK model has been used to characterise the population pharmacokinetics of serplulimab, to evaluate the interindividual variability of PK parameters, and to evaluate the effects of demographic and physiological covariates that might affect exposure in individual patients.

Of a total of 6791 observations in 1156 subjects, 1.68% (outliers, BLQ, data errors) were excluded from the popPK analysis. The final popPK data set consisted of 6677 observations from 1144 cancer patients, including 389 (34%) ES-SCLC patients who were administered the proposed dose of 4.5 mg/kg Q3W (study ASTRUM-005). The data set contained data from 917 (80.1%) male and 227 (19.8%) female cancer patients. Mean (range) weight and age were 64.5 kg (33 to 131 kg) and 61 years (23 to 83 years), respectively. The main body of PK data origins from patients below 65 years, and 348 (30.4%) of patients were aged ≥65-<75 years, 30 (2.6%) were ≥75 years old, and no patients were 85 years or older. Age was missing for 2 (0.2%) of patients. Patients were Asians (897, 78.4%) or Whites (247, 21.6%), and most patients had ECOG status 0 (306, 26.8%) or 1 (835, 73%). A total of 817 (71.4%) patients had lung cancer (NSCLC or SCLC), and 125 (10.9%), 86 (7.5%) and 116 (10.1%) had hepatic, colorectal or other cancers, respectively. The data set included 176 (15.4%) and 2 (0.2%) patients with mild and moderate hepatic impairment, respectively, and 448 (39.2%), 102 (8.9%) and 1 (0.1%) patient(s) with mild, moderate and severe renal impairment, respectively. Hepatic and renal function status were not known for 10 (0.9%) and 2 (0.1%) of patients, respectively.

The structural model is based on an empirical two-compartment model with time-varying clearance (Hill function), see Figure 1. Body weight was added as a predefined covariate on CL and VC in the final base model. Univariate analysis of potential covariates (i.e. age, body weight, body surface area, BMI, sex, race, albumin, total bilirubin, ALT, AST, ALP, LDH, creatinine, creatinine clearance (CRCL), tumour burden, tumour type, ECOG, ADA, combination chemotherapeutic drugs, combination antitumor treatment) on the PK of serplulimab were initially performed. Statistically significant covariates were then further investigated by stepwise forward selection and backward deletion. In the final model, statistically significant covariates were BW on CL and Vc, albumin on CL, gender on Vc and tumour type (lung vs non-lung cancer) on Vc. The final parameters estimates are listed in Table 5.

Figure 1. Final popPK model for serplulimab



IV = Intravenous;
$K_{10} = CL/V_c$;
$K_{12} = Q/V_c$;
$K_{21} = Q/V_p$;

$$\frac{dA_1}{dt} = K_{21} \times A_2 - (K_{10} + K_{12}) \times A_1 + IV$$

$$\frac{dA_2}{dt} = K_{12} \times A_1 - K_{21} \times A_2$$

CL = Clearance;
Q = Inter-compartmental clearance;
V_c = Central volume;
V_p = Peripheral compartment volume;
A_1 = Central dose;
A_2 = Peripheral compartment dose;

$$CL = CL_0 * exp\left(\frac{Tmax*(\frac{time}{Tc50})^{\lambda}}{1+(\frac{time}{Tc50})^{\lambda}}\right),$$

$$CL_i(L/day) = 0.225 \times \exp(T_{maxi} \times \frac{TIME^{2.05}}{TIME^{2.05}+106^{2.05}} + 0.531 \times ln\left(\frac{WT}{65}\right) - 0.783 \times ln\left(\frac{ALB}{41.3}\right) + \eta_{CL,i})$$

$$Vc_i(\mathrm{L}) = 3.52 \times \exp(0.450 \times ln\left(\frac{WT}{65}\right) - 0.0887 \times TUMTP - 0.121 \times \mathrm{SEX} + \eta_{Vc,i})$$

$$Tmax_i = -0.364 + \eta_{Tmax,i}$$

Table 5. Comparison of final popPK model of serplulimab estimates and Bootstrap results

Parameter	Parameter Description	Final model estimate (95% CI)	Bootstrap estimate median (2.5-97.5%tiles)
$exp(\theta_1)$	Clearance at baseline, CL_0 (L/day)	0.225 (0.213; 0.238)	0.224 (0.209; 0.24)
$exp(\theta_2)$	central volume, V_c (L)	3.52 (3.46; 3.58)	3.52 (3.46; 3.58)
$exp(\theta_3)$	Inter-compartmental clearance, Q (L/day)	0.463 (0.412; 0.52)	0.463 (0.38; 0.568)
$exp(\theta_4)$	Peripheral volume, V_p (L)	2.21 (1.91; 2.55)	2.22 (1.92; 2.58)
$exp(\theta_5)$	maximum magnitude change in CL, $exp(T_{max})$	0.695 (0.636; 0.759)	0.698 (0.63; 0.779)
θ_6	Time when clearance change equals 50%, TC_{50} (day)	106 (83.2; 129)	108 (82.8; 139)
θ_7	Sigmoid factor of time-varying CL, λ	2.05 (1.48; 2.62)	2.07 (1.55; 3.14)
θ_8	Influence of body weight on CL	0.531 (0.403; 0.658)	0.533 (0.452; 0.619)
θ_9	Influence of body weight on V_c	0.450 (0.385; 0.514)	0.452 (0.383; 0.516)
θ_{10}	Influence of albumin on CL	-0.783 (-0.893; -0.674)	-0.782 (-0.943; -0.626)
θ_{11}	Influence of sex on V_c	-0.121 (-0.152; -0.0891)	-0.119 (-0.15; -0.0866)
θ_{12}	Influence of tumor type on V_c	-0.0887 (-0.116; -0.0617)	-0.0881 (-0.116; -0.0604)
$\omega CL, V_c$	Covariance (CL,V_c)	0.017 (0.0128; 0.0212)	0.0169 (0.0131; 0.0213)
$IIVCL$	Inter-Individual Variability of CL (%)	25.8 (23.5; 27.9)	25.7 (23.6; 27.9)
$IIVV_c$	Inter-Individual Variability of V_c (%)	15.4 (13.7; 17.0)	15.4 (13.7; 17.1)
$IIVQ$	Inter-Individual Variability of Q (%)	49.7 (17; 68.1)	50.0 (20.4; 66.4)
$IIVV_p$	Inter-Individual Variability of V_p (%)	51.5 (41.7; 59.7)	50.9 (41.1; 61.9)
$IIVT_{max}$	Inter-Individual Variability of T_{max} (%)	26.3 (21.1; 30.6)	26.3 (21.5; 32.2)
σ	Residual (%)	16.6 (15.7; 17.4)	16.5 (15.5; 17.5)

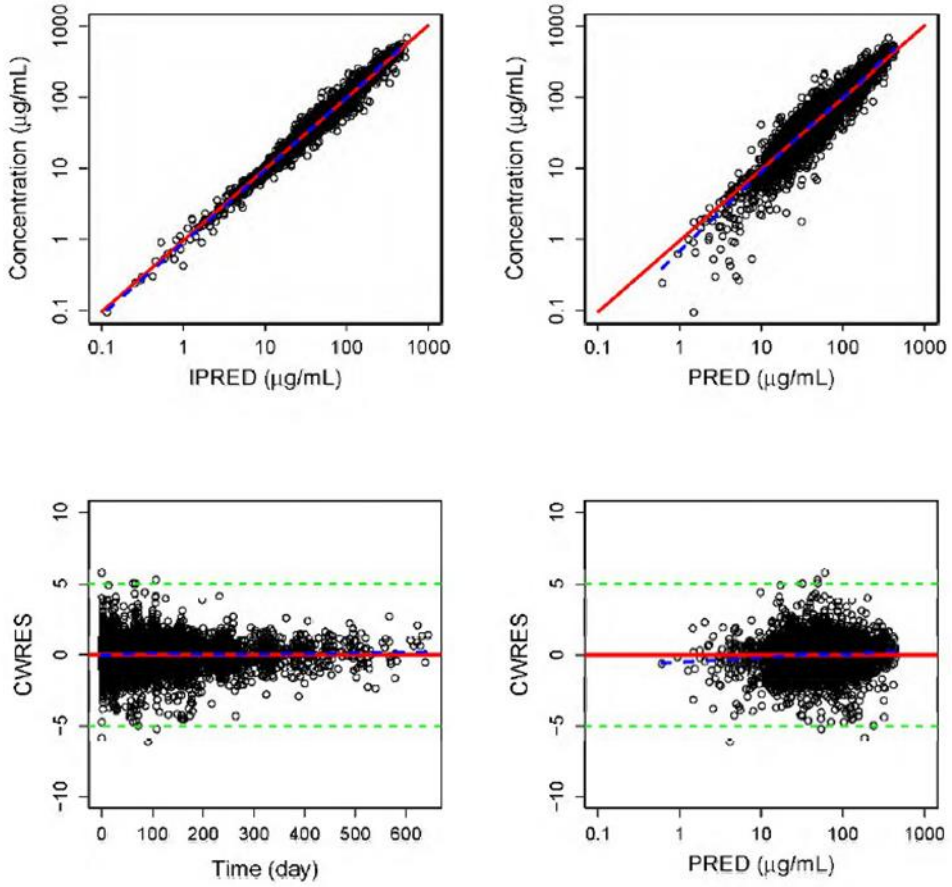
Bootstrap convergence rate was 78.7% (787/1000 runs).

Interindividual variability (IIV) for structural parameters CL, Vc, Q, Vp and Tmax in the *base* model and *final base* model were 29.4%, 20.6%, 56.6%, 49.7% and 27.3%, respectively, and 27.5%, 17.2%, 59.1%, 50.9% and 26.6%, respectively.

Shrinkage was assessed for each interindividual random effect (η) and residual random error (ε) term in the final model. Eta (η) shrinkage for CL, Vc, Q, Vp and $Tmax_{Hill\ function}$ were 13.7%, 27.7%, 72.2%, 45.2% and 46.5%, respectively. Epsilon (ε) shrinkage was 17.4%.

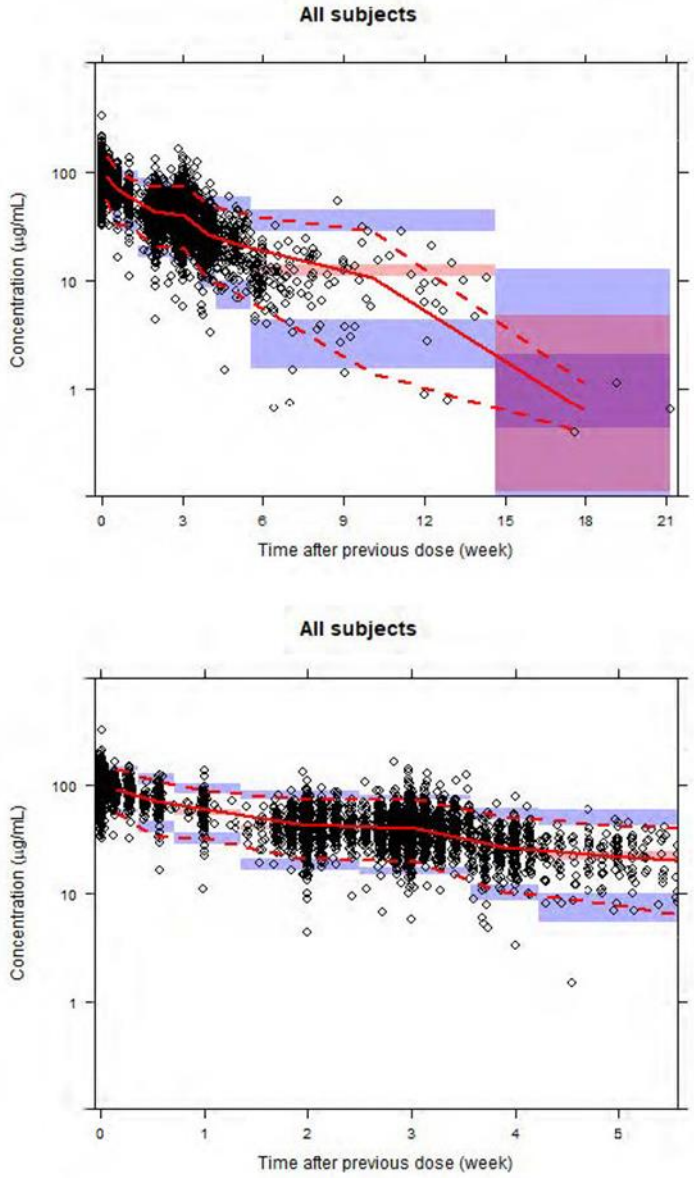
Selected goodness-of fit plots for the final serplulimab popPK model are presented in Figure 2, Figure 3 and Figure 4.

Figure 2. Diagnostic plot for the final popPK model of serplulimab



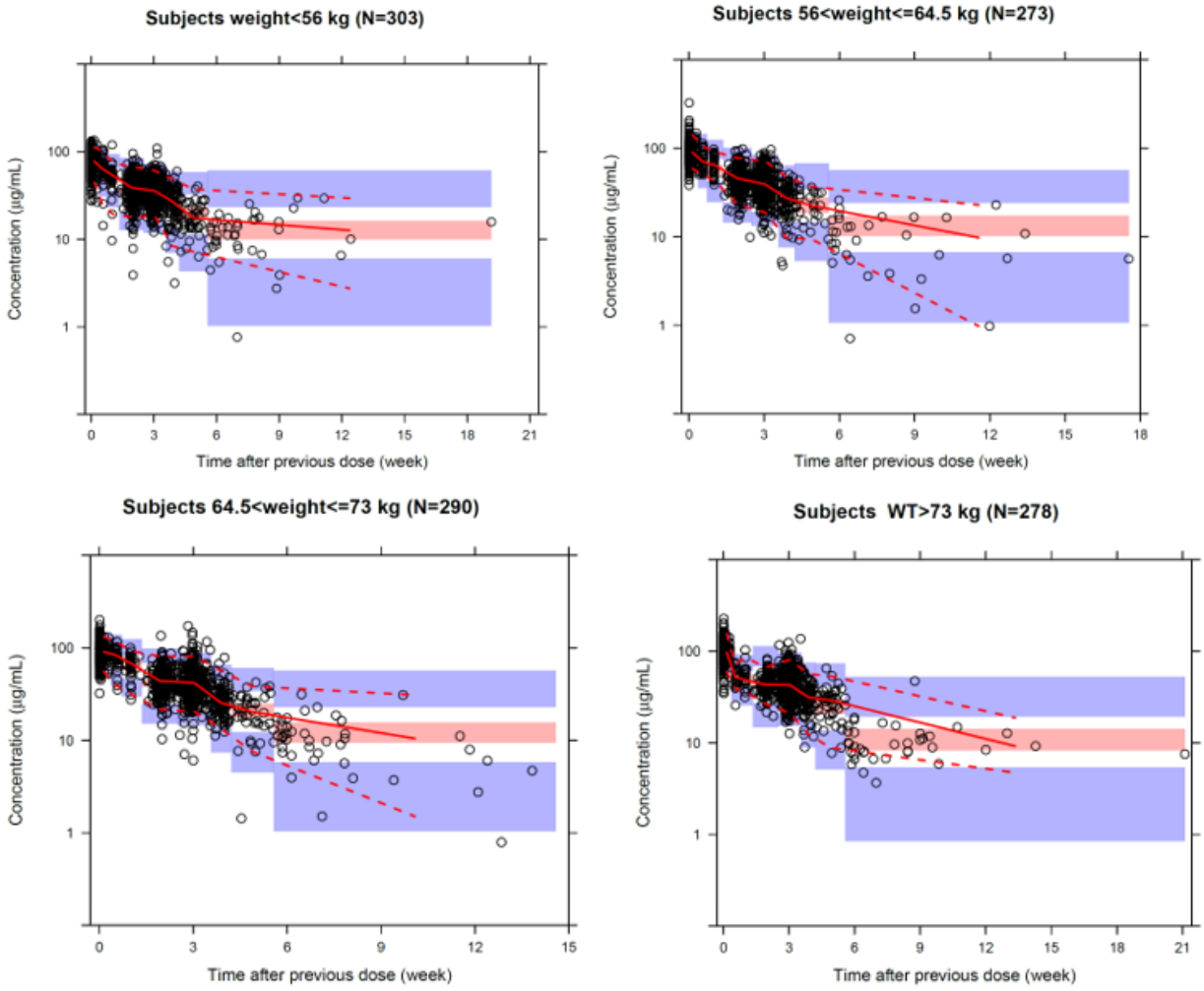
Observed versus individual predicted concentrations (upper left) and observed versus population predicted concentrations (upper right) for the final PopPK model. Points are individual data. The black and red lines represent the unit diagonal and linear regression, respectively. Conditional weighted residuals (CWRES) versus time (lower left) and PRED (lower right). Black solid lines and red dashed lines represent the unit line at zero and loess fit line, respectively. Blue dashed lines represent |CWRES| of 5.

Figure 3. Prediction-corrected visual predictive check (pc-VPC) of serplulimab concentration-time profiles



Points are observed prediction corrected concentrations, the solid red line represents the median observed value, and dashed red lines represent the 2.5th and 97.5th percentiles of the observed values. Pink shaded area represents the spread of the median predicted values (2.5th and 97.5th percentiles), and purple shaded areas represent the spread (2.5th and 97.5th percentiles) of the 2.5th and 97.5th predicted percentile concentrations. Top: the longest time after previous dose is 21 weeks. Bottom: the longest time after previous dose is 5 weeks.

Figure 4. Prediction-corrected visual predictive check (pc-VPC) stratified by body weight (with individual observations)



Note: Points are observed prediction corrected concentrations, the solid red line represents the median observed value, and dashed red lines represent the 2.5th and 97.5th percentiles of the observed values. Pink shaded area represents the spread of the median predicted values (2.5th and 97.5th percentiles), and purple shaded areas represent the spread (2.5th and 97.5th percentiles) of the 2.5th and 97.5th predicted percentile concentrations.

Absorption

Not applicable. Serplulimab is administered via IV infusion.

Distribution

The estimated volume of distribution of serplulimab in PopPK analysis for the typical subject is approximately 5.73 L, with a Vc of 3.52 L and Vp of 2.21 L.

Elimination

As a protein product, serplulimab is expected to be catabolised into amino acids by general protein degradation process and is not expected to be eliminated by renal or biliary excretion. Metabolism does not contribute to its clearance.

Based on a popPK analysis, serplulimab clearance (CL) after the first dose is 0.225 L/day in a typical subject (male lung cancer patient with body weight of 65 kg and albumin of 41.3 g/L). The clearance

decreases over time by a maximum of 30.5% (CV 26.3%) with 106 days to reach half of the maximum effect. The half-life at steady state is approximately 24.3 days.

Dose proportionality and time dependencies

The analysis of dose proportionality was based on rich pharmacokinetic data collected at C1D1 and C3D1 in the ongoing phase 1, first-in-human, dose escalation and dose expansion study HLX10-001. As of the cut-off date (1 Aug 2022), a total of 57 subjects received serplulimab and provided PK data. In the dose-escalation part, 4 dose groups (0.3, 1, 3, and 10 mg/kg Q2W [4 weeks treatment cycle]) were enrolled and treated with serplulimab. In the dose-expansion part, flat-dose groups (200 mg Q2W [4 weeks treatment cycle], 300 mg Q3W [6 weeks treatment cycle], and 400 mg Q4W [4 weeks treatment cycle] was evaluated.

Dose proportionality of serplulimab serum exposure was evaluated following a single dose and following multiple doses using a power function regression, and results for the dose-escalation cohorts are shown in Table 6. According to the applicant, serplulimab exhibited linear PK in a dose range of 0.3 mg/kg to 10 mg/kg both after single dose and approximate linear PK after multiple doses.

Table 6. Statistical assessment of dose proportionality for serplulimab (power model)

Period	Dose Range	Parameter (Unit)	N/Nx*	Slope Estimate (SE)	90% CI of Slope	P-value[1]
Single dose (Cycle 1 first infusion)	13.26 mg - 1146 mg	Cmax (ug/mL)	57/58	1.03 (0.05)	(0.94, 1.11)	<0.0001
		AUC0-∞ (h*ug/mL)	57/56	1.13 (0.05)	(1.04, 1.22)	<0.0001
Steady state (Cycle 3 first infusion)	13.26 mg - 1146 mg	Cmax,ss (ug/mL)	57/35	1.04 (0.05)	(0.95, 1.12)	<0.0001
		AUC0-∞,ss (h*ug/mL)	57/35	1.18 (0.15)	(0.92, 1.43)	<0.0001

Note:
Assessment based on the power model (linear regression of natural log transformed parameter and dose). N: number of subjects; Nx: number of reliable PK parameters included in this analysis. SE: standard error.
[1] The P-value is used to test the relationship between PK exposure parameters and dose. The H0 hypothesis is that there is no correlation between the two ($\beta1=0$), and the H1 hypothesis is that there is correlation between the two ($\beta1\neq0$). The P-value in the results is much less than 0.05, indicating that the H0 hypothesis should be rejected and the H1 hypothesis should be accepted, that is, the PK parameter is correlated with dose.
[2] Dose proportionality will be concluded as linear in specified dose range if Slope Estimate is near 1 and its 90% CI include 1.

Time-dependent clearance was observed and described by popPK model analysis (see 'Elimination').

Across the dose escalation and expansion cohorts, the mean accumulation ratio for Cmax ranged from 1.262 to 1.793, and the mean accumulation ratio for AUCss ranged from 1.403 to 2.158 (Cycle 3/Cycle 1). In study ASTRUM-005, the accumulation ratios (Cycle 8/Cycle 1) for Cmax and Ctrough were 1.850 and 3.056, respectively.

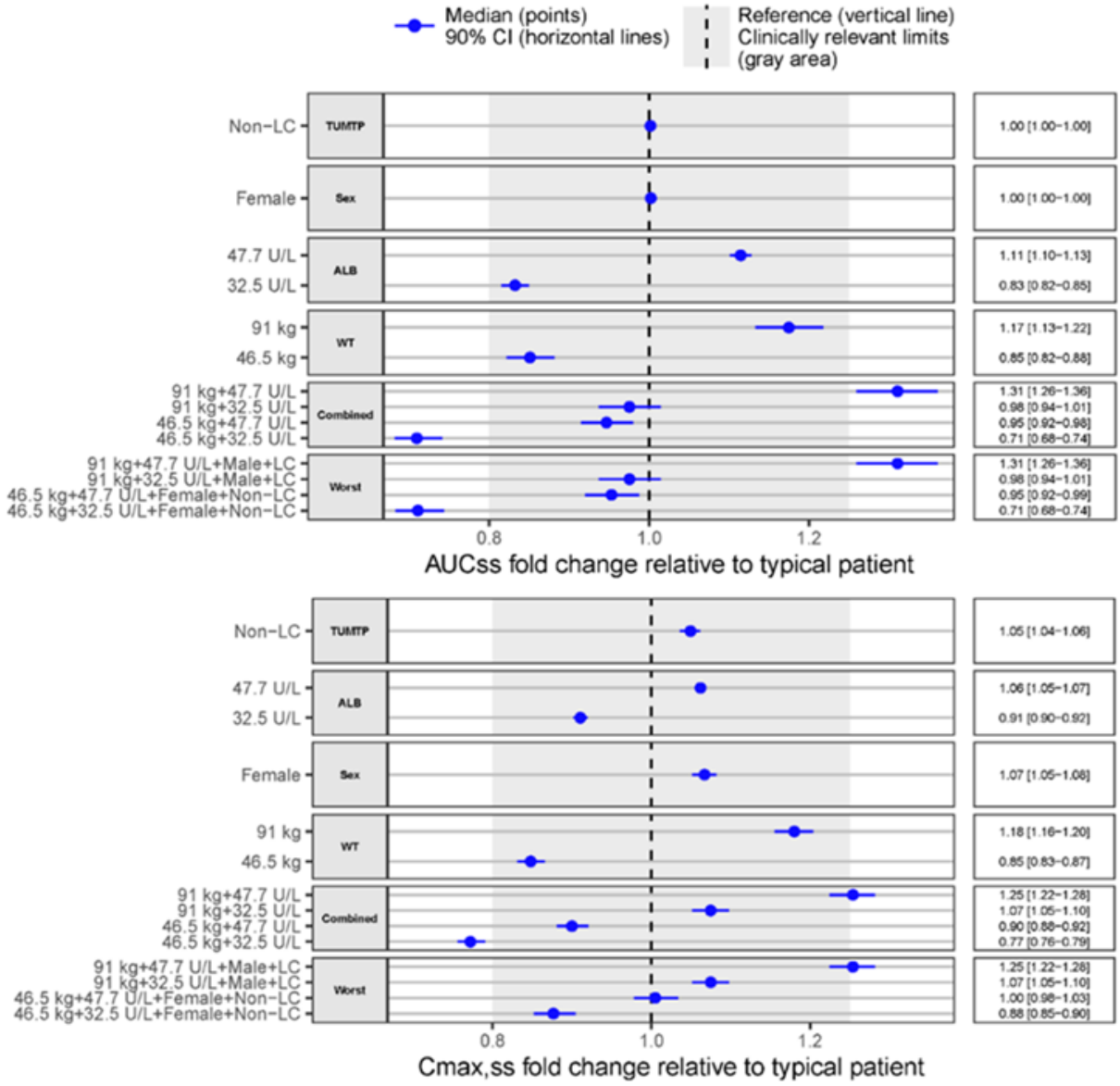
Intra- and inter-individual variability

Based on popPK final model, the interindividual variability of CL, Vc, Q, Vp, and Tmax were 25.8%, 15.4%, 49.7%, 51.5%, and 26.3%, respectively.

Special populations

Dedicated clinical studies to investigate the PK in special populations have not been performed. Intrinsic factors were investigated as covariates in the popPK analysis. The predicted impact of significant covariates (tumour type, sex, albumin and body weight) on steady state PK exposure compared to the reference patient (male, lung cancer patient with body weight of 65 kg and albumin of 41.3 g/L) following 4.5 mg/kg Q3W dosing is shown in Figure 5.

Figure 5. Model-predicted impact of covariates (single and combined) on steady state AUC and Cmax



The impact of renal (mild and moderate) and hepatic (mild) impairment on serplulimab exposure was evaluated by simulations using the Bayesian post-hoc PK parameters following administration of 4.5 mg/kg Q3W. The effects of these factors on Cavg,ss, Cmax,ss, and Cmin,ss were <±15% and were by the applicant considered small and not clinically significant.

No dose adjustments in special populations have been proposed. The sought indication is only relevant in adults, and no paediatric PK data are available.

Table 7. PK studies in elderly patients

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	351 (30.5%)	31 (2.7%)	0

Pharmacokinetic interaction studies

No pharmacokinetic drug-drug interactions studies have been conducted with serplulimab. Serplulimab is not expected to be a victim or perpetrator of pharmacokinetic DDIs.

2.6.2.2. Pharmacodynamics

Mechanism of action

Serplulimab is a recombinant humanised IgG4 monoclonal antibody targeted against human PD-1. Anti-PD-1 monoclonal antibody blocks PD-1/PD-L1 negative immune checkpoints, which causes T-cell activation and proliferation, reverses the tumour immunosuppressive microenvironment, and enhances antitumor immune response. Nonclinical data have confirmed that serplulimab binds to PD-1 on activated human T cells in vitro in a concentration-dependent manner and blocks the interaction of cell surface PD-1 to both natural ligands PD-L1 and PD-L2, with 50% receptor occupancy achieved at 0.47 ± 0.48 μg/mL. Additionally, serplulimab induces IL-2 release and T cell proliferation in a concentration dependent manner in human CD4+ T cell/DC mixed lymphocyte reaction assay.

Primary and secondary pharmacology

Primary pharmacology

The clinical pharmacodynamic properties of serplulimab have been investigated in the Phase I study in Asian patients with advanced or metastatic tumours refractory to standard therapy (study HLX10-001) and in the ongoing phase III efficacy study comprising previously untreated Asian and non-Asian patients with ES-SCLC (study ASTRUM-005).

PD parameters in study HLX10-001 included PD-1 receptor occupancy, IL-2 release, and the exploratory biomarkers PD-L1, DNA mismatch repair (MMR) proteins, Microsatellite instability (MSI) and Total mutation burden (TMB, optional). The results are described below.

An almost full PD-1 receptor occupancy was achieved at Cycle 1 Day 1 24 hours post-dose in all dose cohorts, with mean values ranging from 98.13% to 102.4%, and high receptor occupancy throughout the study for all dose cohorts.

Results from the ex vivo IL-2 release measurements were presented as IL-2 stimulation ratio as a surrogate for target engagement. For all dose cohorts, the stimulation ratio decreased from values around 2 pre-dose to values around 1 from 24 hours after the first dose and throughout the study, suggesting high level of target activity.

None of the exploratory biomarkers, including tumour expression of PD-L1, was associated with tumour burden changes following treatment.

PD parameters in ASTRUM-005 were the primary biomarkers PD-L1 expression, MSI and TMB. Other markers were also analysed to determine potential SCLC subtypes and immune parameters which are potential serplulimab response biomarkers. Furthermore, blood samples were analysed for a number of

potential novel protein markers (LIF, IL6, IL8, MIA, GDF-15, PD-L1, MET, EGFR, BCL2, TP53, STK11, CXCL12, MMP9, and SLIT2) by the Olink Explore 3072 Platform.

Higher baseline soluble PD-L1 levels correlated with worse patient outcomes in both HLX10 and placebo treatment groups (data not shown). In both treatment groups, patients with PD-L1 NPX≤0.4 tended to have longer OS than patients with PD-L1 NPX>0.4. The p-value for the treatment-by-biomarker interaction term was not significant (p=0.381), indicating that soluble PD-L1 was prognostic biomarker rather than predictive biomarkers for ES-SCLC.

Baseline tumour PD-L1 expression level and MSI status are not considered predictive biomarkers for effect of HLX10 treatment on SCLC.

Exposure-efficacy analyses

The exposure-response analyses for efficacy included data from 389 ES-SCLC patients who received a dose of 4.5 mg/kg Q3W in the ASTRUM-005 study. The Kaplan-Meier curves stratified by quartiles of exposures (Cavg1 and Cmin1) indicated a slightly shorter OS in the lowest exposure quartile. There was no relationship between exposure and OS in a Cox proportional hazards model when significant predictors for OS were included as covariates (albumin, aspartate aminotransferase, total bilirubin, tumour burden, and lactate dehydrogenase) (data not shown).

Exposure-safety analyses

The exposure-response analyses for safety included data from 1144 cancer patients from eight clinical studies (Table 4). There was no apparent trend between serplulimab exposure (Cavg1 and Cmax1) and the probability of grade ≥3 TEAE, serplulimab related grade ≥3 ADR, serious AE, immune-related AE, or AE of special interest.

A retrospective concentration-QTc analysis based on 265 matched PK and ECG measurements from study HLX10-001 was conducted. The model-predicted effect on QTc at serplulimab concentrations achieved following a dose of 4.5 mg/kg Q3W did not meet the threshold of regulatory concern (data not shown).

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical methods

All bioanalytical methods were validated according to EMEA/EWP/1922117/2009, Rev.1 and cover selectivity, specificity, MRD, LLOQ, accuracy, precision, stability, linearity and where applicable cut points, Hook effect and drug tolerance. The presented bioanalytical method approach is considered overall acceptable, though issues related to PK and ADA method cross-validation were identified.

Several test facilities were involved in the different studies and the PK data were obtained from different methods across the studies. Nevertheless, cross-validation data was not included in the original submission. Upon request by the CHMP, the applicant conducted cross-validation studies for the PK methods BTM 2516, 19BASM016 and SHBTM-1749 compared with the method AP-HLX10PK01 and later has provided study reports for the cross-validation. Regarding cross-validation between the four listed ADA methods employed in the eight clinical studies, the applicant argues that due to method differences, cross-validation is not possible. Thus, uncertainty remains regarding the comparability of ADA results across studies.

PopPK

In the final model Vc and CL increased with increasing body weight, CL decreased with increasing albumin levels, and females and non-lung cancer patients were shown to have a lower Vc compared to males and lung cancer patients, respectively. Addition of covariates to the popPK model explained ≤25% of the observed variability in structural parameters, and BW appeared to be the largest driver of this variability. Estimated variability in serplulimab CL and Vc was low to moderate (<26%) in the final model. The model captures the observed drug exposure in plasma well in the overall population.

The regulatory impact of the model was low as it was mainly used to describe serplulimab PK in cancer patients and to inform the SmPC. However, the popPK report was not very detailed for secondary assessment. The applicant provided, as requested, the data analysis plan (DAP). Of note, the strategy for the base model development, including the use of body weight as structural parameter, and the investigation of covariates were poorly described in the DAP. Thus, it may seem that the development of the base and covariate models was largely based on subjective considerations which reduces credibility of the modelling exercise. These issues were not further pursued considering the use of the model, as well as general knowledge of the PK of therapeutic drug proteins and the model's ability to describe the observed serplulimab PK. The popPK model should not be used for extrapolation purposes.

The statistical significance of all PK parameters was confirmed based on the 95% confidence interval from the bootstrap analysis. In general, model predictions described the observations well for the first 3-4 weeks. Since the drug is administered every three weeks, the predictions were considered adequate. The applicant presented additional pcVPCs plots stratified by covariates, which showed that the model can be used to evaluate the impact of these covariates (in the ranges for which predictive abilities are shown) on serplulimab PK.

ADME

Serplulimab pharmacokinetics are similar to other mAbs, with an estimated volume of distribution of 5.73 L and a steady-state half-life of approximately 24 days. Like other therapeutic proteins, serplulimab is expected to be cleared through receptor mediated endocytosis or non-specific endocytosis followed by proteolytic degradation. Also, target mediated drug elimination is expected to contribute to the total clearance. The baseline clearance is 0.225 L/day based on the popPK analysis, and it decreases over time. The lowest clearance is 0.695 times of the baseline (i.e. 0.156 L/day). Interindividual variability was mostly low to moderate for CL and Vc (25.8% and 15.4%, respectively) in the final popPK model.

An unexpectedly broad range of observed Tmax values up to 407 hours were reported in study HLX10-001. Based on comparison of exposures within each cohort, these abnormalities are not considered to affect the evaluation of Cmax, but the data nevertheless raises a general concern about the reliability of PK data from this study. Furthermore, the GCP inspection of the pivotal study ASTRUM-005 revealed several events of unexpected PK results. No valid explanation for the PK discrepancies was identified at the individual site(s) or at the central laboratory for PK analyses. Overall, the odd PK results without valid explanations observed both in the phase 1 study (main study used to support PK characterisation of serplulimab) and the phase 3 study (pivotal efficacy and safety study) indicate that one or possibly more of the procedures established for the sampling of PK-data (whether it be during collection, preparation, shipment or analysis) must be insufficient. The credibility of the PK data provided is consequently reduced, and the applicant should carefully consider the PK procedures in ongoing and future studies to reduce the occurrence of obvious errors in the PK analyses. Still, based on the overall evaluation of the non-compartmental analysis and popPK analysis of the available data, the PK of serplulimab is considered adequately characterised.

Dose proportionality/Time dependency

Serplulimab exposure exhibits dose linearity across the investigated dose levels of 13.26-1146 mg (0.3 mg/kg-10 mg/kg Q2W and 200 mg Q2W, 300 mg Q3W and 400 mg Q4W) following single and multiple doses. An accumulation ratio of ~2-3 was indicated by data from studies HLX10-001 and ASTRUM-005. Serplulimab clearance decreases during the course of treatment. For the 0.3 mg/kg - 10.0 mg/kg Q2W dose finding cohort and the 300 mg Q3W cohort, serplulimab trough concentrations suggest that steady state was achieved by the fifth infusion (Cycle 3, Day 15). Model predictions and observed Ctrough data for up to 48 treatment cycles in study ASTRUM-005 indicate that steady-state is achieved following approximately 24 weeks.

Target population

Sparse sampling was performed in the target population included in the pivotal study and ES-SCLC was not formally investigated as a covariate in the popPK analysis. To substantiate that the PK parameters estimated with the popPK model are representative for the target population, additional pcVPC plots have been provided demonstrating that the popPK model is able to capture the PK observed in the ES-SCLC patients reasonably well. Also, the overall distribution of post-hoc estimated PK parameters and single- and multiple- dose exposure metrics (AUC, Cmax) appear similar in the target population and in the pooled overall population. However, due to shrinkage, these values need to be interpreted with caution. Nevertheless, the totality of data indicates similar PK in the target and the pooled overall population.

Special populations

Instead of dedicated clinical studies, PK in special populations have been investigated by popPK modelling which is supported. The predicted impact of albumin, tumour type and sex on serplulimab exposure is limited and does not warrant dose adjustment.

Baseline hepatic function-related covariates (AST, ALT, and BIL) and CRCL (Cockcroft Gault) as measure of renal function were not found to be statistically significant covariates on serplulimab CL. Model-derived single dose and steady state individual PK parameters (CL) and exposures (AUC, Cmax, Cmin) in patients with normal renal/hepatic function and in patients with different categories of renal/hepatic impairment did not indicate major differences in PK, however body weight imbalances across the organ function groups might have influenced the comparison. Nevertheless, considering the general elimination routes of mAbs, no impact of mild to moderate renal impairment (CRCL ≥30 mL/min) and mild hepatic impairment (BIL ≤ ULN and AST > ULN or BIL > 1 to 1.5 × ULN and any AST) on serplulimab PK is expected, and no dose adjustment is needed. There is insufficient data in patients with moderate hepatic impairment (BIL > 1.5 to 3 × ULN and any AST) and severe renal impairment (CRCL <30 mL/min) for dosing recommendations. Serplulimab has not been studied in patients with severe hepatic impairment (BIL > 3 × ULN and any AST).

In the popPK data set, 78.4% of patients were Asians, while 21.6% were White (data not shown). Race did not show a statistically significant impact on the pharmacokinetics of serplulimab in the popPK analysis. Overall, there is no clear indication for an effect of race on the pharmacokinetics.

The effect of body weight on serplulimab PK is of special interest considering the weight-based dose. The predictive ability of the model across body weights appears adequate (Figure 4), and the model can thus be used for simulations to support the rationale for a weight-based dose. Simulations indicate that the variability in exposure across weight quartiles is similar for the weight-based dose (4.5 mg Q3W) and the flat dose (300 mg Q3W). For the weight-based dose, exposure increase with increasing body weight, while with a flat dose, exposure will decrease with increasing body weight. A flat dose offers several advantages over a weight-based dose. However, the pivotal study was conducted with the weight-based dose, and only very limited clinical data is available from the flat dose. Further, dose-

exposure-response relationships have not been appropriately characterised and the therapeutic range for serplulimab is not known. Still, the predicted magnitude of impact of body weight on serplulimab exposure indicate that a flat dose could be considered pursued in the future, if adequately justified.

Age (23-83 years) did not show a statistically significant impact on the pharmacokinetics of serplulimab in the popPK analysis. No special precautions or dose adjustments are warranted in the elderly (≥65 years) from a pharmacokinetic perspective. Please also see the section 'Discussion on Clinical Safety'. There is no relevant use of serplulimab in the paediatric population in the indication of small cell lung cancer (SCLC).

The impact of ADAs on serplulimab is further discussed in the Clinical safety section.

Drug-drug interactions

Serplulimab is not expected to be a victim or perpetrator of pharmacokinetic DDIs. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition, or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of serplulimab.

Pharmacodynamics

Primary pharmacology

PD parameters in study HLX10-001 included PD-1 receptor occupancy, IL-2 release, and the exploratory biomarkers PD-L1, DNA mismatch repair (MMR) proteins, Microsatellite instability (MSI) and Total mutation burden (TMB, optional). None of the exploratory biomarkers, including tumour expression of PD-L1, was associated with tumour burden changes following treatment. In the study report it is further noted that some of the samples analysed for receptor occupancy failed for different reasons, being due to failure in baseline data and incubator error leading to missing RO data for a total of three subjects. In addition, shortage of antibodies for analysis resulted in lack of single pre-dose data points for seven subjects. These failures are considered of low impact on the final results. The result showed that serplulimab could stably maintain the saturation state of receptor occupation and sustained functional blockage at the dosage from 0.3 mg/kg to 10 mg/kg every 2 weeks interval.

PD parameters in study ASTRUM-005 were the primary biomarkers PD-L1 expression, MSI and TMB. Baseline tumour PD-L1 expression level and MSI status are not considered predictive biomarkers for effect of serplulimab treatment on SCLC. While PD-L1 expression in tumour tissue does not necessarily correlate with circulating PD-L1 levels (Oh et al, 2021), soluble PD-L1 (sPD-L1) is suggested as a potential predictive and prognostic biomarker in advanced cancer patients who receive immune checkpoint blockade treatment. Pooled data from selected studies showed that a high circulating concentration of sPD-L1 in cancer patients correlates with worse survival, suggesting that it may be a helpful prognostic biomarker for the selection of cancer patients before immunotherapy (Scirocchio et al, 2022).

The applicant has provided an updated biomarker analysis based on sPD-L1 proteomics and OS data in a subgroup of the ITT population in study ASTRUM-005. The results do indicate that sPD-L1 is a prognostic biomarker, with longer OS in patients with PD-L1 NPX≤0.4 than PD-L1 NPX>0.4. The data further indicate that soluble PD-L1 is not to be considered as predictive biomarker for effect of treatment.

Pharmacodynamic interactions

The use of systemic corticosteroids or immunosuppressants before starting serplulimab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy.

However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting serplulimab (see safety section).

Secondary pharmacology

No thorough QT study (TQT) is required for monoclonal antibodies given the generally low likelihood of direct ion channel interactions. However, patients in the serplulimab group in study ASTRUM-005 had larger increases in their QTcF interval than patients in the placebo arm (see Safety section). The requested concentration-QTc analysis based on phase 1 data has some limitations which prevents a firm conclusion regarding the potential of serplulimab to prolong the QTc interval. However, there is no known mechanistic rationale for an effect of serplulimab on QTc and no signals from these investigations that raise concern of a concentration dependent effect.

Dose-exposure-response relationships

The E-R analyses could suggest that efficacy and safety is similar across the range of exposure achieved following a 4.5 mg Q3W dose but must be interpreted with caution due to the narrow exposure range studied, and the well-known confounding effects of baseline prognostic factors and response on the E-R relationships for mAbs.

As a proper dose-finding study as advised by the CHMP has not been conducted, the D-E-R relationships for serplulimab in terms of efficacy and safety is to a large extent uncharacterised, and it is not known whether the most optimal dose has been chosen. As the benefit-risk evaluation for the proposed serplulimab dose regimen of 4.5 mg/kg Q3W is supported by pivotal efficacy and safety data from the ASTRUM-005 study (refer to section 5), the issue is not pursued. In conclusion, the recommended dose as indicated in section 4.2 of the SmPC is 4.5 mg/kg serplulimab every 3 weeks until disease progression or unacceptable toxicity.

2.6.4. Conclusions on clinical pharmacology

Characterisation of clinical pharmacology of serplulimab is based on data from eight studies, including a dose escalation study and the pivotal study ASTRUM-005. The pharmacokinetics of serplulimab are comparable to other therapeutic IgG4 antibodies. Overall, the information provided can be considered satisfactory and is adequately reflected in the SmPC.

Clinical PD data indicate almost full PD-1 receptor occupancy at all dose cohorts. None of the exploratory biomarkers, including PD-L1 expression in tumour tissue and soluble PD-L1, were considered predictive biomarkers for effect of serplulimab treatment.

The dose-exposure-response relationship for serplulimab is not well characterised. The exposure-response analyses suggest that efficacy and safety is similar across the range of exposure achieved following a 4.5 mg/kg Q3W dose.

2.6.5. Clinical efficacy

Two clinical studies have been submitted in support of the current application, including one pivotal trial (ASTRUM-005) and one dose escalation study (HLX10-001), see Table 3.

The intended indication for serplulimab in combination with carboplatin and etoposide is the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

2.6.5.1. Dose response studies

The HLX10-001 is a prospective, open-label FIH study of serplulimab in patients with advanced or metastatic tumours refractory to standard therapy, with different histological types and anatomical locations. Two cohorts were included: a dose-finding cohort and a dose expansion cohort. In total 57 subjects received serplulimab as of cut-off date Aug-2022. The distribution of patients in the different dose cohorts and efficacy results are shown in the table below.

Table 8. Distribution of treatment with serplulimab in HLX10-001 (at least 1 dose)

Dose	N	Efficacy results
0.3 mg/kg Q2W	3	DCR 66.7%, mPFS 51.0
1 mg/kg Q2W	4	DCR 50.0%, mPFS 81.5
3 mg/kg Q2W	6	DCR 50.0%, mPFS 114.5, ORR 16.7%
10 mg/kg Q2W	16	DCR 56.3%, mPFS 61.0
200 mg flat Q2W	9	mPFS 57.0
300 mg flat Q3W	9	DCR 77.8%, mPFS 332.5, ORR 22.2%
400 mg flat Q4W	10	DCR 55.6%, mFPS 92.0, ORR 44.4%

Q2W: Once every 2 weeks, DCR: Disease control rate, mPFS: median Progression-free survival in days, ORR: Objective response rate.

As of the cut-off date, all subject in dose escalating cohort and 93% of dose expansion cohort experienced at least one treatment-emergent adverse events. Only 1 (3.7%) subject (3 mg/kg cohort) experienced dose-limiting toxicity (DLT) during the first cycle, which met DLT criteria 3. The maximum tolerated dose was not determined.

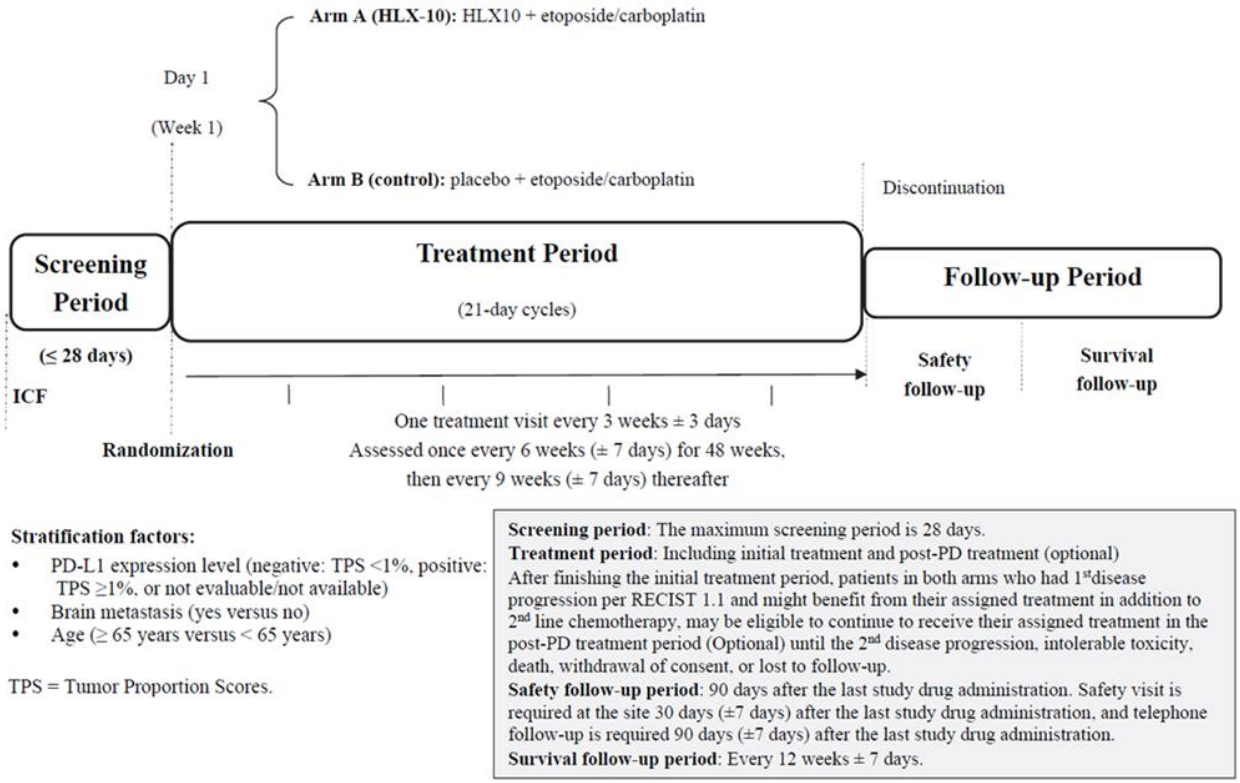
The overall percentage of patients with at least one positive ADA, as reported in the original submission, was 3.4% in the dose-finding cohorts and 67.9% in the dose-expansion cohorts. After an update to the ADA assay cut-points, and inclusion of ADA data from the 600mg Q6W expansion cohort, the ADA levels were adjusted in the dose-expansion cohort, to 32.4% (12/37 patients).

2.6.5.2. Main study(ies)

ASTRUM-005 study (HLX10-005-SCLC301): A Randomised, Double-blind, Placebo Controlled Phase III Study to Investigate Efficacy and Safety of serplulimab + Chemotherapy (Carboplatin- Etoposide) in Patients With Extensive Stage Small Cell Lung Cancer (ES-SCLC) (NCT04063163).

ASTRUM-005 is a randomised, double-blind, multicentre, phase III study to compare clinical efficacy, safety, and tolerability of serplulimab in combination with carboplatin-etoposide chemotherapy in previously untreated patients with ES-SCLC. A schematic diagram of the study design is shown in the figure below.

Figure 6. Overall study design including all phases of the trial ASTRUM-005



HLX10 = serplulimab

Subjects were randomised to either treatment Arm A or B at a 2:1 ratio and were treated with serplulimab or placebo in combination with chemotherapy once every 3 weeks, until disease progression, death, intolerable toxicity, withdrawal of informed consent, or occurrence of other reasons specified in the protocol.

Subjects with first disease progression could receive second-line chemotherapy at discretion of investigator to continue treatment if the subject was clinically stable and willing to continue treatment, and treatment was in accordance with NCCN/ESMO guidelines.

Methods

- **Study participants**

The main inclusion and exclusion criteria are summarised below.

Inclusion criteria

- Male or female aged ≥18 years at the time of signing the consent form.
- Histologically or cytologically diagnosed with ES-SCLC (according to the Veterans Administration Lung Study Group [VALG] staging system).
- No prior systemic therapy for ES-SCLC (including systemic chemotherapy, molecular targeted therapy, biological therapy, and other investigational therapies).

- Patients who had received chemoradiotherapy for previous limited stage SCLC had to have been treated with curative intent and had had a treatment-free interval of at least 6 months from the last course of chemotherapy, radiotherapy, or chemoradiotherapy to the diagnosis of ES-SCLC.
- At least one measurable lesion as assessed by the Independent Radiology Review Committee (IRRC) according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 within 4 weeks prior to randomisation. Measurable lesions were not from previously irradiated sites.
- Tumour tissues had to be provided that met the requirements for the determination of PD-L1 expression levels.
- Prior antineoplastic therapy had to have been ≥2 weeks from the first dose in this study with treatment-related AEs resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 (except for Grade 2 alopecia).
- An Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 or 1.
- An expected survival ≥12 weeks.
- Normal major organ functions defined by protocol (no blood transfusions, or treatment with albumin, recombinant human thrombopoietin or colony-stimulating factor within 14 days prior to the first dose in the study).
- Female subjects had to agree to sexual abstinence or take contraception measures. Breastfeeding was not allowed.

Exclusion criteria

- Histologically or cytologically confirmed mixed SCLC.
- Other active malignancies within 5 years or at the same time. Localized tumours that had been cured, such as basal cell carcinoma, squamous-cell skin cancer, superficial bladder cancer, prostate carcinoma in situ, cervical cancer in situ and breast cancer in situ were acceptable.
- Patients with known or documented active CNS metastases and/or carcinomatous meningitis at screening. However, the following subjects were allowed to be enrolled: 1) Subjects with asymptomatic brain metastases (BM) could be included but were required to receive regular brain imaging. 2) Subjects with treated BM which had been stable for at least 2 months, without evidence of new/ enlarging BM, and with discontinued steroids 3 days prior to study drug administration. Stable BM had to be confirmed before the first dose of study drug.
- Patients with myocardial infarction within half a year before the first dose of the study drug, poorly controlled arrhythmia (including QTc intervals by Fridericia's formula ≥450 ms for males and ≥470 ms for females).
- Class III to IV cardiac insufficiency according to NYHA classification or a left ventricular ejection fraction < 50% by cardiac color Doppler.
- Subject had uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN).
- Subjects with previous and concurrent interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis and severe impaired pulmonary function that might interfere with the detection and management of suspected drug-related pulmonary toxicity, as judged by the investigator.
- Subjects requiring treatment with systemic corticosteroids (>10 mg/day prednisone efficacy dose) or other immunosuppressive drugs within 14 days prior to the first dose or during the study. However, topical or inhaled steroids and adrenal hormone replacement therapy at doses equivalent to ≤10 mg/day of prednisone efficacy were allowed to use.
- Any active infection requiring systemic anti-infective therapy within 14 days. Subjects with a history of COVID-19 infection had to have a negative RT-PCR test prior to the first dose of the study drug.

- Radical radiation therapy within 3 months prior to study medications. Palliative radiotherapy to bone or palliative radiotherapy to superficial lesions was allowed.
- Known active or suspected autoimmune diseases. Subjects in a stable state with no need for systemic immunosuppressant therapy were allowed to enroll.
- Subjects requiring treatment with systemic corticosteroids (> 10 mg/day prednisone efficacy dose) or other immunosuppressive drugs within 14 days prior to the first dose or during the study. However, in the absence of active autoimmune disease, subjects were allowed to use topical or inhaled steroids and adrenal hormone replacement therapy at doses equivalent to ≤ 10 mg/day of prednisone efficacy.
- Active or latent pulmonary tuberculosis.
- Human immunodeficiency virus (HIV) infection, positive test for HIV antibody.
- Hepatitis B or Hepatitis C. Hepatitis B and C co-infection.
- Treatment with live vaccines and all COVID-19 vaccines (fully administered to the required number of doses) within 28 days prior to study drug administration; inactivated viral vaccines for seasonal influenza were allowed.
- Known history of severe allergy to any monoclonal antibody

Locations and settings

The ASTRUM-005 study was conducted in 6 countries: China, Russia, Ukraine, Poland, Turkey, and Georgia. The number of patients enrolled at each is site is shown in. A total of 103 oncological hospital study sites enrolled subjects.

- **Treatments**

Subjects were to receive serplulimab in combination with chemotherapy (Arm A) or placebo in combination with chemotherapy (Arm B).

Dosing scheme was as follows:

- Serplulimab was administered at the dose of 4.5 mg/kg via IV infusion over a period of 30 to 90 minutes on Day 1 of each cycle, once every 3 weeks (21 days).
- Placebo was administered via IV infusion on Day 1 of each cycle, once every 3 weeks (21 days).
- Chemotherapy agents (all subjects):
    - Etoposide: 100 mg/m^2 via IV infusion on Days 1, 2, and 3 of each cycle (21 days). On Day 1, etoposide was administered following infusion of carboplatin.
    - Carboplatin: Area under the curve (AUC)=5, up to a dose of 750 mg via IV infusion on Day 1 of each cycle (21 days). Dose of carboplatin was calculated according to the Calvert formula: Dose (mg) = target AUC x [(creatinine clearance (mL/min) + 25)]

All medications were administered intravenously. The combination of serplulimab or placebo with carboplatin + etoposide was administered in a 3-week treatment cycle. Carboplatin and etoposide were administered until completion of 4 cycles, or progressive disease or unacceptable toxicity, whichever occurred first. Serplulimab was administered until loss of clinical benefit as assessed by investigator. Serplulimab or placebo was allowed to continue as maintenance therapy. After finishing the initial treatment period, patients in both study arms who had disease progression and might benefit from

their assigned treatment in addition to second line chemotherapy, could be eligible to continue with their assigned treatment in the post-PD treatment period as optional by the Investigator.

- **Objectives**

Primary Objective

- To compare the clinical efficacy of serplulimab in combination with chemotherapy versus placebo in combination with chemotherapy in previously untreated patients with ES-SCLC.

Secondary Objective(s)

- To compare the safety and tolerability of serplulimab in combination with chemotherapy versus placebo in combination with chemotherapy in previously untreated patients with ES-SCLC.
- To measure the exposure following serplulimab administration.

Hypotheses

This study was designed to test for superiority. For time-to-event endpoints (e.g., PFS, OS), the null hypothesis (H0) and the alternative hypothesis (H1) were expressed as follows:

H0: $SA(t)=SB(t)$ for all t

H1: $SA(t)\neq SB(t)$ for some t

where $SA(t)$ and $SB(t)$ were the rates of time-to-event for Arm A (serplulimab + chemotherapy) and Arm B (Placebo + chemotherapy) at time t, $t>0$.

- **Outcomes/endpoints**

Primary Efficacy Endpoint

- Overall survival (OS)

OS was defined as a period from randomisation through death regardless of causality. Patients were followed until death according to ITT.

Table 9. The event and censoring scheme for OS

Situation	Date of Death or Censoring	Outcome
Death	Date of Death	Death
Alive at the cut-off	Date of cutoff date	Censored
Alive or study discontinued before the cut-off	Date of last known alive	Censored

Secondary Efficacy Endpoints

- Progression-free survival (PFS) (assessed by the IRRC based on RECIST 1.1)
- PFS (assessed by the investigator based on RECIST 1.1 and iRECIST)
- PFS2 (assessed by the investigator based on RECIST 1.1)
- Objective response rate (ORR) (assessed by the IRRC and investigator based on RECIST 1.1)
- Duration of response (DOR) (assessed by the IRRC and the investigator based on RECIST 1.1)

PFS was defined as a period from randomisation initiation to the first documentation of PD by RECIST 1.1 or iRECIST or death regardless of causality (whichever to occur first).

PFS2 was defined as the time from randomisation to objective tumour progression by RECIST 1.1 on next-line treatment or death from any cause. It was to be analysed using the same method as that for PFS.

ORR was defined as the proportion of subjects with a best overall response of CR or PR, according to RECIST 1.1. The best overall response was defined as the best response across all time points in the order of CR, PR, SD, PD, and not NE.

DOR was defined as the period from the first documentation of response (CR or PR) through the first documentation of PD by RECIST 1.1 or death (whichever to occur first). DOR was to be analysed only for patients whose best overall response was evaluated as CR or PR.

For tumour imaging CT or MRI was used, and the images were to be assessed by IRRC and by the investigators.

Follow-up Period

After the EOT visit, subjects were to be followed up. If a subject terminated the study for other reasons than PD, then radiologic assessment should be further performed according to an established schedule, where possible, until disease progression, initiation of a new anti-tumour therapy, ICF withdrawal, death, or study completion (whichever to occur first).

Intercurrent events

PFS by RECIST 1.1:

Table 10. The event and censoring scheme for PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumour assessments	Date of Randomisation	Censored
No post-baseline tumour assessments and no death	Date of Randomisation	Censored
No post-baseline tumour assessments and death	Date of Death	Progressed
Progression documented between scheduled visits	Date of first progression assessment	Progressed
New anticancer treatment started	Date of last evaluable tumour assessment before start of new treatment	Censored
Death between assessment visits before first PD assessment	Date of death	Progressed
No progression/death at the end of study or the cut-off date	Date of last evaluable tumour assessment	Censored
Progression assessed by IRRC after the 2nd line anti-cancer therapy	Date of the last evaluable tumour assessment prior to the day of 2nd line chemotherapy, only applicable for subjects who assigned the 2nd line anti-cancer therapy after 1st PD assessed by investigator.	Censored

PFS assessed by the investigator based on iRECIST (modified RECIST 1.1 for immune-based therapeutics):

If immune unconfirmed progressive disease (iUPD) was observed and the subsequent tumour assessment was not within the scheduled 4-8 weeks' time window, the PFS was to be calculated as follows:

- If immune confirmed progressive disease (iCPD) was less than 4 weeks after iUPD, the iCPD was to be disregarded.
- If there were multiple iUPD before the iCPD, the latest iUPD date was to be used to calculate PFS.
- If iUPD was followed by "Death" without any iCPD, the iUPD was to be treated as an event, and the latest iUPD date before death was to be used to calculate PFS.
- If there was no iCPD or "Death" after iUPD, the PFS was to be censored to the day of last effective tumour assessment.

PFS2:

For PFS2 the intercurrent events defined for PFS (Table 10) were used as applicable. In addition, the following specific rules applied:

- If a patient died without any progression events, the patient's PFS and PFS2 event dates would be equivalent.
- If a patient died after their primary PFS event, but prior to the initiation of subsequent anti-cancer therapy, their death date was considered their PFS2 event. Patients alive and for whom a second disease progression was not observed should be censored at the last tumour assessment date.

DOR:

For DOR the intercurrent events defined for PFS (Table 10) were used as applicable. In addition, the following specific rules applied:

- Data of patients not experiencing PD or death after achieving response were to be censored on the day of the final tumour assessment.
- Subjects with no tumour assessment performed after response achievement, were to be censored on the day of tumour assessment when response was achieved.

- **Sample size**

The randomisation ratio for this study was 2:1. The sample size was estimated based on the assumption that the median OS for treatment with placebo + chemotherapy (carboplatin–etoposide) was 10 months and the hazard ratio (HR) of (serplulimab + chemotherapy) group versus the control group was 0.7, and it was further assumed that when the enrolment period was 24 months and the whole study period was 34 months, to achieve a confidence level of 85% at an overall significance level α = 0.05 (two-sided), at least 342 OS events had to be observed. Considering a dropout rate of 20%, a total of 567 subjects (378 in treatment arm and 189 in control arm) were to be enrolled in the 2 arms.

In this study it was planned that, when 378 subjects (about 2/3 of the subjects planned to be included) was enrolled under supervision of the Independent Data Monitoring Committee (IDMC), the sponsor would consider performing a blinded sample size estimation, and if the blinded overall median OS was lower than the expected value, then the sponsor would communicate with principal investigator and regulatory authorities about the necessary increase in the sample size (number of OS events).

- **Randomisation and blinding (masking)**

This was a double blind randomised controlled study. All subjects were centrally randomised by block randomisation using an interactive Web response system, IWRS/IVRS. Each subject was assigned a unique number (randomisation number) that encoded the subject's assignment to one of the two arms of the study, according to the randomisation schedule generated by Medidata using a validated computer program. Subjects were randomly assigned to the following two groups using the IWRS/IVRS at 2:1 ratio:

• Arm A (serplulimab): Serplulimab + chemotherapy (carboplatin-etoposide)

• Arm B (control): Placebo + chemotherapy (carboplatin-etoposide)

Stratification factors for randomisation included PD-L1 expression level (negative: TPS <1%, positive: TPS ≥ 1%, or not evaluable/not available), brain metastasis (yes versus no), and age (≥65 years versus <65 years).

The blinding was to be performed by the Statistical Unit during study treatment. The subjects, investigator, sponsor, and designated personnel were not to be aware of the randomisation and treatment allocation. This study was to perform overall unblinding after the last subject completed the end of study visit. Unblinding was to be performed only in case of emergency or as required by regulatory authorities. Otherwise, blinding had to be maintained. All randomisation numbers were to be unblinded only after all data were entered into the database, all data queries were resolved, and subjects were included in analysis sets.

- **Statistical methods**

Analysis Sets

The analysis sets of this study were defined as follows:

- Enrolled Population was defined as all participants who signed the informed consent form (ICF) (including screening failures).
- The Intent-to-Treat Population (ITT) comprised all participants to whom study intervention was randomised. Statistical analyses were to be based on study intervention groups as per randomisation, irrespective of the study intervention actually received. The ITT Population served as the primary population of efficacy assessment in this study. ITT Population was to be analysed based on planned treatment arms.
- The Per Protocol Set (PPS) comprised a subset of the ITT. The PPS consisted of all randomised subjects without any major protocol deviation that would impact the primary efficacy significantly. The protocol deviations that significantly affect evaluation for the primary efficacy were to be determined based on a blinded data review prior to interim/final database lock. Analyses for the PPS were to be based on actual treatment received.
- The Safety Set (SS) was defined as all subjects who received at least one dose of study intervention.

Statistical analyses

The comparison of the time-to-event between treatment and control were to be performed by a two-sided stratified log-rank test with α=0.05 and the prespecified stratification factors. Time-to-event distributions were to be estimated using the Kaplan-Meier (KM) product-limit method. If median event time was evaluated, the corresponding two-sided 95% confidence interval (CI) was to be computed using the Brookmeyer-Crowley approach. The standard error of the survival rate at a fixed time point (e.g., PFS rate at 6 months) was to be estimated using Greenwood's formula. The hazard ratio and its

95% CI were to be estimated by stratified Cox proportional hazards model. Efron's method was to be used to handle ties.

For binomial proportions endpoints (e.g., ORR), considering the stratified randomisation, the stratified Cochran-Mantel-Haenszel method was used to test the between-group variation in the ORR and to estimate the odds ratio and its 95% CI. For each single arm, the 95% CI for the proportion was to be derived using Clopper-Pearson method.

Any major protocol deviation potentially affecting the efficacy analysis would be discussed in DRM. If there was any doubt about the efficacy data involving major protocol deviation, the efficacy data was to be available up to the last efficacy assessment prior to the major protocol deviation.

All analyses of efficacy endpoints were to be stratified as described above. If a subject is assigned in a wrong stratum, he/she would be analysed per "randomised stratum". A sensitivity analysis was to be performed for PFS and OS using "actual stratum".

Multiplicity

One primary variable was defined for this study, one critical treatment contrast (Arm A vs. Arm B). The secondary variables defined were intended to provide supportive evidence relating to the primary objective and no labelling claims were intended. Hence, except the interim analysis, no adjustments for multiplicity were required.

Interim Analysis

This study planned to carry out an interim analysis. An IDMC was to be established for the interim analysis. The O'Brien-Fleming type alpha-spending function (using the Lan-DeMets method to approximate) was to be used to control overall type I error rate. The stopping boundary for OS interim and final analyses are shown in the table below.

Table 11. Analysis Timing and Stopping Boundary of Overall Survival

Analysis Timing	Information Fraction (Number of Events)	Estimated Time (month)	Stopping Boundary (p-value)
OS interim analysis	66% (226)	19	<0.012
OS final analysis	100% (342)	34	<0.046

- The first interim analysis was scheduled to be conducted when 66% (~ 226) of OS events were observed, and the interim analysis was to assess the safety and efficacy of the trial group. The α for the first interim analysis was to be 0.012 (two-tailed) based on the O'Brien Fleming type alpha-spending function.
- The updated analysis of OS was to be performed when a target number of OS events (~ 342) were observed, and the α for the updated analysis was to be 0.046 (two tailed) based on the O'Brien-Fleming type alpha-spending function.

Independent Data Monitoring Committee

The IDMC was to be assembled to evaluate safety data for the study. The IDMC was also assigned to evaluate efficacy data, such as OS for the planned interim analysis. Following the data review, the IDMC was to provide a recommendation as to whether the study may continue, whether amendments to the protocol should be implemented, or whether the study should be stopped. The final decision was with the sponsor. The details of procedures including roles and responsibility, composition, meetings,

data package of meeting, decision making and confidentiality, was referred to a separate IDMC charter.

Subgroup analysis

To assess the consistency of the study OS, PFS and PFS2, results in subgroups were to be examined. The following subgroups were being considered:

- Age (≥ 65 years vs. < 65 years)
- Sex (Male vs. Female)
- Race (Asian vs. non-Asian)
- Ethnicity (Hispanic of Latino vs. non-Hispanic of Latino)
- Baseline ECOG performance status (0, 1)
- Baseline smoking status
- Baseline brain metastasis (yes vs. no)

To explore the efficacy under different PD-L1 expression level, the following subgroups were examined.

- PD-L1 expression level based on tumour proportion score (positive TPS ≥1% vs. negative TPS <1%)
- PD-L1 expression level based on combined positive score (positive CPS ≥1% vs. negative CPS < 1%)

In the pivotal study, the PD-L1 expression level was determined by pharmDx kit 22C3.

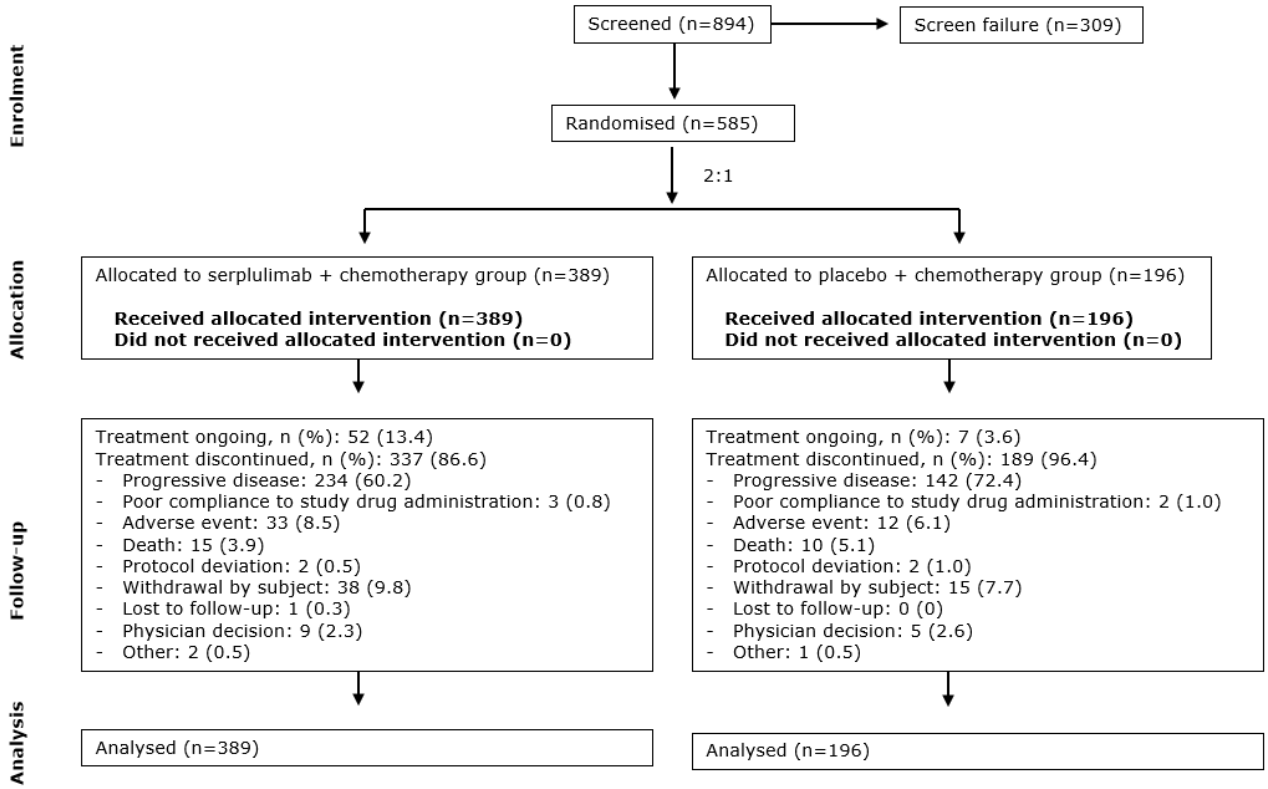
Summaries of OS, PFS and PFS2, including unstratified HRs estimated from Cox proportional hazards models were to be displayed in a forest plot. Kaplan-Meier estimates of median OS, PFS and PFS2 were to be produced separately for each level of the categorical variables for the comparisons between treatment arms.

- The survival curve and median survival time were to be estimated by Kaplan-Meier approach for subgroups (including Age, Baseline brain metastasis, PD-L1 expression level based on TPS and CPS). The Brookmeyer-Crowley method was to be used to construct the 95% CI for the median survival time.
- One primary variable was defined for this study with one critical treatment comparison (Arm A vs Arm B). The secondary variables defined were intended to provide supportive evidence relating to the primary objective and no labelling claims were intended. No adjustments for multiplicity were conducted in this analysis.

Results

- **Participant flow**

Figure 7. Allocation of study subjects (DCO 13 Jun 2022)



- **Recruitment and data cut-off time**

The first study subject was enrolled on 12 Sep 2019.

The last study subject was enrolled on 27 Apr 2021.

Interim analysis data cut-off date was 22 Oct 2021.

Data cut-off date for the updated analysis was 13 Jun 2022.

At time of the planned interim analysis, 246 OS events (corresponding to the prespecified event threshold of 66%) were observed. The efficacy results at interim analysis met the pre-specified stopping boundary, as determined by the IDMC. Therefore, the Sponsor performed a database lock 15 Dec 2021 (data cut-off: 22 October 2021), unblinded the study and conducted statistical analyses to evaluate the efficacy and safety of serplulimab. Thus, the interim analysis is the inferential analysis, and the updated analysis results will be considered supportive to the primary analysis.

- **Conduct of the study**

The first version of the protocol is dated Mar 2019. The fifth and final protocol version is dated Apr 2022. The major changes in study conduct were:

Changes from version 1.0 (04 Mar 2019) to 2.0 (27 Sep 2019):

- Re-structuring the text in accordance with ICH guideline.
- Addition of iRECIST to PFS assessment.

Changes from version 2.0 (27 Sep 2019) to 3.0 (08 Apr 2020):

- The primary efficacy endpoint was changed from PFS to OS, and PFS became a secondary efficacy endpoint.
- Post-PD treatment was clarified to allow second-line chemotherapy and avoid exposing subjects to placebo only.
- Carboplatin dose was revised to a maximum of 750 mg according to NCCN guidelines.
- Addition of myocardial enzymogram for safety monitoring.
- Addition of drug-induced liver injury.
- Addition of AESIs.
- Sample size was recalculated due to change of primary endpoint to OS.
- Addition of subgroup analyses.
- Remove upper age limit as patients older than 75 years in inclusion criteria.
- Increase the value of creatinine clearance to take into account the renal toxicity of carboplatin in inclusion criteria.
- Extending of time limits of using birth control methods or maintain abstinence after the final dose of study drug in inclusion criteria.

Changes from version 3.0 (08 Apr 2020) to 4.0 (05 Feb 2021):

- PFS2, defined as time from randomisation to second/subsequent objective tumour progression on next-line treatment or death from any cause, was added as a secondary efficacy endpoint.
- Addition of tuberculosis testing at time of screening and latent tuberculosis as an exclusion criterion, as requested by the Bulgarian Drug Agency for Bulgarian subjects.
- The inclusion criterion for CrCl for subjects with creatinine levels >1.5xULN was revised from 60 mL/min to 50 mL/min as requested by EMA.
- Addition of eligibility criteria for subjects with current or a history of COVID-19 infection.
- Addition of information relating to subjects with or a history of COVID-19 infection in exclusion criteria.

Changes from version 4.0 (05 Feb 2021) to 5.0 (22 Apr 2022):

- Addition of an exploratory objective to determine the relationship between SCLC subtypes and the treatment outcome and to determine the biomarkers which potentially respond to serplulimab treatment in objectives and endpoints section.
- Addition of two rarely seen AEs of PD-1/PD-L1 inhibitors in identified and potential risks section.
- Update definition of PFS as OS is the primary endpoint in populations for analyses section.
- Addition of a paragraph in the interim analysis section, clarifying that Sponsor would unblind data and conduct a full analysis at interim.

Protocol deviations

A table of major protocol deviations in all comers is shown below.

Table 12. Major protocol deviations in all comers (ITT Population) (Primary Analysis - DCO 13 Jun 2022)

	Serplulimab Group (N=389)	Placebo Group (N=196)	Total (N=585)
Number of Subjects with at Least One Major Protocol Deviations, n (%) [a]	217 (55.8)	105 (53.6)	322 (55.0)
AE/SAE, n (%) [b]	6 (2.8)	4 (3.8)	10 (3.1)
Disallowed Medications, n (%) [b]	3 (1.4)	2 (1.9)	5 (1.6)
Incl/excl Criteria, n (%) [b]	5 (2.3)	3 (2.9)	8 (2.5)
Informed Consent, n (%) [b]	12 (5.5)	7 (6.7)	19 (5.9)
IP Administration/Treatment, n (%) [b]	50 (23.0)	23 (21.9)	73 (22.7)
Other, n (%) [b]	1 (0.5)	0	1 (0.3)
Procedures/Tests, n (%) [b]	137 (63.1)	57 (54.3)	194 (60.2)
Visit Schedule, n (%) [b]	71 (32.7)	40 (38.1)	111 (34.5)
Withdrawal criteria, n (%) [b]	1 (0.5)	0	1 (0.3)
Unknown, n (%) [b]	1 (0.5)	1 (1.0)	2 (0.6)
Major COVID-19 deviation, n (%) [a]	3 (0.8)	0	3 (0.5)

a. The percentages were calculated using the total number of subjects in the ITT set as the denominator. b. All subcategory percentages were calculated using the number of subjects with at least one major protocol deviation in the ITT set as the denominator. Abbreviations: AE: adverse event, incl/excl: inclusion/exclusion, IP: investigational product, ITT: intent to treat, SAE: serious adverse event.

In the non-Asian and Asian subgroups, the number of subjects with at least one major protocol deviations was 126 (67%) vs. 196 (49%), respectively. The major protocol deviations due to visit schedules was 52% vs. 23%, respectively. Major COVID-19 deviations were found in 0.5% in both subgroups.

Table 13. Unblinding levels in ASTRUM-005

Unblinding Level	Unblinding Procedure
Sponsor Level	The complete unblinding was done on 15th Dec 2021 after interim analysis database lock and the steps were as below: The statistician sent the request about 'the release form of the randomisation list' to IRT (Interactive Response Technology) vendor after database lock was announced. The IRT designee released the randomisation list to the statistician.

	The statistician checked the randomisation list and notified the study management team that the unblinding was completed. The randomisation list was applied in the statistical analysis.
Investigator and/or subjects Level	After sponsor level unblinding, the applicant generated a Memo of Individual Subject Treatment Code Disclose. This memo was to document the process by which investigator could request individual subject's treatment arm for subject's further treatment to ensure that the subject's right was protected. This procedure was in parallel with emergency unblinding process after sponsor level unblinding.

- **Baseline data**

Demographic and baseline characteristics of study subjects and their SCLC diagnosis are shown in tables below.

Table 14. Summary of demographic characteristics in all comers (ITT Population)

	Serplulimab Group (N=389)	**Placebo Group (N=196)**	**Total (N=585)**
Age at Screening (years)			
N	389	196	585
Mean (SD)	61.0 (8.64)	61.1 (8.75)	61.1 (8.67)
Median (Q1, Q3)	63.0 (56.0, 67.0)	62.0 (55.0, 68.0)	62.0 (55.0, 67.0)
Min, Max	28, 76	31, 83	28, 83
Gender, n (%)			
Male	317 (81.5)	164 (83.7)	481 (82.2)
Female	72 (18.5)	32 (16.3)	104 (17.8)
Fertile [a]	9 (12.5)	3 (9.4)	12 (11.5)
Non-fertile [a]	63 (87.5)	29 (90.6)	92 (88.5)
Race, n (%)			
Asian	262 (67.4)	139 (70.9)	401 (68.5)
White	127 (32.6)	57 (29.1)	184 (31.5)
Height (cm)			
N	387	194	581
Mean (SD)	167.3 (8.61)	167.3 (8.10)	167.3 (8.43)
Median (Q1, Q3)	168.0 (162.0, 173.0)	168.0 (162.0, 173.0)	168.0 (162.0, 173.0)
Min, Max	142.0, 191.0	140.0, 185.0	140.0, 191.0
Weight (kg)			
N	389	196	585
Mean (SD)	68.8 (15.51)	67.7 (14.30)	68.4 (15.11)

Median (Q1, Q3)	67.0 (58.0, 78.0)	65.7 (58.0, 76.0)	66.5 (58.0, 76.2)
Min, Max	33.0, 120.0	37.0, 120.0	33.0, 120.0
BMI (kg/m^2)			
N	387	194	581
Mean (SD)	24.5 (4.53)	24.1 (4.17)	24.3 (4.41)
Median (Q1, Q3)	23.8 (21.4, 26.7)	23.5 (21.3, 26.1)	23.7 (21.3, 26.4)
Min, Max	13.7, 42.3	17.0, 40.2	13.7, 42.3
PD-L1 expression level, n (%)			
Negative	308 (79.2)	152 (77.6)	460 (78.6)
Positive	64 (16.5)	35 (17.9)	99 (16.9)
Not evaluable/available	17 (4.4)	9 (4.6)	26 (4.4)
Brain metastasis, n (%)			
No	338 (86.9)	169 (86.2)	507 (86.7)
Yes	51 (13.1)	27 (13.8)	78 (13.3)
Age, n (%)			
< 65 years	236 (60.7)	119 (60.7)	355 (60.7)
≥ 65 years	153 (39.3)	77 (39.3)	230 (39.3)

[a] Percentages were calculated with ITT female subjects as the denominator. Abbreviations: BMI=body mass index, ITT=intent to treat, Q=quartile, SD=standard deviation.

Table 15. Baseline characteristics of SCLC diagnosis in all comers (ITT Population)

	Serplulimab Group (N=389)	**Placebo Group (N=196)**	**Total (N=585)**
Time from first diagnosis of SCLC (month)			
N	389	196	585
Mean (SD)	1.2 (4.62)	0.6 (2.02)	1.0 (3.95)
Median (Q1, Q3)	0.2 (0.1, 0.6)	0.2 (0.1, 0.5)	0.2 (0.1, 0.5)
Min, max	-0.3, 46.2	-0.3, 19.7	-0.3, 46.2
<6 months	376 (96.7)	193 (98.5)	569 (97.3)
≥6 months	13 (3.3)	3 (1.5)	16 (2.7)
VALG Stage at initial diagnosis, n (%)			
Extensive	369 (94.9)	190 (96.9)	559 (95.6)
Limited	19 (4.9)	6 (3.1)	25 (4.3)
Missing	1 (0.3)	0	1 (0.2)
VALG Stage at study entry, n (%)			

Extensive	388 (99.7)	196 (100)	584 (99.8)
Limited	1 (0.3)	0	1 (0.2)
Overall stage at initial diagnosis, n (%) [b]			
I	1 (0.3)	0	1 (0.2)
II	1 (0.3)	0	1 (0.2)
III	49 (12.6)	23 (11.7)	72 (12.3)
IV	286 (73.5)	143 (73.0)	429 (73.3)
Unknown	52 (13.4)	30 (15.3)	82 (14.0)
Overall Stage at study entry, n (%) [b]			
III	33 (8.5)	18 (9.2)	51 (8.7)
IV	318 (81.7)	155 (79.1)	473 (80.9)
Unknown	38 (9.8)	23 (11.7)	61 (10.4)
Tumour metastasis, n (%)			
Yes	378 (97.2)	187 (95.4)	565 (96.6)
Site of metastasis [c]			
Lung	164 (42.2)	83 (42.3)	247 (42.2)
Liver	99 (25.4)	51 (26.0)	150 (25.6)
Bone	115 (29.6)	49 (25.0)	164 (28.0)
Lymph	298 (76.6)	167 (85.2)	465 (79.5)
Skin	2 (0.5)	0	2 (0.3)
Other	117 (30.1)	77 (39.3)	194 (33.2)
CNS	50 (12.9)	28 (14.3)	78 (13.3)

[a] Calculated as: (Date of informed consent – Date of SCLC First Diagnosed+1) x 12/365.25. [b] Stage I includes I, IA, IB, IC; Stage II includes II, IIA, IIB, IIC; Stage III includes III, IIIA, IIIB, IIIC. [c] A subject may have more than one site of metastasis. Abbreviations: CNS: central nervous system, ITT: intent to treat, Q: quartile, SCLC: small cell lung cancer, SD: standard deviation, VALG: Veterans Administration Lung Study Group.

Table 16. Baseline characteristics at clinical assessment (ITT Population)

	Serplulimab Group (N=389)	**Placebo Group (N=196)**	**Total (N=585)**
ECOG status, n (%)			
0	71 (18.3)	32 (16.3)	103 (17.6)
1	318 (81.7)	164 (83.7)	482 (82.4)
Echocardiogram, n (%)			
Normal	175 (45.0)	89 (45.4)	264 (45.1)
Abnormal, clinically significant	43 (11.1)	23 (11.7)	66 (11.3)
Abnormal, not clinically significant	171 (44.0)	84 (42.9)	255 (43.6)

Biomarker, n (%)			
MSS	156 (40.1)	83 (42.3)	239 (40.9)
MSI-L	26 (6.7)	17 (8.7)	43 (7.4)
MSI-H	13 (3.3)	10 (5.1)	23 (3.9)
Missing	194 (49.9)	86 (43.9)	280 (47.9)
Biomarker, tumour mutation burden			
N (%)	195 (50.1)	110 (56.1)	305 (52.1)
Mean (SD)	5.7 (3.77)	5.2 (3.06)	5.5 (3.52)
Median (Q1, Q3)	4.4 (3.2, 7.3)	5.0 (3.2, 6.9)	4.8 (3.2, 6.9)
Min, Max	0.0, 21.8	0.81, 22.6	0.0, 22.6
Smoking Status			
Never	81 (20.8)	35 (17.9)	116 (19.8)
Former	206 (53.0)	114 (58.2)	320 (54.7)
Current	102 (26.2)	47 (24.0)	149 (25.5)

Abbreviations: ECOG: Eastern Cooperative Oncology Group, ITT: intent to treat, MSS: Microsatellite stability, MSI: Microsatellite instability, MSI-H: MSI-High, MSI-L: MSI-Low, SD=standard deviation, TMB: Tumour mutation burden.

Table 17. Summary of demographic characteristics in the non-Asian subgroup (ITT Population)

	Serplulimab Group (N=127)	**Placebo Group (N=57)**	**Total (N=184)**
Age at Screening (years)			
N	127	57	184
Mean (SD)	60.7 (8.09)	61.1 (8.30)	60.8 (8.13)
Median (Q1, Q3)	62.0 (56.0, 66.0)	61.0 (56.0, 66.0)	62.0 (56.0, 66.0)
Min, Max	36, 76	38, 83	36, 83
Gender, n (%)			
Male	109 (85.8)	51 (89.5)	160 (87.0)
Female	18 (14.2)	6 (10.5)	24 (13.0)
Fertile [a]	2 (11.1)	0	2 (8.3)
Non-fertile [a]	16 (88.9)	6 (100)	22 (91.7)
Race, n (%)			
White	127 (100)	57 (100)	184 (100)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0

Not Hispanic or Latino	126 (99.2)	57 (100)	183 (99.5)
Other	1 (0.8)	0	1 (0.5)
Height (cm)			
N	127	57	184
Mean (SD)	171.2 (8.52)	171.4 (6.73)	171.3 (7.99)
Median (Q1, Q3)	172.0 (166.0, 176.0)	172.0 (167.0, 176.0)	172.0 (166.0, 176.0)
Min, Max	146.0, 191.0	150.0, 185.0	146.0, 191.0
Weight (kg)			
N	127	57	184
Mean (SD)	78.7 (17.60)	79.2 (15.24)	78.8 (16.87)
Median (Q1, Q3)	76.0 (67.0, 92.0)	80.0 (68.2, 86.0)	77.0 (67.0, 89.5)
Min, Max	40.1, 120.0	51.0, 120.0	40.1, 120.0
BMI (kg/m^2)			
N	127	57	184
Mean (SD)	26.8 (5.71)	26.9 (4.89)	26.8 (5.46)
Median (Q1, Q3)	26.0 (22.5, 30.3)	25.7 (23.9, 29.6)	26.0 (22.9, 30.2)
Min, Max	14.6, 42.3	18.9, 40.2	14.6, 42.3
PD-L1 expression level, n (%)			
Negative	86 (67.7)	34 (59.6)	120 (65.2)
Positive	34 (26.8)	20 (35.1)	54 (29.3)
Not evaluable/ available	7 (5.5)	3 (5.3)	10 (5.4)
Brain metastasis, n (%)			
No	110 (86.6)	52 (91.2)	162 (88.0)
Yes	17 (13.4)	5 (8.8)	22 (12.0)
Age, n (%)			
< 65 years	86 (67.7)	40 (70.2)	126 (68.5)
≥ 65 years	41 (32.3)	17 (29.8)	58 (31.5)

Table 18. Prior systemic anti-cancer therapy (ITT Population)

Number of Subject with	HLX10 (N=389)	Placebo (N=196)	Total (N=585)
Any Prior Systemic Anti-Cancer Therapy, n(%)	10 (2.6)	5 (2.6)	15 (2.6)
Number of Systemic Anti-Cancer Therapy, n(%)			
1	1 (0.3)	2 (1.0)	3 (0.5)
2	4 (1.0)	1 (0.5)	5 (0.9)
3	1 (0.3)	1 (0.5)	2 (0.3)
>=4	4 (1.0)	1 (0.5)	5 (0.9)
Type, n(%)			
Chemotherapy	9 (2.3)	3 (1.5)	12 (2.1)
Immunotherapy	0	0	0
Chemotherapy/ Immunotherapy	0	0	0
Other	1 (0.3)	2 (1.0)	3 (0.5)
Line of Therapy, n(%)			
1st-Line	8 (2.1)	2 (1.0)	10 (1.7)
2nd-Line	0	0	0
3rd-Line	0	0	0
4th-Line	0	0	0
Other	2 (0.5)	3 (1.5)	5 (0.9)
Best Response, n(%)			
Complete Response (CR)	2 (0.5)	1 (0.5)	3 (0.5)
Partial Response (PR)	2 (0.5)	0	2 (0.3)
Progressive Disease (PD)	2 (0.5)	0	2 (0.3)
Stable Disease (SD)	0	0	0
Not Applicable (NA)	4 (1.0)	3 (1.5)	7 (1.2)
Not Evaluable (NE)	0	1 (0.5)	1 (0.2)
Prior Systemic Anti-Cancer Therapy, n(%)			
ANTINEOPLASTIC AGENTS	9 (2.3)	3 (1.5)	12 (2.1)
ETOPOSIDE	9 (2.3)	2 (1.0)	11 (1.9)
CISPLATIN	7 (1.8)	1 (0.5)	8 (1.4)
CARBOPLATIN	2 (0.5)	1 (0.5)	3 (0.5)
DOCETAXEL	1 (0.3)	0	1 (0.2)
FLUOROURACIL	0	1 (0.5)	1 (0.2)
GEMCITABINE	1 (0.3)	0	1 (0.2)
LOBAPLATIN	1 (0.3)	0	1 (0.2)
OXALIPLATIN	0	1 (0.5)	1 (0.2)

HLX10 = serplulimab

- **Numbers analysed**

Table 19. Data sets analysed

	Serplulimab Group (N=389)	**Placebo Group (N=196)**	**Total (N=585)**
Randomised, n	389	196	585
Intent to treat set, n (%)	389 (100)	196 (100)	585 (100)
Per protocol set, n (%)	387 (99.5)	195 (99.5)	582 (99.5)
Excluded from PPS due to major protocol deviation, n (%)	2 (0.5)	1 (0.5)	3 (0.5)
Safety Set, n (%)	389 (100)	196 (100)	585 (100)
PKS, n (%)	389 (100)	0	389 (66.5)

Abbreviations: ITT: intent to treat, PKS: pharmacokinetic set, PPS: per protocol set.

- **Outcomes and estimation**

Primary endpoint: Overall Survival

At the time of the interim analysis (primary analysis) cut-off on 22 October 2021 when 66% OS events were observed (defined approximately 226, actual 246 OS events), patients had a median survival follow-up time of 12.3 months.

Table 20. Primary efficacy analysis: Overall survival in all comers (ITT Population) (Primary Analysis - DCO 22 Oct 2021)

	Serplulimab Group (N=389)	Placebo Group (N=196)
Number of Event (Deaths), n (%)	146 (37.5)	100 (51.0)
Number of Censor, n (%)	243 (62.5)	96 (49.0)
Alive	228 (58.6)	86 (43.9)
Lost to Follow-up	15 (3.9)	10 (5.1)
Overall Survival (Months)		
Median (95% CI) [a]	15.38 (13.27, NA)	10.91 (9.96, 14.32)
Min, Max	0.2, 24.8	0.4, 24.7
Stratified [b]		
Hazard Ratio (95% CI) [c]	0.63 (0.49, 0.82)	
p-Value [d]	< 0.001	
Survival Rate up to [e]		
3 Months	0.96 (0.93, 0.97)	0.94 (0.90, 0.97)
6 Months	0.89 (0.85, 0.92)	0.78 (0.71, 0.83)
12 Months	0.61 (0.55, 0.66)	0.48 (0.40, 0.56)
18 Months	0.46 (0.38, 0.53)	0.30 (0.20, 0.40)
21 Months	0.43 (0.34, 0.52)	0.24 (0.12, 0.38)
24 Months	0.43 (0.34, 0.52)	0.08 (0.01, 0.27)

[a] The Brookmeyer-Crowley method was used to construct the 95% CI for the median OS.
[b] Stratification factors: PD-L1 expression level (TPS < 1%, TPS 2: 1%, not evaluable/ not available), brain metastasis (yes versus no), and age (2: 65 years versus < 65 years).
[c] The hazard ratio and its 95% CI were estimated by Cox proportional hazards model. Efron's method was used to handle ties.
[d] The comparison of OS between the two arms was performed by a two-sided stratified log-rank test.
[e] The standard error of the survival rate was calculated using Greenwood's formula.

Updated analysis after unblinding with longer follow-up duration (median: 19.7 months) was conducted by the cut-off date 13 June 2022 when 100% of predefined OS events were observed (defined approximately 342, actual 363 OS events).

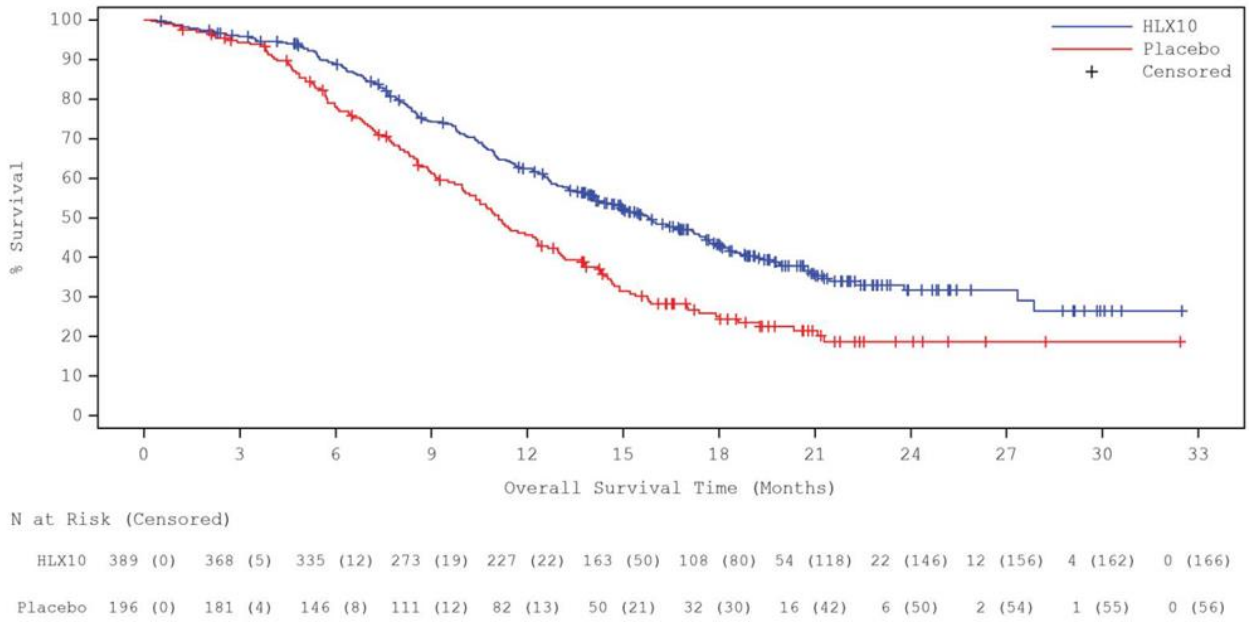
Table 21. Overall survival in all comers (ITT Population) (Updated analysis - DCO 13 Jun 2022)

	HLX10 Group (N=389)	Placebo Group (N=196)
Number of Event (Deaths), n (%)	223 (57)	140 (71)
Number of Censor, n (%)	166 (43)	56 (29)
Alive	142 (37)	43 (22)
Lost to Follow-up	24 (6)	13 (7)
Overall Survival (Months)		
Median (95% CI) [a]	15.8 (14.13, 17.58)	11.1 (9.96, 12.35)
Min, Max	0.2, 32.5	0.4, 32.4
Stratified [b]		
Hazard Ratio (95% CI) [c]	0.62 (0.496, 0.763)	
p-Value [d]	< 0.001	
Survival Rate up to [e]		
3 Months	0.959 (0.933, 0.974)	0.944 (0.900, 0.968)
6 Months	0.890 (0.854, 0.917)	0.780 (0.714, 0.832)
12 Months	0.625 (0.573, 0.672)	0.456 (0.383, 0.526)
24 Months	0.317 (0.256, 0.379)	0.187 (0.125, 0.259)
30 Months	0.264 (0.184, 0.351)	0.187 (0.125, 0.259)

[a] The Brookmeyer-Crowley method was used to construct the 95% CI for the median OS. [b] Stratification factors: PD-L1 expression level (TPS < 1%, TPS 2: 1%, not evaluable/ not available), brain metastasis (yes versus no), and age (2: 65 years versus < 65 years). [c] The hazard ratio and its 95% CI were estimated by Cox proportional hazards model. Efron's method was used to handle ties. [d] The comparison of OS between the two arms was performed by a two-sided stratified log-rank test. [e] The standard error of the survival rate was calculated using Greenwood's formula.

HLX10 = serplulimab

Figure 8. Kaplan-Meier curve of OS in all comers (ITT Population) (Updated Analysis - DCO 13 Jun 2022)



HLX10 = serplulimab

Secondary endpoint: Progression-free survival (PFS)

Table 22. Progression-free survival (RECIST 1.1) by IRRC (ITT Population) (Primary Analysis - DCO 22 Oct 2021)

Characteristic	HLX10 (N=389)	Placebo (N=196)	Total (N=585)
Number of Event (PD/ Deaths), n(%)	223 (57.3)	151 (77.0)	374 (63.9)
Progression	177 (45.5)	133 (67.9)	310 (53.0)
Deaths	46 (11.8)	18 (9.2)	64 (10.9)
Number of Censor, n(%)	166 (42.7)	45 (23.0)	211 (36.1)
No Baseline or Post Baseline	5 (1.3)	3 (1.5)	8 (1.4)
No Progression nor Death	100 (25.7)	21 (10.7)	121 (20.7)
New Anticancer Treatment Started Prior to Documented Disease Progression or Death on Study	61 (15.7)	21 (10.7)	82 (14.0)
Significant Major Protocol Deviation	0	0	0
Progression Free Survival (Months)			
Median (95% CI) [1]	5.72 (5.520, 6.899)	4.34 (4.205, 4.501)	5.45 (4.698, 5.552)
Min, Max	0.0, 23.3	0.0, 23.6	0.0, 23.6
Stratified [2]			
Hazard Ratio (95% CI) [3]	0.48 (0.383, 0.590)		
p-Value [4]	<0.001		
Unstratified			
Hazard Ratio (95% CI) [3]	0.49 (0.400, 0.609)		
p-Value [4]	<0.001		
PFS Rate at [5]			
3 Months	0.892 (0.855, 0.920)	0.785 (0.717, 0.838)	0.856 (0.824, 0.883)
6 Months	0.481 (0.425, 0.535)	0.197 (0.139, 0.262)	0.384 (0.341, 0.428)
9 Months	0.333 (0.277, 0.390)	0.101 (0.058, 0.157)	0.253 (0.212, 0.296)
12 Months	0.238 (0.182, 0.299)	0.060 (0.024, 0.118)	0.178 (0.138, 0.222)

15 Months	0.196 (0.138, 0.261)	0.060 (0.024, 0.118)	0.149 (0.108, 0.196)
18 Months	0.196 (0.138, 0.261)	0.060 (0.024, 0.118)	0.149 (0.108, 0.196)
21 Months	0.196 (0.138, 0.261)	0.060 (0.024, 0.118)	0.149 (0.108, 0.196)

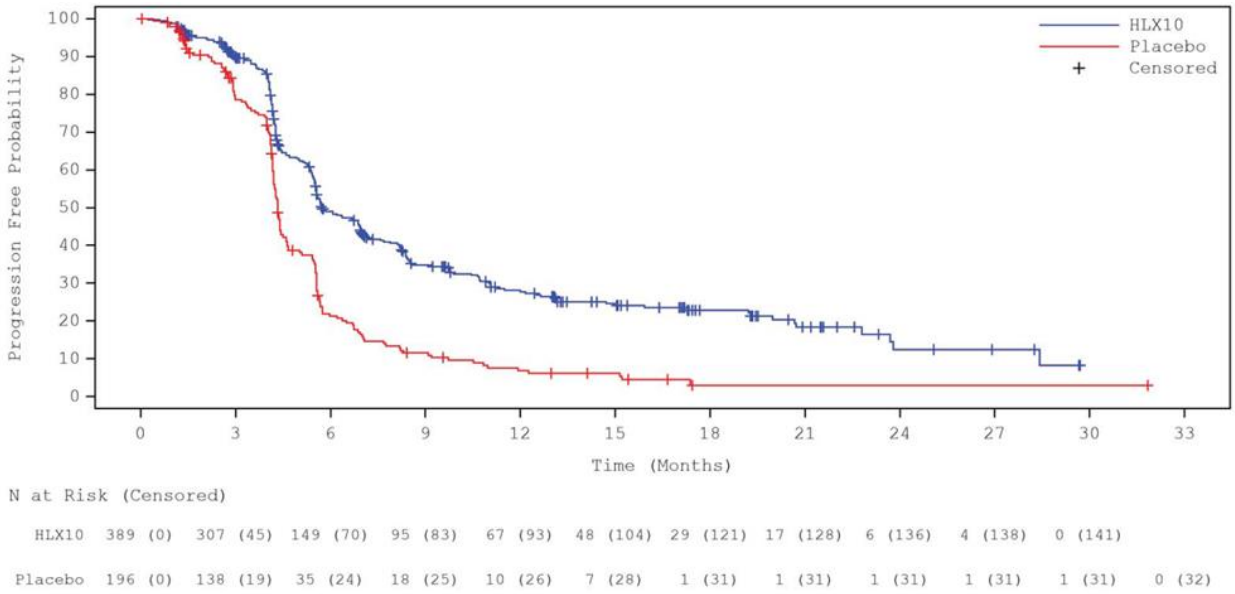
HLX10 = serplulimab

Table 23. Progression-free survival (RECIST 1.1) by Investigator (ITT Population) (Primary Analysis - DCO 22 Oct 2021)

Characteristic	HLX10 (N=389)	Placebo (N=196)	Total (N=585)
Number of Event (PD/ Deaths), n(%)	279 (71.7)	168 (85.7)	447 (76.4)
Progression	245 (63.0)	154 (78.6)	399 (68.2)
Deaths	34 (8.7)	14 (7.1)	48 (8.2)
Number of Censor, n(%)	110 (28.3)	28 (14.3)	138 (23.6)
No Baseline or Post Baseline	2 (0.5)	4 (2.0)	6 (1.0)
No Progression nor Death	94 (24.2)	20 (10.2)	114 (19.5)
New Anticancer Treatment Started Prior to Documented Disease Progression or Death on Study	14 (3.6)	4 (2.0)	18 (3.1)
Significant Major Protocol Deviation	0	0	0
Progression Free Survival (Months)			
Median (95% CI) [1]	5.49 (4.994, 5.684)	4.34 (4.205, 4.435)	4.90 (4.402, 5.454)
Min, Max	0.0, 23.3	0.0, 23.6	0.0, 23.6
Stratified [2]			
Hazard Ratio (95% CI) [3]	0.58 (0.476, 0.707)		
p-Value [4]	<0.001		
Unstratified			
Hazard Ratio (95% CI) [3]	0.59 (0.482, 0.711)		
p-Value [4]	<0.001		
PFS Rate at [5]			
3 Months	0.816 (0.773, 0.851)	0.776 (0.709, 0.829)	0.803 (0.767, 0.833)
6 Months	0.423 (0.371, 0.473)	0.213 (0.156, 0.276)	0.353 (0.312, 0.393)
9 Months	0.267 (0.220, 0.316)	0.083 (0.046, 0.133)	0.206 (0.171, 0.243)
12 Months	0.196 (0.151, 0.245)	0.042 (0.016, 0.089)	0.146 (0.114, 0.182)
15 Months	0.162 (0.118, 0.213)	0.028 (0.007, 0.076)	0.119 (0.087, 0.155)
18 Months	0.162 (0.118, 0.213)	0.028 (0.007, 0.076)	0.119 (0.087, 0.155)
21 Months	0.162 (0.118, 0.213)	0.028 (0.007, 0.076)	0.119 (0.087, 0.155)

HLX10 = serplulimab

Figure 9. Kaplan-Meier curve of progression-free survival by IRRC, according to RECIST 1.1 (ITT Population) (Updated Analysis - DCO 13 Jun 2022)



HLX10 = serplulimab

Secondary endpoint: PFS (iRECIST) by investigator (Primary Analysis - DCO 22 Oct 2021)

PFS according to iRECIST as evaluated by investigator was 5.7 (5.5, 6.9) months in the serplulimab group and 4.4 (4.3, 4.6) months in the placebo group. The stratified HR (95% CI) was 0.56 (0.45, 0.68).

Secondary endpoint: PFS2 (Primary Analysis - DCO 22 Oct 2021)

The median PFS2 (95% CI) according to RECIST 1.1 as evaluated by investigators was 11.0 (9.8, 12.9) months in the serplulimab group and 8.3 (7.6, 9.0) months in the placebo group. The stratified HR (95% CI) was 0.61 (0.46, 0.82).

Secondary endpoint: Unconfirmed and confirmed ORR by IRRC (Primary Analysis - DCO 22 Oct 2021)

According to RECIST 1.1, as evaluated by the IRRC, 1.8% and 79.2% of subjects in the serplulimab group had unconfirmed CR and PR, respectively, compared with 0 and 70.4% in the Placebo group.

The unconfirmed ORR was 81.0% in the serplulimab group and 70.4% in the placebo group, resulting in an odds ratio (95% CI) of 1.80 (1.21, 2.68).

In the serplulimab group, 0.8% and 66.6% of subjects had confirmed CR and PR, respectively, compared with 0 and 58.7% in the placebo group. The confirmed ORR was 67.4% in the serplulimab group and 58.7% in the Placebo group, resulting in an odds ratio (95% CI) of 1.46 (1.02, 2.09).

Secondary endpoint: Duration of response (Primary Analysis - DCO 22 Oct 2021)

Table 24. Duration of response (RECIST 1.1) by IRRC (ITT Population) (Primary Analysis - DCO 22 Oct 2021)

Characteristic	HLX10 (N=389)	Placebo (N=196)	Total (N=585)
Subjects with CR or PR	262	115	377
Number of Event (PD/ Deaths), n(%)	140 (53.4)	86 (74.8)	226 (59.9)
Progression	126 (48.1)	82 (71.3)	208 (55.2)
Deaths	14 (5.3)	4 (3.5)	18 (4.8)
Number of Censor, n(%)	122 (46.6)	29 (25.2)	151 (40.1)
No Further Progression and Death after the First CR/PR	89 (34.0)	21 (18.3)	110 (29.2)
New Anticancer Treatment Started Prior to Documented Disease Progression or Death on Study	33 (12.6)	8 (7.0)	41 (10.9)
Major Protocol Deviation Occurred Prior to Unblinding	0	0	0
Duration of Response (Months)			
Median (95% CI) [1]	5.78 (5.158, 7.524)	4.14 (3.023, 4.205)	4.47 (4.238, 5.520)
Min, Max	1.2, 22.0	0.0, 22.3	0.0, 22.3
Stratified [2]			
Hazard Ratio (95% CI) [3]	0.44 (0.331, 0.582)		
p-Value [4]	<0.001		
Unstratified			
Hazard Ratio (95% CI) [3]	0.47 (0.357, 0.617)		
p-Value [4]	<0.001		

HLX10 = serplulimab

Secondary endpoint: Quality of Life Analysis

Different quality of life-tools were applied to measure patient reported outcomes (EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-LC13). According to the applicant, serplulimab in combination with chemotherapy improved overall QoL in terms of self-assessed VAS.

Table 25. Example of QoL result: EQ-5D-5L VAS score in all comers (ITT Population)

Item	Visit	Statistics	HLX10 (N=389)	Placebo (N=196)	Total (N=585)
		Min, Max	10, 100	25, 100	10, 100
	END OF TREATMENT-Changen from Baseline		205	124	329
		Mean (SD)	-2.9 (18.47)	-1.2 (18.51)	-2.3 (18.48)
		Median (Q1, Q3)	0.0 (-11.0, 6.0)	0.0 (-10.0, 10.0)	0.0 (-10.0, 10.0)
		Min, Max	-65, 61	-55, 60	-65, 61

Table 26. Summary of subsequent treatment in all comers (ITT Population)

	HLX10 Group (n=389)									
	No Subsequent Treatment (n=139, 35.7%)	Chemo/Other (n=80, 20.6%)			HLX10 Continue (n=107, 27.5%)			Continue with Other Anti-PD-1/PD-L1 Treatment excluding HLX10 (n=20, 5.1%)			Total (n=346, 88.9%)
		Only Chemo (n=36, 9.3%)	Chemo+Others (n=28, 7.2%)	Others (n=16, 4.1%)	HLX10 Monotherapy (n=55, 14.1%)	HLX10+1L Chemo (n=20, 5.1%)	HLX10+2L Chemo (n=32, 8.2%)	Other Anti-PD-1/PD-L1+1L Chemo/1L Chemo+Target Therapy (n=7, 1.8%)	Other Anti-PD-1/PD-L1+2L Chemo/2L Chemo+Others (n=12, 3.1%)	Other Anti-PD-1/PD-L1+Target Therapy (n=1, 0.3%)	
OS	10.02 (8.148, 12.320)	12.11 (9.626, 17.577)	18.04 (12.715, NA)	16.03 (9.791, 18.070)	17.87 (12.945, 23.786)	10.97 (6.998, 20.665)	18.30 (14.949, NA)	21.26 (11.499, NA)	14.09 (8.542, 21.454)	10.97 (NA, NA)	13.90 (12.517, 15.474)

	Placebo Group (n=196)							
	No Subsequent Treatment (n=94, 48.0%)	Chemo/Other (n=77, 39.3%)			Continue with Other Anti-PD-1/PD-L1 Treatment (n=20, 10.2%)			Total (n=191, 97.4%)
		Only Chemo (n=47, 24.0%)	Chemo+Others (n=22, 11.2%)	Others (n=8, 4.1%)	Other Anti-PD-1/PD-L1+1L Chemo/1L Chemo+Others (n=4, 2.0%)	Other Anti-PD-1/PD-L1+2L Chemo/2L Chemo+Others (n=12, 6.1%)	Other Anti-PD-1/PD-L1+Target Therapy (n=4, 2.0%)	
OS	9.99 (7.754, 11.400)	11.20 (7.984, 13.832)	12.48 (8.444, 21.092)	8.23 (3.877, 12.945)	12.98 (6.899, NA)	15.80 (12.156, NA)	10.02 (5.257, NA)	10.91 (9.725, 12.320)

HLX10 = serplulimab

Table 27. Subsequent second line chemotherapy following disease progression (ITT Population)

Number of Subject with	Serplulimab Group (N=389)	Placebo Group (N=196)
Therapy type, n (%)		
CHEMOTHERAPY	95 (24.4)	64 (32.7)
IRINOTECAN	31 (8.0)	17 (8.7)
CISPLATIN	21 (5.4)	11 (5.6)
IRINOTECAN HYDROCHLORIDE TRIHYDRATE	16 (4.1)	15 (7.7)
PACLITAXEL	21 (5.4)	6 (3.1)
IRINOTECAN HYDROCHLORIDE	10 (2.6)	10 (5.1)
CARBOPLATIN	13 (3.3)	6 (3.1)
DOCETAXEL	10 (2.6)	8 (4.1)
PACLITAXEL NANOPARTICLE ALBUMIN-BOUND	7 (1.8)	10 (5.1)
ETOPOSIDE	9 (2.3)	3 (1.5)
LOBAPLATIN	7 (1.8)	1 (0.5)
TOPOTECAN	5 (1.3)	3 (1.5)
NEDAPLATIN	1 (0.3)	5 (2.6)
TEMOZOLOMIDE	2 (0.5)	3 (1.5)
GEMCITABINE HYDROCHLORIDE	0	4 (2.0)
MITOXANTRONE HYDROCHLORIDE	2 (0.5)	1 (0.5)
VINORELBINE TARTRATE	3 (0.8)	0
CYCLOPHOSPHAMIDE	2 (0.5)	0
IFOSFAMIDE	2 (0.5)	0
PACLITAXEL LIPOSOME	1 (0.3)	1 (0.5)
TOPOTECAN HYDROCHLORIDE	1 (0.3)	1 (0.5)
DIANHYDROGALACTITOL	1 (0.3)	0
DOXORUBICIN	1 (0.3)	0

DOXORUBICIN HYDROCHLORIDE	1 (0.3)	0
LOMUSTINE	1 (0.3)	0
OTHER ANTINEOPLASTIC AGENTS	0	1 (0.5)
OXALIPLATIN	1 (0.3)	0
THIOTEPA	0	1 (0.5)
VINCRISTINE	1 (0.3)	0
VINCRISTINE SULFATE	1 (0.3)	0

Table 28. Summary of follow-up treatment in the placebo group (n=196) (ITT Population) (Updated analysis - DCO 13 Jun 2022)

		OS
No Subsequent Treatment (n=79, 40.3%)		9.95 (7.655, 10.710)
Chemo/Other (n=50, 25.5%)	Only Chemo (n=23, 11.7%)	8.15 (6.998, 13.832)
	Chemo+ Others (n=19, 9.7%)	12.65 (8.871, 21.290)
	Others (n=8, 4.1%)	8.23 (3.877, 12.945)
Placebo Continue (n=46, 23.5%)	Placebo Monotherapy (n=15, 7.7%)	15.21 (6.111, NA)
	Placebo+ Chemo/Others (n=27, 13.8%)	11.47 (6.439, 17.018)
	Placebo+ Other Anti-PD-1/PD-L1 (n=4, 2.0%)	NA (15.376, NA)
Continue with Other Anti-PD-1/PD-L1 Treatment (n=16, 8.2%)	Other Anti-PD-1/PD-L1+1L Chemo/1L Chemo+Others (n=4, 2.0%)	12.98 (6.899, NA)
	Other Anti-PD-1/PD-L1+2L Chemo/2L Chemo+Others (n=8, 4.1%)	15.80 (5.979, NA)
	Other Anti-PD-1/PD-L1+Targeted Therapy (n=4, 2.0%)	10.02 (5.257, NA)
Total (n=191, 97.4%)		10.91 (9.725, 12.320)

Subgroup analyses

Non-Asian subgroup

OS

As of the primary analysis (DCO 22 Oct 2021), overall survival data are shown in table below. Forest plot is shown in Figure 15.

Table 29. Overall survival in non-Asian (ITT Population) (Primary Analysis – 22 Oct 2021)

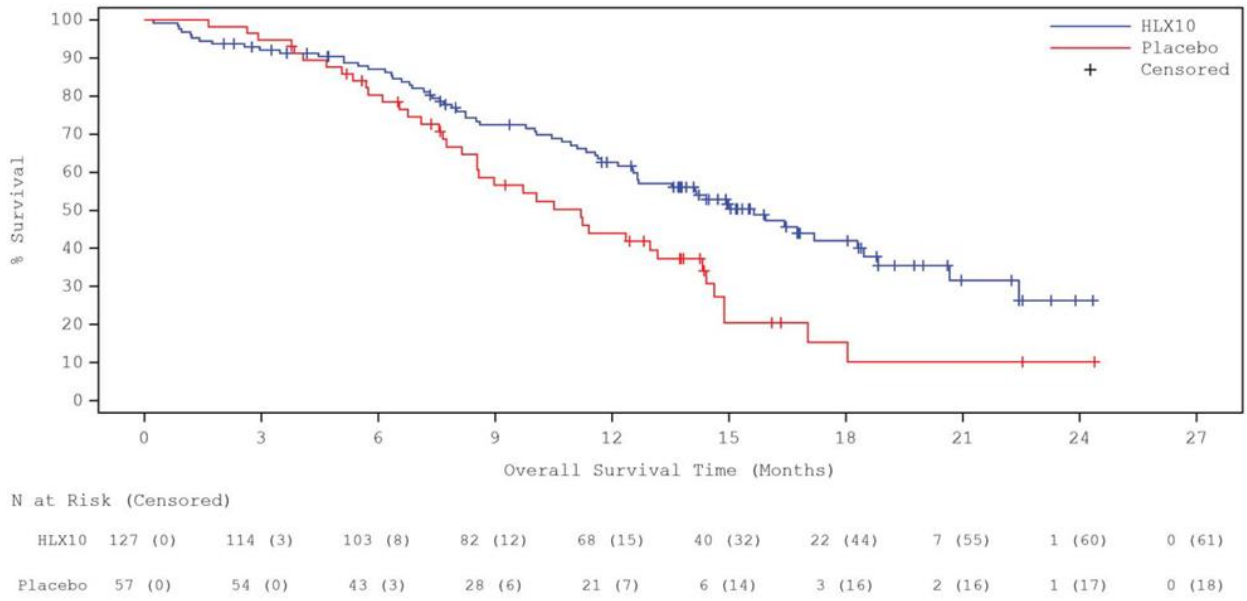
	Serplulimab Group (N=127)	**Placebo Group (N=57)**
Number of Event (Deaths), n (%)	43 (33.9)	26 (45.6)
Number of Censor, n (%)	84 (66.1)	31 (54.4)
Alive	76 (59.8)	27 (47.4)

Lost to Follow-up	8 (6.3)	4 (7.0)
Overall Survival (Months)		
Median (95% CI) [a]	12.5 (11.3, NA)	10.5 (8.1, 14.6)
Min, Max	0.2, 18.0	1.6, 16.7
Stratified [b]		
Hazard Ratio (95% CI) [c]	0.70 (0.41, 1.18)	
p-Value [d]	0.18	
Survival Rate up to [e]		
3 Months	0.92 (0.86, 0.96)	0.95 (0.85, 0.98)
6 Months	0.87 (0.80, 0.92)	0.80 (0.67, 0.89)
9 Months	0.69 (0.59, 0.77)	0.50 (0.33, 0.65)
12 Months	0.55 (0.43, 0.66)	0.46 (0.29, 0.61)
18 Months	0.38 (0.21, 0.55)	NA (NA, NA)

[a] The Brookmeyer-Crowley method was used to construct the 95% CI for the median OS. [b] Stratification factors: PD-L1 expression level (TPS < 1%, TPS 2: 1%, not evaluable/ not available), brain metastasis (yes versus no), and age (2: 65 years versus < 65 years). [c] The hazard ratio and its 95% CI were estimated by Cox proportional hazards model. Efron's method was used to handle ties. [d] The comparison of OS between the two arms was performed by a two-sided stratified log-rank test. [e] The standard error of the survival rate was calculated using Greenwood's formula.

Updated analysis (DCO 13 Jun 2022): median overall survival (95% CI) in non-Asian subgroup at updated analysis, was 15.6 (12.7, 18.5) months in the serplulimab group and 11.2 (8.5, 14.3) months in the placebo group. The stratified HR (95% CI) was 0.51 (0.34, 0.79). The Kaplan-Meier curve for the updated OS analysis is shown below.

Figure 10. Kaplan-Meier curve of overall survival in non-Asian (ITT Population) (Updated Analysis – DCO 13 Jun 2022)



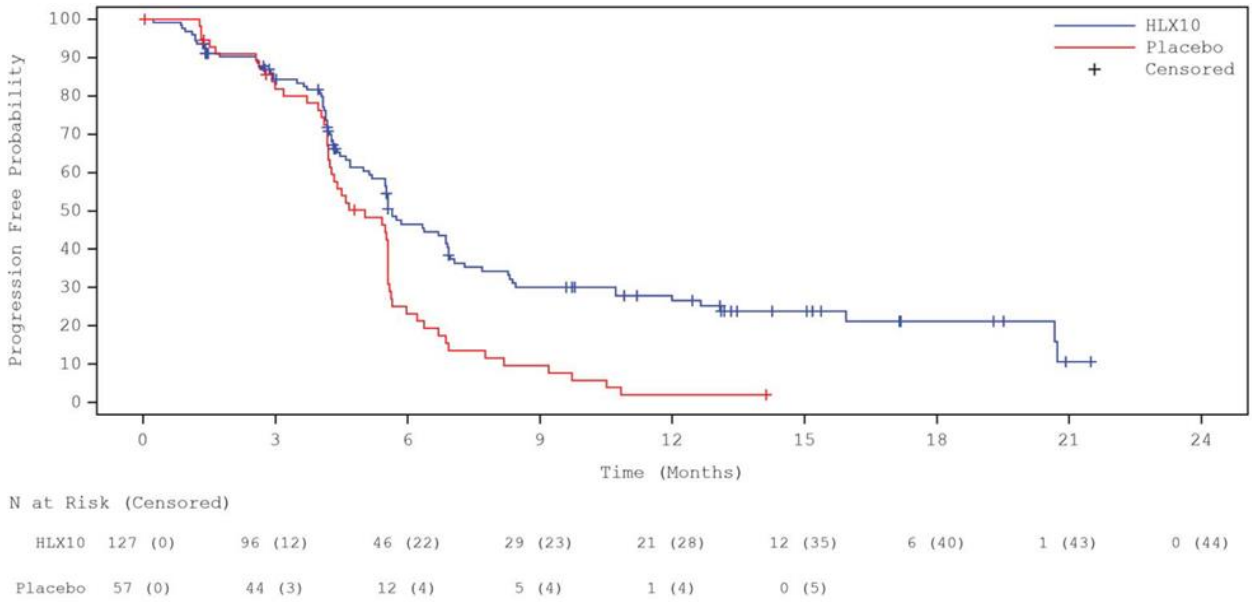
PFS

Primary analysis (DCO 22 Oct 2021): Analysis of PFS was assessed by IRRC according to RECIST 1.1 at interim analysis. The median PFS (95% CI) was 5.6 (4.4, 6.1) months in the serplulimab group and 4.7 (4.2, 5.6) months in the placebo group. The stratified HR (95% CI) was 0.76 (0.52, 1.10).

Updated analysis (DCO 13 Jun 2022): The median PFS (95% CI) according to RECIST 1.1 as evaluated by IRRC was 5.7 (5.1, 6.9) months in the serplulimab group and 5.0 (4.2, 5.6) months in the placebo group. The stratified HR (95% CI) was 0.54 (0.37, 0.79). PFS by IRRC is shown in Kaplan-Meier curve below.

The median PFS (95% CI) according to RECIST 1.1 by investigators was 5.6 (4.4, 6.1) months in the Serplulimab group and 4.7 (4.2, 5.6) months in the placebo group. The stratified HR (95% CI) was 0.70 (0.50, 0.997).

Figure 11. Kaplan-Meier curve of progression-free survival by IRRC according to RECIST 1.1 in non-Asian (ITT Population) (Updated Analysis – DCO 13 Jun 2022)



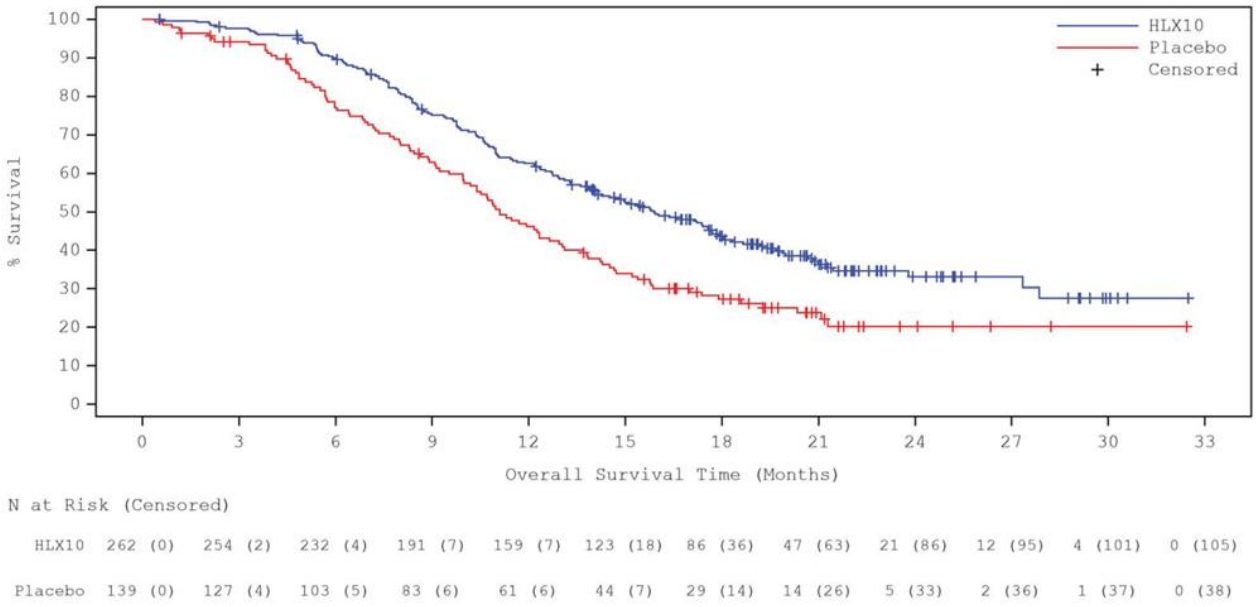
Asian subgroup

OS

Primary analysis (DCO 22 Oct 2021): the median survival (95% CI) was 16.0 (13.3, NA) in the serplulimab group versus 11.1 (10.0, 14.5) in the placebo group [HR 0.62 (95% CI: 0.46, 0.85)]. Forest plot is shown in Figure 16.

Updated analysis (DCO 13 Jun 2022): the median duration of follow-up in Asian population was 21.0 months. The median survival (range) was 15.9 (13.9, 17.9) in the serplulimab group vs. 11.1 (10.0, 13.0) in the placebo group [HR 0.65 (95% CI: 0.51, 0.84)]. Kaplan-Meier curve is shown below.

Figure 12. Kaplan-Meier curve of overall survival in Asian (ITT Population) (Final Analysis – 13 June 2022)

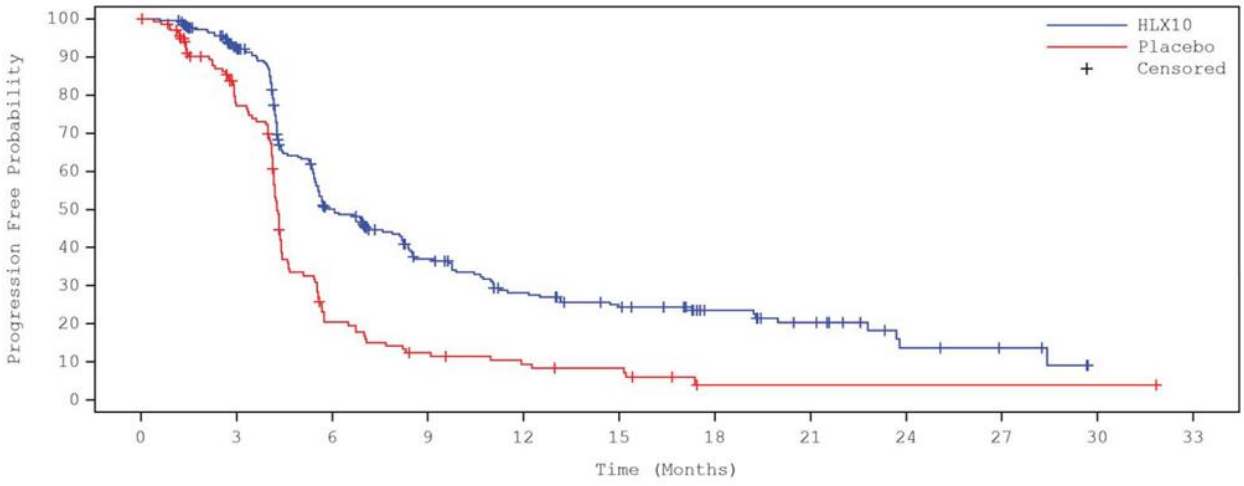


PFS

Primary analysis (DCO 22 Oct 2021): analysis of PFS was assessed by IRRC according to RECIST 1.1. The median (95% CI) PFS according to RECIST 1.1 as evaluated by IRRC was 5.8 (5.5, 7.6) months in the serplulimab group and 4.3 (4.2, 4.4) months in the placebo group. The stratified HR (95% CI) was 0.45 (0.35, 0.59).

Updated analysis (DCO 13 Jun 2022): analysis of PFS was assessed by IRRC according to RECIST 1.1. The median (95% CI) PFS according to RECIST 1.1 as evaluated by IRRC was 6.1 (5.5, 8.1) months in the serplulimab group and 4.3 (4.2, 4.4) months in the placebo group. The stratified HR is unchanged from interim analysis.

Figure 13. Kaplan-Meier curve of progression-free survival by IRRC according to RECIST 1.1 in the Asian subgroup (ITT Population) (Updated Analysis – DCO 13 June 2022)



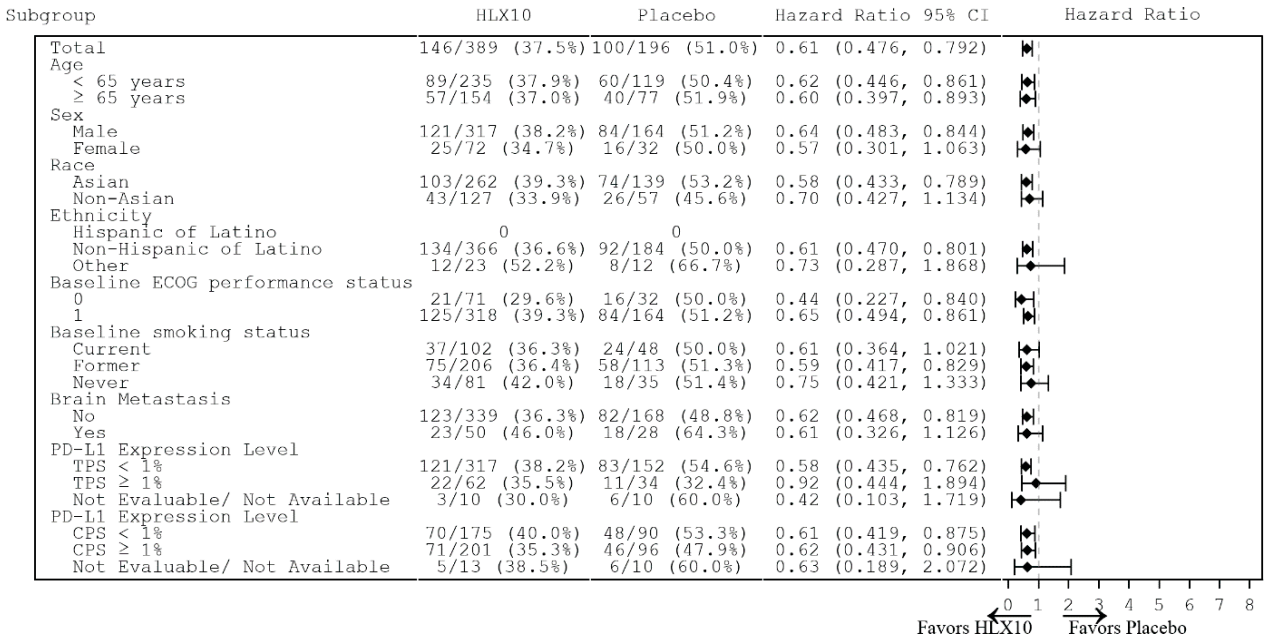
N at Risk (Censored)

HLX10	262 (0)	211 (33)	103 (48)	66 (60)	46 (65)	36 (69)	23 (81)	16 (85)	6 (92)	4 (94)	0 (97)	
Placebo	139 (0)	94 (16)	23 (20)	13 (21)	9 (22)	7 (23)	1 (26)	1 (26)	1 (26)	1 (26)	1 (26)	0 (27)

- **Ancillary analyses**

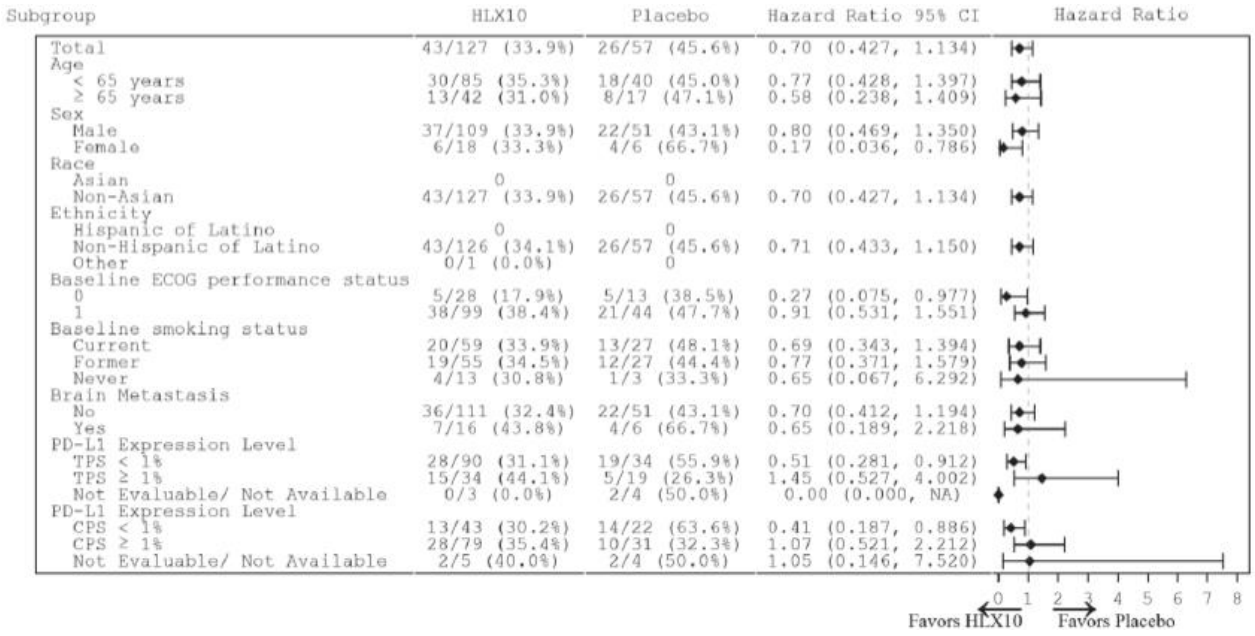
Forest plots of OS for subgroup analyses for all comers, non-Asians and Asians are shown below.

Figure 14. Forest plot of OS (ITT Population) (Primary Analysis – DCO 22 Oct 2021)



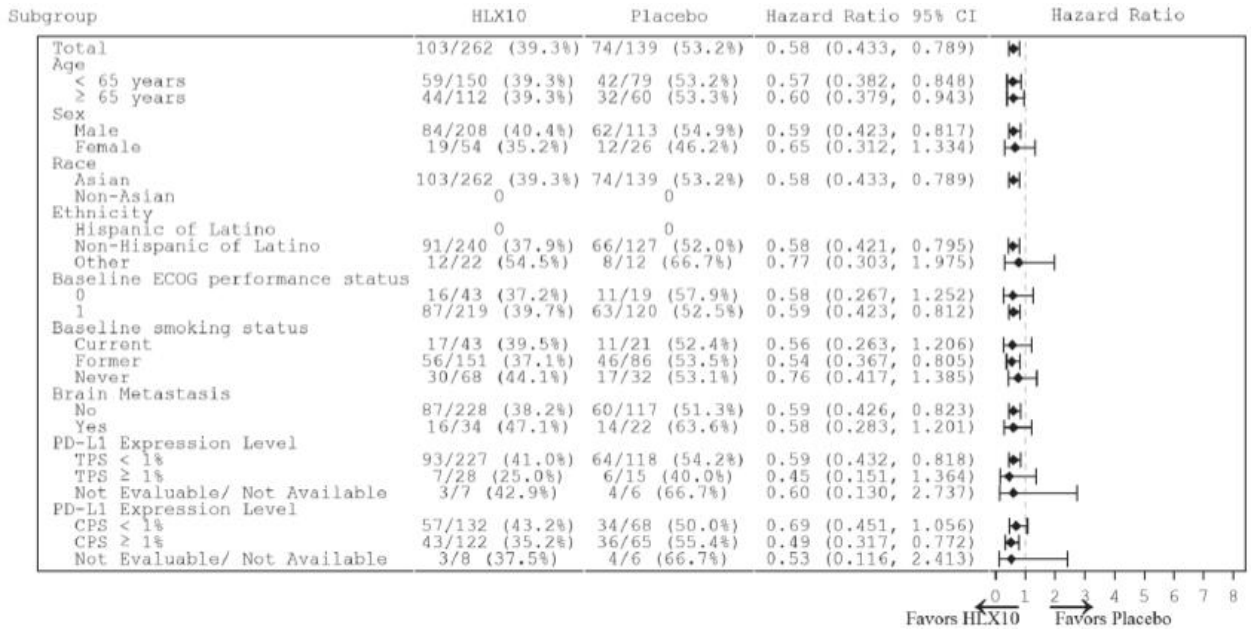
Abbreviations: CI: confidence interval, CPS: combined positive score, ECOG: Eastern Cooperative Oncology Group, ITT: intent to treat, OS: overall survival, PD-L1: programmed death ligand 1, TPS: tumour proportion score.

Figure 15. Forest plot of OS in non-Asian subgroup (ITT Population) (Primary Analysis – DCO 22 Oct 2021)



Abbreviations: TPS: Tumour proportion score, CPS: Combined positive score.

Figure 16. Forest plot of OS in Asian subgroup (ITT Population) (Primary Analysis – DCO 22 Oct 2021)



Abbreviations: TPS: Tumour proportion score, CPS: Combined positive score.

- **Summary of main efficacy results**

The following table summarise the efficacy results from the main study supporting the present application. This summary 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 ASTRUM-005

Title: A randomised, double-blind, multicentre, phase III study to compare clinical efficacy and safety of serplulimab (recombinant humanised anti-PD-1 monoclonal antibody injection) in combination with chemotherapy (carboplatin-etoposide) in previously untreated patients with extensive stage small cell lung cancer (ES-SCLC)		
Study identifier	EudraCT Number: 2019-003063-21	
Design	Randomised, double-blind, placebo-controlled, multicentre, phase III study to compare the clinical efficacy, safety, and tolerability of serplulimab (recombinant humanised anti-PD-1 monoclonal antibody injection) with placebo in combination with chemotherapy in patients with previously untreated ES-SCLC.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 Sep 2019–present not applicable not applicable
Hypothesis	Superiority	

Treatments groups	Serplulimab group		Serplulimab + chemotherapy (carboplatin-etoposide). N=389 Chemotherapy was administered for a maximum of 4 cycles. Subjects were treated with serplulimab in combination with chemotherapy once every 3 weeks, until disease progression, death, intolerable toxicity, withdrawal of informed consent (whichever occurs first).
	Placebo group		Placebo + chemotherapy (carboplatin-etoposide) N=196 Chemotherapy was administered for a maximum of 4 cycles. Subjects were treated with placebo in combination with chemotherapy once every 3 weeks, until disease progression, death, intolerable toxicity, withdrawal of informed consent (whichever occurs first).
Endpoints and definitions	Primary endpoint	OS	Defined as a period from randomisation to death regardless of causality.
	Secondary endpoint	PFS by IRRC	PFS assessed by the independent radiology review committee based on RECIST 1.1.
	Secondary endpoint	PFS by investigators	PFS assessed by investigators based on RECIST 1.1.
	Secondary endpoint	Confirmed ORR by IRRC / investigators	Confirmed objective response rate assessed by the IRRC/Investigator based on RECIST 1.1. Confirmed CR/PR may be claimed if the CR/PR criteria are met at a subsequent time point of at least 4-week.
	Secondary endpoint	DOR by IRRC	Duration of confirmed response assessed by the IRRC based on RECIST 1.1
	Secondary endpoint	DOR by investigators	Duration of confirmed response assessed by the investigator based on RECIST 1.1.
Results and Analysis			
Analysis description	**Primary Analysis**		
Database lock	22 October 2021		
Analysis population and time point description	Intent-to-treat (ITT) population. The ITT population was defined as all subjects who were randomised. Results from the interim analysis		
Descriptive statistics and estimate variability	Treatment group	Serplulimab group	Placebo group
	Number of subjects	389	196

	Median OS, months	15.4	10.9
	95% CI	13.3, NA	10.0, 14.3
	Median PFS by IRRC	5.7	4.3
	95% CI	5.5, 6.9	4.2, 4.5
	Median PFS by investigators	5.5	4.3
	95% CI	4.9, 5.7	4.2, 4.4
	Confirmed ORR by IRRC (%)	67.4	58.7
	95% CI	62.4, 72.0	51.4, 65.6
	Median DOR by IRRC	5.8	4.1
	95% CI	5.2, 7.5	3.0, 4.2
Effect estimates per comparison	OS	Comparison groups	Serplulimab group vs placebo group
		Hazard Ratio	0.63
		95% CI	0.49, 0.82
		P-value	< 0.001
	PFS by IRRC	Comparison groups	Serplulimab 10 group vs placebo group
		Hazard Ratio	0.48
		95% CI	0.38, 0.59
	PFS by investigators	Comparison groups	Serplulimab 10 group vs placebo group
		Hazard Ratio	0.58
		95% CI	0.48, 0.71
	Confirmed ORR by IRRC	Comparison groups	Serplulimab group vs placebo group
		Odds Ratio	1.58
		95% CI	1.10, 2.26
	DOR by IRRC	Comparison groups	Serplulimab group vs placebo group
		Hazard Ratio	0.48
		95% CI	0.33, 0.58
Notes	The primary endpoint reached prespecified statistical significance (alpha: 0.012) in the interim analysis. The median OS showed an improvement of 4.5 months in the seriplulimab group.		
Analysis description	**Updated analysis**		
Database lock	13 June 2022		

Analysis population and time point des.	Intent to treat population. The ITT population was defined as all subjects who were randomised. Results from the updated analysis		
Descriptive statistics and estimate variability	Treatment group	Serplulimab group	Placebo group
	Number of subjects	389	196
	Median OS, months	15.8	11.1
	95% CI	14.1, 17.6	10.0, 12.4
	Median PFS by IRRC	5.8	4.3
	95% CI	5.5, 6.9	4.2, 4.5
	Median PFS by investigators	5.5	4.3
	95% CI	5.0, 5.7	4.2, 4.4
Effect estimates per comparison	OS	Comparison groups	Serplulimab group vs placebo group
		Hazard Ratio	0.62
		95% CI	0.50, 0.76
	PFS by IRRC	Comparison groups	Serplulimab group vs placebo group
		Hazard Ratio	0.47
		95% CI	0.38, 0.58
	PFS by investigators	Comparison groups	Serplulimab group vs placebo group
		Hazard Ratio	0.58
		95% CI	0.48, 0.70

2.6.5.3. Clinical studies in special populations

Of the 389 study subjects in treatment arm from the overall population, 153 (39%) were older than 65 years. According to the applicant, no overall differences in efficacy were observed between elderly and younger study subjects.

Table 31. Summary of age profile

Type	**Age <65 n(%)**	**Age 65-74 n(%)**	**Age 75-84 n(%)**	**Age >=85 n(%)**
Controlled trials[a]	488 (59.2)	308 (37.4)	28 (3.4)	0
Non-controlled trials[b]	293 (84.2)	51 (14.7)	4 (1.1)	0
All	781 (66.6)	359 (30.6)	32 (2.7)	0

a: Applicable studies including HLX10-004-NSCLC303, HLX10-005-SCLC301.
b: Applicable studies including HLX10-001, HLX10-008-HCC201, HLX10-010-MSI201, HLX10-011-CC201, HLX10HLX04-001, HLX10HLX07-001.
- Percentage is based on the safety population as denominator.
- Total patients include all the patients treated at least one dose with serplulimab.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

The distribution of PD-L1 expression level in pivotal study population is shown in table below.

Table 32. Distribution of PD-L1 expression level in ES-SCLC according to TPS and CPS (ITT Population)

	Serplulimab Group (N=389)	Placebo Group (N=196)	Total (N=585)
TPS, n (%)			
TPS < 1%	322 (82.8)	154 (78.6)	476 (81.4)
1% ≤ TPS < 5%	29 (7.5)	18 (9.2)	47 (8.0)
5% ≤ TPS < 10%	16 (4.1)	3 (1.5)	19 (3.2)
10% ≤ TPS < 25%	6 (1.5)	7 (3.6)	13 (2.2)
25% ≤ TPS < 50%	5 (1.3)	1 (0.5)	6 (1.0)
TPS ≥ 50%	2 (0.5)	3 (1.5)	5 (0.9)
Not Evaluable/Available	9 (2.3)	10 (5.1)	19 (3.2)
CPS, n (%)			
CPS < 1%	175 (45.0)	90 (45.9)	265 (45.3)
1% ≤ CPS < 5%	89 (22.9)	49 (25.0)	138 (23.6)
5% ≤ CPS < 10%	42 (10.8)	22 (11.2)	64 (10.9)
10% ≤ CPS < 25%	47 (12.1)	12 (6.1)	59 (10.1)
25% ≤ CPS < 50%	12 (3.1)	9 (4.6)	21 (3.6)
CPS ≥ 50%	11 (2.8)	4 (2.0)	15 (2.6)
Not Evaluable/Available	13 (3.3)	10 (5.1)	23 (3.9)

Abbreviations: TPS: Tumour proportion score, CPS: Combined positive score. Source: CSR, table 99.

Tumour proportion score (TPS)

The HR (95% CI) of OS was 0.59 (0.47, 0.75) in subjects with baseline TPS < 1% and 0.76 (0.42, 1.38) in those with baseline TPS ≥1%. Outcomes of tumour proportion score are shown for all comers in the ITT analysis set for overall survival below.

Figure 17. Kaplan-Meier curves of OS by TPS score in all comers (ITT Population) (DCO 22 Oct 2021)

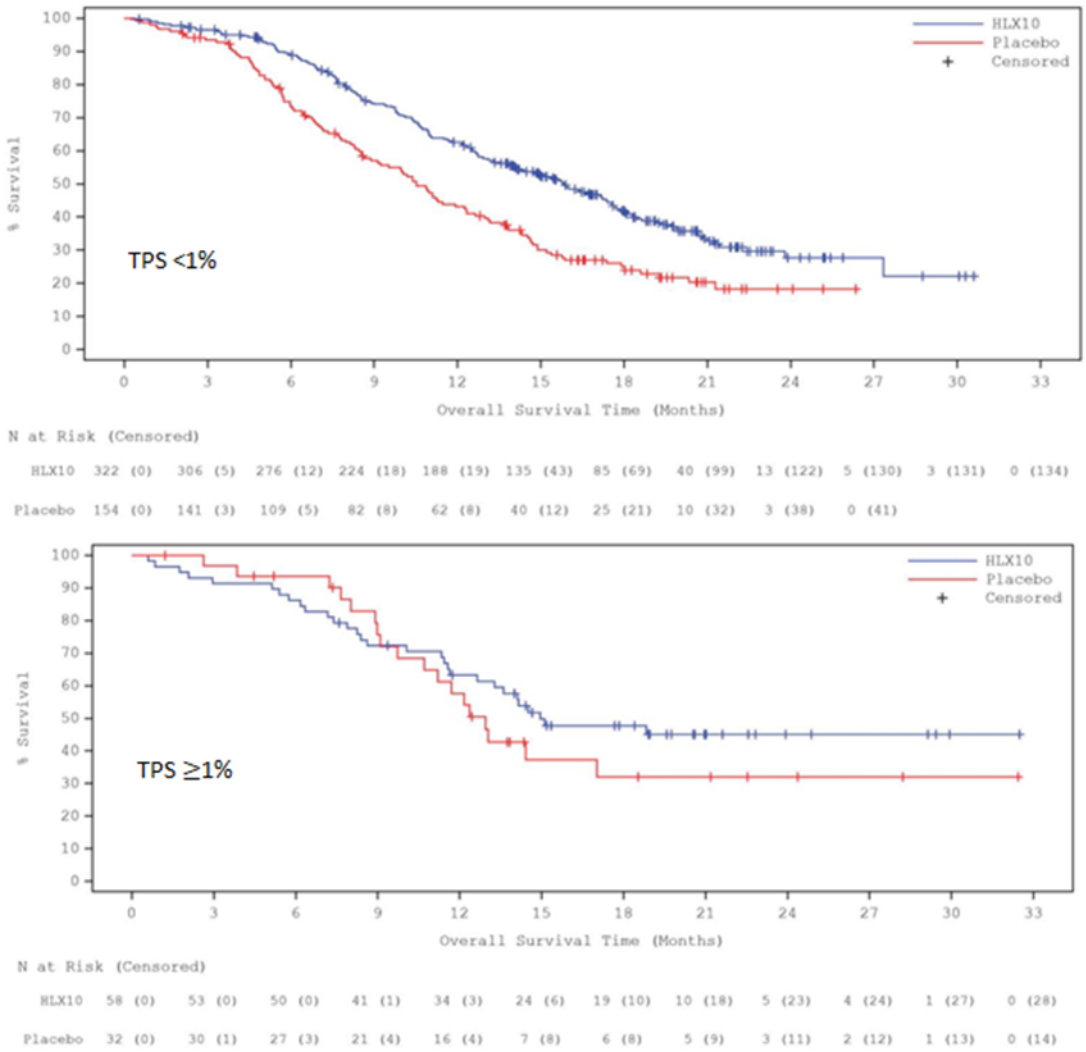


Table 33. OS according to PD-L1 expression level (CPS) subgroup analysis in all comers (ITT Population) (Updated Analysis - DCO 13 Jun 2022)

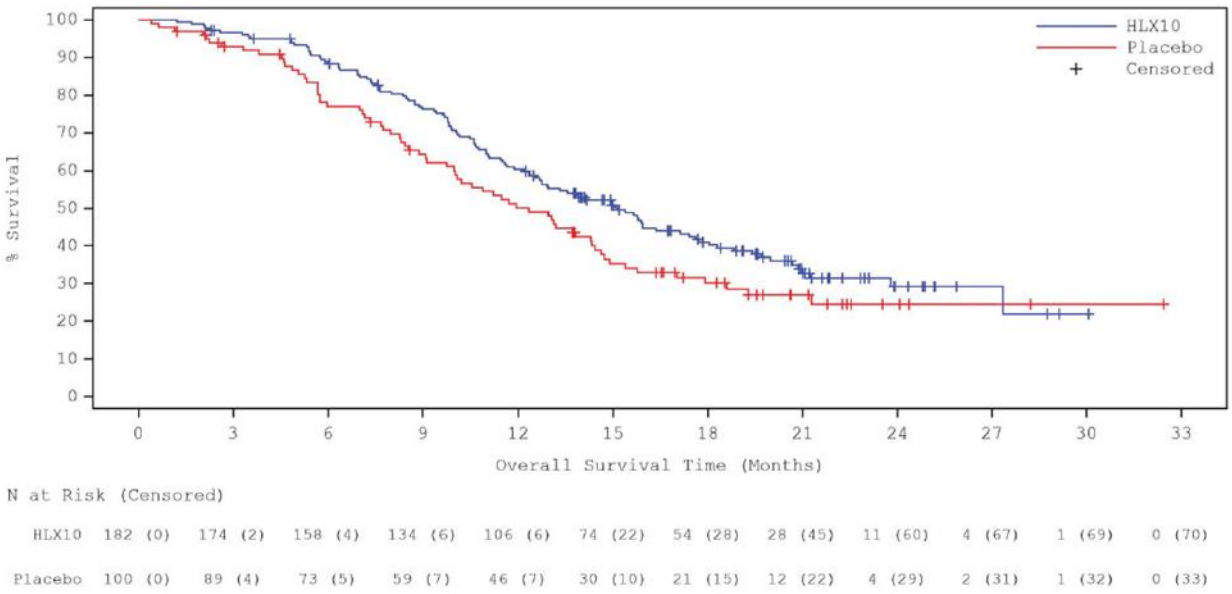
	HLX10 (N=389)				Placebo (N=196)				
Characteristic	n (%)	Events	Median[1] (Month)	95% CI	n (%)	Events	Median[1] (Month)	95% CI	Hazard Ratio[2] (95% CI)
PD-L1 Expression Level									
CPS < 1%	175 (45.0)	110	14.16	(12.517, 16.427)	90 (45.9)	66	9.99	(7.688, 11.926)	0.65 (0.477, 0.879)
1%≤ CPS < 10%	131 (33.7)	77	15.93	(12.945, 18.825)	71 (36.2)	52	11.10	(9.101, 13.799)	0.61 (0.427, 0.866)
CPS ≥ 10%	70 (18.0)	29	NA	(14.423, NA)	25 (12.8)	13	14.65	(10.053, NA)	0.65 (0.338, 1.259)

[1] Median was product-limited (Kaplan-Meier) estimate. [2] The hazard ratio and its 95% CI were estimated by (unstratified) Cox proportional hazards model. HLX10 = serplulimab

Microsatellite status instability (MSI)

The HR (95% CI) of OS was 0.75 (0.55, 1.01) in subjects with MSS or MSI-L and 0.41 (0.13, 1.26) in those with MSI-H. The HR (95% CI) after adjusting for TMB at baseline was 0.76 (0.57, 1.01).

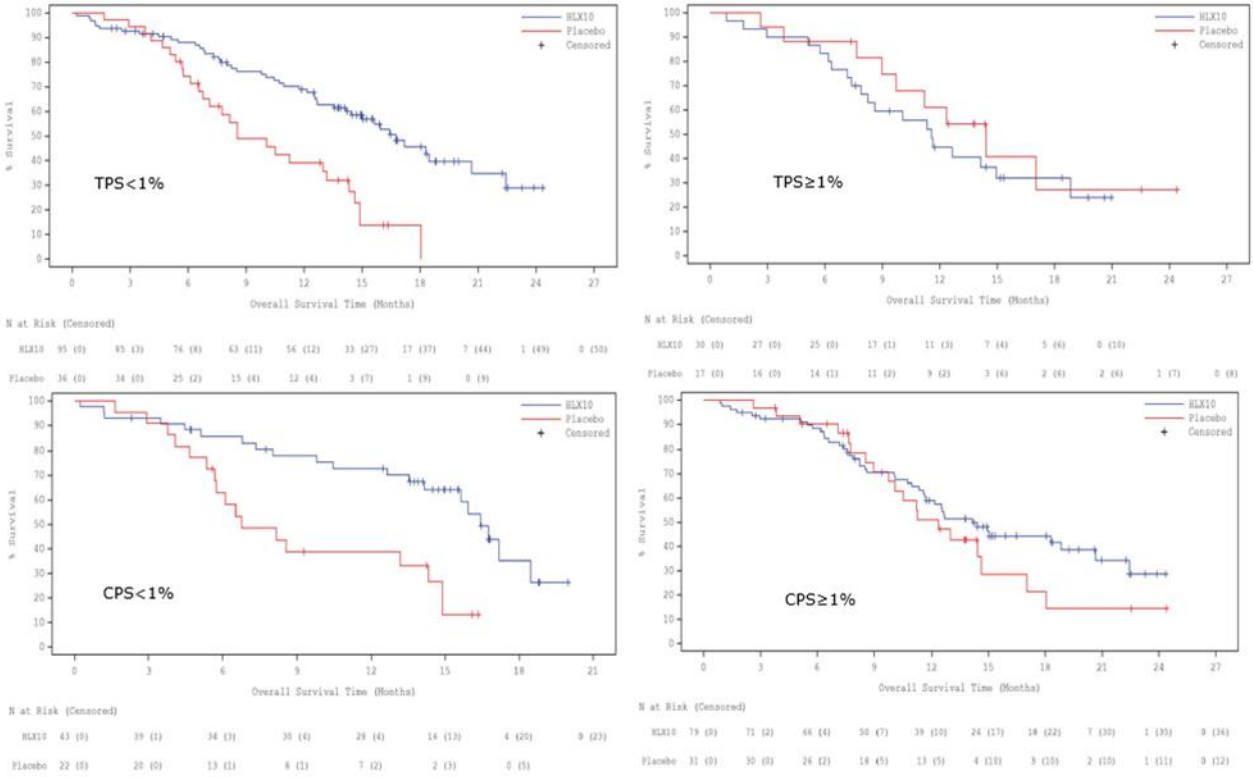
Figure 18. Kaplan-Meier curve of OS according to MSI status at baseline in all comers (ITT Population) (DCO 13 Jun 2022)



Non-Asian subgroup

The overall survival according to TPS and CPS in the non-Asian subgroup are shown in the figure below.

Figure 19. Kaplan-Meier curves of OS in non-Asians according to TPS and CPS score (DCO 13 Jun 2022)



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

Not applicable.

2.6.5.6. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

<u>HLX10-001 (dose response study)</u>

A saturation of PD effects was observed already at the lowest dose of 0.3 mg/kg. The relationship between IL-2 secretion/receptor occupancy and efficacy has, however, not been established. Consequently, the dose-exposure-response relationship for serplulimab has not been well characterised, and limited data are available for identifying the therapeutic range and the most well-balanced dose regimen with respect to efficacy and safety. Notably, there is a large discrepancy between the lowest dose needed to achieve a high level of PD1 receptor occupancy and the pivotal study dose, which is 11 to 12 times higher than the receptor occupancy dose. Also, results of the D-E-R study HLX10-001 may encumber uncertainty, since the proportion of discontinuations was as high as 91% and 1/3 of study participants are not accounted for (16 subjects [28% of included]). For further assessment of the dose rationale, refer to the Clinical pharmacology section.

The recommended dose as indicated in section 4.2 of the SmPC is 4.5 mg/kg serplulimab every 3 weeks until disease progression or unacceptable toxicity.

ASTRUM-005 / HLX10-005-SCLC301 (main study)

Study design

The pivotal study (ASTRUM-005) was a phase III, randomised, double-blind and placebo-controlled trial. The objective of the study was to compare the efficacy and safety of serplulimab in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy in treatment-naïve patients with ES-SCLC. The ASTRUM-005 trial was designed to show superiority using 2:1 allocation of patients to the serplulimab and placebo groups.

A total of 585 subjects were included, of whom 389 subjects were randomised to serplulimab and chemotherapy and 196 subjects were randomised to placebo and chemotherapy. The platinum-based chemotherapy consisted of carboplatin and etoposide for up to 4 cycles, while serplulimab/placebo was continued as maintenance. The selected background chemotherapy regimen is considered appropriate. However, for the EU patients, the treatment regimen for the comparator arm may have limitations. According to the 2021 ESMO treatment guideline, for patients who respond to chemotherapy, cranial prophylactic irradiation and consolidation thoracic radiation are treatment options. It is unclear if such treatments could be offered in ASTRUM-005. Therefore, subjects may have received a suboptimal treatment according to protocol. The applicant claims that consolidation thoracic radiation is a palliative radiotherapy (non-target) option. Further, the applicant states that cranial prophylactic irradiation was allowed in the pivotal study, which are in line with earlier studies in ES-SCLC. Yet, according to the CSR, it is not clear that these therapies were allowed. Even though current standard-of-care in first line is carbo/cisplatin + etoposide + anti-PD-L1 treatment (atezolizumab or durvalumab), this was not the case when the pivotal trial for serplulimab was designed and carried out, so the selected chemotherapy regimen for the control arm is acceptable.

Subsequent serplulimab/placebo treatment following progressive disease was implemented as optional by choice of the investigators. From a methodological point of view, continuation of study treatment post-progression is problematic as it may introduce heterogeneity to treatment as well as potential bias (e.g., investigator-introduced and/or protocol-introduced selection bias), especially since the study treatment was unblinded following interim analysis. In addition, there could be risk of early treatment unblinding due to reconsideration of treatment effects and AEs by the investigators. Furthermore, second-line treatment with serplulimab is beyond the sought indication, and it may obscure the true magnitude of efficacy in 1L setting. Whilst subsequent treatment is usually challenging in most cancer trials, it may be warranted in some clinical situations such as pseudo-progression.

Overall, the design of Study ASTRUM-005 is in line with the Scientific Advice (SA). The primary endpoint OS is a valid and reliable measure of clinical benefit in the intended patient population. Of note, the primary endpoint was changed from PFS to OS following the initial SA. Most patients (82%) had vital status ascertainment within the last 3 months of DCO. There was a slight imbalance between treatment arms with 84% in the serplulimab arm and 73% in the placebo arm. Patients with more than 6 months since vital status ascertainment were mainly lost to follow-up or withdrawn.

The SCLC diagnosis was based on tumour tissue, preferably larger formalin-fixed samples, and a pathology report. The SCLC diagnosis and biomarker status was confirmed by the central laboratory in the majority of study subjects. In all-comers, histology samples were the basis of diagnosis (n=579, 99%) and cytology samples were only infrequently applied (n=6, ~1%). The central analysis of re-examined pathology samples was consistent with the local SCLC-diagnosis in 94.7%.

In general, the inclusion/exclusion criteria are appropriate, except from inclusion of patients relapsing to ES-SCLC after having received systemic therapy for limited disease. These subjects are expected to

benefit less from a new systemic therapy compared to treatment-naïve subjects. As only 2.1% of patients fulfilled this criterion at study inclusion, the impact on serplulimab-efficacy is likely negligible.

The IRRC that assessed imaging before randomisation (i.e., to determine whether at least one measurable lesion was present) was the same team that assessed post-baseline imaging. The IRRC consisted of two independent radiologists that were blinded to patient identification and treatment allocation. In case of disagreement the assessment most agreed upon with justifying comments was chosen by a third independent radiologist. The concordance between the two radiologists was approximately 80% which is considered acceptable.

In the pivotal study, the potential for interval censoring and interval detected progression is substantial, due to the rapid progression of ES-SCLC and relatively extended interval (i.e., 6 weeks) between tumour imaging and assessment. The applicant has provided sensitivity analyses of PFS, PFS2 and DOR where progression is imputed at the midpoint time between two scheduled assessments and at the day after the previous assessment. The sensitivity analyses are generally consistent with the original analyses (data not shown).

Patient population

In general, the study population reflects well the intended treatment population. The study population comprised Asian patients (n= 401, 69%) and non-Asian (Caucasian) patients (n=184, 31%). Non-Asian subjects were included from study sites in Georgia, Russia, Ukraine, Turkey, and Poland. Initially, study sites outside China were planned in the US and Italy, among other sites, but these sites were never included. Only 7 subjects from the EU were included in the study, of whom 4 received serplulimab (1.2% of study population). The low number of European patients was considered insufficient in SA to adequately demonstrate the relevance of results for EU patients. Of note, the applicant's proposal to largely perform the study in China, with about 65% of patients in this region, was not rejected by the SAWP (EMEA/H/SA/4295/2/2019/II). However, the applicant was to demonstrate that the efficacy and safety results were relevant for EU patients and medical practice.

According to the applicant, the PK and PD properties of serplulimab could indicate that it is less likely to be sensitive to intrinsic ethnic factors based on the ICH guideline (CPMP/ICH/289/95) and hence, no additional clinical bridging study would be required to allow extrapolation of the foreign clinical data to the EU. Nevertheless, due to potential ethnic differences in response to study treatment between Asian and non-Asian subjects, extrapolation of overall results to patients of non-Asian origin may be challenging. Cumulative evidence suggests that Asian and Caucasian patients with lung cancer are different in terms of epidemiology, genetic susceptibility, molecular profiles, and clinical outcomes in terms of response or toxicity to chemotherapy and targeted agents, and prognosis. In several reported clinical studies, ethnical differences have been observed between Asian and non-Asian ES-SCLC patients. A meta-analysis (Peng, 2020) showed improved survival benefit of PD-1/PD-L1 inhibitor-based therapy in Asians compared to non-Asians. In addition, a US cohort study (Zhou, 2021) of subjects with limited stage SCLC suggests a more favourable efficacy outcome in Asian patients compared to non-Asian patients. It may thus be assumed that the efficacy results for serplulimab could be subject to the same trend in Asian vs. non-Asian subgroups.

Study conduct

The interim analysis was pre-planned and discussed in SA. The IDMC did at its 7 December 2021 meeting review the interim analysis and concluded that the study met its primary objective. They recommended that the study continue as planned, but also recommended for sponsor to communicate with regulatory authorities. The sponsor was given access to randomisation codes and unblinded data

and opted to file the interim analysis for MA application to Chinese authorities with unblinding and database lock dated to 15 December 2021. The interim analysis is therefore the primary analysis. The study was nevertheless continued as recommended by IDMC and more mature data from the updated analysis support the interim findings. It cannot be excluded that interim results became available to investigators as well, and data collected after interim must be considered open label and treated as supportive of the primary analysis.

In total 35% of the 894 subjects screened were screening failures. Most of the patients who failed screening did not fulfil eligibility requirements. There was an unusually high proportion of patients who could not provide informed consent or complete all trial procedures (22%).

Due to a concern regarding the reliability of study results based on the applicant's documentation and lack of regulatory experience with studies conducted outside of the EU/EEA, GCP inspections of the pivotal study ASTRUM-005 were requested. Three onsite GCP inspections were conducted Feb to April 2024, one in Georgia, one in China, and the Chinese sponsor site. The outcomes of those GCP inspections were concluded by the reporting inspector in IIR (Integrated Inspection Report, EMA/IN/0000162716), which was released to the sponsor Jul 2024. A total of 22 findings were cited, including 2 critical, 7 major and 13 minor. The inspection team did not identify any restrictions on the usability of the reported efficacy or safety data, and they recommended that the data of the pivotal trial could be used for evaluation and assessment of the application.

Efficacy data and additional analyses

Baseline characteristics

Only 18% of the participants enrolled in the pivotal study were females. Notably, in the non-Asian subgroup only 24 of 184 subjects (13%) were females. In comparison with the studies of atezolizumab and durvalumab, the proportion of females were 35% and 30%, respectively. The low proportion of female participants enrolled may not reflect a future proportion of female subjects in the intended EU population.

Additionally, ~20% of study subjects were never-smokers, which highly contrasts to the fact that SCLC has the strongest association with smoking among all lung cancers and that only ~2-3% of patients with SCLC are expected to be never-smokers. This cannot be explained by the expected cultural differences in smoking habits between Asian and Caucasian subjects. In published studies comparing OS in smoker and never-smoker SCLC patients, different efficacy outcomes have been reported. While some suggest comparable outcomes, some reported more favourable efficacy in the latter. Some authors speculated that the reasons of more favourable OS in never-smokers may be associated with potential misdiagnosis (i.e., inclusion of patients with other than SCLC). Although the subgroup analyses of ASTRUM-005 suggest no clear differences in OS between smokers and never-smokers, these data could potentially be biased due to e.g., error in diagnosis. The applicant claims that 111 of 116 never-smokers, the SCLC diagnosis was confirmed at central lab.

In the non-Asian subgroup of the serplulimab arm, mean time from diagnosis was longer compared to the placebo arm (1.2 months vs 0.6 months, respectively), and more subjects with long observation time (≥6 months) were included in the serplulimab arm (3.9% vs 0%, respectively). This could possibly be related to early deaths observed in the non-Asian subgroup which is clearly evidenced in the KM curve (refer to OS outcomes below for further information).

In total, 37 (6%) subjects were reported as lost to follow-up, and equally balanced between treatment and control. This is within what may be expected in a phase III clinical trial. However, there is a large difference in the proportion of subjects lost to follow-up in the non-Asian subgroup (11.4%) vs. the Asian subgroup (4%).

As a further illustration of the multifaceted interpretation uncertainty, most non-Asian patients likely received a higher dose of serplulimab as consequence of the weight-based posology and higher weight in non-Asians compared to Asians (see section 'Discussion of clinical pharmacology').

OS outcomes

The **interim analysis** of the primary endpoint was planned at 226 events and conducted when 246 events had occurred. The OS maturity was 42% in the overall population, 38% in the non-Asian subgroup and 44% in the Asian subgroup at data cut-off date of Oct-2021.

At DCO for the **primary analysis**, the median follow-up time was 12.3 months. The median OS for the overall population was 15.4 months in the serplulimab group and 10.9 months in the placebo group, with HR (95% CI) of 0.63 (0.49, 0.82), p<0.001. The increase in median OS of 4.5 months in the serplulimab group is considered clinically meaningful for the intended population. Notably, the KM survival curves demonstrated a separation after ~ 4 months of treatment in favour of the serplulimab group. This suggests a relatively early onset of efficacy following add-on immunotherapy with serplulimab and is considered clinically relevant, having in mind the poor prognosis of patients with ES-SCLC. In the non-Asian subgroup, the median follow-up time was 9.1 months. The median OS was 12.5 months in the serplulimab group and 10.5 months in the placebo group with a difference between medians of 2.0 months and HR (95% CI) of 0.70 (0.41, 1.18). These findings show a trend in line with the overall population. However, the KM curve for the non-Asian subgroup differs from that for the overall population for the first 4 months due to more events in the serplulimab arm. At ~4 months the curves cross. According to the applicant, the early deaths are not likely caused by Covid-19. This imbalance could be by chance or possibly due to differences between the study arms in baseline characteristics such as maximum time from diagnosis. This phenomenon of early deaths following immunotherapy is evident in other studies as well and may indicate slow onset of effect. Notably, the slow onset of immunotherapy effect does not explain the more frequent deaths.

The **updated analysis** of the primary endpoint was planned at 342 events and was conducted when a total of 363 events had occurred. The OS maturity was 62% in the overall population, 57% in the non-Asian subgroup and 64% in the Asian subgroup at data cut-off date (DCO) of Jun-2022.

At DCO for the updated analysis, the median follow-up time was 19.7 months. The median OS for the overall population was 15.8 months in the serplulimab group and 11.1 months in the placebo group, with HR (95% CI) of 0.62 (0.50, 0.76). The mature data of the updated analysis from the pivotal study are concordant with the primary analysis. For the non-Asian subgroup, these findings were consistent with the observed efficacy in the overall population.

Findings from previously reported studies in SCLC patients indicate that the efficacy of immunotherapy including PD-L1 inhibitors may be less favourable in non-Asians compared to Asians. Study ASTRUM-005 was designed and powered to demonstrate efficacy in the overall population, and the results of the non-Asian and Asian subpopulations are well within the observed efficacy in the overall population and what is to be expected of subpopulations with equivalent response. This study was not designed to elucidate potential ethnical differences in response and the findings do not give rise to a concern that there could be a difference in response for the non-Asian subgroup. Consequently, although the non-Asian (Caucasian) subgroup included only 4 European patients receiving serplulimab and the magnitude of the OS estimate is associated with uncertainty, the OS data can be considered relevant for the intended population in the EU, as serplulimab is less likely to be sensitive to intrinsic ethnic factors as described above.

Secondary outcomes

PFS and the other secondary endpoints (PFS2, ORR, DOR) were treated as exploratory in this study. At data cut-off Jun-2022 the observed benefit of PFS by IRRC in the overall population showed a difference in median PFS of 1.4 months in the serplulimab group compared to the placebo group with HR (95% CI): 0.47 (0.38-0.58). For the non-Asian subgroup, the difference in median PFS was 0.7 months in favour of serplulimab with HR (95% CI): 0.54 (0.37, 0.79), and for the Asian subgroup the difference in median PFS was 1.8 months in favour of serplulimab with HR (95% CI): 0.45 (0.35, 0.59). The KM curves separated at ~ 4-5 months in all groups. Despite an apparent discrepancy in difference in median PFS for the subgroups, the HRs are within what is observed in the overall population and what is to be expected of subpopulations with equivalent response.

The intercurrent events and censoring rules presented in the CSR were not agreed and the applicant presented updated analyses for PFS, DOR and PFS2 based on treatment policy strategy. Specifically, there was a concern that there was a large discrepancy in number of patients censored in the IRRC and Investigator analyses because patients who were assessed as PD by investigator and thereby started on next line therapy were censored by IRRC if they had not assessed these patients to PD prior to new therapy. In the original hypothetical PFS analysis 82 patients were censored by IRRC and 18 patients were censored by investigator when starting next line therapy prior to progression. Of these patients, 10 patients were censored by investigator and 45 patients were censored by IRRC at database lock using treatment policy. It seems that many of the patients assessed as PD by investigator and started on next line therapy were never assessed as PD by IRRC. There is therefore still a large discrepancy in assessment by investigator and IRRC. The updated analysis of PFS by IRRC according to treatment policy at data cut-off Jun-2022 showed a difference in median PFS of 2.4 months in the serplulimab group compared to the placebo group with HR (95% CI): 0.47 (0.39-0.57). For the non-Asian subgroup, the difference in median PFS was 0.8 months in favour of serplulimab with HR (95% CI): 0.54 (0.37, 0.79). Assessment by IRRC shows a slight increase in median PFS difference, but HR remains the same when using treatment policy compared to the hypothetical strategy. The change is even less by investigator. The same pattern is seen for PFS2 and DOR. Sensitivity analyses where all informative censoring was replaced with an event showed that PFS and DOR by IRRC moved closer to investigator assessment as would be expected since the main difference in the assessments was censoring. Finally, a sensitivity analysis where censoring was handled as event in the treatment arm and censored on last day of follow-up in the placebo arm was provided. This resulted in no difference in PFS between the two arms (results not shown). The tipping point where the two treatments no longer differed was not given.

The applicant has provided concordance estimates for PFS assessment between IRRC and investigator as requested (data not shown). There is low concordance which is a concern considering this is a double-blind study. The applicant has not offered a discussion of the discord as requested. Of note, there seems to be agreement in assessment for the placebo patients, but the patients on serplulimab tend to be assessed as progressing at a higher rate by investigator and thereby given next line treatment. Of note, the treatment policy analysis supplied does not explain the discord as many of the patients originally censored due to next line treatment following PD by investigator were never assessed as PD by IRRC. However, this was not considered to impact the overall benefit-risk assessment, since PFS was a secondary endpoint and OS the primary endpoint.

All secondary endpoints results were generally supportive of the primary endpoint outcomes.

Subgroup analyses

Several exploratory analyses on PD-L1 status have been performed by the applicant: The expression of PD-L1 in tumour tissue (TPS) and in tumour and immune cells combined (CPS). Most study subjects

had low PD-L1 expression, in tumour (TPS<1%: 81%) and in tumour and immune cells (CPS<1%: 45%). The distribution of CPS is, in general, at a higher level compared to the distribution of TPS in pivotal study subjects. This unequal distribution may be interpreted as a noteworthy involvement of immune cells with positive PD-L1 expression. Further, a higher proportion of subjects in the non-Asian subgroup (29%) were PD-L1 positive, compared to the Asian subgroup (11%). In conclusion, the PD-L1 expression status as a prognostic biomarker was of limited value in the pivotal study since PD-L1 expression status seems to be independent of the clinical benefit of serplulimab. This is in line with earlier research findings regarding the association between SCLC treatment with a PD-L1 inhibitor and PD-L1 expression status. The assay applied in the pivotal study is established and the rationale for scoring system and definition of cut-point is reasonable.

External validity

External validity is supported by similar results in trials IMpower133 (atezolizumab + carboplatin + etoposide in a similar patient population) and CASPIAN (durvalumab + cis/carboplatin + etoposide in a similar population). The applicant is recommended to report the results of the study HLX10-005-SCLC301-E, in order to accumulate further information on the efficacy in a non-Asian population and clarify the efficacy size of serplulimab (**REC**). HLX10-005-SCLC301-E is a randomised, open-label study that compares serplulimab in combination with carboplatin and etoposide versus atezolizumab plus chemotherapy in previously untreated US patients with ES-SCLC.

Wording of the indication

The efficacy is considered established in the finally agreed indication, and this has been included in the section 4.1 of the SmPC:

> *Hetronifly in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).*

2.6.7. Conclusions on the clinical efficacy

ASTRUM-005 met its primary endpoint at the interim analysis and showed a significant survival advantage from the addition of serplulimab to carboplatin and etoposide in the first line treatment of patients with ES-SCLC. Survival benefits were observed regardless of tumoral PD-L1 expression and were comparable between Asian and non-Asian patients. Secondary endpoints of PFS, ORR and DOR supported the benefits of added serplulimab.

Mature data from the updated analysis of this pivotal trial are supportive to the primary analysis. Despite the uncertainties related to subsequent treatment and late protocol amendments that might impact data integrity, the difference in median OS of 4.7 months is considered clinically relevant for the intended population.

2.6.8. Clinical safety

The safety of serplulimab for the targeted indication, first-line treatment of adult patients with extensive stage-small cell lung cancer (ES-SCLC), in combination with carboplatin and etoposide, was based primarily on the safety data obtained in the pivotal trial ASTRUM-005 (HLX10-005-SCLC301). In addition, safety data collected from a total of 8 clinical trials of serplulimab in subjects with various types of solid tumours, including the pivotal trial ASTRUM-005, were pooled for analyses.

The original cut-off for safety for the individual studies included in the pooled safety population was 1-2 years ago. The applicant has provided updated summary tables of AEs with cut-off 13 June 2023 for the pivotal study, and for the pooled safety population where cut-off dates of the individual studies

vary (Table 34). As of 13 June 2022, a total of 59 (10.1%) subjects were receiving ongoing treatment in the pivotal study, while 526 (89.9%) subjects had discontinued the study treatment. There are no notable differences in frequencies of adverse events between the cut-off dates 13 June 2022 and 13 June 2023.

The majority of the patients in the clinical trials are Asian. In the pivotal trial, ~30% were non-Asian (White), while in the pooled safety population 22% were non-Asian. In the pivotal trial, 7 subjects from the EU were included, all from Poland.

Table 34. Overview of 8 Clinical Trials of Serplulimab Pooled in Safety Evaluations

Study No.	Title	Study Treatment	Control	Serplulimab Dose	No. of Subjects in Analysis[a]	Study Status	Cutoff Date for Safety Data
HLX10-005-SCLC301 (Pivotal trial for targeted indication)	A Randomized, Double-Blind, Multicenter, Phase III Study to Evaluate HLX10 in Combination with Chemotherapy (Carboplatin-Etoposide) in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC)	Serplulimab with carboplatin-etoposide combination therapy	Placebo with carboplatin-etoposide	4.5 mg/kg, Q3W	Serplulimab: 389 Placebo: 196 Total: 585	Ongoing	13 Jun 2023
HLX10-001	A Prospective Open-label Dose-Escalation Phase I Study to Investigate the Safety and Tolerability, and to Determine the Maximum Tolerated Dose and Recommended Phase II Dose, of HLX10 in Patients with Advanced Solid Tumors	Serplulimab monotherapy	None	0.3 mg/kg Q2W, 1 mg/kg Q2W, 3 mg/kg Q2W, 10 mg/kg Q2W 200 mg Q2W, 300 mg Q3W, 400 mg Q4W	3 4 6 16 9 9 10 Total: 57	Ongoing	1 Aug 2022
HLX10-010-MSI201	A Single-arm, Multi-center, Phase II Clinical Study to Evaluate the HLX10 Monotherapy for the Treatment of Unresectable or Metastatic Microsatellite Instability-high (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors That Failed to Respond to Standard Therapy	Serplulimab monotherapy	None	3 mg/kg, Q2W	108	Ongoing	10 Jul 2021

Study No.	Title	Study Treatment	Control	Serplulimab Dose	No. of Subjects in Analysis[a]	Study Status	Cutoff Date for Safety Data
HLX10-004-NSCLC303	A randomized, double-blind, multicenter, Phase III clinical study of HLX10 + chemotherapy (carboplatin-nanoparticle albumin-bound (nab)-paclitaxel) vs. placebo + chemotherapy (carboplatin-nab-paclitaxel) as first-line therapy for locally advanced or metastatic squamous NSCLC	Serplulimab with carboplatin-paclitaxel combination therapy	Placebo with carboplatin-paclitaxel	4.5 mg/kg, Q3W	Serplulimab: 358/435[b] Placebo: 179 Total: 537	Ongoing	30 Mar 2021
HLX10-008-HCC201	A Single-arm, Open, Multicenter, Phase II Clinical Study Evaluating the Use of HLX10 (Recombinant Anti-pd-1 Humanized Monoclonal Antibody Injection) in Combination with HLX04 (Recombinant Anti-VEGF Humanized Monoclonal Antibody Injection) for the Treatment of Advanced Hepatocellular Carcinoma (HCC) Patients	Serplulimab with HLX04 combination therapy	None	3 mg/kg, Q2W	Monotherapy : 21 Combination therapy: 102 Total: 123	Completed	07 Feb 2023
HLX10-011-CC201	A Single-Arm, Open-Label, Multicenter, Phase II Clinical Study to Evaluate Efficacy and Safety of HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) Combined with Albumin-Bound Paclitaxel in Patients with Advanced Cervical Cancer Who Have Progressive Disease or Intolerable Toxicity After First-Line Standard Chemotherapy	Serplulimab with paclitaxel combination therapy	None	4.5 mg/kg, Q3W	21	Completed	22 Sep 2022
HLX10HLX04-001	A Phase I clinical study to evaluate the safety, tolerability and pharmacokinetics of recombinant anti-PD-1 humanized monoclonal antibody injection (HLX10) in combination with recombinant anti-VEGF humanized monoclonal antibody injection (HLX04) in patients with advanced solid tumors	Serplulimab with HLX04 combination therapy	None	1 mg/kg Q2W, 3 mg/kg Q2W, 10 mg/kg Q2W	3 3 20 Total: 26	Completed	11 Oct 2022
HLX10HLX07-001	A Multiple-center, Open-label, Phase II clinical trial to Evaluate the Efficacy and Safety of HLX10 in Combination with HLX07 in Patients with Advanced Head and Neck Tumors	Serplulimab with HLX07 combination therapy	None	3 mg/kg, Q2W	13	Completed	16 Sep 2022

Abbreviations: NSCLC=non-small cell lung cancer, Q2W=once every 2 weeks, Q3W=once every 3 weeks, Q4W=once every 4 weeks.

In the HLX10-004-NSCLC303 study, subjects randomised to the placebo group either ended treatment or were allowed to crossover to receive serplulimab after the first progressive disease. As of the cutoff date, 77 subjects in the placebo group crossed over to receive serplulimab monotherapy. Therefore, 435 (serplulimab + chemotherapy 358 subjects, serplulimab monotherapy 77 subjects) subjects received serplulimab.

2.6.8.1. Patient exposure

Pivotal trial – Study ASTRUM-005

By the cutoff date of 13 June 2023, the serplulimab group had received a median (range) of 8 (1, 58) cycles of serplulimab, while the placebo group had received a median (range) of 6 (1, 47) cycles of placebo. The median treatment durations of carboplatin and etoposide were 4 cycles in both groups as specified per the protocol. The mean (SD) relative dose intensity was 91.97% (8.97%) for serplulimab and 91.43% (9.22%) for placebo. The relative dose intensity of carboplatin and etoposide was similar for the serplulimab and placebo groups.

Overall, 46.8% of the subjects in the serplulimab group and 43.9% of the subjects in the placebo group had TEAEs that led to the interruption of serplulimab/placebo.

Pooled safety population

A total of 1172 subjects treated with serplulimab were included in the pooled safety population (389 from the pivotal trial), including 10 who received the doses of 0.3 mg/kg or 1 mg/kg serplulimab Q2W and 1162 who received the doses of 3 mg/kg Q2W, 4.5 mg/kg Q3W (recommended dose), 10 mg/kg Q2W, 200 mg Q2W, 300 mg Q3W, or 400 mg Q4W. The median (range) number of doses of serplulimab administered was 7.0 (1 to 58).

Table 35. Summary of demographic characteristics (Pooled safety population)

	<RP2D/3D			≥RP2D/3D				
	Monotherapy (N=7)	**Other Combination (N=3)**	**Total (N=10)**	**Monotherapy (N=256)**	**Chemotherapy Combination (N=768)**	**Other Combination [a] (N=138)**	**Total (N=1162)**	**Total Population [b] (N=1172)**
Age (year)								
n	7	3	10	256	768	138	1162	1172
Mean (SD)	60.3 (2.69)	46.3 (13.28)	56.1 (9.46)	56.8 (11.12)	61.4 (8.50)	54.0 (10.53)	59.5 (9.78)	59.5 (9.78)
Median	60.0	54.0	58.5	58.0	63.0	55.0	61.0	61.0
Q1, Q3	57, 63	31, 54	54, 61	52, 64	56, 68	49, 61	54, 66	54, 66
Age Group								
<65	7 (100)	3 (100)	10 (100)	195 (76.2)	460 (59.9)	116 (84.1)	771 (66.4)	781 (66.6)
≥65	0	0	0	61 (23.8)	308 (40.1)	22 (15.9)	391 (33.6)	391 (33.4)
Sex								
Male	4 (57.1)	1 (33.3)	5 (50.0)	180 (70.3)	638 (83.1)	117 (84.8)	935 (80.5)	940 (80.2)
Female	3 (42.9)	2 (66.7)	5 (50.0)	76 (29.7)	130 (16.9)	21 (15.2)	227 (19.5)	232 (19.8)
Height (cm)								
n	7	3	10	255	763	138	1156	1166
Mean (SD)	158.50 (6.817)	164.00 (8.544)	160.15 (7.366)	164.76 (7.947)	167.33 (8.350)	166.23 (6.920)	166.63 (8.166)	166.58 (8.178)
Median	160.00	163.00	160.50	165.00	168.00	167.25	168.00	168.00
Q1, Q3	150.0, 164.0	156.0, 173.0	156.0, 164.0	160.0, 170.0	162.0, 173.0	161.0, 170.5	161.0, 172.0	161.0, 172.0

	<RP2D/3D			≥RP2D/3D				
	Monotherapy (N=7)	Other Combination (N=3)	Total (N=10)	Monotherapy (N=256)	Chemotherapy Combination (N=768)	Other Combination [a] (N=138)	Total (N=1162)	Total Population [b] (N=1172)
Missing	0	0	0	1	5	0	6	6
Weight (kg)								
n	7	3	10	256	767	138	1161	1171
Mean (SD)	57.34 (10.951)	85.20 (5.897)	65.70 (16.393)	61.26 (11.728)	67.53 (14.864)	62.98 (9.506)	65.61 (13.937)	65.61 (13.951)
Median	53.50	82.90	63.85	61.00	66.00	62.70	64.00	64.00
Q1, Q3	48.3, 64.0	80.8, 91.9	52.0, 80.8	53.0, 68.0	57.0, 76.0	56.0, 69.0	56.0, 73.0	56.0, 73.0
Missing	0	0	0	0	1	0	1	1
BMI (kg/m^2)								
n	7	3	10	255	762	138	1155	1165
Mean (SD)	22.99 (5.337)	31.70 (1.321)	25.61 (6.089)	22.49 (3.544)	24.02 (4.377)	22.76 (2.910)	23.53 (4.107)	23.55 (4.129)
Median	22.84	31.20	23.87	22.21	23.46	22.87	23.08	23.12
Q1, Q3	19.3, 24.1	30.7, 33.2	20.3, 31.2	20.1, 24.6	21.0, 26.4	20.6, 24.6	20.7, 25.7	20.7, 25.7
Missing	0	0	0	1	6	0	7	7
ECOG at Baseline								
0	3 (42.9)	1 (33.3)	4 (40.0)	94 (36.7)	143 (18.6)	65 (47.1)	302 (26.0)	306 (26.1)
1	3 (42.9)	2 (66.7)	5 (50.0)	160 (62.5)	625 (81.4)	73 (52.9)	858 (73.8)	863 (73.6)
2	1 (14.3)	0	1 (10.0)	2 (0.8)	0	0	2 (0.2)	3 (0.3)
Disease Stage								
I	0	0	0	1 (0.4)	1 (0.1)	0	2 (0.2)	2 (0.2)
II	0	0	0	1 (0.4)	1 (0.1)	8 (5.8)	10 (0.9)	10 (0.9)
III	0	0	0	25 (9.8)	148 (19.3)	0	173 (14.9)	173 (14.8)
IV	7 (100)	3 (100)	10 (100)	208 (81.3)	545 (71.0)	23 (16.7)	776 (66.8)	786 (67.1)
Missing	0	0	0	21 (8.2)	73 (9.5)	107 (77.5)	201 (17.3)	201 (17.2)

Abbreviations: BMI=body mass index, ECOG=Eastern Cooperative Oncology Group, Q=quartile, RP2D/3D=recommended Phase II/III dose, SD=standard deviation.

Notes: <RP2D/3D: doses included 0.3 mg/kg/2 weeks and 1 mg/kg/2 weeks. ≥RP2D/3D: doses included 3 mg/kg/2 weeks, 4.5 mg/kg/3 weeks, 10 mg/kg/2 weeks, 200 mg/2 weeks, 300 mg/3 weeks and 400 mg/4 weeks.

[a] Other combination include all other kinds of combinations with serplulimab except chemotherapy.

[b] Total Population include all the subjects treated at least one dose with serplulimab.

In the pooled safety population, 918 subjects were Asian and 254 were non-Asian, including 184 non-Asian subjects (all White) in the ASTRUM-005 study and 70 non-Asian subjects (all White) in the HLX10-004-NSCLC303 study.

Table 36. Summary of exposure to serplulimab (Pooled safety population)

	<RP2D/3D			≥RP2D/3D				
	Monotherapy (N=7)	Other Combination (N=3)	Total (N=10)	Monotherapy (N=256)	Chemotherapy Combination (N=768)	Other Combination [a] (N=138)	Total (N=1162)	Total Population [b] (N=1172)
Treated subjects	7	3	10	256	768	138	1162	1172
Duration of treatment (months)								
N	7	3	10	256	768	138	1162	1172
Mean (SD)	2.05 (1.867)	8.47 (2.957)	3.97 (3.726)	6.45 (5.710)	7.28 (7.577)	7.68 (7.909)	7.15 (7.254)	7.12 (7.236)
Median	1.41	9.69	3.06	4.73	4.91	4.17	4.86	4.86
Q1, Q3	0.49, 3.25	5.09, 10.61	0.95, 5.32	1.91, 9.92	2.58, 9.00	1.41, 11.99	2.20, 9.23	2.17, 9.23
Min, Max	0.0, 5.3	5.1, 10.6	0.0, 10.6	0.0, 22.1	0.0, 41.8	0.1, 26.9	0.0, 41.8	0.0, 41.8
≥3 months	2 (28.6%)	3 (100%)	5 (50.0%)	156 (60.9%)	552 (71.9%)	82 (59.4%)	790 (68.0%)	795 (67.8%)
≥6 months	0	2 (66.7%)	2 (20.0%)	113 (44.1%)	327 (42.6%)	56 (40.6%)	496 (42.7%)	498 (42.5%)
≥9 months	0	2 (66.7%)	2 (20.0%)	71 (27.7%)	196 (25.5%)	43 (31.2%)	310 (26.7%)	312 (26.6%)

2.6.8.2. Adverse events

Table 37. Overview of TEAEs (Safety Set) – ASTRUM-005 (DCO 13 Jun 2023)

	Serplulimab (N=389)	Placebo (N=196)	Total (N=585)
	n (%)	n (%)	n (%)
Any Treatment-emergent adverse events (TEAEs)	375 (96.4)	192 (98.0)	567 (96.9)
TEAE by Grade			
Grade 1	11 (2.8)	3 (1.5)	14 (2.4)
Grade 2	35 (9.0)	26 (13.3)	61 (10.4)
Grade 3	156 (40.1)	65 (33.2)	221 (37.8)
Grade 4	134 (34.4)	71 (36.2)	205 (35.0)
Grade 5	39 (10.0)	27 (13.8)	66 (11.3)
Grade 3 or 4	290 (74.6)	136 (69.4)	426 (72.8)
⩾Grade 3	329 (84.6)	163 (83.2)	492 (84.1)
TEAEs Related to Any Study Drug	365 (93.8)	188 (95.9)	553 (94.5)
Related to Serplulimab/ Placebo	279 (71.7)	113 (57.7)	392 (67.0)
Related to Carboplatin or Etoposide	363 (93.3)	186 (94.9)	549 (93.8)
Serious TEAEs	152 (39.1)	77 (39.3)	229 (39.1)
Serious TEAEs Related to Any Study Drug	99 (25.4)	44 (22.4)	143 (24.4)
Serplulimab / Placebo	71 (18.3)	28 (14.3)	99 (16.9)
Carboplatin or Etoposide	80 (20.6)	42 (21.4)	122 (20.9)
TEAEs Leading to Any Study Drug Interruption	182 (46.8)	86 (43.9)	268 (45.8)
Serplulimab / Placebo	172 (44.2)	82 (41.8)	254 (43.4)

	Serplulimab (N=389)	Placebo (N=196)	Total (N=585)
	n (%)	n (%)	n (%)
Carboplatin or Etoposide	113 (29.0)	62 (31.6)	175 (29.9)
TEAEs Related to Serplulimab / Placebo Leading to Any Study Drug Interruption	90 (23.1)	34 (17.3)	124 (21.2)
Serplulimab / Placebo	85 (21.9)	33 (16.8)	118 (20.2)
Carboplatin or Etoposide	42 (10.8)	19 (9.7)	61 (10.4)
TEAEs Leading to Any Study Drug Discontinuation	38 (9.8)	19 (9.7)	57 (9.7)
Serplulimab / Placebo	35 (9.0)	18 (9.2)	53 (9.1)
Carboplatin or Etoposide	13 (3.3)	9 (4.6)	22 (3.8)
TEAEs Related to Serplulimab / Placebo Leading to Any Study Drug Discontinuation	24 (6.2)	10 (5.1)	34 (5.8)
Serplulimab / Placebo	22 (5.7)	9 (4.6)	31 (5.3)
Carboplatin or Etoposide	6 (1.5)	6 (3.1)	12 (2.1)
Treatment-Emergent Injection Reaction (IRR)	7 (1.8)	1 (0.5)	8 (1.4)
TEAE of Immune-related (irAE)	148 (38.0)	37 (18.9)	185 (31.6)
TEAEs Leading to Death	39 (10.0)	27 (13.8)	66 (11.3)
TEAEs Leading to Death Related to Any Study Drug	7 (1.8)	2 (1.0)	9 (1.5)
Related to Serplulimab / Placebo	5 (1.3)	1 (0.5)	6 (1.0)
Related to Carboplatin or Etoposide	5 (1.3)	2 (1.0)	7 (1.2)
TEAEs and Received systemic corticosteroids (+ high-dose)	59 (15.2)	22 (11.2)	81 (13.8)
TEAEs and received endocrine therapy	141 (36.2)	44 (22.4)	185 (31.6)
TEAEs with outcome resolved	14 (3.6)	7 (3.6)	21 (3.6)
TEAEs with outcome not resolved	322 (82.8)	158 (80.6)	480 (82.1)

Note: E= Frequency of specified adverse events.
Note: TEAEs were AEs occurring on or after first date of study drug administered OR AEs occurring before the first dose of study drug and worsening during study treatment.
Note: If a subject had multiple events of the same severity or relationship, then they were counted only once in that severity or relationship. If a subject had multiple events with different severity or relationship, then the subject was counted only once for more severe adverse event or related adverse event.
Note: Subjects may have one or more than one irAE applied.
Reasons of NOT RECOVERED/NOT RESOLVED, RECOVERING/RESOLVING, and UNKNOWN map to an outcome of Not Resolved. Reasons of RECOVERED/RESOLVED, RECOVERED/RESOLVED WITH SEQUELAE map to an outcome of Resolved. If a subject had multiple events with different outcome, then the subject was counted only once for more severe outcome with this order: fatal, not resolved, resolved.

The number of patients who received high-dose corticosteroids for immune-related AEs were 26 (6.7%) and 4 (2.0%) in the two study arms, respectively.

Treatment emergent adverse events (TEAEs) – Pivotal trial (ASTRUM-005)

Overall, 96.4% and 98.0% of the patients reported at least one TEAE, respectively in the serplulimab arm and the placebo arm. TEAEs that occurred in ≥5% of subjects are summarised in the table below.

Table 38. Summary of common TEAEs with incidence ≥5% by SOC and PT – ASTRUM-005 (DCO 13 Jun 2023)

System Organ Class (SOC) Preferred Term (PT)	Serplulimab Group (N=389)	Placebo Group (N=196)	Total (N=585)
Any TEAE with incidence ≥5%, n (%)	371 (95.4)	190 (96.9)	561 (95.9)
Blood and lymphatic system disorders, n (%)	324 (83.3)	165 (84.2)	489 (83.6)
Anaemia	281 (72.2)	140 (71.4)	421 (72.0)
Neutropenia	116 (29.8)	63 (32.1)	179 (30.6)
Leukopenia	95 (24.4)	41 (20.9)	136 (23.2)
Thrombocytopenia	72 (18.5)	30 (15.3)	102 (17.4)
Investigations, n (%)	301 (77.4)	143 (73.0)	444 (75.9)
Neutrophil count decreased	219 (56.3)	101 (51.5)	320 (54.7)
White blood cell count decreased	210 (54.0)	100 (51.0)	310 (53.0)
Platelet count decreased	162 (41.6)	88 (44.9)	250 (42.7)
Alanine aminotransferase increased	72 (18.5)	37 (18.9)	109 (18.6)
Lymphocyte count decreased	71 (18.3)	29 (14.8)	100 (17.1)
Aspartate aminotransferase increased	63 (16.2)	33 (16.8)	96 (16.4)
Blood alkaline phosphatase increased	51 (13.1)	17 (8.7)	68 (11.6)
Weight decreased	45 (11.6)	18 (9.2)	63 (10.8)
Blood lactate dehydrogenase increased	43 (11.1)	18 (9.2)	61 (10.4)
Weight increased	44 (11.3)	14 (7.1)	58 (9.9)
Gamma-glutamyltransferase increased	39 (10.0)	13 (6.6)	52 (8.9)
Blood cholesterol increased	39 (10.0)	4 (2.0)	43 (7.4)
Blood creatinine increased	22 (5.7)	10 (5.1)	32 (5.5)
Blood bilirubin increased	20 (5.1)	12 (6.1)	32 (5.5)
Metabolism and nutrition disorders, n (%)	261 (67.1)	106 (54.1)	367 (62.7)
Decreased appetite	110 (28.3)	56 (28.6)	166 (28.4)
Hyponatraemia	99 (25.4)	26 (13.3)	125 (21.4)
Hypoalbuminaemia	74 (19.0)	29 (14.8)	103 (17.6)
Hypertriglyceridaemia	65 (16.7)	24 (12.2)	89 (15.2)
Hypokalaemia	61 (15.7)	14 (7.1)	75 (12.8)
Hyperglycaemia	52 (13.4)	16 (8.2)	68 (11.6)
Hypercholesterolaemia	44 (11.3)	19 (9.7)	63 (10.8)
Hyperuricaemia	43 (11.1)	17 (8.7)	60 (10.3)
Hypocalcaemia	42 (10.8)	10 (5.1)	52 (8.9)
Hypomagnesaemia	34 (8.7)	9 (4.6)	43 (7.4)

System Organ Class (SOC) Preferred Term (PT)	Serplulimab Group (N=389)	Placebo Group (N=196)	Total (N=585)
Hypoproteinaemia	33 (8.5)	8 (4.1)	41 (7.0)
Hypochloraemia	29 (7.5)	11 (5.6)	40 (6.8)
Hyperlipidaemia	23 (5.9)	2 (1.0)	25 (4.3)
Hypophosphataemia	20 (5.1)	5 (2.6)	25 (4.3)
Hyperkalaemia	20 (5.1)	3 (1.5)	23 (3.9)
Gastrointestinal disorders, n (%)	227 (58.4)	118 (60.2)	345 (59.0)
Nausea	141 (36.2)	86 (43.9)	227 (38.8)
Constipation	96 (24.7)	58 (29.6)	154 (26.3)
Vomiting	79 (20.3)	58 (29.6)	137 (23.4)
Diarrhoea	40 (10.3)	13 (6.6)	53 (9.1)
Abdominal pain upper	20 (5.1)	5 (2.6)	25 (4.3)
Skin and subcutaneous tissue disorders, n (%)	223 (57.3)	113 (57.7)	336 (57.4)
Alopecia	211 (54.2)	111 (56.6)	322 (55.0)
Rash	30 (7.7)	9 (4.6)	39 (6.7)
General disorders and administration site conditions, n (%)	161 (41.4)	84 (42.9)	245 (41.9)
Pyrexia	62 (15.9)	26 (13.3)	88 (15.0)
Asthenia	46 (11.8)	26 (13.3)	72 (12.3)
Fatigue	34 (8.7)	15 (7.7)	49 (8.4)
Non-cardiac chest pain	24 (6.2)	17 (8.7)	41 (7.0)
Malaise	26 (6.7)	9 (4.6)	35 (6.0)
Disease progression	16 (4.1)	10 (5.1)	26 (4.4)
Chest discomfort	13 (3.3)	10 (5.1)	23 (3.9)
Respiratory, thoracic and mediastinal disorders, n (%)	84 (21.6)	54 (27.6)	138 (23.6)
Cough	51 (13.1)	24 (12.2)	75 (12.8)
Dyspnoea	28 (7.2)	28 (14.3)	56 (9.6)
Haemoptysis	19 (4.9)	18 (9.2)	37 (6.3)
Productive cough	20 (5.1)	10 (5.1)	30 (5.1)
Musculoskeletal and connective tissue disorders, n (%)	79 (20.3)	33 (16.8)	112 (19.1)
Back pain	34 (8.7)	16 (8.2)	50 (8.5)
Pain in extremity	35 (9.0)	14 (7.1)	49 (8.4)
Arthralgia	34 (8.7)	13 (6.6)	47 (8.0)
Endocrine disorders, n (%)	90 (23.1)	14 (7.1)	104 (17.8)
Hypothyroidism	67 (17.2)	7 (3.6)	74 (12.6)
Hyperthyroidism	47 (12.1)	7 (3.6)	54 (9.2)
Infections and infestations, n (%)	62 (15.9)	28 (14.3)	90 (15.4)

System Organ Class (SOC) Preferred Term (PT)	Serplulimab Group (N=389)	Placebo Group (N=196)	Total (N=585)
Pneumonia	40 (10.3)	16 (8.2)	56 (9.6)
Urinary tract infection	27 (6.9)	14 (7.1)	41 (7.0)
Nervous system disorders, n (%)	46 (11.8)	23 (11.7)	69 (11.8)
Dizziness	29 (7.5)	10 (5.1)	39 (6.7)
Headache	25 (6.4)	14 (7.1)	39 (6.7)
Psychiatric disorders, n (%)	43 (11.1)	17 (8.7)	60 (10.3)
Insomnia	43 (11.1)	17 (8.7)	60 (10.3)
Renal and urinary disorders, n (%)	27 (6.9)	13 (6.6)	40 (6.8)
Proteinuria	27 (6.9)	13 (6.6)	40 (6.8)
Vascular disorders, n (%)	18 (4.6)	11 (5.6)	29 (5.0)
Hypertension	18 (4.6)	11 (5.6)	29 (5.0)
Cardiac disorders, n (%)	22 (5.7)	6 (3.1)	28 (4.8)
Sinus tachycardia	22 (5.7)	6 (3.1)	28 (4.8)
Hepatobiliary disorders, n (%)	13 (3.3)	12 (6.1)	25 (4.3)
Hepatic function abnormal	13 (3.3)	12 (6.1)	25 (4.3)

Abbreviations: PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event.
Source: SCS Table 7.

Treatment emergent adverse events (TEAEs) – Pooled Safety Population

A total of 96.5% of the patients in the pooled safety population had at least one TEAE. Among the grouped categories, the TEAEs that occurred in ≥20% of subjects were anaemia (59.9%), neutropenia (55.8%), leukopenia (54.2%), thrombocytopenia (44.7%), hypoproteinaemia (23.1%), and fatigue (20.9%).

Among the ungrouped PTs, the TEAEs that occurred in ≥20% of subjects were alopecia (37.3%), decreased appetite (25.4%), nausea (25.1%), aspartate aminotransferase increased (21.1%), and alanine aminotransferase increased (20.8%).

Treatment related TEAEs – Pivotal trial (ASTRUM-005)

As of 13 June 2023, the overall incidences of TEAEs considered related to serplulimab/placebo was 71.7% and 57.7% in the two treatment arms, respectively. Common TEAEs with an incidence ≥10% in the serplulimab group that were considered related to serplulimab/placebo were anaemia (serplulimab vs placebo: 23.1% vs 18.9%), white blood cell count decreased (20.6% vs 16.8%), neutrophil count decreased (19.8% vs 17.9%), hypothyroidism (16.2% vs 2.6%), platelet count decreased (15.7% vs 18.4%), nausea (13.4% vs 14.3%), alanine aminotransferase increased (12.3% vs 9.7%), hyperthyroidism (12.1% vs 3.1%) and decreased appetite (10.0% vs 9.7%).

See table below of TEAEs considered related to serplulimab/placebo in ≥5% of the patients by cut-off 13 June 2022 (updated summary table has not been provided).

Table 39. Summary of Common treatment related TEAEs (Incidence ≥5%) Related to serplulimab/placebo by SOC and PT (Safety Set) – ASTRUM-005 (DCO 13 June 2022)

System Organ Class (SOC) Preferred Term (PT)	HLX10 Group (N=389)	Placebo Group (N=196)	Total (N=585)
Any TEAE with incidence ≥5% and related to HLX10/placebo, n (%)	231 (59.4)	87 (44.4)	318 (54.4)

System Organ Class (SOC) Preferred Term (PT)	HLX10 Group (N=389)	Placebo Group (N=196)	Total (N=585)
Investigations, n (%)	137 (35.2)	68 (34.7)	205 (35.0)
White blood cell count decreased	79 (20.3)	33 (16.8)	112 (19.1)
Neutrophil count decreased	76 (19.5)	35 (17.9)	111 (19.0)
Platelet count decreased	61 (15.7)	36 (18.4)	97 (16.6)
Alanine aminotransferase increased	48 (12.3)	19 (9.7)	67 (11.5)
Aspartate aminotransferase increased	38 (9.8)	21 (10.7)	59 (10.1)
Lymphocyte count decreased	27 (6.9)	8 (4.1)	35 (6.0)
Blood lactate dehydrogenase increased	18 (4.6)	10 (5.1)	28 (4.8)
Blood alkaline phosphatase increased	21 (5.4)	3 (1.5)	24 (4.1)
Blood and lymphatic system disorders, n (%)	100 (25.7)	42 (21.4)	142 (24.3)
Anaemia	85 (21.9)	37 (18.9)	122 (20.9)
Neutropenia	26 (6.7)	10 (5.1)	36 (6.2)
Leukopenia	22 (5.7)	10 (5.1)	32 (5.5)
Gastrointestinal disorders, n (%)	65 (16.7)	36 (18.4)	101 (17.3)
Nausea	51 (13.1)	28 (14.3)	79 (13.5)
Vomiting	27 (6.9)	15 (7.7)	42 (7.2)
Constipation	18 (4.6)	13 (6.6)	31 (5.3)
Metabolism and nutrition disorders, n (%)	69 (17.7)	28 (14.3)	97 (16.6)
Decreased appetite	39 (10.0)	19 (9.7)	58 (9.9)
Hyperglycaemia	25 (6.4)	6 (3.1)	31 (5.3)
Hypoalbuminaemia	18 (4.6)	10 (5.1)	28 (4.8)
Endocrine disorders, n (%)	83 (21.3)	11 (5.6)	94 (16.1)
Hypothyroidism	60 (15.4)	5 (2.6)	65 (11.1)
Hyperthyroidism	45 (11.6)	6 (3.1)	51 (8.7)
Skin and subcutaneous tissue disorders, n (%)	49 (12.6)	16 (8.2)	65 (11.1)
Alopecia	29 (7.5)	13 (6.6)	42 (7.2)
Rash	22 (5.7)	3 (1.5)	25 (4.3)
General disorders and administration site conditions, n (%)	42 (10.8)	17 (8.7)	59 (10.1)
Asthenia	22 (5.7)	12 (6.1)	34 (5.8)
Pyrexia	22 (5.7)	7 (3.6)	29 (5.0)

HLX10 = serplulimab

Treatment related TEAEs - Pooled Safety Population

A total of 848 (72.4%) subjects had TEAEs related to serplulimab. In the ≥RP2D/3D dose group, 69.5% of the subjects who received serplulimab monotherapy, 70.7% of the subjects who received serplulimab in combination with chemotherapy, and 85.5% of the subjects who received serplulimab in combination with other monoclonal antibodies had serplulimab-related TEAEs.

Among the grouped categories, the serplulimab-related TEAEs that occurred in ≥10% of subjects were anaemia (21.8%), leukopenia (21.1%), neutropenia (20.4%), thrombocytopenia (18.7%), fatigue (10.6%), and protein urine present (10.2%).

Among the ungrouped PTs, the serplulimab-related TEAEs that occurred in ≥10% of subjects were alanine aminotransferase increased (13.8%), aspartate aminotransferase increased (13.7%), hypothyroidism (12.8%), and decreased appetite (10.2%).

Adverse drug reactions

A summary of all ADRs based on all-cause AE frequency by SOC and PT for serplulimab and chemotherapy combination in ASTRUM-005 study was provided as part of this application and is the basis for the table in section 4.8 of the SmPC. The frequencies of ADRs are based on all-cause AE frequency identified in 389 patients with ES-SCLC from the pivotal study.

Strategy for identifying ADRs:

All observed adverse events from the eight studies were re-assessed by the sponsor based on all facts relevant to known pathophysiology of the event, reporter's opinion of causality if available, known clinical course of the disease, known medical history of the subject (including underlying illnesses, treatment, complications of surgical procedures, etc.), known pharmacologic and toxicologic profiles of the suspect product and relevant class of compounds, known AE profile of the suspect product and relevant class of compounds, temporal relationship of suspect product (dosing and the onset of the AEs; time lag between suspect product discontinuation and the onset of the SAEs, if event occurred after cessation of treatment), information on action taken with the suspect product and outcome, information relative to any dechallenge/rechallenge with the suspect product or concomitant medications to any administration of an antagonist and the outcome if applicable, evaluation of suspected product interacting, presence or absence of other potential causative factors (such as progression or complication of underlying illness) and temporal relationship of concomitant medication dosing. The rationale was described as follows:

1. The AE consistent with pharmacology of the investigational drug, timing of AE relative to time of drug exposure and known to be caused by related drug, such as thyroiditis, dermatitis and colitis are recorded as ADRs.
2. AE with other causative factors and no causality between the investigational drug and AE identified based on multiple assessment factors, will be excluded from ADR listing, such as arteriosclerosis coronary artery (relevant to medical history) or lymphocytosis (relevant to concomitant medication).
3. When making an assessment in the presence of inadequate information, the sponsor will make all efforts to dig deeper, give best-evidence assessment and specify the rationale for causality assessment. If no further evidence has been received, the case is managed as if the

investigator’s assessment was that a reasonable possibility exists that the event was related to the study product, as a cautionary measure and for reporting purposes.

The most common adverse reactions were neutropenia (82.8%), leukopenia (74.0%), anaemia (72.8%), thrombocytopenia (56.0%), alopecia (54.2%), nausea (36.2%), hyperlipidaemia (32.1%), decreased appetite (28.3%), hypoproteinaemia (25.4%), and hyponatraemia (25.4%).

The most common Grade ≥3 adverse reactions were neutropenia (65.3%), leukopenia (33.7%), thrombocytopenia (23.1%), anaemia (19.8%), hyponatraemia (10.0%), and lymphopenia (5.1%).

The most common serious adverse reactions were thrombocytopenia (9.3%), neutropenia (7.7%), leukopenia (6.7%), pneumonia (3.3%), and hyperglycaemia or diabetes mellitus (2.3%).

The most common immune-related adverse reactions (incidence ≥1.5%) were hypothyroidism (13.1%), hyperthyroidism (10.8%), immune-related skin adverse reactions (7.5%), abnormal liver function (4.1%), immune-related lung disease (3.1%), anaemia (2.8%), malaise (2.1%), hyperglycaemia or diabetes mellitus (1.8%), immune-related colitis (1.8%), and platelet count decreased (1.5%).

Adverse reactions leading to discontinuation of serplulimab occurred in 5.4% of patients.

Table 40. Summary of ADRs based on all-cause AEs frequency by SOC and PT for serplulimab and chemotherapy combination in ASTRUM-005

SOC PT	Serplulimab +Chemotherapy (N=389)
At least one ADR	368 (94.6%)
Combined ADR	363 (93.3%)
Neutropenia	322 (82.8%)
Neutrophil count decreased	219 (56.3%)
Neutropenia	116 (29.8%)
Febrile neutropenia	8 (2.1%)
Neutrophil percentage decreased	2 (0.5%)
Leukopenia	288 (74.0%)
White blood cell count decreased	210 (54.0%)
Leukopenia	95 (24.4%)
Anaemia	283 (72.8%)
Anaemia	281 (72.2%)
Haemoglobin decreased	3 (0.8%)
Red blood cell count decreased	2 (0.5%)
Thrombocytopenia	218 (56.0%)
Platelet count decreased	162 (41.6%)
Thrombocytopenia	72 (18.5%)
Hyperlipidaemia	125 (32.1%)
Hypertriglyceridaemia	65 (16.7%)
Hypercholesterolaemia	44 (11.3%)
Blood cholesterol increased	39 (10.0%)
Hyperlipidaemia	23 (5.9%)
Decreased appetite	110 (28.3%)
Decreased appetite	110 (28.3%)
Hyponatraemia	99 (25.4%)
Hyponatraemia	99 (25.4%)
Hypoproteinaemia	99 (25.4%)
Hypoalbuminaemia	74 (19.0%)
Hypoproteinaemia	33 (8.5%)
Constipation	96 (24.7%)
Constipation	96 (24.7%)
Lymphopenia	78 (20.1%)
Lymphocyte count decreased	71 (18.3%)
Lymphopenia	10 (2.6%)

SOC PT	Serplulimab +Chemotherapy (N=389)
Hypothyroidism	76 (19.5%)
Hypothyroidism	67 (17.2%)
Blood thyroid stimulating hormone increased	6 (1.5%)
Thyroxine free decreased	2 (0.5%)
Central hypothyroidism	1 (0.3%)
Tri-iodothyronine decreased	1 (0.3%)
Pyrexia	65 (16.7%)
Pyrexia	62 (15.9%)
Body temperature increased	3 (0.8%)
Hyperglycemia or diabetes mellitus	60 (15.4%)
Hyperglycaemia	52 (13.4%)
Diabetes mellitus	8 (2.1%)
Diabetic ketoacidosis	2 (0.5%)
Glucose tolerance impaired	2 (0.5%)
Blood ketone body increased	1 (0.3%)
Ketoacidosis	1 (0.3%)
Cough	58 (14.9%)
Cough	51 (13.1%)
Productive cough	20 (5.1%)
Insomnia	48 (12.3%)
Insomnia	43 (11.1%)
Poor quality sleep	5 (1.3%)
Asthenia	46 (11.8%)
Asthenia	46 (11.8%)
Hyperuricaemia	46 (11.8%)
Hyperuricaemia	43 (11.1%)
Blood uric acid increased	3 (0.8%)
Musculoskeletal pain	45 (11.6%)
Back pain	34 (8.7%)
Musculoskeletal chest pain	6 (1.5%)
Neck pain	5 (1.3%)
Myalgia	4 (1.0%)
Spinal pain	2 (0.5%)
Arrhythmia	42 (10.8%)
Supraventricular tachycardia	10 (2.6%)
Arrhythmia	8 (2.1%)
Atrial fibrillation	8 (2.1%)
Supraventricular extrasystoles	8 (2.1%)
Ventricular extrasystoles	6 (1.5%)
Sinus arrhythmia	3 (0.8%)
Ventricular arrhythmia	3 (0.8%)
Atrial tachycardia	2 (0.5%)
Arrhythmia supraventricular	1 (0.3%)
Bradyarrhythmia	1 (0.3%)
Early repolarisation syndrome	1 (0.3%)
Hypocalcaemia	42 (10.8%)
Hypocalcaemia	42 (10.8%)

SOC PT	Serplulimab +Chemotherapy (N=389)
Blood calcium decreased	1 (0.3%)
Abdominal pain	41 (10.5%)
Abdominal pain upper	20 (5.1%)
Abdominal pain	13 (3.3%)
Abdominal discomfort	9 (2.3%)
Abdominal pain lower	2 (0.5%)
Diarrhoea	40 (10.3%)
Diarrhoea	40 (10.3%)
Pneumonia	40 (10.3%)
Pneumonia	40 (10.3%)
Pneumonia fungal	1 (0.3%)
Rash	39 (10.0%)
Rash	30 (7.7%)
Rash maculo-papular	6 (1.5%)
Erythema	3 (0.8%)
Eczema	2 (0.5%)
Drug eruption	1 (0.3%)
Skin toxicity	1 (0.3%)
Protein urine present	35 (9.0%)
Proteinuria	27 (6.9%)
Protein urine present	9 (2.3%)
Albuminuria	1 (0.3%)
Hypomagnesaemia	34 (8.7%)
Hypomagnesaemia	34 (8.7%)
Hyperbilirubinaemia	33 (8.5%)
Blood bilirubin increased	20 (5.1%)
Bilirubin conjugated increased	8 (2.1%)
Hyperbilirubinaemia	7 (1.8%)
Blood bilirubin unconjugated increased	1 (0.3%)
Chest discomfort	29 (7.5%)
Non-cardiac chest pain	24 (6.2%)
Chest pain	5 (1.3%)
Hypochloraemia	29 (7.5%)
Hypochloraemia	29 (7.5%)
Dyspnoea	28 (7.2%)
Dyspnoea	28 (7.2%)
Sinus tachycardia	28 (7.2%)
Sinus tachycardia	22 (5.7%)
Tachycardia	7 (1.8%)
Urinary tract infection	28 (7.2%)
Urinary tract infection	27 (6.9%)
Asymptomatic bacteriuria	1 (0.3%)
Liver injury	22 (5.7%)
Hepatic function abnormal	13 (3.3%)
Liver injury	5 (1.3%)
Drug-induced liver injury	4 (1.0%)
Immune-mediated hepatitis	1 (0.3%)

SOC PT	Serplulimab +Chemotherapy (N=389)
Blood creatine phosphokinase increased	21 (5.4%)
Blood creatine phosphokinase increased	19 (4.9%)
Blood creatine phosphokinase MB increased	3 (0.8%)
Coagulation function test abnormal	21 (5.4%)
Activated partial thromboplastin time prolonged	19 (4.9%)
Activated partial thromboplastin time shortened	2 (0.5%)
Activated partial thromboplastin time	1 (0.3%)
International normalised ratio decreased	1 (0.3%)
Prothrombin level increased	1 (0.3%)
Upper respiratory tract infection	21 (5.4%)
Upper respiratory tract infection	19 (4.9%)
Pharyngotonsillitis	1 (0.3%)
Tonsillitis	1 (0.3%)
Hyperkalaemia	20 (5.1%)
Hyperkalaemia	20 (5.1%)
Blood potassium increased	1 (0.3%)
Edema	18 (4.6%)
Oedema peripheral	9 (2.3%)
Face oedema	6 (1.5%)
Swelling face	5 (1.3%)
Peripheral swelling	1 (0.3%)
Swelling	1 (0.3%)
Hypertension	18 (4.6%)
Hypertension	18 (4.6%)
Electrocardiogram abnormal	17 (4.4%)
Electrocardiogram QT prolonged	14 (3.6%)
Electrocardiogram repolarisation abnormality	3 (0.8%)
Electrocardiogram T wave abnormal	2 (0.5%)
Flatulence	17 (4.4%)
Abdominal distension	13 (3.3%)
Flatulence	4 (1.0%)
Haematuria	16 (4.1%)
Haematuria	13 (3.3%)
Urinary occult blood positive	3 (0.8%)
Red blood cells urine positive	2 (0.5%)
Paraesthesia	15 (3.9%)
Hypoaesthesia	8 (2.1%)
Paraesthesia	7 (1.8%)
Pneumonitis	15 (3.9%)
Pneumonitis	7 (1.8%)
Immune-mediated lung disease	5 (1.3%)
Interstitial lung disease	3 (0.8%)
Sinus bradycardia	15 (3.9%)
Sinus bradycardia	15 (3.9%)
Granulocytopenia	13 (3.3%)
Granulocytopenia	12 (3.1%)
Granulocyte count decreased	1 (0.3%)

SOC PT	Serplulimab +Chemotherapy (N=389)
Neutrophilia	12 (3.1%)
Neutrophil count increased	12 (3.1%)
Conduction defects	11 (2.8%)
Bundle branch block right	7 (1.8%)
Atrioventricular block first degree	3 (0.8%)
Bundle branch block left	3 (0.8%)
Atrial conduction time prolongation	2 (0.5%)
Defect conduction intraventricular	2 (0.5%)
Renal injury	11 (2.8%)
Renal failure	5 (1.3%)
Acute kidney injury	3 (0.8%)
Renal impairment	2 (0.5%)
Renal injury	1 (0.3%)
Hypermagnesaemia	10 (2.6%)
Hypermagnesaemia	10 (2.6%)
Thyroid function test abnormal	9 (2.3%)
Blood thyroid stimulating hormone decreased	5 (1.3%)
Tri-iodothyronine increased	2 (0.5%)
Anti-thyroid antibody positive	1 (0.3%)
Thyroglobulin increased	1 (0.3%)
Thyroxine increased	1 (0.3%)
Dermatitis	7 (1.8%)
Dermatitis allergic	3 (0.8%)
Autoimmune dermatitis	1 (0.3%)
Dermatitis	1 (0.3%)
Dermatitis bullous	1 (0.3%)
Immune-mediated dermatitis	1 (0.3%)
Seborrhoeic dermatitis	1 (0.3%)
Neuropathy peripheral	7 (1.8%)
Neuropathy peripheral	7 (1.8%)
Peripheral sensorimotor neuropathy	1 (0.3%)
Troponin increased	7 (1.8%)
Troponin T increased	3 (0.8%)
Troponin I increased	2 (0.5%)
Troponin increased	2 (0.5%)
Glycosuria	6 (1.5%)
Glycosuria	6 (1.5%)
Infusion-related reaction	6 (1.5%)
Infusion related reaction	3 (0.8%)
Drug hypersensitivity	2 (0.5%)
Anaphylactic reaction	1 (0.3%)
Musculoskeletal discomfort	6 (1.5%)
Muscular weakness	5 (1.3%)
Musculoskeletal discomfort	1 (0.3%)
Cardiac failure	5 (1.3%)
Cardiac failure	2 (0.5%)
Left ventricular failure	2 (0.5%)

SOC PT	Serplulimab +Chemotherapy (N=389)
Cardiac failure acute	1 (0.3%)
Gastroenteritis	5 (1.3%)
Gastritis	5 (1.3%)
Gastrointestinal disorder	5 (1.3%)
Gastrointestinal disorder	2 (0.5%)
Gastrointestinal haemorrhage	2 (0.5%)
Lower gastrointestinal haemorrhage	1 (0.3%)
Stomatitis	5 (1.3%)
Stomatitis	5 (1.3%)
Thyroiditis	5 (1.3%)
Thyroid disorder	4 (1.0%)
Thyroiditis	1 (0.3%)
Vasculitis	5 (1.3%)
Phlebitis	4 (1.0%)
Phlebitis superficial	1 (0.3%)
Brain natriuretic peptide increased	4 (1.0%)
N-terminal prohormone brain natriuretic peptide increased	4 (1.0%)
Leukocyturia	4 (1.0%)
White blood cells urine positive	4 (1.0%)
Adrenal insufficiency	3 (0.8%)
Adrenal insufficiency	2 (0.5%)
Cortisol decreased	1 (0.3%)
Arthritis	3 (0.8%)
Arthritis	2 (0.5%)
Joint effusion	1 (0.3%)
Coagulopathy	3 (0.8%)
Coagulopathy	3 (0.8%)
Immune-mediated encephalitis	3 (0.8%)
Immune-mediated encephalitis	2 (0.5%)
Encephalitis autoimmune	1 (0.3%)
Lipoprotein abnormal	3 (0.8%)
Low density lipoprotein increased	2 (0.5%)
Lipoprotein increased	1 (0.3%)
Cardiomyopathy	2 (0.5%)
Cardiomyopathy	1 (0.3%)
Metabolic cardiomyopathy	1 (0.3%)
Hypersomnia	2 (0.5%)
Somnolence	2 (0.5%)
Hypophysitis	2 (0.5%)
Hypophysitis	2 (0.5%)
Pigmentation disorder	2 (0.5%)
Skin hyperpigmentation	1 (0.3%)
Vitiligo	1 (0.3%)
Septic shock	2 (0.5%)
Septic shock	2 (0.5%)
Thyroid disorder	2 (0.5%)
Euthyroid sick syndrome	1 (0.3%)

SOC PT	Serplulimab +Chemotherapy (N=389)
Ultrasound thyroid abnormal	1 (0.3%)
Vertigo	2 (0.5%)
Motion sickness	2 (0.5%)
Chills	1 (0.3%)
Chills	1 (0.3%)
Colitis	1 (0.3%)
Enteritis	1 (0.3%)
Hyperadrenocorticism	1 (0.3%)
Cortisol increased	1 (0.3%)
Hyperadrenocorticism	1 (0.3%)
Myositis	1 (0.3%)
Autoimmune myositis	1 (0.3%)
Pancreatitis	1 (0.3%)
Immune-mediated pancreatitis	1 (0.3%)
Skin infection	1 (0.3%)
Skin infection	1 (0.3%)
Transaminases increased	1 (0.3%)
Transaminases increased	1 (0.3%)
Other ADR	330 (84.8%)
Skin and subcutaneous tissue disorders	220 (56.6%)
Alopecia	211 (54.2%)
Pruritus	14 (3.6%)
Hyperhidrosis	4 (1.0%)
Psoriasis	2 (0.5%)
Dry skin	1 (0.3%)
Investigations	168 (43.2%)
Alanine aminotransferase increased	72 (18.5%)
Aspartate aminotransferase increased	63 (16.2%)
Blood alkaline phosphatase increased	51 (13.1%)
Weight decreased	45 (11.6%)
Gamma-glutamyltransferase increased	39 (10.0%)
Blood creatinine increased	22 (5.7%)
Blood urea increased	16 (4.1%)
Myoglobin blood increased	9 (2.3%)
Myocardial necrosis marker increased	3 (0.8%)
Blood creatine increased	2 (0.5%)
Gastrointestinal disorders	167 (42.9%)
Nausea	141 (36.2%)
Vomiting	79 (20.3%)
Dysphagia	14 (3.6%)
Dyspepsia	7 (1.8%)
Dry mouth	3 (0.8%)
Gingival bleeding	2 (0.5%)
Metabolism and nutrition disorders	87 (22.4%)
Hypokalaemia	61 (15.7%)
Hypophosphataemia	20 (5.1%)

SOC PT	Serplulimab +Chemotherapy (N=389)
Hyperphosphataemia	11 (2.8%)
Hypercalcaemia	5 (1.3%)
Hypoglycaemia	5 (1.3%)
Acidosis	2 (0.5%)
General disorders and administration site conditions	57 (14.7%)
Fatigue	34 (8.7%)
Malaise	26 (6.7%)
Musculoskeletal and connective tissue disorders	56 (14.4%)
Pain in extremity	35 (9.0%)
Arthralgia	34 (8.7%)
Nervous system disorders	49 (12.6%)
Dizziness	29 (7.5%)
Headache	25 (6.4%)
Neurotoxicity	2 (0.5%)
Motor dysfunction	1 (0.3%)
Endocrine disorders	47 (12.1%)
Hyperthyroidism	47 (12.1%)
Cardiac disorders	7 (1.8%)
Myocardial ischaemia	3 (0.8%)
Pericardial effusion	3 (0.8%)
Myocardial injury	1 (0.3%)
Infections and infestations	4 (1.0%)
Enteritis infectious	1 (0.3%)
Lip infection	1 (0.3%)
Lower respiratory tract infection	1 (0.3%)
Meningoencephalitis herpetic	1 (0.3%)
Blood and lymphatic system disorders	3 (0.8%)
Myelosuppression	2 (0.5%)
Lymphadenitis	1 (0.3%)
Eye disorders	2 (0.5%)
Vision blurred	2 (0.5%)
Renal and urinary disorders	1 (0.3%)
Microalbuminuria	1 (0.3%)

Percentage is based on the safety population as denominator.
ADR does not include disease progression.

Adverse events by severity – Pivotal trial (ASTRUM-005)

A total of 462 (79.0%) subjects in the pivotal trial had at least one TEAE of ≥Grade 3 in severity (excluding disease progression and COVID-19), 79.9% of subjects in the serplulimab group and 77.0% of subjects in the placebo group.

The total number of patients with ≥Grade 3 TEAEs related to serplulimab/placebo in the serplulimab and placebo arms of the pivotal study were 133 (34.2%) and 57 (29.1%), respectively.

Table 41. Summary of Common (Incidence ≥5%) and Severe (≥Grade 3) TEAEs Related to serplulimab/Placebo (Safety Set) - ASTRUM-005 (DCO 13 June 2023)

System Organ Class (SOC) Preferred Term (PT)	HLX10 Group (N=389)	Placebo Group (N=196)	Total (N=585)
Any TEAE with incidence ≥5% and ≥Grade 3 and related to HLX10/placebo, n (%)	72 (18.5)	36 (18.4)	108 (18.5)
Investigations, n (%)	66 (17.0)	33 (16.8)	99 (16.9)
Neutrophil count decreased	55 (14.1)	27 (13.8)	82 (14.0)
White blood cell count decreased	33 (8.5)	17 (8.7)	50 (8.5)
Platelet count decreased	24 (6.2)	16 (8.2)	40 (6.8)
Blood and lymphatic system disorders, n (%)	21 (5.4)	11 (5.6)	32 (5.5)
Anaemia	21 (5.4)	11 (5.6)	32 (5.5)

Adverse events by severity - Pooled safety population

A total of 828 (70.6%) subjects had ≥Grade 3 TEAEs in the pooled safety population. In the ≥RP2D/3D dose group, 43.4% of the subjects who received serplulimab monotherapy and 54.3% of the subjects who received serplulimab in combination with other monoclonal antibodies had ≥Grade 3 TEAEs. The incidence of ≥ Grade 3 TEAEs was 82.7% in patients who received serplulimab in combination with chemotherapy.

Among the grouped categories of TEAEs, ≥Grade 3 TEAEs that occurred in ≥10% of all subjects were neutropenia (39.7%), leukopenia (24.4%), anaemia (19.5%), and thrombocytopenia (14.7%). Among the ungrouped PTs, none occurred in ≥10% subjects.

A total of 363 (31.0%) subjects had serplulimab-related TEAEs with a severity of ≥Grade 3 in the pooled safety population. In the ≥RP2D/3D dose group, 20.7% of the subjects who received serplulimab monotherapy, 34.0% of the subjects who received serplulimab in combination with chemotherapy, and 33.3% of the subjects who received serplulimab in combination with other monoclonal antibodies had serplulimab-related TEAEs with a severity of ≥Grade 3.

Adverse Events of Special Interest (AESI)

Immune-related AEs – Pivotal trial (ASTRUM-005)

AESIs included infusion-related reactions (IRRs) and immune-related adverse events (irAEs). An irAE referred to an AE that was related to drug exposure and consistent with immune mediated mechanism of action without any other definitive pathological factor. Serological, immunological, and histological (biopsy) data had to be used to support diagnosis of irAE when appropriate. Appropriate methods were used to exclude pathological factors of irAE such as tumour, infection, metabolism, toxin.

Table 42. Summary of Immune-related TEAEs Occurring in ≥2 Subjects by SOC and PT (Safety Set) – ASTRUM-005 (DCO 13 Jun 2023)

	Serplulimab (N=389)	Placebo (N=196)	Total (N=585)
	n (%)	n (%)	n (%)
Any Immune-related TEAEs (irAEs)	148 (38.0)	37 (18.9)	185 (31.6)
Immune-related myocarditis			
Any irAE	1 (0.3)	0	1 (0.2)
Any Grade 3 or 4 irAE	0	0	0
Serious irAEs	0	0	0
Outcome Resolved	1 (0.3)	0	1 (0.2)
Outcome not resolved	0	0	0
Outcome death	0	0	0
Immune-related pancreatitis			
Any irAE	1 (0.3)	0	1 (0.2)
Any Grade 3 or 4 irAE	1 (0.3)	0	1 (0.2)
Serious irAEs	1 (0.3)	0	1 (0.2)
Outcome Resolved	1 (0.3)	0	1 (0.2)
Outcome not resolved	0	0	0
Outcome death	0	0	0
Immune-related lung disease			
Any irAE	12 (3.1)	3 (1.5)	15 (2.6)
Any Grade 3 or 4 irAE	4 (1.0)	1 (0.5)	5 (0.9)
Serious irAEs	6 (1.5)	3 (1.5)	9 (1.5)
Outcome Resolved	3 (0.8)	0	3 (0.5)
Outcome not resolved	8 (2.1)	3 (1.5)	11 (1.9)
Outcome death	1 (0.3)	0	1 (0.2)
Immune-related colitis			
Any irAE	7 (1.8)	0	7 (1.2)
Any Grade 3 or 4 irAE	1 (0.3)	0	1 (0.2)
Serious irAEs	1 (0.3)	0	1 (0.2)
Outcome Resolved	4 (1.0)	0	4 (0.7)
Outcome not resolved	3 (0.8)	0	3 (0.5)
Outcome death	0	0	0
Hepatitis			
Any irAE	1 (0.3)	1 (0.5)	2 (0.3)
Any Grade 3 or 4 irAE	1 (0.3)	1 (0.5)	2 (0.3)
Serious irAEs	1 (0.3)	1 (0.5)	2 (0.3)
Outcome Resolved	0	0	0
Outcome not resolved	1 (0.3)	1 (0.5)	2 (0.3)
Outcome death	0	0	0
abnormal liver function			
Any irAE	16 (4.1)	9 (4.6)	25 (4.3)
Any Grade 3 or 4 irAE	4 (1.0)	0	4 (0.7)
Serious irAEs	4 (1.0)	0	4 (0.7)
Outcome Resolved	2 (0.5)	7 (3.6)	9 (1.5)
Outcome not resolved	14 (3.6)	2 (1.0)	16 (2.7)
Outcome death	0	0	0

	Serplulimab (N=389)	Placebo (N=196)	Total (N=585)
	n (%)	n (%)	n (%)
Immune-related nephritis and renal dysfunction			
Any irAE	5 (1.3)	1 (0.5)	6 (1.0)
Any Grade 3 or 4 irAE	0	0	0
Serious irAEs	0	0	0
Outcome Resolved	1 (0.3)	1 (0.5)	2 (0.3)
Outcome not resolved	4 (1.0)	0	4 (0.7)
Outcome death	0	0	0
Diabetes mellitus/hyperglycemia			
Any irAE	7 (1.8)	1 (0.5)	8 (1.4)
Any Grade 3 or 4 irAE	5 (1.3)	0	5 (0.9)
Serious irAEs	5 (1.3)	0	5 (0.9)
Outcome Resolved	0	1 (0.5)	1 (0.2)
Outcome not resolved	7 (1.8)	0	7 (1.2)
Outcome death	0	0	0
Thyroiditis			
Any irAE	2 (0.5)	2 (1.0)	4 (0.7)
Any Grade 3 or 4 irAE	0	0	0
Serious irAEs	0	0	0
Outcome Resolved	1 (0.3)	1 (0.5)	2 (0.3)
Outcome not resolved	1 (0.3)	1 (0.5)	2 (0.3)
Outcome death	0	0	0
Hyperthyroidism			
Any irAE	42 (10.8)	7 (3.6)	49 (8.4)
Any Grade 3 or 4 irAE	0	0	0
Serious irAEs	0	0	0
Outcome Resolved	28 (7.2)	2 (1.0)	30 (5.1)
Outcome not resolved	14 (3.6)	5 (2.6)	19 (3.2)
Outcome death	0	0	0
Hypothyroidism			
Any irAE	51 (13.1)	4 (2.0)	55 (9.4)
Any Grade 3 or 4 irAE	1 (0.3)	0	1 (0.2)
Serious irAEs	1 (0.3)	0	1 (0.2)
Outcome Resolved	13 (3.3)	2 (1.0)	15 (2.6)
Outcome not resolved	38 (9.8)	2 (1.0)	40 (6.8)
Outcome death	0	0	0
Abnormal thyroid function			
Any irAE	0	0	0
Any Grade 3 or 4 irAE	0	0	0
Serious irAEs	0	0	0
Outcome Resolved	0	0	0
Outcome not resolved	0	0	0
Outcome death	0	0	0
Pituitary disorders			
Any irAE	3 (0.8)	0	3 (0.5)
Any Grade 3 or 4 irAE	0	0	0
Serious irAEs	0	0	0

	Serplulimab (N=389)	Placebo (N=196)	Total (N=585)
	n (%)	n (%)	n (%)
Outcome Resolved	0	0	0
Outcome not resolved	3 (0.8)	0	3 (0.5)
Outcome death	0	0	0
Adrenal gland disorders			
Any irAE	2 (0.5)	0	2 (0.3)
Any Grade 3 or 4 irAE	0	0	0
Serious irAEs	0	0	0
Outcome Resolved	0	0	0
Outcome not resolved	2 (0.5)	0	2 (0.3)
Outcome death	0	0	0
Immune-related skin adverse reactions			
Any irAE	29 (7.5)	4 (2.0)	33 (5.6)
Any Grade 3 or 4 irAE	2 (0.5)	1 (0.5)	3 (0.5)
Serious irAEs	1 (0.3)	0	1 (0.2)
Outcome Resolved	13 (3.3)	1 (0.5)	14 (2.4)
Outcome not resolved	16 (4.1)	3 (1.5)	19 (3.2)
Outcome death	0	0	0
Immune-related uveitis			
Any irAE	0	0	0
Any Grade 3 or 4 irAE	0	0	0
Serious irAEs	0	0	0
Outcome Resolved	0	0	0
Outcome not resolved	0	0	0
Outcome death	0	0	0
Other immune-related adverse reactions			
Any irAE	73 (18.8)	18 (9.2)	91 (15.6)
Any Grade 3 or 4 irAE	15 (3.9)	10 (5.1)	25 (4.3)
Serious irAEs	18 (4.6)	7 (3.6)	25 (4.3)
Outcome Resolved	24 (6.2)	7 (3.6)	31 (5.3)
Outcome not resolved	44 (11.3)	10 (5.1)	54 (9.2)
Outcome death	5 (1.3)	1 (0.5)	6 (1.0)

Immune-related AEs - Pooled safety population

In the pooled safety population, a total of 399 (34.0%) subjects had at least one irAE. In the ≥RP2D/3D dose group, 31.6% subjects who received serplulimab monotherapy had irAEs, compared to 32.8% of those who received serplulimab in combination with chemotherapy, and 44.9% of the subjects who received serplulimab in combination with other monoclonal antibodies.

By grouped categories, AESI that occurred in ≥2.0% of all subjects in the pooled safety population were hypothyroidism (11.2%), immune-related skin adverse reactions (8.7%), hyperthyroidism (6.3%), abnormal liver function (4.5%), immune-related lung disease (3.5%), immune-related nephritis and renal dysfunction (2.4%), and immune-related colitis (2.4%).

Among the subjects who experienced immune-related TEAEs, 67 (5.7%) subjects received high dose corticosteroids.

- **Immune-related myocarditis**: 0.6% (7/1172) of patients developed immune-related myocarditis, of these patients there was one (0.1%) patient with a fatal outcome, 3 (0.3%) patients with ≥Grade 3 immune-related myocarditis. The median time to onset was 1.87 months (range: 0.26-25.36 months). The median duration was 0.89 months (range: 0.72-4.57 months). 0.3% of patients received high-dose corticosteroid treatment. Immune-related myocarditis led to discontinuation in 0.2% of patients.
- **Immune-related pancreatitis**: 1.1% (13/1172) of patients developed immune-related pancreatitis, of these patients there was one (0.1%) patient with a fatal outcome, 7 (0.6%) patients with ≥Grade 3 immune-related pancreatitis. The median time to onset was 2.30 months (range: 0.23-12.42 months). The median duration was 0.76 months (range: 0.16-10.12 months). 0.2% of patients received high-dose corticosteroid treatment. Immune-related pancreatitis led to discontinuation in 0.2% of patients.
- **Immune-related lung disease:** 3.5% (41/1172) of patients developed immune-related lung disease, including Grade 3, 4 or 5 in 0.9%, 0.1%, and 0.3% of patients, respectively. The median time to onset was 3.25 months (range: 0.03-34.53 months). The median duration was 1.91 months (range: 0.26-13.34 months). 1.6% of patients received high-dose corticosteroid treatment. Immune-related lung disease led to discontinuation in 1.0% of patients..
- **Immune-related colitis:** 2.4% (28/1172) of patients developed immune-related colitis, including Grade 3 in 0.6% of patients and Grade 5 in 0.1% of patient. The median time to onset was 3.01 months (range: 0.03-20.11 months). The median duration was 0.43 months (range: 0.03-4.40 months). 0.5% of patients received high-dose corticosteroid treatment. Immune-related colitis led to discontinuation in 0.3% of patients..
- **Immune-related hepatitis and abnormal liver function:** 0.7% (8/1172) of patients developed immune-related hepatitis, including Grade 3 in 0.3% of patients, Grade 4 in 0.2% of patients, and Grade 5 in 0.2% of patients. The median time to onset was 2.48 months (range: 0.43-6.60 months). The median duration was 0.95 months (range: 0.53-1.51 months). 0.2% of patients received high-dose corticosteroid treatment. Hepatitis led to discontinuation in 0.3% of patients..

  Additionally, 4.5% (53/1172) of patients developed abnormal liver function, including Grade 3 in 1.0% of patients. The median time to onset was 1.51 months (range: 0.07-29.73 months). The median duration was 1.41 months (range: 0.26-17.54 months). 0.3% of patients received high-dose corticosteroid treatment. Abnormal liver function led to discontinuation in 0.3% of patients..
- **Immune-related nephritis and renal dysfunction:** 2.4% (28/1172) of patients developed immune-related nephritis and renal dysfunction, including Grade 3 in 0.3% of patients and Grade 4 in 0.1% of patient. The median time to onset was 2.78 months (range: 0.23-17.28 months). The median duration was 1.12 months (range: 0.13-5.32 months). 0.2% of patients received high-dose corticosteroid treatment. Immune-related nephritis and renal dysfunction led to discontinuation in 0.2% of patients..
- **Diabetes mellitus/hyperglycaemia**: 1.0% (12/1172) of patients developed diabetes mellitus/ hyperglycaemia, of these patients there was no patient with a fatal outcome, 7 (0.6%) patients with ≥Grade 3 diabetes mellitus/hyperglycaemia. The median time to onset was 4.09 months (range: 0.69-11.10 months). The median duration was 2.96 months. 0.6% of patients received insulin replacement therapy. Diabetes mellitus/hyperglycaemia led to discontinuation in 0.1% of patient.

- **Thyroiditis**: 0.7% (8/1172) of patients developed thyroiditis, of these patients there was no patient with a fatal outcome or with ≥Grade 3 thyroiditis. The median time to onset was 5.65 months (range: 1.94-13.50 months). The median duration was 5.93 months (range: 0.56-11.30 months). 0.2% of patients received thyroid hormone replacement therapy. No patients discontinued serplulimab due to thyroiditis.
- **Hyperthyroidism**: 6.3% (74/1172) of patients developed hyperthyroidism, of these patients there was no patient with a fatal outcome or with ≥Grade 3 hyperthyroidism. The median time to onset was 1.79 months (range: 0.69-31.18 months). The median duration was 1.41 months (range: 0.07-4.21 months). No patients discontinued serplulimab due to hyperthyroidism.
- **Hypothyroidism**: 11.2% (131/1172) of patients developed hypothyroidism, including Grade 3 in 0.1% of patient. The median time to onset was 3.84 months (range: 0.62-34.10 months). The median duration was 2.76 months (range: 0.53-7.49 months). 5.9% of patients received thyroid hormone replacement therapy. No patients discontinued serplulimab due to hypothyroidism..
- **Pituitary disorders**: 0.9% (11/1172) of patients developed pituitary disorders, of these patients there was no patient with a fatal outcome, 2 (0.2%) patients with ≥Grade 3 pituitary disorders. The median time to onset was 6.97 months (range: 1.41-20.53 months). The median duration was 2.43 months. 0.3% of patients received high-dose corticosteroid treatment. Pituitary disorders led to discontinuation in 0.2% of patients.
- **Adrenal gland disorders:** 0.3% (3/1172) of patients developed adrenal gland disorders, all of which were Grade 2. The median time to onset was 5.78 months (range: 5.75-6.93 months). No patients discontinued serplulimab due to adrenal gland disorders.
- **Immune-related skin adverse reactions:** 8.7% (102/1172) of patients developed immune-related skin adverse reactions, of these patients there was no patient with a fatal outcome, 9 (0.8%) patients with ≥Grade 3 immune-related skin adverse reactions. The median time to onset was 2.10 months (range: 0.03-30.52months). The median duration was 0.82 months (range: 0.07-12.39 months). 1.4% of patients received high-dose corticosteroid treatment. Immune-related skin adverse reactions led to discontinuation in 0.4% of patients.
- **Immune-related uveitis:** 0.1% (1/1172) of patient developed Grade 1 immune-related uveitis. The time to onset was 6.90 months. The duration of immune-related uveitis was 1.35 months. The event resolved for the patient.
- **Other immune-related adverse reactions:** 15.1% (177/1172) of patients developed other immune-related adverse reactions, of these patients there were 9 (0.8%) patients with fatal outcomes, 448(4.1%) patients with ≥Grade 3 other immune-related adverse reactions.

  The other clinically significant immune-related adverse reactions reported in patients who received serplulimab were as follows. Severe or fatal cases have been reported for some of these adverse reactions.
  - Blood and lymphatic system: Anaemia, leukopenia, thrombocytopenia, neutropenia.
  - Nervous system: Dizziness, immune-mediated encephalitis, neuropathy peripheral.
  - Eye disorders: Vision blurred.
  - Cardiac/Vascular: Acute coronary syndrome, myocardial infarction, cardiac failure acute, cardiotoxicity, troponin increased.
  - Respiratory, thoracic and mediastinal: Dyspnoea, chronic obstructive pulmonary disease, respiratory failure.
  - Gastrointestinal: Mouth ulceration, vomiting, proctitis.
  - General disorders and administration site conditions: Asthenia, fatigue, pyrexia.

- Other: Panic disorder, tinnitus, cholangitis acute, sepsis, cortisol decreased, blood alkaline phosphatase increased, electrolyte imbalance.

The applicant has included warnings and precautions regarding immune-related and infusion-related adverse reactions in the product information in line with other substances in the same pharmacological and chemical subgroup.

Infusion-related reactions - Pooled safety population

Infusion-related reactions occurred in 1.4% of patients, including Grade 3 in 0.2% of patients and Grade 4 in 0.1% of patient. The median time to onset was 1.02 months (range: 0.03-9.86 months). The median duration was 0.07 months (range: 0.03-0.53 months). No patients discontinued serplulimab due to infusion-related reactions.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths – Pivotal trial (ASTRUM-005)

Table 43. Summary of TEAEs Leading to Death by SOC and PT (Safety Set) – ASTRUM-005 (DCO 13 June 2023)

System Organ Class (SOC) Preferred Term (PT)	Serplulimab Group (N=389)	Placebo Group (N=196)	Total (N=585)
Any TEAE leading to death, n (%)	39 (10.0)	27 (13.8)	66 (11.3)
TEAE leading to death a, n (%)	24 (6.2)	17 (8.7)	41 (7.0)
TEAE leading to death b, n (%)	21 (5.4)	15 (7.7)	36 (6.2)
General disorders and administration site conditions, n (%)	27 (6.9)	17 (8.7)	44 (7.5)
Disease progression	15 (3.9)	10 (5.1)	25 (4.3)
Death	7 (1.8)	7 (3.6)	14 (2.4)
Sudden death	3 (0.8)	0	3 (0.5)
Multiple organ dysfunction syndrome	1 (0.3)	0	1 (0.2)
Pyrexia	1 (0.3)	0	1 (0.2)
Infections and infestations, n (%)	4 (1.0)	3 (1.5)	7 (1.2)
COVID-19	3 (0.8)	1 (0.5)	4 (0.7)
Sepsis	1 (0.3)	0	1 (0.2)
COVID-19 pneumonia	0	1 (0.5)	1 (0.2)
Intracranial infection	0	1 (0.5)	1 (0.2)
Septic shock	0	1 (0.5)	1 (0.2)
Respiratory, thoracic and mediastinal disorders, n (%)	3 (0.8)	2 (1.0)	5 (0.9)
Pulmonary embolism	1 (0.3)	1 (0.5)	2 (0.3)
Immune-mediated lung disease	1 (0.3)	0	1 (0.2)
Respiratory failure	1 (0.3)	0	1 (0.2)
Dyspnoea	0	1 (0.5)	1 (0.2)
Cardiac disorders, n (%)	2 (0.5)	2 (1.0)	4 (0.7)

System Organ Class (SOC) Preferred Term (PT)	Serplulimab Group (N=389)	Placebo Group (N=196)	Total (N=585)
Acute coronary syndrome	1 (0.3)	0	1 (0.2)
Cardiopulmonary failure	1 (0.3)	0	1 (0.2)
Cardiac arrest	0	1 (0.5)	1 (0.2)
Myocardial infarction	0	1 (0.5)	1 (0.2)
Nervous system disorders, n (%)	2 (0.5)	0	2 (0.3)
Diabetic hyperosmolar coma	1 (0.3)	0	1 (0.2)
Immune-mediated encephalitis	1 (0.3)	0	1 (0.2)
Gastrointestinal disorders, n (%)	1 (0.3)	1 (0.5)	2 (0.3)
Intestinal obstruction	1 (0.3)	0	1 (0.2)
Upper gastrointestinal haemorrhage	0	1 (0.5)	1 (0.2)
Vascular disorders, n (%)	0	2 (1.0)	2 (0.3)
Aortic dissection rupture	0	1 (0.5)	1 (0.2)
Hypovolaemic shock	0	1 (0.5)	1 (0.2)
Investigations, n (%)	1 (0.3)	0	1 (0.2)
Platelet count decreased	1 (0.3)	0	1 (0.2)
Blood and lymphatic system disorders, n (%)	0	1 (0.5)	1 (0.2)
Thrombocytopenia	0	1 (0.5)	1 (0.2)
Hepatobiliary disorders, n (%)	0	1 (0.5)	1 (0.2)
Cholecystitis	0	1 (0.5)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n(%)	0	1 (0.5)	1 (0.2)
Malignant neoplasm progression	0	1 (0.5)	1 (0.2)

a Excluded the case that reported as disease progression.
b Excluded the case that reported as disease progression or COVID-19.
In overall population, 25 patients died due to disease progression, of which 15 patients in the serplulimab group, 10 patients in the placebo group; 5 patients died due to COVID-19, of which 3 patients in the serplulimab group, 2 patients in the placebo group.
Abbreviations: irAE=immune-related adverse event, TEAE=treatment-emergent adverse event

Deaths considered treatment related

In the pivotal trial, 5 (1.3%) subjects in the serplulimab group and 1 (0.5%) subject in the placebo group died due to TEAEs that were considered related to serplulimab/placebo. For the serplulimab arm, these TEAEs belonged to the Preferred Terms Pyrexia, Immune-mediated lung disease, Immune-mediated encephalitis, Acute coronary syndrome, and Platelet count decreased.

Deaths - Pooled safety population

22 (1.9%) subjects had TEAEs leading to death that were considered related to serplulimab. No clear trends or patterns were observed in these events.

SAEs – Pivotal trial (ASTRUM-005)

A total of 229 (39.1%) subjects had at least one SAE during the trial, 152 (39.1%) subjects in the serplulimab group and 77 (39.3%) in the placebo group and they were predominantly related to haematological toxicity. Furthermore, pneumonia was reported as SAE in 3.3% and 3.6% in the two treatment arms, respectively. SAEs considered related to serplulimab/placebo were reported in 18.3% vs 14.3% of subjects, respectively (Table 44).

Table 44. Summary of SAEs Related to Serplulimab/Placebo by SOC and PT – ASTRUM-005 (DCO 13 June 2023)

System Organ Class (SOC) Preferred Term (PT)	Serplulimab Group (N=389)	Placebo Group (N=196)	Total (N=585)
Any SAE related to serplulimab/placebo, n (%)	71 (18.3)	28 (14.3)	99 (16.9)
Investigations, n (%)	26 (6.7)	13 (6.6)	39 (6.7)
Platelet count decreased	14 (3.6)	10 (5.1)	24 (4.1)
Neutrophil count decreased	9 (2.3)	11 (5.6)	20 (3.4)
White blood cell count decreased	10 (2.6)	6 (3.1)	16 (2.7)
Alanine aminotransferase increased	6 (1.5)	0	6 (1.0)
Aspartate aminotransferase increased	3 (0.8)	0	3 (0.5)
Blood ketone body increased	1 (0.3)	0	1 (0.2)
Gamma-glutamyltransferase increased	1 (0.3)	0	1 (0.2)
Metabolism and nutrition disorders, n (%)	10 (2.6)	2 (1.0)	12 (2.1)
Hyperglycaemia	5 (1.3)	0	5 (0.9)
Diabetic ketoacidosis	2 (0.5)	0	2 (0.3)
Decreased appetite	1 (0.3)	1 (0.5)	2 (0.3)
Diabetes mellitus	1 (0.3)	0	1 (0.2)
Hypoglycaemia	1 (0.3)	0	1 (0.2)
Hyponatraemia	0	1 (0.5)	1 (0.2)
General disorders and administration site conditions, n (%)	6 (1.5)	5 (2.6)	11 (1.9)
Pyrexia	3 (0.8)	1 (0.5)	4 (0.7)
Fatigue	1 (0.3)	1 (0.5)	2 (0.3)
Asthenia	0	2 (1.0)	2 (0.3)
General physical health deterioration	1 (0.3)	0	1 (0.2)
Multiple organ dysfunction syndrome	1 (0.3)	0	1 (0.2)
Non-cardiac chest pain	0	1 (0.5)	1 (0.2)
Blood and lymphatic system disorders, n (%)	5 (1.3)	6 (3.1)	11 (1.9)
Neutropenia	3 (0.8)	2 (1.0)	5 (0.9)
Thrombocytopenia	3 (0.8)	2 (1.0)	5 (0.9)
Leukopenia	3 (0.8)	1 (0.5)	4 (0.7)
Febrile neutropenia	1 (0.3)	1 (0.5)	2 (0.3)

System Organ Class (SOC) Preferred Term (PT)	Serplulimab Group (N=389)	Placebo Group (N=196)	Total (N=585)
Anaemia	0	2 (1.0)	2 (0.3)
Infections and infestations, n (%)	8 (2.1)	2 (1.0)	10 (1.7)
Pneumonia	5 (1.3)	2 (1.0)	7 (1.2)
Lip infection	1 (0.3)	0	1 (0.2)
Lower respiratory tract infection	1 (0.3)	0	1 (0.2)
Meningoencephalitis herpetic	1 (0.3)	0	1 (0.2)
Septic shock	1 (0.3)	0	1 (0.2)
Nervous system disorders, n (%)	7 (1.8)	0	7 (1.8)
Immune-mediated encephalitis	2 (0.5)	0	2 (0.3)
Cognitive disorder	1 (0.3)	0	1 (0.2)
Lacunar infarction	1 (0.3)	0	1 (0.2)
Neuropathy peripheral	1 (0.3)	0	1 (0.2)
Neurotoxicity	1 (0.3)	0	1 (0.2)
Peripheral sensorimotor neuropathy	1 (0.3)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders, n (%)	5 (1.3)	2 (1.0)	7 (1.2)
Immune-mediated lung disease	4 (1.0)	2 (1.0)	6 (1.0)
Pneumothorax	1 (0.3)	0	1 (0.2)
Hepatobiliary disorders, n (%)	3 (0.8)	4 (2.0)	7 (1.2)
Drug-induced liver injury	1 (0.3)	2 (1.0)	3 (0.5)
Hepatic function abnormal	1 (0.3)	0	1 (0.2)
Immune-mediated hepatitis	1 (0.3)	0	1 (0.2)
Hepatic failure	0	1 (0.5)	1 (0.2)
Jaundice	0	1 (0.5)	1 (0.2)
Gastrointestinal disorders, n (%)	6 (1.5)	0	6 (1.0)
Vomiting	2 (0.5)	0	2 (0.3)
Diarrhoea	1 (0.3)	0	1 (0.2)
Gastrointestinal haemorrhage	1 (0.3)	0	1 (0.2)
Immune-mediated pancreatitis	1 (0.3)	0	1 (0.2)
Intestinal obstruction	1 (0.3)	0	1 (0.2)
Nausea	1 (0.3)	0	1 (0.2)
Cardiac disorders, n (%)	4 (1.0)	0	4 (0.7)
Acute coronary syndrome	2 (0.5)	0	2 (0.3)
Acute myocardial infarction	1 (0.3)	0	1 (0.2)
Cardiac failure acute	1 (0.3)	0	1 (0.2)
Immune system disorders, n (%)	2 (0.5)	0	2 (0.3)
Anaphylactic reaction	1 (0.3)	0	1 (0.2)
Drug hypersensitivity	1 (0.3)	0	1 (0.2)

System Organ Class (SOC) Preferred Term (PT)	Serplulimab Group (N=389)	Placebo Group (N=196)	Total (N=585)
Endocrine disorders, n (%)	1 (0.3)	0	1 (0.2)
Hypothyroidism	1 (0.3)	0	1 (0.2)
Eye disorders, n (%)	1 (0.3)	0	1 (0.2)
Vision blurred	1 (0.3)	0	1 (0.2)
Psychiatric disorders, n (%)	1 (0.3)	0	1 (0.2)
Panic disorder	1 (0.3)	0	1 (0.2)
Renal and urinary disorders, n (%)	1 (0.3)	0	1 (0.2)
Acute kidney injury	1 (0.3)	0	1 (0.2)
Skin and subcutaneous tissue disorders, n (%)	1 (0.3)	0	1 (0.2)
Rash	1 (0.3)	0	1 (0.2)
Vascular disorders, n (%)	0	1 (0.5)	1 (0.2)
Aortic arteriosclerosis	0	1 (0.5)	1 (0.2)

Abbreviations: PT=preferred term, SAE=serious adverse event, SOC=system organ class, TEAE=treatment-emergent adverse event.

SAEs - Pooled safety population

As of 13 June 2023, treatment-emergent SAEs had occurred in 454 (38.7%) subjects in the pooled safety population. In the ≥RP2D/3D dose group, 32.8% subjects who received serplulimab monotherapy had treatment-emergent SAEs, compared to 42.2% subjects who received serplulimab in combination with chemotherapy, and 29.7% of the subjects who received serplulimab in combination with other monoclonal antibodies.

SAEs that were considered related to serplulimab were reported in 195 (16.6%) subjects in the pooled safety population. Among the grouped categories, the serplulimab-related SAEs that occurred in ≥2% of all subjects were thrombocytopenia (3.4%), pneumonitis (3.1%), and leukopenia (2.0%). Among the ungrouped PTs, none occurred in ≥2% subjects.

2.6.8.4. Laboratory findings

Laboratory abnormalities

In the pooled safety population, the proportion of patients who experienced a shift from baseline to a Grade ≥ 3 laboratory abnormality was as follows: 0.6% for platelet count decreased, 0.4% for neutrophil count decreased, 0.3% for blood creatine phosphokinase increased, 0.2% for white blood cell count decreased, 0.1% for blood lactate dehydrogenase increased, and 0.1% for blood cholesterol increased.

Haematology

Haematological changes occurred frequently in the pivotal trial, with similar trends for the serplulimab and placebo group. In the pooled safety population, shifts from normal to clinically significant (CS) abnormal results for haemoglobin were observed in 38.6% of the patients. For neutrophils, 46.5% of the patients with normal baseline values had CS abnormalities after treatment.

Chemistry

The chemistry-related TEAEs under the SOC of Investigations with an incidence of ≥5% in the serplulimab group included ALT increased (serplulimab 18.5% vs placebo 18.9%), AST increased

(16.2% vs 16.8%), blood alkaline phosphatase increased (13.1% vs 8.7%), blood lactate dehydrogenase increased (11.1% vs 9.2%), gamma glutamyltransferase increased (10.0% vs 6.6%), blood cholesterol increased (10.0% vs 2.0%), blood bilirubin increased (5.1% vs 6.1%), and blood creatinine increased (5.7% vs 5.1%).

In the pooled safety population, shifts from normal at baseline to CS abnormalities were observed for ALT (20.5% of the subjects), AST (20.2%) and bilirubin (8.9%). No apparent trends were observed in other chemistry parameters.

Thyroid hormones

In the pooled safety population, shifts from normal at baseline to CS abnormalities were observed in free T3 (10.4%), free T4 (11.2%), and TSH (14.4%).

12-Lead ECG

12-lead ECG revealed that patients in the serplulimab group had larger increases in their QTcF interval than patients in the placebo arm, including more patients with QTcF >500 msec, 3.6% vs 1.0%.

No dedicated QT study was performed with serplulimab.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Non-Asians

There were 184 non-Asian subjects in the pivotal trial, 127 in the serplulimab group and 57 in the placebo group.

In the non-Asian subset, the incidence of TEAEs was 89.0% in the serplulimab group and 93.0% in the placebo group. Common TEAEs with an incidence of ≥20% in the serplulimab group were anaemia (44.9% vs 45.6%), alopecia (43.3% vs 36.8%), neutropenia (41.7% vs 47.4%), neutrophil count decreased (24.4% vs 21.1%), and nausea (20.5% vs 24.6%). TEAEs were considered related to serplulimab/placebo in 29.1% and 26.3% of subjects in the two arms, respectively.

Excluding disease progression and COVID-19, TEAEs that resulted in death occurred in 7 (5.5%) subjects in the serplulimab group and 6 (10.5%) subjects in the placebo group.

Treatment-emergent SAEs occurred in 40 (31.5%) subjects in the serplulimab group and 22 (38.6%) subjects in the placebo group. Seven patients were reported to have SAEs related to serplulimab/placebo, 2.4% (3/127) in the serplulimab arm and 7.0% (4/57) in the placebo arm.

A total of 21 (11.4%) subjects had TEAEs that led to the discontinuation of serplulimab or placebo, 14 (11.0%) in the serplulimab group and 7 (12.3%) in the placebo group.

Regarding AESI, no infusion reactions were reported in any subjects. Treatment-emergent irAEs occurred more often in the serplulimab group than in the placebo group, 25.2% vs 10.5%.

Gender

Details of the safety profile according to gender have been provided and an overview of the safety profile in men and women is shown in the table below.

Table 45. Overview of TEAEs by gender (ASTRUM-005) (DCO 13 June 2023)

	Male			Female		
	Serplulimab (N=317) n (%)	Placebo (N=164) n (%)	Total (N=481) n (%)	Serplulimab (N=72) n (%)	Placebo (N=32) n (%)	Total (N=104) n (%)
Any Treatment-emergent adverse events (TEAEs)	301 (95.0)	159 (97.0)	460 (95.6)	72 (100)	32 (100)	104 (100)
TEAE by Grade						
Grade 1	11 (3.5)	3 (1.8)	14 (2.9)	0	1 (3.1)	1 (1.0)
Grade 2	28 (8.8)	24 (14.6)	52 (10.8)	10 (13.9)	3 (9.4)	13 (12.5)
Grade 3	127 (40.1)	56 (34.1)	183 (38.0)	28 (38.9)	9 (28.1)	37 (35.6)
Grade 4	103 (32.5)	58 (35.4)	161 (33.5)	31 (43.1)	15 (46.9)	46 (44.2)
Grade 5	32 (10.1)	18 (11.0)	50 (10.4)	3 (4.2)	4 (12.5)	7 (6.7)
Grade 3 or 4	230 (72.6)	114 (69.5)	344 (71.5)	59 (81.9)	24 (75.0)	83 (79.8)
≥Grade 3	262 (82.6)	132 (80.5)	394 (81.9)	62 (86.1)	28 (87.5)	90 (86.5)
TEAEs Related to Any Study Drug	292 (92.1)	155 (94.5)	447 (92.9)	72 (100)	32 (100)	104 (100)
Related to Serplulimab/ Placebo	215 (67.8)	91 (55.5)	306 (63.6)	58 (80.6)	22 (68.8)	80 (76.9)
Related to Carboplatin or Etoposide	291 (91.8)	153 (93.3)	444 (92.3)	71 (98.6)	32 (100)	103 (99.0)
Serious TEAEs	115 (36.3)	57 (34.8)	172 (35.8)	31 (43.1)	14 (43.8)	45 (43.3)
Serious TEAEs Related to Any Study Drug	75 (23.7)	36 (22.0)	111 (23.1)	23 (31.9)	7 (21.9)	30 (28.8)
Serplulimab/ Placebo	53 (16.7)	23 (14.0)	76 (15.8)	18 (25.0)	5 (15.6)	23 (22.1)
Carboplatin or Etoposide	62 (19.6)	34 (20.7)	96 (20.0)	17 (23.6)	7 (21.9)	24 (23.1)
TEAEs Leading to Any Study Drug Interruption	142 (44.8)	69 (42.1)	211 (43.9)	37 (51.4)	17 (53.1)	54 (51.9)
Serplulimab / Placebo	135 (42.6)	65 (39.6)	200 (41.6)	35 (48.6)	17 (53.1)	52 (50.0)
Carboplatin or Etoposide	92 (29.0)	56 (34.1)	148 (30.8)	21 (29.2)	6 (18.8)	27 (26.0)
TEAEs Related to Serplulimab / Placebo Leading to Any Study Drug Interruption	68 (21.5)	28 (17.1)	96 (20.0)	21 (29.2)	6 (18.8)	27 (26.0)
Serplulimab/ Placebo	65 (20.5)	27 (16.5)	92 (19.1)	20 (27.8)	6 (18.8)	26 (25.0)
Carboplatin or Etoposide	32 (10.1)	19 (11.6)	51 (10.6)	10 (13.9)	0	10 (9.6)
TEAEs Leading to Any Study Drug Discontinuation	26 (8.2)	17 (10.4)	43 (8.9)	12 (16.7)	1 (3.1)	13 (12.5)

Serplulimab/ Placebo	25 (7.9)	16 (9.8)	41 (8.5)	9 (12.5)	1 (3.1)	10 (9.6)
Carboplatin or Etoposide	7 (2.2)	8 (4.9)	15 (3.1)	7 (9.7)	0	7 (6.7)
TEAEs Related to Serplulimab/ Placebo Leading to Any Study Drug Discontinuation	14 (4.4)	9 (5.5)	23 (4.8)	9 (12.5)	1 (3.1)	10 (9.6)
Serplulimab/ Placebo	14 (4.4)	8 (4.9)	22 (4.6)	7 (9.7)	1 (3.1)	8 (7.7)
Carboplatin or Etoposide	2 (0.6)	6 (3.7)	8 (1.7)	4 (5.6)	0	4 (3.8)
Treatment-Emergent Injection Reaction (IRR)	4 (1.3)	1 (0.6)	5 (1.0)	3 (4.2)	0	3 (2.9)
TEAE of Immune-related (irAE)	112 (35.3)	32 (19.5)	144 (29.9)	33 (45.8)	6 (18.8)	39 (37.5)
TEAEs Leading to Death	32 (10.1)	18 (11.0)	50 (10.4)	3 (4.2)	4 (12.5)	7 (6.7)
TEAEs Leading to Death Related to Any Study Drug	7 (2.2)	1 (0.6)	8 (1.7)	0	0	0
Related to Serplulimab/ Placebo	5 (1.6)	1 (0.6)	6 (1.2)	0	0	0
Related to Carboplatin or Etoposide	5 (1.6)	1 (0.6)	6 (1.2)	0	0	0
TEAEs and Received systemic corticosteroids (+ high-dose)	46 (14.5)	20 (12.2)	66 (13.7)	12 (16.7)	2 (6.3)	14 (13.5)
TEAEs and Received endocrine therapy	106 (33.4)	39 (23.8)	145 (30.1)	31 (43.1)	4 (12.5)	35 (33.7)
TEAEs with outcome resolved	14 (4.4)	8 (4.9)	22 (4.6)	0	0	0
TEAEs with outcome not resolved	255 (80.4)	133 (81.1)	388 (80.7)	69 (95.8)	28 (87.5)	97 (93.3)

Age

Table 46. Safety profile by age group (Pooled safety population)

MedDRA Terms	Age <65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
Total TEAEs	757 (96.9%)	344 (95.8%)	30 (93.8%)	0
Serious TEAEs - Total	282 (36.1%)	161 (44.8%)	11 (34.4%)	0
- Fatal	72 (9.2%)	48 (13.4%)	2 (6.3%)	0
- Hospitalization/prolong existing hospitalization	232 (29.7%)	138 (38.4%)	9 (28.1%)	0
- Life-threatening	36 (4.6%)	21 (5.8%)	3 9.4%)	0
- Disability/incapacity	3 (0.4%)	0	0	0
- Other (medically significant)	12 (1.5%)	4 (1.1%)	0	0
AE leading to drop-out	80 (10.2%)	46 (12.8%)	1 3.1%)	0
Psychiatric disorders	86 (11.0%)	42 (11.7%)	3 (9.4%)	0
Nervous system disorders	171 (21.9%)	73 (20.3%)	9 (28.1%)	0
Accidents and injuries	34 (4.4%)	16 (4.5%)	2 (6.3%)	0
Cardiac disorders	152 (19.5%)	77 (21.4%)	3 (9.4%)	0
Vascular disorders	81 (10.4%)	42 (11.7%)	5 (15.6%)	0
Cerebrovascular disorders	18 (2.3%)	4 (1.1%)	1 (3.1%)	0
Infections and infestations	250 (32.0%)	105 (29.2%)	9 (28.1%)	0
Anticholinergic syndrome	197 (25.2%)	92 (25.6%)	8 (25.0%)	0

MedDRA Terms	Age <65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	46 (5.9%)	30 (8.4%)	2 (6.3%)	0
Other AE appearing more frequently in older patients	652 (83.5%)	310 (86.4%)	26 (81.3%)	0
Anaemia	426 (54.5%)	244 (68.0%)	19 (59.4%)	0
Neutrophil count decreased	302 (38.7%)	164 (45.7%)	12 (37.5%)	0
White blood cell count decreased	319 (40.8%)	168 (46.8%)	11 (34.4%)	0
Alopecia	275 (35.2%)	152 (42.3%)	10 (31.3%)	0
Decreased appetite	177 (22.7%)	111 (30.9%)	10 (31.3%)	0
Platelet count decreased	264 (33.8%)	148 (41.2%)	8 (25.0%)	0
Dyspnoea	56 (7.2%)	31 (8.6%)	8 (25.0%)	0
Neutropenia	121 (15.5%)	93 (25.9%)	7 (21.9%)	0
Alanine aminotransferase increased	187 (23.9%)	50 (13.9%)	7 (21.9%)	0
Asthenia	98 (12.5%)	45 (12.5%)	7 (21.9%)	0
Cough	92 (11.8%)	41 (11.4%)	7 (21.9%)	0
Leukopenia	105 (13.4%)	73 (20.3%)	6 (18.8%)	0
Thrombocytopenia	85 (10.9%)	62 (17.3%)	3 (9.4%)	0
Hypotension	8 (1.0%)	9 (2.5%)	2 (6.3%)	0
Rhinorrhoea	9 (1.2%)	3 (0.8%)	2 (6.3%)	0
Nasopharyngitis	13 (1.7%)	1 (0.3%)	2 (6.3%)	0
Urinary incontinence	3 (0.4%)	1 (0.3%)	2 (6.3%)	0

AEs leading to drop-out are TEAES leading to permanent treatment discontinuation.
The "Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures" includes the PTs of Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia, and the HLGT of Fractures.
The following AE categories have been analyzed by MedDRA SMQs (broad and narrow): Accidents and injuries (SMQ: Accidents and Injuries), Cerebrovascular disorders (SMQ: Central nervous system vascular disorders), and Anticholinergic syndrome (SMQ: Anticholinergic syndrome).
>5% difference between the <65, 65-74, 75-84 and ≥85 age categories.

2.6.8.7. Immunological events

Immunogenicity data were collected in the eight clinical studies constituting the safety pool. The presence of anti-serplulimab antibodies (ADA) in serum was evaluated with a 3-tier approach composed of screening, confirmation, and titre determination. ELISA and electrochemiluminescence immunoassays were employed to detect NAb against serplulimab.

In study HLX10-001, for the dose finding cohorts and the 200 mg, 300 mg flat dose cohorts, immunogenicity samples were collected at pre-dose before 1st and 2nd infusion in cycle 1, and pre-dose before 1st infusion in cycles 2-6 or up to 24 weeks, whichever came first, and on the 28-day follow-up visit. For the 400 mg flat dose cohort, immunogenicity samples were collected at pre-dose in cycles 1-6 and on the 28-day follow-up visit. In ASTRUM-005, ADA samples were collected within 7 days pre-dose in Cycle 1, within 3 days pre-dose in Cycles 2, 4, 6, 8 and every 4 cycles thereafter, at EOT visit and safety follow-up. Samples were analysed by the central laboratory in a blinded manner.

In study HLX10-001, the originally reported incidence of treatment-emergent ADAs was 3.4% (1/29) in the dose finding cohorts and 35.7% (10/28) in the dose expansion cohorts. The percentage of patients with at least one positive ADA was 3.4% in the dose finding cohorts and 67.9% in the dose expansion cohorts. Following an adjustment in cut-point, the percent of patients with at least one positive ADA measurement in study HLX10-001 was reduced to 3.4% (1/29) in the dose finding cohorts and 35.71% (10/28) in the dose expansion cohort (Table 43). The applicant provided satisfactory justification for the modification of the cut-point. Further, the applicant provided ADA results from the 600 mg Q6W expansion cohort of study HLX10-001, where two out of nine patients were found to be ADA positive at any time. NAbs were not originally tested for in study HLX10-001, however, in the course of the procedure, Nabs were also measured in ADA-positive samples in study HLX10-001, and results presented (data not shown). No Nabs were detected in this study.

For C3D1, the exposure of serplulimab (AUC, Cmax, Cmin) in the ADA positive subjects in 0.3 mg/kg Q2W and 200 mg Q2W cohorts were lower and had quicker clearance compared with the ADA negative subjects in these two cohorts.

Cross-validation of ADA methods between studies has not been performed, thus comparisons of immunogenicity results across studies are not possible.

In ASTRUM-005, 1.5% (6/389 subjects) had at least one post-treatment ADA-positive sample. No neutralising activity was found in any of the ADA-positive samples from ASTRUM-005. Overall, 96.4% and 98.0% of the patients reported at least one TEAE, respectively in the serplulimab arm and the placebo arm. TEAEs that occurred in ≥5% of subjects are summarised in the table below.

Table 47. Summary of the number and percentage of patients with at least one positive ADA by dose level, study HLX10-001

Study	Treatment Group	*ADA positive n (%)		#treatment-emergent ADA positive n (%)	
		previous	updated	previous	updated
Dose finding cohorts	0.3 mg/kg Q2W (N = 3)	1	1	1	1
	1 mg/kg Q2W (N = 4)	0	0	0	0
	3 mg/kg Q2W (N = 6)	0	0	0	0
	10 mg/kg Q2W (N = 16)	0	0	0	0
	Total (N = 29)	1 (3.4)	1 (3.4)	1 (3.4)	1 (3.4)
Dose expansion cohorts	200 mg Q2W (N = 9)	2	**1**	2	**1**
	300 mg Q3W (N = 9)	7	**4**	4	**4**
	400 mg Q4W (N = 10)	10	**5**	4	**3**
	Total (N = 28)	19 (67.9)	**10(35.71)**	10 (35.71)	**8 (28.57)**
All	Total (N =57)	20 (35.09)	**11 (19.30)**	11 (19.30)	**9 (15.79)**

Note: * subjects with at least one ADA positive at any visit including baseline. # subjects with at least one ADA positive at any visit after HLX10 treatment.

In the pooled safety population of eight serplulimab trials, 43 (3.6%) of 1181 subjects had at least 1 positive ADA result at any visit.

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

Pharmacokinetic interactions are not expected with serplulimab.

2.6.8.9. Discontinuation due to adverse events

In the pivotal trial, 5.4% of the patients in the serplulimab arm discontinued treatment due to TEAEs related to serplulimab. The related TEAEs leading to discontinuation and occuring more often in the

serplulimab arm were classified into the following SOCs (serplulimab arm vs placebo arm): Investigations (1.0%/0.5%), Nervous system disorders (1.0%/0), Skin and subcutaneous tissue disorders (0.8%/0.5%), Gastrointestinal disorders (0.8%/0), Cardiac disorders (0.3%/0), Endocrine disorders (0.3%/0), Eye disorders (0.3%/0). A similar rate of discontinuation due to serpulimab-related TEAEs was seen in the pooled safety population, 5.3%, and belonged to the following grouped categories (≥0.5%): pneumonitis (1.2%), thrombocytopenia (0.5%), and liver injury (0.5%).

2.6.8.10. Post marketing experience

Serplulimab as a monotherapy was approved by China's NMPA in 2022 for the treatment of unresectable or metastatic solid tumours with a high degree of metastatic microsatellite instability (MSI-H). As a combination therapy, serplulimab was approved by China's NMPA in 2022 for the first-line treatment of patients with squamous NSCLC combined with chemotherapy, and in 2023 for the first-line treatment of patients with ES-SCLC combined with chemotherapy. Marketing of the product began in March 2022.

2.6.9. Discussion on clinical safety

The safety of serplulimab for the targeted indication, first-line treatment of adult patients with extensive stage-small cell lung cancer (ES-SCLC), in combination with carboplatin and etoposide (4 cycles), is based primarily on the safety data obtained in the placebo-controlled pivotal trial ASTRUM-005 (n=585). This study was conducted in China, Russia, Ukraine, Poland, Turkey, and Georgia. The first subject was enrolled 12 September 2019.

With safety data collected from a total of 8 ongoing clinical trials of serplulimab in subjects with various types of solid tumours, the pooled safety population comprises a total of 1172 serplulimab treated patients. Of these, 254 are Caucasian (127 from the pivotal trial), while the remaining are Asian. The safety database is considered sufficiently large. As of the cut-off of 13 June 2023, in the pooled safety population, 67.8%, 42.5%, 26.6% of subjects had serplulimab exposure for at least 3 months, 6 months, and 9 months, respectively. Cut-off for safety for the individual studies included in the pooled safety population was 1-2 years ago. The safety database is considered large enough to sufficiently describe the safety profile of serplulimab.

The recommended dose of serplulimab is 4.5 mg/kg every 3 weeks until disease progression or unacceptable toxicity. Adverse drug reactions should be handled by treatment interruption or discontinuation and/or symptomatic treatment (e.g., glucocorticoids) could be given. In the pivotal study, use of corticosteroids to handle adverse reactions was reported for 15.2% and 11.2% of the patients in the serplulimab arm and the placebo arm, respectively. The numbers of patients who received high-dose corticosteroids for immune-related AEs were 26 (6.7%) and 4 (2.0%) in the two study arms, respectively.

Adequate description of how to manage immune-mediated adverse reactions has been included in the product information (section 4.4 of the SmPC).

In the pivotal trial, the overall safety profiles (cut-off 13 June 2023) for the two treatment arms are quite similar, with similar frequencies of **SAEs** (39.1% vs 39.3%) and **≥Grade 3 AEs** (84.6% vs 83.2%). As expected, there were more infusion-related reactions (IRRs) (1.8% vs 0.5%) and immune-related TEAEs (38.0% vs 18.9%) in the serplulimab arm (data not shown). This is in line with the frequencies reported for other ICIs, e.g., durvalumab and atezolizumab.

In the pooled safety population, **IRRs** were reported in 14 (1.2%) subjects. Most events were Grade 1-2 in severity. Two patients had Grade 3 IRRs reported as anaphylactic reaction and infusion-related reaction. In addition, one subject had a Grade 4 event of drug hypersensitivity (data not shown).

In the pivotal study, there were slightly more patients with **SAEs** related to any study drug (25.4% vs 22.4%) in the serplulimab treated patients, and the difference was caused by SAEs considered related to serplulimab (18.3% vs 14.3%). A quite similar, small difference between treatment arms was also seen for TEAEs leading to any study drug interruption (46.8% vs 43.9%). There was no difference in the rates of TEAEs leading to any study drug discontinuation (9.8% vs 9.7%), and TEAEs have not led to more discontinuation of chemotherapy. The large proportion of TEAEs reported as related to serplulimab in the placebo arm (57.7%) indicates that most of the TEAEs are not related to the study drug, or they are caused by the chemotherapy backbone in both study arms.

There were more **TEAEs reported as leading to death** in the control arm (13.8%) than in the serplulimab arm (10.0%); however, they were considered related to serplulimab in more patients in the serplulimab arm than in the control arm (1.3% vs 0.5%). There is no apparent trend in the cause of death in the pivotal trial; however, in the pooled safety population there were 7 cases of pneumonitis leading to death (0.6%; 7/1172). There are 41 deaths due to AEs labelled as "other" in the serplulimab arm and 13 in the placebo arm of the pivotal study. Individual narratives for the serplulimab treated patients do not rule out that some of those deaths could be related to AEs from serplulimab. No Asian patients were declared to have died as a result of COVID-19 infection in the pivotal study which has been explained by the strict lock-down in China.

The most predominant **TEAEs** in the pivotal trial were haematological events and there were only slightly more of these reported in the serplulimab arm: anaemia (serplulimab 72.2% vs placebo 71.4%), neutrophil count decreased (56.3% vs 51.5%), alopecia (54.2% vs 56.6%), WBC count decreased (54.0% vs 51.0%), platelet count decreased (41.6% vs 44.9%), nausea (36.2% vs 43.9%), neutropenia (29.8% vs 32.1%), decreased appetite (28.3% vs 28.6%), hyponatraemia (25.4% vs 13.3%), leukopenia (24.4% vs 20.9%), constipation (24.7% vs 29.6%), and vomiting (20.3% vs 29.6%). Common TEAEs (≥10%) considered related to serplulimab/placebo and occurring more frequently in the serplulimab arm than in the placebo arm were anaemia (21.9% vs 18.9%), WBC count decreased (20.3% vs 16.8%), neutrophil count decreased (19.5% vs 17.9%), hypothyroidism (15.4% vs 2.6%), ALT increased (12.3% vs 9.7%), hyperthyroidism (11.6% vs 3.1%), and decreased appetite (10.0% vs 9.7%). Hypo- and hyperthyroidism, liver enzyme elevations, thrombocytopenia and hyponatraemia are associated with other immune therapies, e.g., atezolizumab and durvalumab. Anaemia and other haematological toxicity have also been reported for other checkpoint inhibitors. When taking into consideration the level of these AEs in the control arm, serplulimab seems to be causing limited additional haematological toxicity. For comparison, among the 256 patients who had received serplulimab monotherapy (≥RP2D/3D) in the pooled safety population, many of the common TEAEs were much less frequent than in the chemotherapy combination group, i.e., neutropenia, leukopenia, thrombocytopenia, decreases in WBC count, platelet count and neutrophil count were reported in 1-10% while anaemia was reported in 29% (76% for combination with chemotherapy).

The **SAEs** with incidence ≥2% occurring at a similar rate or more frequently in the serplulimab arm were pneumonia (3.3% vs 3.6%), neutropenia (2.8% vs 2.0%), thrombocytopenia (2.8% vs 2.0%), and leukopenia (2.3% vs 1.5%) (data not shown).
A number of **deaths** were labelled as "other", i.e. 41 in the serplulimab arm and 13 in the placebo arm. Individual narratives for the serplulimab treated patients do not rule out that some of those deaths could be related to AEs from serplulimab.

QT prolongation

12-lead ECG revealed that patients in the serplulimab group had larger increases in their QTcF interval than patients in the placebo arm, including more patients with QTcF >500 msec, 3.6% vs 1.0%. The latter may be attributed to the higher frequency of ECG examinations in the serplulimab arm. No dedicated QT study was performed with serplulimab which is acceptable for monoclonal antibodies with low potential for direct ion channel interactions. However, the applicant has provided a concentration-QTc analysis which did not show any concentration-QTc relationship with serplulimab. There are some SAEs and deaths (including sudden deaths) that could be related to disturbances in cardiac conduction caused by serplulimab, although considered related to the underlying disease by the investigator. In the SmPC section 4.8, arrhythmia is listed as a very common ADR, while sinus tachycardia, sinus bradycardia, conduction defects and cardiac failure are listed as common ADRs.

Non-Asians

In the non-Asian subset (n=184) of the pivotal trial, there were generally less TEAEs than in the Asian subset, and also less treatment related TEAEs, less ≥Grade 3 TEAEs (58% serplulimab/49.1% placebo), less SAEs (31.5%/38.6%), and less SAEs considered related to serplulimab/placebo (2.4%/7.0%). In the serplulimab arm the following SAEs were reported (once each): General physical health deterioration, pyrexia, fatigue, immune-mediated lung disease, peripheral sensorimotor neuropathy, acute kidney injury (data not shown). There was a lower incidence of immune-related AEs/IRR in the non-Asian subset than in the Asian subset, with 25.2% in the serplulimab arm and 10.5% in the placebo arm.

Overall, non-Asians seem to have a better tolerability towards both chemotherapy and serplulimab compared to Asians. It is a recognised fact that there are differences in response to chemotherapy between Asians and Caucasians. The rather small Caucasian population in the overall safety pool is not considered a problem as there are clear indications that the safety profile is acceptably tolerated by these patients.

Gender

80% of the patients are male both in the pivotal trial and the pooled safety set. Across the eight studies in the pooled safety population, 232 females have been treated with serplulimab. In the pivotal trial, 72 females were treated with serplulimab, of which 18 were Caucasian. Based on the pooled safety population, the safety profile seems slightly worse in men than in women. However, based on the pivotal trial, the opposite tendency is seen, (with an exception for TEAEs leading to death). This might be caused by the specific combination of serplulimab and chemotherapy, with women being less tolerant to chemotherapy. Based on the provided data, the impression is that Caucasian women seem to tolerate the treatment better than the Asian women, in line with previous findings that Asians are more sensitive to certain anticancer treatments than Caucasians. Albeit a small population of Caucasian women in the pooled safety population (n=31), it may be concluded that the combination of serplulimab and chemotherapy provides an acceptable safety profile in this population.

Age

In the pivotal trial, 40% of the patients are ≥ 65 years, with a median age of 63 years. In the pooled safety set, 33% are ≥ 65 years, with a median of 61 years. In the pooled safety population, there are generally more TEAEs Grade ≥3, SAEs and deaths in patients ≥65 years than in patient <65 years. The <65 age group had a numerically higher incidence of irAEs (34.2% vs 28.9%), which is not unexpected. Similar numbers for irAEs were found in the pooled safety population 36.0% vs 30.2%). The TEAEs that appear more frequently in the older patients in the pooled safety population could be related to the chemotherapy backbone, i.e. anaemia, neutropenia, leukopenia, thrombocytopenia, alopecia, and decreased appetite. Considering the toxicity profile reported for serplulimab in general,

high age may not be a hindrance for treatment if the patient is considered fit for chemotherapy. Furthermore, based on pharmacokinetic analysis no special precautions are warranted in the elderly; this information has been included in section 4.8 of the SmPC.

Immunogenicity

An Integrated Summary of Immunogenicity (ISI) was provided upon request by the CHMP.

Both PK and immunogenicity assays are seemingly adequately validated, however cross-validation of the employed ADA methods has not been performed and any cross-study comparisons of immunogenicity are therefore hampered by uncertainty.

More frequent ADA sampling during the first treatment cycles would have been preferred. Specifically, no ADA sampling was performed at C1D15, leaving this first important month without immunogenicity monitoring, thereby introducing further uncertainty to reported ADA results.

In study HLX10-001, there is a high incidence of ADA-positive patients, especially in the dose expansion cohorts. An apparent discrepancy in immunogenicity is observed between the HLX10-001 and ASTRUM-005 studies.

While the applicant has provided some discussion of factors potentially influencing immunogenicity, including dosing, the discrepancy in immunogenicity between the HLX10-001 and ASTRUM-005 is still not fully explained. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however data are still limited.

The applicant also introduced, upon request by the CHMP, a new in-study cut-point for study HLX10-001, resulting in apparently lower immunogenicity rates across all doses in this study. The applicant also provided satisfactory justification for the need and appropriateness of a new, in-study cut-point, along with a comparative overview of ADA results for in-study samples using either the former cut point values or the newly established values. In dose escalation and dose expansion study HLX10-001, ADAs were observed in 13 out of 66 patients (19.7%).

Neutralising activity should always be tested when new biologics are administered to obtain an appropriate characterisation of potential ADAs in patients (EMEA/CHMP/BMWP/14327/2006 Rev 1). Nabs were originally not tested for in study HLX10-001, but in the course of the procedure, Nab testing results were submitted for all ADA positive samples from this study and no Nab positive samples were found. However, no validation or bioanalytical reports were provided. Similarly, no Nabs were found in the ADA positive samples from ASTRUM-005.

In study HLX10-001, ADA positive patients had lower systemic serplulimab exposure and higher CL compared to ADA negative patients based on Cycle 3 Day 1 data, but this finding should be interpreted with caution due to the small sample size. No clear differences in serplulimab concentrations according to ADA status were observed across studies. The effect, or lack thereof, of ADAs on serplulimab PK cannot be definitely concluded based on the available data. However, there is no strong indication of a large impact of ADAs on the systemic exposure of serplulimab. Overall, no clear evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however data are still limited.

An overview of AEs by comparison between subjects with at least one positive ADA and subjects without positive ADA in the pooled safety population has been presented, showing no overall obvious differences. Any interpretation of differences in percentage of individual AEs or by SOC should be performed with caution since the group of patients with ADAs only comprises 41 patients, compared to 1131 patients that were found to be ADA negative.

Overdose

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

Contraindications

Hetronifly is contraindicated in patients with hypersensitivity to the active substance (serplulimab) or any of its excipients.

2.6.10. Conclusions on the clinical safety

The dossier provides data from a population large enough to assess the safety of serplulimab. The reported safety profile is overall comparable to other anti-PD-1/PD-L1 antibodies. For the intended indication, it is likely that haematological toxicities and other frequent events are attributable to the chemotherapy backbone, whereas immune-related events attributable to serplulimab were mostly of low-grade nature and treatable with dose interruptions or corticosteroids. There is uncertainty regarding the immunogenicity profile of serplulimab, due to discrepancies in immunogenicity between the two key studies HLX10-001 and HLX10-005-SCLC301. A low level of ADAs was seen in the pivotal study. Overall, the safety profile of serplulimab is considered acceptable.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	• Immune-mediated adverse reactions • Severe infusion reactions
Important potential risks	• None
Missing information	• Long-term safety in immunocompromised patients

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Immune-mediated adverse reactions	**Routine risk minimisation measures:** Routine risk communication:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

	• Immune-mediated adverse reactions added in SmPC section 4.4. • Immune-mediated adverse reactions listed as adverse reactions in SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance for withholding or permanently discontinuing serplulimab based on the severity of adverse reactions provided in SmPC section 4.2. • Warning to monitor for signs and symptoms of immune-mediated adverse reactions and treatment advice based on severity included in SmPC section 4.4. • Warning for the patient to talk to their doctor if they have inflammation provided in Package leaflet. Other routine risk minimisation measures: • Legal status: subject to restricted medical prescription. **Additional risk minimisation measures:** Patient Card	**Additional pharmacovigilance activities:** None
Severe infusion reactions	**Routine risk minimisation measures:** Routine risk communication: • Description of the infusion-related reactions observed in clinical trials provided in SmPC section 4.4. • Infusion-related reaction listed as adverse reaction in SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance for withholding or discontinuing serplulimab based on the severity of the infusion-related reaction provided in SmPC section 4.2. • Warning to monitor for signs and symptoms of infusion-related reactions and treatment	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

	advice based on severity included in SmPC section 4.4. • Warning for the patient to talk to their doctor if they have infusion-related reactions provided in Package leaflet. Other routine risk minimisation measures: • Legal status: subject to restricted medical prescription. **Additional risk minimisation measures:** Patient Card	
Long-term safety in immunocompromised patients	**Routine risk minimisation measures:** Routine risk communication: • Information that patients with a history of active or prior documented autoimmune disease or active HIV infection, conditions requiring systemic immunosuppressive medicinal products within 2 weeks prior to receiving serplulimab were excluded from clinical trials provided in SmPC section 4.4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance for the patient to check with their doctor before receiving serplulimab if they have an autoimmune disease in Package leaflet. Other routine risk minimisation measures: • Legal status: subject to restricted medical prescription. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

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 22.03.2022. The new EURD list entry will therefore use the IBD 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. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The applicant has requested to omit Braille because the medicinal product is to be administered by healthcare professionals only. The request is found acceptable as the medicinal product are to be prepared and handled by healthcare professionals only.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Hetronifly (serplulimab) is included in the additional monitoring list as it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

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 is as follows: *"Hetronifly in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)".* The aim of the therapy is to prolong overall survival, which is the primary efficacy endpoint of the pivotal study.

3.1.2. Available therapies and unmet medical need

For decades, the available treatment for ES-SCLC has been chemotherapy, often a platinum agent (carboplatin or cisplatin) in combination with etoposide. In case of response to first-line treatment, consolidation thoracic radiation therapy and prophylactic cranial irradiation are treatment options. Addition of immunotherapy to conventional chemotherapy has been explored as first-line strategy in ES-SCLC. Currently, two anti-PD-L1 immune checkpoint inhibitors (atezolizumab and durvalumab) are approved in the EU for this indication, while no anti-PD-1 antibodies are approved for the claimed indication. Of note, OS benefit could not be demonstrated in study KEYNOTE-604 with pembrolizumab (PD-1 inhibitor), but this may be due to different immunotherapy strategies and differences in study design (Rudin CM et al 2020).

The use of PD-L1 immunohistochemistry as a predictive biomarker does not appear to be related to response to immunochemotherapy (Liu et al 2021).

Despite available therapies, there is still need for additional treatment options to prolong survival in this aggressive disease setting, for which long-term prognosis has historically been dismal.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase III, multicentre, 2:1 randomised and double-blind study (ASTRUM-005) comparing serplulimab plus chemotherapy (n=389) versus placebo plus chemotherapy (n=196) in previously untreated patients with ES-SCLC.

The safety profile of serplulimab is based on the safety data obtained from the pivotal trial in patients with ES-SCLC, and safety data collected from 8 clinical trials of serplulimab in subjects with various types of solid tumours, including the pivotal trial, with a total of 1172 patients having received at least one dose of serplulimab. Of these patients, 78% were Asian and the remaining 22% were Caucasians. A total of 263 patients have been treated with serplulimab as monotherapy in the pooled safety population, while 768 were treated with serplulimab in combination with chemotherapy and 141 in combination with a monoclonal antibody.

3.2. Favourable effects

The primary endpoint OS was met in the ITT population with a stratified HR (95% CI) of 0.63 (0.49, 0.82) in favour of serplulimab in the primary analysis (DCO date of 22 Oct 2021). The median OS (95% CI) was 15.4 (13.3, NA) months for the serplulimab group versus 10.9 (10.0, 14.3) months in the placebo group. The difference in median OS was 4.5 months between the serplulimab group and

the placebo group. The Kaplan-Meier survival curves demonstrated a separation after ~4 months of treatment in favour of serplulimab.

In the non-Asian subgroup, OS results showed a trend in line with the primary analysis. Updated results confirmed this trend: The median OS (95% CI) was 15.6 (12.7, 18.5) months for the serplulimab arm versus 11.2 (8.5, 14.3) months in the placebo arm, HR (95% CI) of 0.51 (0.34, 0.79). The difference in median OS was 4.4 months between the serplulimab group and the placebo group. The Kaplan-Meier survival curves demonstrated a separation after ~4 months of treatment in favour of serplulimab.

The survival benefit of serplulimab compared to placebo is seen in Forest plots across all subgroups in all comers and the non-Asian subgroup.

The secondary endpoint of PFS by IRRC was supportive of the primary endpoint, with a stratified HR (95% CI) of 0.48 (0.38, 0.59) in all comers at updated analysis. The median PFS was (95% CI) 5.7 (5.6, 6.9) months in the serplulimab arm versus 4.3 (4.2, 4.5) months in the placebo arm. Results of other secondary endpoints (PFS by Investigator, ORR, PFS2 and DOR) were also supportive of the primary endpoint in all comers and the non-Asian subgroup.

3.3. Uncertainties and limitations about favourable effects

Study population

The non-Asian subgroup comprised 31% of study participants and only 7 participants were included from study sites in the EU. Only 18% of the study participants were females. Since smoking habits are more comparable between genders in the European population, the proportion of females is expected to be higher in the non-Asian study population. The gender distribution between the study arms was balanced. The proportion of never-smokers included in the study was ~20%, which is much higher than expected according to literature (2-3% of patients with SCLC). The proportion of never-smokers (n=67) among the included Asian females (n=80) was 84%. The proportion of patients with PD-L1 expression >1% was three times higher in the non-Asian subgroup vs the Asian subgroup (29% vs 11%, respectively). The above-mentioned baseline characteristics may have an impact on the generalisability of the study outcomes to the European patient population.

In order to accumulate further information on the efficacy in the non-Asian population, the applicant is recommended to report the results of the study HLX10-005-SCLC301-E (**REC**).

3.4. Unfavourable effects

As of cut-off date 13 June 2023 for the pivotal trial, 96.4% and 98.0% of the patients reported at least one TEAE, respectively in the serplulimab arm and the placebo arm. The rates of ≥Grade 3 TEAEs were 84.6% and 83.2%, respectively. There were slightly more patients with SAEs related to any study drug in the serplulimab treated patients than in the control arm (25.4% vs 22.4%), and the difference was caused by SAEs considered related to serplulimab/placebo (18.3% vs 14.3%). A similar rate of study drug discontinuation was observed in the two study arms (9.8% vs 9.7%). TEAEs caused by serplulimab did not lead to more discontinuation of the chemotherapy backbone.

The majority of the common TEAEs was typical of chemotherapy treatment: anaemia (serplulimab 72.2% vs placebo 71.4%), neutrophil count decreased (56.3% vs 51.5%), alopecia (54.2% vs 56.6%), WBC count decreased (54.0% vs 51.0%), platelet count decreased (41.6% vs 44.9%), nausea (36.2% vs 43.9%), neutropenia (29.8% vs 32.1%), decreased appetite (28.3% vs 28.6%), hyponatraemia

(25.4% vs 13.3%), leukopenia (24.4% vs 20.9%), constipation (24.7% vs 29.6%), and vomiting (20.3% vs 29.6%).

The most common TEAEs reported as related to serplulimab were anaemia (21.9% vs placebo arm 18.9%), WBC count decreased (20.3% vs 16.8%), neutrophil count decreased (19.5% vs 17.9%), platelet count decreased (15.7% vs 18.4%), hypothyroidism (15.4% vs 2.6%), nausea (13.1% vs 14.3%), ALT increased (12.3% vs 9.7%), hyperthyroidism (11.6% vs 3.1%) and decreased appetite (10.0% vs 9.7%). The TEAEs ≥5% that stand out as caused by serplulimab treatment are hypothyroidism and hyperthyroidism, which are common immune-mediated AEs reported for other immune checkpoint inhibitors.

Immune-related adverse events (irAEs) and infusion related reactions (IRR) were adverse events of special interest (AESI) for serplulimab. Immune-related TEAEs occurred in 38.0% of the patients in the serplulimab arm and 18.9% of the patients in the placebo arm. The most common irAEs by PT were hypothyroidism (serplulimab vs placebo: 13.1% vs 2.0%), hyperthyroidism (10.8% vs 3.6%), and rash (3.1% vs 1.0%). There were more infusion reactions with serplulimab (1.8%) vs the control arm (0.5%).

Non-Asians

Of the non-Asian subjects in the pivotal trial, 89.0% in the serplulimab group and 93.0% in the placebo group experienced at least one TEAE. There was overall less reporting of ≥Grade 3 TEAEs (58% serplulimab/49.1% placebo), less SAEs (31.5%/38.6%), less related SAEs (2.4%/7.0%), and less AESI (25.2%/10.5%) compared to Asians. No IRR were reported in the non-Asians. Otherwise, the safety profile was qualitatively similar between non-Asians and Asians.

3.5. Uncertainties and limitations about unfavourable effects

The studies included in the pooled safety population, including the pivotal trial, have been ongoing since before the Covid-pandemic. Whether reporting of adverse events was hampered by the COVID-19 lock-down remains unanswered.

3.6. Effects Table

Table 48. Effects Table for serplulimab in combination with carboplatin and etoposide in previously untreated patients with extensive-stage small cell lung cancer (DCO: Jun-2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ASTRUM-005 (Primary analysis, DCO 22 Oct 2021) - All comers ITT, n=585						
			Ser + CE n=389	CE n=196		
Overall Survival		Months	15.4	10.9	Stratified HR 0.63 (0.49, 0.82), p<0.001	Clinical efficacy section
Progression Free Survival by IRRC		Months	5.7	4.3	Stratified HR 0.48 (0.38, 0.59), p<0.001	
Unfavourable Effects (treatment emergent adverse events, all-cause incidences)						
ASTRUM-005 (DCO 13 Jun 2023) – Safety set, n=585						

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			Ser + CE n=389	CE n=196		
Anaemia		%	72.8	71.4	The majority of these adverse events are likely related to chemotherapy, taking into consideration the similar incidences in the two treatment arms and the known safety profile of the chemotherapy backbone.	
White blood cell count decreased		%	54.0	51.0		
Immune-mediated TEAEs		%	38.0	18.9		
SAEs		%	39.1	39.3		
Grade 3/4 AEs		%	74.6	69.4		
TEAEs leading to discontinuation		%	9.8	9.7		

Abbreviations: Ser: Serplulimab, CE: carboplatin and etoposide, ITT: Intention-to-treat, IRRC: Independent Radiology Review Committee.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In ES-SCLC, PD-L1 inhibitors, atezolizumab and durvalumab, were approved as first-line treatment in combination with platinum-based chemotherapy in 2021. The modest OS benefit of 2 months (HR 0.76, 95% CI: 0.60-0.95) and 2.4 months (HR 0.75, 95%CI: 0.63-0.91), respectively, was considered clinically meaningful due to the poor prognosis and unmet medical need in patients with ES-SCLC.

Being the first PD-1 inhibitor in ES-SCLC, serplulimab in combination with chemotherapy demonstrated a statistically significant benefit in terms of OS compared to placebo in addition to chemotherapy in ASTRUM-005. The difference in median OS of 4.5 months (HR 0.63, 95%CI: 0.49-0.82) in favour of serplulimab in the overall population is considered clinically meaningful for ES-SCLC in the context of ~9 months survival prognosis with a solely chemotherapy-based regimen. However, the diversity of treatments in subsequent lines in both arms and the possibility to continue serplulimab following progressive disease complicates the interpretation of the OS data. A GCP inspection was conducted and did not identify restrictions on the usability of the reported efficacy or safety data.

The low proportion of female participants enrolled, especially in the non-Asian subgroup, may not reflect the intended EU population. To address this uncertainty and to gather additional information on the efficacy in a non-Asian population and clarify the effect size of serplulimab, the applicant is recommended to submit the results of the study HLX10-005-SCLC301-E (**REC**).

Although the difference in median PFS was limited (i.e., 1.4 months in favour of serplulimab (HR 0.48) using treatment policy in overall population), the result was supportive of OS findings.

Overall, despite the uncertainties, the observed OS benefit in favour of serplulimab in the overall population is established in first line ES-SCLC patients and the efficacy of serplulimab in combination with chemotherapy is considered clinically meaningful for the intended indication.

The PD-L1 expression (per 22C3 assay) as a biomarker has not demonstrated any predictive value in ES-SCLC patients, despite confirmation of PD-L1 expression at a central laboratory and a high proportion of tested study participants (96%).

The safety profile presented for serplulimab is similar to other immune checkpoint inhibitors approved for the same indication. Some of the immune-related AEs can be serious and potentially lethal; however, as for other PD-1/PD-L1 inhibitors immune-related adverse drug reactions are considered manageable with adequate warnings and precautions including dose reduction and interruption as reflected in the SmPC. The safety data is mainly obtained in an Asian population. However, the safety profile of serplulimab is not expected to be significantly different in the non-Asian patient population.

3.7.2. Balance of benefits and risks

The improvement of median overall survival by 4.5 months in patients who received serplulimab is considered clinically relevant for ES-SCLC patients who have a poor prognosis. The reported safety profile of serplulimab is similar to that of other immune checkpoint inhibitors used for the same condition and is considered manageable.

The benefit-risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Hetronifly 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 Hetronifly is favourable in the following indication(s):

Hetronifly in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

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 Hetronifly is marketed, all patients/caregivers who use Hetronifly are provided with the patient educational material.

• **Composition of educational material package:**
- Summary of product characteristics/package leaflet (will be voluntarily provided)
- Patient card

• **Risks covered by the educational material:**
- Immune-mediated adverse reactions
- Severe infusion reactions

The Education Material includes information on the signs and symptoms of immune-related adverse reactions and infusion-related reactions, as well as the guidance for the importance of patient monitoring and the clinical management of these events. The material will be distributed to relevant HCPs as a package and patients will receive their materials through the HCP.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Serplulimab 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.

Refer to Appendix on new active substance (NAS).