21 May 2026
EMADOC-1700519818-3134594
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hetronifly

International non-proprietary name: Serplulimab

Procedure No. EMA/VR/0000290021

Note

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

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List of abbreviations

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ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BIL	Bilirubin
BMI	Body mass index
BNP	Brain natriuretic peptide
BOIN	Bayesian Optimal Interval
BSA	Body surface area
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
dMMR	Mismatch repair deficient
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ESCC	Esophageal Squamous Cell Carcinoma
ESMO	European Society for Medical Oncology
ES-SCLC	Extensive-stage small cell lung cancer
EU	European Union
HCC	Hepatocellular carcinoma
HXL10	Serplulimab
HLX04	a biosimilar to bevacizumab
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
irAE	Immune-related adverse event

IRR	Infusion-related reaction
iRECIST	immune Response Evaluation Criteria in Solid Tumors
ITT	Intention-to-treat
IV	Intravenous
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	Microsatellite instability-high
MTD	Maximum tolerated dose
NAb	Neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMPA	National Medical Products Administration
NSCLC	Non-small cell lung cancer
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death-ligand 1
PK	Pharmacokinetic(s)
PT	Preferred term
Q	Quartile
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
Q4W	Once every 4 weeks
Q6W	Once every 6 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D/3D	Recommended phase II/III dose
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SS	Safety set
TEAE	Treatment-emergent adverse event

TESAE	Treatment-emergent serious adverse event
TPS	Tumor proportion score
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Accord Healthcare S.L.U. submitted to the European Medicines Agency on 30 July 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include HETRONIFLY in combination with carboplatin and nab-paclitaxel is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic squamous non-small cell lung carcinoma based on final results from study HLX10-004-NSCLC303; this is a randomized, double-blind, multi-center, phase III pivotal study, was conducted to compare the clinical efficacy and safety of serplulimab combined with chemotherapy (carboplatin and nab-paclitaxel) versus placebo combined with chemotherapy (carboplatin and nab-paclitaxel). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP Version 1.3 has been submitted.

The variation requested amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision No. P/0471/2020 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

Scientific advice

The MAH received Scientific Advice from the CHMP in 2019 and 2020 (EMEA/H/SA/4295/1/2019/III, EMEA/H/SA/4295/1/FU/1/2020/III). The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and PRAC rapporteur appointed by the CHMP were:

Rapporteur: Eva Skovlund

Timetable	Actual dates
Submission date	30 July 2025
Start of procedure:	16 August 2025
CHMPRapporteur's preliminary assessment report circulated on:	10 October 2025
PRAC Rapporteur's preliminary assessment report circulated on:>	16 October 2025
Joint Rapporteur's updated assessment report circulated on:	06 November 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	13 November 2025
MAH's responses submitted to the CHMP on:>	19 October 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	02 February 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	19 February 2026
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	26 February 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	21 April 2026
CHMP opinion:	21 May 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Worldwide, primary lung cancers were the most commonly diagnosed malignancies in 2020, with over 2.2 million new patients. In Europe, the age-standardized incidence rate of all lung cancers is 63.5 per 100,000 (97.6 per 100,000 among men and 38.3 per 100,000 among women) (Dyba et al 2021). Lung cancer is the leading cause of cancer-related mortality (National Cancer Institute, 2025).

Non-small-cell lung cancer (NSCLC) accounts for 80%-90% of all lung cancers (Torre LA et al, 2012). The main histological subtypes are adenocarcinoma (40%), squamous cell carcinoma (25%), and large cell carcinoma (10%) (National Cancer Institute 2025). The distribution of NSCLC histological types has been changing by a continuous increase in lung adenocarcinoma (LUAD) and a decrease in squamous-cell carcinoma rates (Barta JA et al, 2019).

Lung cancer is often diagnosed at an advanced stage, resulting in a poor prognosis; the 5-year OS rate in NSCLC declines with advanced stage. However, treatment has changed markedly in the past

decade with wider lung cancer screening, improved radiation techniques, and treatment advances. These changes have likely resulted in the reported decline in NSCLC mortality (Ganti et al 2021).

State the claimed therapeutic indication

Non-small cell lung carcinoma (NSCLC)

HETRONIFLY in combination with carboplatin and nab-paclitaxel is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic squamous non-small cell lung carcinoma.

Epidemiology and risk factors, screening tools/prevention

Lung cancer was the most frequently diagnosed cancer and the leading cause of cancer deaths in males worldwide. In females, lung cancer was the second most frequently diagnosed cancer and the third leading cause of death (Sung H et al 2021).

The highest incidence rates of lung cancer in males are observed in Micronesia/Polynesia, Eastern and Southern Europe, and Eastern and Western Asia, and among women in North America, Northern and Western Europe, Micronesia/Polynesia, and Australia/New Zealand (Sung et al 2021). In Europe, the age-standardized incidence rate of all lung cancers is 63.5 per 100,000 (97.6 per 100,000 among men and 38.3 per 100,000 among women) (Dyba et al 2021).

Tobacco smoking remains the main cause of lung cancer. Therefore, smoking prevention and smoking cessation by active tobacco control measures and campaigns can lead to a reduction in lung cancer rates. (Torre LA et al, 2012, Barta JA et al, 2019). Particularly in males, lung cancer incidence and mortality rates have been falling in industrialised countries, while they are still increasing in females in most countries. The increased smoking consumption in females in developed countries has led to increased mortality rates so that it has become the leading cause of cancer death.

Several other lung cancer risk factors have been described, including exposure to asbestos, arsenic, radon, non-tobacco-related polycyclic aromatic hydrocarbons and indoor air pollution (Malhotra J et al, 2016).

Recently, an increasing rate of lung cancer incidence and mortality in never-smokers has been observed. According to ESMO Clinical Practice Guideline on oncogene-addicted metastatic NSCLC, 'non-smoking-associated lung cancer' is considered a distinct disease entity, for which specific molecular and genetic tumour characteristics have been identified (Hendriks LE et al, 2022).

Aetiology and pathogenesis

NSCLC can be divided into two major histologic types: non-squamous and squamous cell carcinoma. Non-squamous histology accounts for more than half of all NSCLC, whereas squamous histology accounts for approximately 25% (National Cancer Institute, 2025). Specific subtyping of all NSCLCs is necessary for therapeutic decision making and should be carried out wherever possible.

Biomarker testing is essential to identify subgroups of NSCLC with oncogenic drivers (EGFR, ALK, ROS, BRAF V600E and others) that can be therapeutically targeted. These molecular alterations that predict response to treatment are present in approximately 30% of patients with NSCLC, mainly found in lung adenocarcinomas (Arbour and Riely 2019). Testing is recommended in all patients with advanced non-squamous-cell carcinoma. Local variation in availability of targeted therapy may influence the testing strategy per region. Testing for oncogenic driver alterations is not recommended in patients with a confident diagnosis of **squamous-cell carcinoma**, except in unusual cases e.g. young (< 50years) patients, never smokers/former light smokers/long-time ex-smokers.

All stage IV NSCLC cases (squamous and non-squamous) are recommended for programmed death-ligand 1 (PD-L1) immunohistochemistry (IHC) testing (ESMO Clinical guideline, Hendriks et al, 2022).

Clinical presentation, diagnosis and stage/prognosis

Lung cancer is often diagnosed at an advanced stage, resulting in a poor prognosis; the 5-year OS rate for patients with advanced NSCLC (2010-2016) ranges from 6% in patients with distant metastases to 17% in patients with stage IIIB (SEER-18 data US, 2017). However, treatment has changed markedly in the past decade with wider lung cancer screening, improved radiation techniques, and treatment advances. These changes have likely resulted in the reported decline in NSCLC mortality (Ganti et al, 2021).

Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status (PS), and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant metastatic disease, which directly contributes to poor survival prospects. More than 30% of NSCLC have poor (ECOG ≥ 2) at baseline (Passaro et al 2021) which is associated with worse survival outcomes than those with favorable (0-1) ECOG PS (Meyers et al 2023).

Management

Over the past decade, there have been considerable advances in the management of NSCLC. Improved understanding of the biology and molecular subtypes of NSCLC has led to development of a number of biomarker-directed therapies for patients with metastatic disease, including drugs targeting EGFR mutations, ALK rearrangements, and other molecular aberrations. These therapies have improved OS for patients with metastatic NSCLC with an oncogenic driver (Arbour and Riely, 2019).

For patients with metastatic NSCLC with no actionable oncogenic driver (EGFR mutations and ALK rearrangements), the development of immune checkpoint inhibitors (ICIs) has transformed the care, providing a survival benefit when administered as monotherapy following disease progression on platinum-based chemotherapy (Rittmeyer et al 2017) or when administered with or without chemotherapy in the first-line setting (Jotte et al 2020, West et al 2019, Wang et al 2023). These changes to the treatment landscape applies to both squamous and non-squamous NSCLC.

In the first-line **squamous** NSCLC setting, pembrolizumab has been approved as first-line treatment therapy for squamous NSCLC, either as monotherapy for the "PD-L1 high" (≥50%) population (and also for the population with PD-L1 ≥1% in the US) (Reck et al 2016) or in combination with platinum-based chemotherapy. More recently, nivolumab/ipilimumab with platinum-doublet chemotherapy has been approved as first-line treatment for NSCLC irrespective of histology, and nivolumab/ipilimumab combination therapy alone was approved in tumours

expressing PD-L1 ≥1% (Opdivo SmPC 2021). Other ICIs approved for treatment in the first-line setting include atezolizumab and cemiplimab as monotherapy for first-line treatment of NSCLC whose tumours have high PD-L1 expression irrespective of histology.

2.1.2. About the product

Serplulimab (Hetronifly) 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. 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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Serplulimab (Hetronifly) has been approved in EU on February 3, 2025 for the first-line treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) in combination with carboplatin and etoposide. In China, serplulimab has been approved by the NMPA for the first-line treatment of patients with squamous NSCLC, non-squamous NSCLC, ES-SCLC and esophageal squamous cell carcinoma (ESCC) combined with chemotherapy.

Multiple clinical studies have been initiated to evaluate the safety and efficacy of serplulimab in a variety of cancers, including cervical cancer, hepatocellular carcinoma (HCC), head and neck tumors, SCLC and NSCLC.

For the squamous NSCLC development, two CHMP Scientific Advices have been given (in 2019 and 2020, respectively) regarding the Chemistry, Manufacturing and Controls (CMC) development, pre-clinical development and pivotal clinical study design [EMEA/H/SA/4295/1/2019/III, EMEA/H/SA/4295/1/FU/1/2020/III]. CHMP discouraged the use of chemotherapy only as a comparator because of recent approvement of pembrolizumab in addition to chemotherapy in this particular 1st line setting of squamous NSCLC. In addition, the use of pembrolizumab in this treatment setting was already implemented in the European treatment guidelines (ESMO). The clinical relevance of a chemotherapy only-arm was questioned for the EU population. To be able to show consistent efficacy across regions, the importance of including a sufficient number of representative EU patients was also stressed.

2.1.4. General comments on compliance with GCP

The pivotal phase 3 efficacy and safety clinical study HLX10-004-NSCLC303 was carried out in 85 sites in China, Poland, Russia, Turkey, Ukraine and Georgia and enrolled a total of 537 subjects. The trial was mainly carried out in China, at 50 sites in total. The MAH included a statement that the trial which was carried out outside the European Union met the ethical requirements of Directive 2001/20/EC.

The CSR for study HLX10-004-NSCLC303 states that the study was conducted according to the protocol and in compliance with International Council for Harmonisation (ICH) guideline on Good Clinical Practice (GCP), the Declaration of Helsinki and other applicable regulatory requirements.

GCP inspections were carried out by the NMPA at 2 sites in relation to the study (both in 2022), both concluding: "On-site inspections of the clinical trial were carried out during the review of this product, and the issues identified in the inspections had no significant impact on the benefit-risk evaluation of this product". Audits of six sites were also carried out by the NMPA in relation to the study, without any critical findings.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

In the case of medicinal products comprised of naturally occurring substances such as vitamins, electrolytes, amino acids, peptides, proteins, nucleotides, carbohydrates and lipids as active pharmaceutical ingredient (API), the ERA may consist of a justification for not submitting ERA studies (Guideline on the environmental risk assessment of medicinal products for human use, EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*).

The applicant has provided a justification, in accordance with current guidance. Serplulimab is a recombinant humanized monoclonal antibody expected to be degraded to small peptides and individual amino acids. The lack of dedicated environmental risk assessment studies is agreed due to the nature of the product which is not expected to pose risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

Considering the above data, serplulimab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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.

As part of the initial MAA review, three onsite GCP inspections were conducted from 15 Feb 2024 to 22 April 2024, including two investigator sites inspections (one in Georgia and one in China, and the sponsor site inspection (Henlius, in China). In conclusion, no critical findings of the efficacy and safety data were reported.

Based on the review of clinical data, CHMP did not identify the need for a further GCP inspection of the clinical trials included in this dossier.

2.3.2. Pharmacokinetics

Serplulimab (HLX10) is a novel recombinant humanised anti-programmed cell death 1 (PD-1) monoclonal antibody (mAb) of IgG4 type developed by Shanghai Henlius Biotech, Inc. and belongs

to the pharmacological class of anti-PD-1 inhibitors. The molecular weight (MW) is approximately 144-146 kDa.

The proposed indication for serplulimab in combination with carboplatin and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) for the first-line treatment of adult patients with unresectable, locally advanced or metastatic squamous non-small cell lung cancer (NSCLC).

Serplulimab is supplied as a sterile solution for injection and should be administered via intravenous (IV) infusion within 30 to 90 minutes, if no infusion reactions occurred. The proposed dosage of serplulimab for the intended indication is 4.5 mg/kg administered once every 3 weeks.

Table 1. Overview of pharmacokinetic properties

Drug product	**Serplulimab 10 mg/mL concentrate for infusion**
Absorption	• Absolute bioavailability: not relevant
Distribution	• Tissue distribution: The mean Vd is in the range from 4.397 L to 7.882 L
Elimination	• The baseline clearance is in the range from 0.171 to 0.211 L/day • The mean half-life T1/2 at steady state is in the range of 25.0-31.2 days.
Metabolism	• Not characterised, expected to be catabolised into small peptides and amino acids by general protein degradation processes
Dose proportionality	• Linear PK established at 0.3 to 10 mg/kg Q2W (including flat doses of 200 mg Q2W, 300 mg Q3W and 400 mg Q4W), both after single and multiple doses • Mean accumulation ratios: 1.2 to 1.5 for C_{max}, 1.2 to 1.8 for AUC_{ss}.
Time dependency	• CL decreases over time with 221 days to reach half of the maximum effect.
Pharmacokinetic variability	• Between subjects: Moderate, CV 24.0% in base CL; high in Q: 54.3%. • Within subjects: Not studied
Sources of variability	• The predicted impact of albumin, alkaline phosphatase, tumour burden, tumour type and sex on exposure is limited.

All clinical studies on serplulimab PD and PK were conducted in patients with various tumour types. Considering the mechanism of action of serplulimab and safety concerns associated with immune checkpoint inhibitors, the Sponsor deemed healthy volunteers unsuitable for assessing PK characteristics.

A summary of the type of cancer in the studies is presented below.

Table 2. Overview of types of cancer in the studies

Variables	HLX10-001 (n=57)	HLX10-002-NSCLC301 (n=491)	HLX10-004-NSCLC303 (n=439)	HLX10-005-SCLC301 (n=389)	HLX10-007-EC301 (n=379)	HLX10-008-HCC201 (n=123)	HLX10-010-MSI201 (n=108)	HLX10-011-CC201 (n=21)	HLX10-015-mCRC301 (n=64)	HLX10-HLX04-001 (n=26)	HLX10-HLX07-001 (n=13)	Total (n=2110)
Colorectal cancer	6 (10.53%)	—	—	—	—	—	74 (68.52%)	—	64 (100.00%)	7 (26.92%)	—	151 (7.16%)
Squamous non-small cell lung cancer	2 (3.51%)	—	439 (100.00%)	—	—	—	—	—	—	—	—	441 (20.90%)
Non-squamous non-small cell lung cancer	7 (12.28%)	491 (100.00%)	—	—	—	—	—	—	—	—	—	498 (23.60%)
Small cell lung cancer	1 (1.75%)	—	—	389 (100.00%)	—	—	—	—	—	—	—	390 (18.48%)
Esophageal squamous cell carcinoma	8 (14.04%)	—	—	—	379 (100.00%)	—	2 (1.85%)	—	—	—	—	389 (18.44%)
Other tumor types	32 (56.14%)	—	—	—	—	—	32 (29.63%)	21 (100.00%)	—	18 (69.23%)	13 (100.00%)	116 (5.50%)

The clinical pharmacology of serplulimab in adult patients with non-squamous non-small cell lung cancer is based primarily on the results from two clinical trials:

1. **HLX10-001**: A phase I, open-label, dose-escalation study of serplulimab monotherapy in patients with metastatic or recurrent solid tumours who failed standard treatment. **PK sampling**: Before the first infusion in Cycle 1 and Cycle 3, at the end of infusion (within 30 minutes post-infusion), and at 2, 6, 24, 48, 96, and 168 hr post-infusion. Additionally, before the second infusion in Cycle 1, before the first infusion in Cycles 2-6, and during the 28-day follow-up.
2. **HLX10-004-NSCLC303**. A phase III pivotal study conducted in the target population (locally advanced or metastatic squamous NSCLC); serplulimab was administered IV at a dose of 4.5 mg/kg once every 3 weeks, in combination with carboplatin and nab-paclitaxel. **PK sampling:** Before infusion in Cycles 1, 2, 4, 6 and 8, at the end of infusion in Cycles 1 and 8 (within 30 minutes post-infusion), and once every 4 cycles thereafter (in Cycles 12, 16 and 20, as well as during the termination follow-up).

However, a PopPK analysis was conducted using available PK data from a total of 11 clinical trials in patients with a variety of cancers including small cell lung cancer, squamous non-small cell lung cancer, non-squamous non-small cell lung cancer, oesophageal squamous cell carcinoma, microsatellite instability-high solid tumours, hepatocellular carcinoma, and colorectal cancer.

Methods

Pharmacokinetic data analysis

A nonlinear mixed-effects modelling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.5 (ICON, Maryland) was used for the population PK analysis.

Evaluation and Qualification of Models

Objectives

The objectives of the main popPK model were to characterise population pharmacokinetics of serplulimab by developing a popPK model based on patient data and to estimate typical values and inter-individual variability of PK parameters.

A PopPK model was also used to evaluate the effects of demographics, renal and hepatic function, anti-drug antibodies, tumour types, tumour burden, ECOG (Eastern Cooperative Oncology Group), and combination treatment on PK parameters of serplulimab, as well as to generate exposures for E-R analysis. Furthermore, the popPK model was employed to simulate and compare the exposures with dosing regimens of 3 mg/kg Q2W, 4.5 mg/kg Q3W, 200 mg Q2W, 300 mg Q3W, and 10 mg/kg Q2W by using individual PK parameters estimated from the final model.

Database

The popPK and exposure-response analyses evaluated data obtained from 11 clinical studies: HLX10-001, HLX10-004-NSCLC303, HLX10-005-SCLC301, HLX10-008-HCC201, HLX10-010-MSI201, HLX10-011-CC201, HLX10HLX04-001, HLX10HLX07-001, HLX10-002-NSCLC301, HLX10-007-EC301, and HLX10-015-mCRC301. A summary is in Table 3.

Table 3. Summary of Clinical Studies Included in the Serplulimab PopPK Analysis

Clinical Study	Design	Serplulimab Regimen	Subject Number	Cut-off Date for Included Analysis Data	
				PK, ADA and Dosing	Safety and Efficacy
HLX10-001	Multiple dose, phase Ⅰ	0.3, 1, 3, 10 mg/kg Q2W, 200 mg Q2W, 300 mg Q3W, 400 mg Q4W	57	2022-08-01	2022-08-01
HLX10-004-NSCLC303	Multicenter, double-blind, phase Ⅲ	4.5 mg/kg, Q3W	439	2023-01-31	2023-01-31
HLX10-008-HCC201	Multicenter, open, single arm, phase Ⅱ	3 mg/kg, Q2W	123	2023-04-26	2023-04-26
HLX10-010-MSI201	Multicenter, single arm, phase Ⅱ	3 mg/kg, Q2W	108	2021-07-10	2021-07-10
HLX10-011-CC201	Multicenter, open, single arm, phase Ⅱ	4.5 mg/kg, Q3W	21	2022-10-24	2022-10-24
HLX10-HLX04-001	Multiple dose, phase Ⅰ	1, 3, 10 mg/kg Q2W	26	2022-10-11	2022-10-11
HLX10-HLX07-001	Multicenter, phase Ⅱ	3 mg/kg, Q2W	13	2022-09-16	2022-09-16
HLX10-005-SCLC301	Multicenter, double-blind, phase Ⅲ	4.5 mg/kg, Q3W	389	2022-06-13	2022-06-13
HLX10-002-NSCLC301	Multicenter, double-blind, phase Ⅲ	4.5 mg/kg, Q3W	491	2023-06-15	2023-06-15
HLX10-007-EC301	Multicenter, double-blind, phase Ⅲ	3 mg/kg, Q2W	389	2022-04-15	2022-04-15
HLX10-015-mCRC301	Multicenter, double-blind, phase Ⅱ/Ⅲ	300 mg, Q3W	64	2022-10-20	2022-10-20

Covariates

The effects of body weight, BSA (Body surface area), BMI (Body mass index), age, sex, ALB (Albumin), ALT (Alanine transaminase), AST (Aspartate aminotransferase), ALP (Alkaline phosphatase), serum creatinine, total bilirubin, creatinine clearance, lactate dehydrogenase, tumour burden, anti-drug antibodies, tumour type, ECOG, concomitant chemotherapy, concomitant antibody-based anti-tumour therapy and race on the PK parameters were investigated during PopPK model development. Covariates were selected using a stepwise forward addition and backward-elimination method (based on a significance level of $p < 0.01$ for the forward steps and $p < 0.001$ for the backward steps).

Data handling

Observations below the LLOQ were omitted (set MDV=1). Only the 3.24% (510/15742) of data points were below the LLOQ for serplulimab considering all the 11 studies.

Suspected data errors or inconsistencies were handled on an individual basis. Suspected data error and outliers were excluded from the analysis, as appropriate.

The PopPK analysis was performed with outliers omitted. Individual data points were considered outliers and were excluded from the covariate screening and parameter estimation of the final model if the absolute value of conditional weighted residuals (CWRES) exceeded 5.

The frequency of missing covariates in the database was determined, and missing covariates were handled as follows:

- Covariates missing for ≤ 15% of the subjects: continuous covariates were imputed as the population median and categorical covariates were imputed as the most frequent category;

- Covariates missing for > 15% of the subjects were excluded from the analysis.

In total, 3.58% (545/15232) were excluded from the PopPK analysis with reasons detailed in Table 4. As a result, the final PopPK analysis dataset included 14,687 serplulimab serum concentration measurements from 2110 subjects.

Table 4. Summary of data exclusions in the PopPK datasets of serplulimab

Study	Original Dataset	Data Exclusions (EXCLFL)									|CWRES|>5	PK Analysis Dataset
		1	2	3	4	5	6	7	8	9		
HLX10-001	57 subjects with 1102 measurable concentrations	1	—	—	3	—	3	1	—	—	5	57 subjects with 1089 measurable concentrations
HLX10-002-NSCLC301	496 subjects with 3978 measurable concentrations	9	13	3	4	156	1	—	1	—	9	491 subjects with 3782 measurable concentrations
HLX10-004-NSCLC303	454 subjects with 2698 measurable concentrations	22	16	5	14	4	2	5	—	1	10	439 subjects with 2619 measurable concentrations
HLX10-005-SCLC301	405 subjects with 2031 measurable concentrations	13	24	6	14	—	—	—	—	—	6	389 subjects with 1968 measurable concentrations
HLX10-007-EC301	423 subjects with 2466 measurable concentrations	41	118	4	6	—	—	1	2	—	4	379 subjects with 2290 measurable concentrations
HLX10-008-HCC201	123 subjects with 898 measurable concentrations	5	—	—	—	—	—	—	—	—	—	123 subjects with 893 measurable concentrations
HLX10-010-MSI201	108 subjects with 591 measurable concentrations	2	—	—	2	—	—	—	—	—	—	108 subjects with 587 measurable concentrations
HLX10-011-CC201	21 subjects with 136 measurable concentrations	—	—	—	—	—	—	—	—	—	—	21 subjects with 136 measurable concentrations
HLX10-015-mCRC301	64 subjects with 708 measurable concentrations	—	—	1	—	—	—	—	—	—	—	64 subjects with 707 measurable concentrations
HLX10-HLX04-001	26 subjects with 355 measurable concentrations	1	—	—	6	—	—	—	—	—	—	26 subjects with 348 measurable concentrations
HLX10-HLX07-001	13 subjects with 269 measurable concentrations	—	—	—	—	—	—	—	—	—	1	13 subjects with 268 measurable concentrations
Total	**2190 subjects with 15232 measurable concentrations**	**94**	**171**	**19**	**49**	**160**	**6**	**7**	**3**	**1**	**35**	**2110 subjects with 14687 measurable concentrations**

Model building

Serplulimab serum concentrations versus time profiles were initially explored graphically. This graphical analysis together with serplulimab PK characteristics provided initial directions to the structural model and the residual error model.

Random effects model

Inter-individual variability (IIV) was modelled for PK parameters as follows:

$$\theta_i = exp\ (\theta_T + \eta_i)$$

Where θ_i is the parameter for the i^{th} subject, θ_T is the natural logarithm of the typical value of the parameter in the population, and η_i is a normally distributed random inter-individual effect with mean 0 and variance ω^2.

Residual variability (RV) was modelled as follows

$$ln(y_{ij}) = ln(\hat{y}_{ij}) + \varepsilon_{ij}$$

where y_{ij} and $\hat{y}_{ij}$ represent the jth observed and predicted concentration, respectively, for the ith subject; and ε_{ij} is the residual error for the ith subject and jth concentration, which is independent and normally distributed with mean zero and variance σ^2.

Logarithmic transformations were applied to the observations during the analysis.

Covariate model

The covariates were selected based on physiological plausibility, clinical relevance, prior knowledge of existing analogues and the feasibility of data included in the analysis. Table 5 and

Table ***6*** below give an overview of selected baseline covariates available for analysis.

Table 5. Baseline population characteristics in the serplulimab PopPK analysis dataset – Continuous covariates

Variables	HLX10-001 (n=57)	HLX10-002-NSCLC301 (n=491)	HLX10-004-NSCLC303 (n=439)	HLX10-005-SCLC301 (n=389)	HLX10-007-EC301 (n=379)	HLX10-008-HCC201 (n=123)	HLX10-010-MSI201 (n=108)	HLX10-011-CC201 (n=21)	HLX10-015-mCRC301 (n=64)	HLX10-HLX04-001 (n=26)	HLX10-HLX07-001 (n=13)	Total (n=2110)
Continuous covariates (median [min, max])												
Age (years)	60.0 (33.0, 83.0)	62.0 (27.0, 75.0)	63.0 (35.0, 81.0)	63.0 (28.0, 76.0)	63.0 (34.0, 75.0)	54.0 (29.0, 73.0)	55.0 (23.0, 74.0)	50.0 (31.0, 64.0)	61.0 (25.0, 74.0)	56.0 (31.0, 77.0)	52.0 (34.0, 68.0)	61.0 (23.0, 83.0)
Body weight (kg)	61.2 (32.9, 115)	61.0 (35.0, 94.2)	65.0 (38.2, 131)	67.0 (33.0, 120)	58.0 (40.0, 92.0)	62.5 (45.0, 86.0)	60.0 (34.0, 89.0)	65.0 (40.0, 79.0)	62.0 (47.0, 86.0)	66.0 (46.5, 91.9)	56.5 (36.1, 72.0)	62.0 (32.9, 131)
Missing	—	—	1 (0.23%)	—	—	—	—	—	—	—	—	1 (0.05%)
Height (cm)	162 (144, 180)	166 (138, 188)	169 (143, 191)	168 (142, 191)	168 (145, 185)	168 (150, 185)	163 (128, 181)	156 (149, 169)	165 (147, 188)	163 (150, 183)	166 (155, 171)	167 (128, 191)
Missing	—	1 (0.20%)	4 (0.91%)	1 (0.26%)	—	1 (0.81%)	—	—	—	—	—	7 (0.33%)
Body mass index (kg/m^2)	23.0 (13.3, 38.3)	22.8 (14.5, 34.4)	23.0 (15.6, 41.3)	23.8 (13.7, 42.3)	20.8 (15.6, 29.7)	23.1 (15.2, 29.3)	21.8 (13.6, 30.4)	26.5 (16.0, 28.9)	23.5 (19.4, 29.4)	23.5 (18.7, 33.2)	20.4 (13.9, 24.6)	22.6 (13.3, 42.3)
Missing	—	1 (0.20%)	5 (1.14%)	1 (0.26%)	—	1 (0.81%)	—	—	—	—	—	8 (0.38%)
Body surface area (m^2)	1.67 (1.19, 2.35)	1.67 (1.21, 2.22)	1.75 (1.26, 2.55)	1.76 (1.19, 2.39)	1.64 (1.28, 2.14)	1.71 (1.38, 2.03)	1.66 (1.22, 2.07)	1.69 (1.32, 1.93)	1.69 (1.39, 2.10)	1.75 (1.39, 2.10)	1.60 (1.27, 1.85)	1.70 (1.19, 2.55)
Missing	—	1 (0.20%)	5 (1.14%)	1 (0.26%)	—	1 (0.81%)	—	—	—	—	—	8 (0.38%)
Albumin (ALB, g/L)	39.0 [26.0, 53.0]	41.7 [23.8, 51.0]	40.4 [25.0, 53.8]	41.1 [23.9, 67.9]	41.4 [27.4, 53.2]	43.2 [30.6, 49.2]	42.5 [30.7, 52.1]	42.9 [31.7, 50.3]	42.3 [32.0, 50.4]	44.9 [37.1, 49.5]	42.1 [37.0, 49.6]	41.4 [23.8, 67.9]
Missing	0 (0%)	0 (0%)	1 (0.2%)	3 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (0.2%)
Aspartate aminotransferase (U/L)	20.0 (10.0, 198)	20.2 (8.00, 105)	18.8 (5.00, 163)	21.9 (7.00, 179)	19.0 (7.30, 106)	39.9 (14.0, 173)	24.0 (3.00, 165)	19.8 (7.00, 63.0)	22.2 (10.2, 151)	22.5 (11.0, 109)	18.7 (12.5, 41.3)	21.0 (3.00, 198)
Alanine aminotransferase (U/L)	15.0 (4.00, 196)	18.0 (5.00, 110)	17.5 (3.00, 144)	20.0 (4.00, 182)	15.3 (3.00, 110)	30.0 (8.20, 229)	16.0 (4.00, 160)	13.1 (6.00, 30.1)	18.3 (4.20, 54.6)	16.5 (7.00, 67.0)	11.2 (5.20, 46.0)	18.0 (3.00, 229)
Alkaline Phosphatase (U/L)	83.0 (33.0, 396)	97.0 (30.0, 910)	96.0 (35.0, 823)	95.0 (10.7, 607)	84.9 (30.0, 831)	104 (37.0, 579)	90.0 (30.0, 641)	90.0 (75.0, 774)	103 (40.6, 565)	98.0 (38.0, 863)	78.9 (50.8, 243)	94.0 (10.7, 910)
Missing	—	—	—	—	1 (0.26%)	—	—	—	—	—	—	1 (0.05%)
Lactate dehydrogenase (U/L)	178 (79.0, 704)	211 (94.0, 2731)	210 (38.0, 1921)	247 (116, 2239)	181 (94.0, 4633)	195 (95.0, 585)	224 (111, 2555)	179 (128, 276)	207 (126, 1432)	—	144 (112, 261)	208 (38.0, 4633)
Missing	—	—	—	2 (0.51%)	1 (0.26%)	—	—	—	—	26 (100.00%)	—	29 (1.37%)
Total bilirubin (μmol/L)	8.55 [3.42, 20.5]	10.2 [2.80, 35.6]	9.40 [2.40, 30.0]	9.80 [1.60, 42.9]	10.9 [2.60, 29.4]	14.3 [4.10, 30.6]	10.6 [3.70, 29.0]	9.08 [2.80, 22.5]	9.55 [5.10, 32.8]	9.95 [4.50, 30.4]	10.1 [6.90, 25.5]	10.3 [1.60, 42.9]
Missing	1 (1.8%)	0 (0%)	3 (0.7%)	3 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (0.3%)
Creatinine (μmol/L)	70.7 [38.0, 133]	66.6 [24.0, 121]	70.4 [33.5, 130]	69.2 [26.7, 156]	68.5 [27.0, 137]	68.0 [30.0, 102]	64.5 [23.0, 124]	55.0 [41.3, 107]	73.8 [39.5, 162]	69.5 [49.0, 106]	70.0 [50.7, 132]	68.7 [23.0, 162]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.1%)
Creatinine clearance (mL/min)	77.6 [30.4, 179]	86.9 [40.0, 227]	89.5 [37.5, 195]	92.2 [26.4, 291]	80.8 [38.8, 200]	99.0 [50.5, 217]	88.3 [36.7, 257]	99.3 [48.4, 152]	86.5 [35.1, 151]	86.8 [55.7, 162]	78.4 [39.5, 139]	87.3 [26.4, 291]
Missing	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)	2 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.1%)
Tumor burden (mm)	72.2 (11.4, 240)	76.0 (0.00, 288)	80.0 (0.00, 298)	118 (13.8, 324)	40.0 (11.0, 250)	60.8 (10.4, 166)	58.5 (10.0, 350)	49.0 (15.0, 98.0)	66.0 (12.0, 241)	67.0 (12.4, 209)	48.5 (15.0, 93.0)	72.9 (0.00, 350)
Missing	—	—	—	6 (1.54%)	—	5 (4.07%)	—	—	1 (1.56%)	—	1 (7.69%)	13 (0.62%)

Table 6. Baseline population characteristics in the serplulimab PopPK analysis dataset – Categorical covariates

Variables	HLX10-001 (n=57)	HLX10-002-NSCLC301 (n=491)	HLX10-004-NSCLC303 (n=439)	HLX10-005-SCLC301 (n=389)	HLX10-007-EC301 (n=379)	HLX10-008-HCC201 (n=123)	HLX10-010-MSI201 (n=108)	HLX10-011-CC201 (n=21)	HLX10-015-mCRC301 (n=64)	HLX10-HLX04-001 (n=26)	HLX10-HLX07-001 (n=13)	Total (n=2110)
Tumor type												
Hepatocellular carcinoma	1 (1.75%)	—	—	—	—	123 (100.00%)	—	—	—	1 (3.85%)	—	125 (5.92%)
Colorectal cancer	6 (10.53%)	—	—	—	—	—	74 (68.52%)	—	64 (100.00%)	7 (26.92%)	—	151 (7.16%)
Squamous non-small cell lung cancer	2 (3.51%)	—	439 (100.00%)	—	—	—	—	—	—	—	—	441 (20.90%)
Non-squamous non-small cell lung cancer	7 (12.28%)	491 (100.00%)	—	—	—	—	—	—	—	—	—	498 (23.60%)
Small cell lung cancer	1 (1.75%)	—	—	389 (100.00%)	—	—	—	—	—	—	—	390 (18.48%)
Esophageal squamous cell carcinoma	8 (14.04%)	—	—	—	379 (100.00%)	—	2 (1.85%)	—	—	—	—	389 (18.44%)
Other tumor types	32 (56.14%)	—	—	—	—	—	32 (29.63%)	21 (100.00%)	—	18 (69.23%)	13 (100.00%)	116 (5.50%)
ECOG												
0	39 (68.42%)	137 (27.90%)	85 (19.36%)	71 (18.25%)	99 (26.12%)	70 (56.91%)	41 (37.96%)	6 (28.57%)	15 (23.44%)	1 (3.85%)	3 (23.08%)	567 (26.87%)
1	15 (26.32%)	353 (71.89%)	354 (80.64%)	318 (81.75%)	280 (73.88%)	53 (43.09%)	67 (62.04%)	15 (71.43%)	49 (76.56%)	25 (96.15%)	10 (76.92%)	1539 (72.94%)
2	3 (5.26%)	—	—	—	—	—	—	—	—	—	—	3 (5.26%)
Missing	—	1 (0.20%)	—	—	—	—	—	—	—	—	—	1 (0.20%)
Chemotherapy combination												
No	57 (100.00%)	60 (12.22%)	83 (18.91%)	—	—	123 (100.00%)	108 (100.00%)	—	—	26 (100.00%)	13 (100.00%)	470 (22.28%)
Yes	—	431 (87.78%)	356 (81.09%)	389 (100.00%)	379 (100.00%)	—	—	21 (100.00%)	64 (100.00%)	—	—	1640 (77.73%)
Antibody-based anti-tumor therapy combination												
No	57 (100.00%)	214 (43.59%)	439 (100.00%)	389 (100.00%)	379 (100.00%)	21 (17.07%)	108 (100.00%)	21 (100.00%)	—	—	—	1628 (77.16%)
Yes	—	277 (56.42%)	—	—	—	102 (82.93%)	—	—	64 (100.00%)	26 (100.00%)	13 (100.00%)	482 (22.84%)
Sex												
Male	37 (64.91%)	358 (72.91%)	399 (90.89%)	317 (81.49%)	325 (85.75%)	109 (88.62%)	55 (50.93%)	—	47 (73.44%)	16 (61.54%)	12 (92.31%)	1675 (79.38%)
Female	20 (35.09%)	133 (27.09%)	40 (9.11%)	72 (18.51%)	54 (14.25%)	14 (11.38%)	53 (49.07%)	21 (100.00%)	17 (26.56%)	10 (38.46%)	1 (7.69%)	435 (20.62%)
Race												
Asian	57 (100.00%)	491 (100.00%)	301 (68.57%)	262 (67.35%)	379 (100.00%)	123 (100.00%)	108 (100.00%)	21 (100.00%)	64 (100.00%)	26 (100.00%)	13 (100.00%)	1845 (87.44%)
White	—	—	138 (31.44%)	127 (32.65%)	—	—	—	—	—	—	—	265 (12.56%)
Anti-drug antibody												
Negative	46 (80.70%)	469 (95.52%)	424 (96.58%)	383 (98.46%)	313 (82.59%)	120 (97.56%)	101 (93.52%)	21 (100.00%)	63 (98.44%)	25 (96.15%)	12 (92.31%)	1977 (93.70%)
Positive	11 (19.30%)	22 (4.48%)	15 (3.42%)	6 (1.54%)	66 (17.41%)	3 (2.44%)	7 (6.48%)	—	1 (1.56%)	1 (3.85%)	1 (7.69%)	133 (6.30%)

Body weight is considered a common covariate that influences the clearance and volumes of distribution, the covariate effects of body weight on PK parameters were investigated firstly. The goodness-of-fit improved by incorporating the effect of body weight and it was determined as the final base model for HLX10.

The impact of continuous and categorical covariates on PK parameters were modelled as follows:

$$\theta_i = exp\left(\theta_T + k_{cov} \cdot ln\left(\frac{Cov_i}{Cov_{pop}}\right) + \eta_i\right)$$

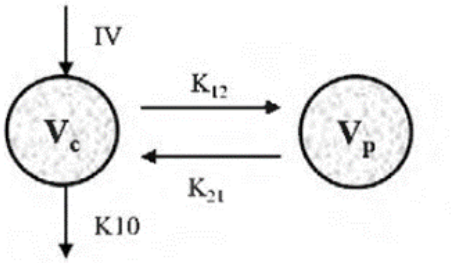
$$\theta_i = exp\left(\theta_T + \sum_j \left(k_{cov,j} \cdot \begin{pmatrix} 1, if\ X_i = j \\ 0, if\ X_i \neq j \end{pmatrix}\right) + \eta_i\right)$$

where θ_i is the individual model parameter for the ith subject, θ_T is the natural logarithm of the typical value of the parameter in the population, and η_i is an interindividual random effect with mean of zero and variance ω^2.

A stepwise forward-addition and backward-elimination strategy was used to determine the final PopPK model. The model obtained at the end of the backward elimination process was to be considered the final PopPK model.

Results

The PopPK structural model for serplulimab started with a one-compartment model. The two-compartment model significantly improved the goodness-of-fit plots, with a notable decrease in OFV. Compared to the two-compartment model, the three-compartment model did not show a significant decrease in OFV ($p > 0.05$). Given the previous application and other PD-1 monoclonal antibodies, the OFV showed a significant decrease using a time-varying clearance, thus the two-compartment model with time-varying clearance was chosen as the structural model.



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

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

IV = infusion rate
K_{10} = elimination rate constant $K_{10} = CL/V_c$
K_{12} = rate constant from central to peripheral $K_{12} = Q/V_c$
K_{21} = rate constant from peripheral to central $K_{21} = Q/V_p$
CL = clearance
Q = inter-compartmental clearance
V_c = central compartment volume
V_p = peripheral compartment volume
A_1 = the quantity of drug in the central compartment
A_2 = the quantity of drug in the peripheral compartment

The relationship between clearance over time was described by the following equation

$$CL = CL_0 \cdot exp\left(\frac{T_{Max} \cdot \left(\frac{time}{Tc_{50}}\right)^{\lambda}}{1 + \left(\frac{time}{Tc_{50}}\right)^{\lambda}}\right)$$

where CL0 is the baseline clearance, exp(T_{max}) is the parameter value for the maximum proportional change in clearance form baseline, Tc_{50} is the time required to reach half of the maximum change in clearance, and λ is the factor that influences the time-dependent change in clearance.

The effects of all the potential covariates on the PK parameters were investigated graphically. The inter-individual random effects of individual Bayesian post-hoc PK parameter generated from the final base PopPK model were plotted versus the covariates to identify potential relationships.

The impact of covariates is summarised in Table 7.

Table 7. Impact of covariates on the Bayesian Post-hoc PK parameters from the final base model of serplulimab

Covariates	etaCL	etaVc	etaQ	etaVp	N*
Age, AGE	0.193	0.00159	0.25	0.116	2110
Sex, SEX (male vs. female)	<0.0001	<0.0001	0.0772	<0.0001	2110
Albumin, ALB	<0.0001	<0.0001	<0.0001	<0.0001	2106
Alanine aminotransferase, ALT	0.146	—	—	—	2110
Aspartate aminotransferase, AST	0.041	—	—	—	2110
Alkaline phosphatase, ALP	<0.0001	—	—	—	2109
Serum creatinine, CREAT	0.0348	—	—	—	2108
Total bilirubin, TBIL	0.852	—	—	—	2103
Creatinine clearance, CRCL	0.00022	—	—	—	2107
Lactate dehydrogenase, LDH	0.00121	—	—	—	2081
Tumor burden, TUMBUR	<0.0001	<0.0001	<0.0001	<0.0001	2097
Anti-drug antibody, ADA (negative vs. positive)	0.177	—	0.0176	—	2110
Tumor type, TUMTP#	<0.0001	<0.0001	—	—	2110
ECOG (0 vs. ⩾1)	<0.0001	—	0.000208	—	2109
Chemotherapy combination, COMB (No vs. Yes)	0.00361	—	0.00472	—	2110
Antibody-based anti-tumor therapy combination, COMBANTI (No vs. Yes)	0.104	—	0.402	—	2110
Race, RACE (Asian vs. White)	0.208	0.77	0.308	0.0181	2110

*Missing covariates were excluded from this correlation analysis. etaCL, etaVc, etaQ and etaVp represent the inter-individual random effects of CL, Vc, Q and Vp respectively. Numbers in the table are p values from linear regression (continuous covariates) or ANOVA testing (categorical covariates). N: sample size. Red = $p < 0.001$, green = $p < 0.01$, blue = $p < 0.05$, white = $p > 0.05$.

#Tumor types are classified as: hepatocellular carcinoma vs. colorectal cancer vs. squamous non-small cell lung cancer vs. non-squamous non-small cell lung cancer vs. small cell lung cancer vs. esophageal squamous cell carcinoma vs. other tumor types.

The full PopPK model included all significant covariate relationships (with a decrease in OFV more than 6.63 ($P < 0.01$)). The non-significant covariates were then excluded using a stepwise backward-elimination method and the final PopPK model was determined. The criterion for retention was a change in likelihood ratio >10.83 for 1 parameter ($P < 0.001$).

Testing of the covariates one at a time using a stepwise forward-addition method in NONMEM showed that the effect of body weight, sex, albumin, alkaline phosphatase, tumour burden and tumour type on CL, body weight, sex, albumin and tumour type on Vc and albumin, tumour burden on Vp were significant ($p < 0.01$). No covariate was removed in the backward-elimination process.

Final PopPK model

The final PopPK model includes the following parameter-covariate relations:

$$CL_{0i}(L/hr) = 0.00852(\text{if TUMTP} = 1) \times 0.00756(\text{if TUMTP} = 2) \times 0.00848(\text{if TUMTP} = 3) \times 0.00768(\text{if TUMTP} = 4) \times 0.00712(\text{if TUMTP} = 5) \times 0.00743(\text{if TUMTP} = 6) \times 0.00878(\text{if TUMTP} = 7) \times exp\,(0.514 \times \ln\left(\frac{WT}{62}\right) - 0.714 \times \ln\left(\frac{ALB}{41.4}\right) + 0.0548 \times \ln\left(\frac{TUMBUR}{73}\right) - 0.145(\text{if SEX} = \text{Female}) + 0.0553 \times \ln\left(\frac{ALP}{94}\right))$$

$$CL_{0i}(L/day) = CL_{0i}(L/hr) \times 24$$

$$CL(L/day) = CL_{0i} * \exp\left(\frac{Tmax * (\frac{time}{Tc50})^{\lambda}}{1 + (\frac{time}{Tc50})^{\lambda}} + \eta_{CL,i}\right)$$

$$Vc_i(\text{L}) = 3.20(\text{if TUMTP} = 1) \times 3.19(\text{if TUMTP} = 2) \times 3.38(\text{if TUMTP} = 3) \times 3.25(\text{if TUMTP} = 4) \times 3.45(\text{if TUMTP} = 5) \times 3.48(\text{if TUMTP} = 6) \times 3.19(\text{if TUMTP} = 7) \times \exp(0.470 \times \ln\left(\frac{WT}{62}\right) - 0.320 \times \ln\left(\frac{ALB}{41.4}\right) - 0.14(\text{if SEX} = \text{Female}) + \eta_{Vc,i})$$

$$Q_i(\text{L/day}) = (0.0169 \times exp(\eta_{Q,i})) \times 24$$

$$Vp_i(\text{L}) = 2.98 \times exp\left(-1.05 \times \ln\left(\frac{ALB}{41.4}\right) + 0.107 \times \ln\left(\frac{TUMBUR}{73}\right) + \eta_{Vp,i}\right)$$

$$Tmax_i = -0.0926 + \eta_{Tmax,i}$$

$$TC50_i(\text{day}) = 221$$

$$\lambda = 2.43$$

WT=body weight, ALB=albumin, TUMBUR=tumor burden, SEX=sex (0=male, 1=female), ALP=alkaline phosphatase, TUMTP=tumor type (1=Hepatocellular carcinoma, 2=colorectal cancer, 3=squamous non-small cell lung cancer, 4= non-squamous non-small cell lung cancer, 5= small cell lung cancer, 6=esophageal squamous cell carcinoma, 7=other tumor types).

A summary of the final population parameters is in Table 8.

The typical subject is a male with a body weight of 62 kg, albumin of 41.4 g/L, tumour burden of 73.0 mm and ALP of 94 U/L, the estimated CL0 and Vc for subjects with oesophageal squamous cell carcinoma was 0.178 L/day and 3.48 L. For a typical subject with any tumour type, the estimated Q, Vp, exp(Tmax), TC50 and λ were 0.405 L/day, 2.98 L, 0.912, 221 days and 2.43. Interindividual variability of CL, Vc, Q, Vp, and Tmax were 24.0%, 16.3%, 54.3%, 45.9%, and 34.1%.

The RSEs for the final model estimates of the PK parameters CL0, Vc, Q, Vp, Tmax, TC50, and λ were no more than 12%, indicating that these parameters were estimated accurately.

Table 8. Summary of serplulimab final population PK parameters

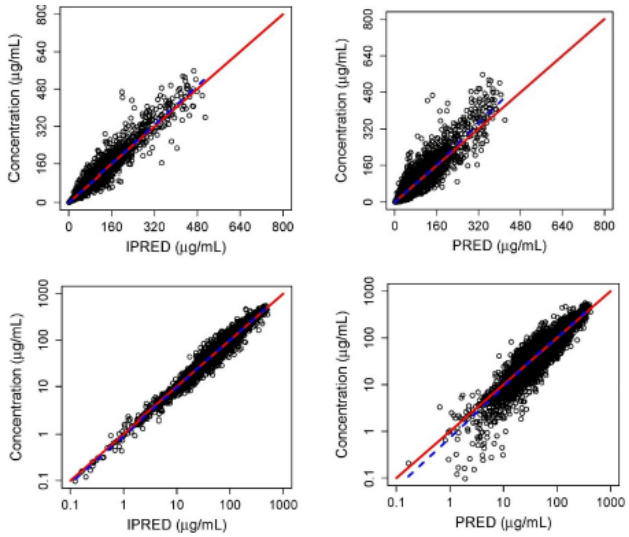
Parameter		Parameter Estimate (RSE%)	Inter-Individual Variability (RSE%)
Baseline clearance, CL_0 (L/day)	Squamous non-small cell lung cancer	0.204 (2.04%)	24.0 (2.9%)
	Hepatocellular carcinoma	0.204 (2.37%)	
	Colorectal cancer	0.182 (2.84%)	
	Non-squamous non-small cell lung cancer	0.184 (1.54%)	
	Small cell lung cancer	0.171 (1.8%)	
	Esophageal squamous cell carcinoma	0.178 (1.98%)	
	Other tumor types	0.211 (3.18%)	
Volume of central compartment, V_c (L)	Squamous non-small cell lung cancer	3.38 (1.1%)	16.3 (3.98%)
	Hepatocellular carcinoma	3.20 (2.02%)	
	Colorectal cancer	3.19 (1.6%)	
	Non-squamous non-small cell lung cancer	3.25 (0.961%)	
	Small cell lung cancer	3.45 (1.22%)	
	Esophageal squamous cell carcinoma	3.48 (1.51%)	
	Other tumor types	3.19 (1.68%)	
Inter-compartment clearance, Q (L/day)		0.405 (6.1%)	54.3 (8.98%)
Volume of peripheral compartment, V_p (L)		2.98 (2.77%)	45.9 (4.6%)
Maximum proportional change in clearance from baseline, exp(T_{max})		0.912 (2.11%)	34.1 (9.11%)
Time to half of the maximum change in clearance, TC_{50} (day)		221 (12.0%)	—
Impact factor of time-dependent clearance, λ		2.43 (6.21%)	—
Influence of body weight on CL		0.514 (6.46%)	—
Influence of body weight on V_c		0.47 (5.81%)	—
Influence of sex on CL		-0.145 (10.8%)	
Influence of sex on V_c		-0.14 (8.6%)	—
Influence of ALB on CL		-0.714 (9.39%)	—
Influence of ALB on V_c		-0.32 (14.2%)	—
Influence of ALB on V_p		-1.05 (15.5%)	—
Influence of ALP on CL		0.0553 (29.9%)	—
Influence of tumor burden on CL		0.0548 (20.8%)	—
Influence of tumor burden on V_p		0.107 (24.6%)	—
Covariance (CL, V_c)		0.0140 (11%)	—
Residual errors (%)		17.6 (1.75%)	—

Model evaluation

The diagnostic plots of the final PopPK model show a good agreement between the predicted concentrations and the observed concentrations, and no apparent bias was observed in the residuals plots over time and across predicted concentrations.

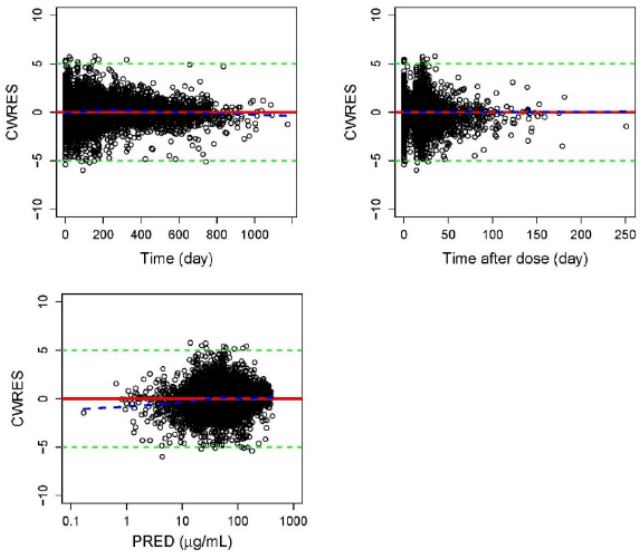
Distributions of inter-individual variability in the final PopPK model show that ETA is nearly symmetric distributed around zero.

Figure 1. Goodness-of-fit diagnostic plots for the final model of serplulimab



Observed versus individual predicted concentrations (upper left: constant coordinates; lower left: logarithmic coordinates) and observed versus population predicted concentrations (upper right: constant coordinates; lower right: logarithmic coordinates) for the final PopPK model. Red solid lines represent the unit diagonal and blue dashed lines represent the lowess smooth curves.

Figure 2. Diagnostic plots of conditional weighted residuals for the final model of serplulimab



Conditional weighted residuals (CWRES) vs time (upper left) and time after the dose (upper right), as well as CWRES vs population predicted concentrations (lower left). Red solid lines represent the unit line at zero. Green dotted lines represent |CWRES| of 5. The blue dashed lines are smooth curves (lowess) showing the relationship between 2 variables.

Bootstrap

The PK parameter estimates of final PopPK model and the median and 95% CIs of the PK parameter estimates derived from bootstrap method are in Table 9.

The success rate of bootstrapping was 86.5%.

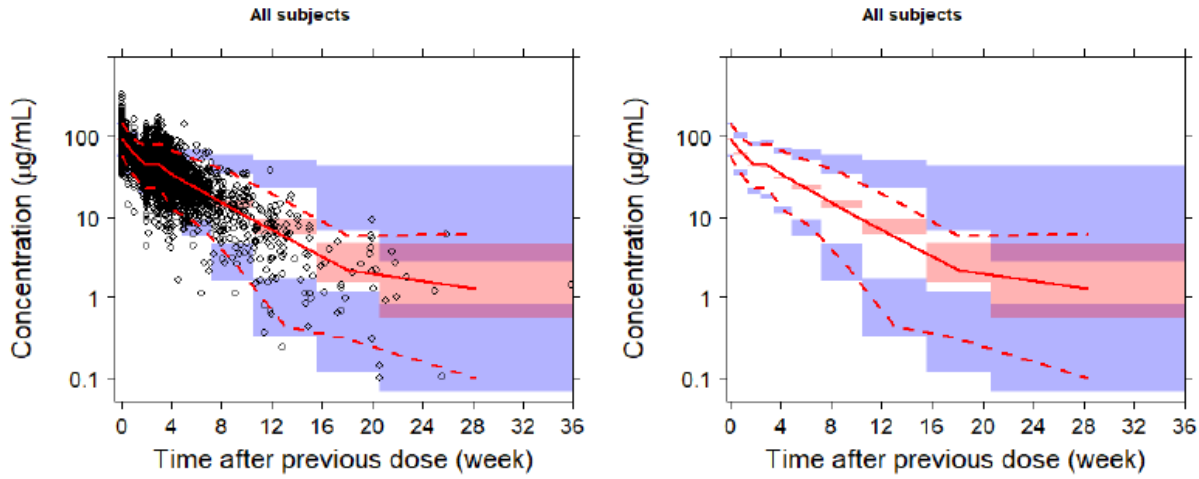
Table 9. Comparison of final model of serplulimab estimates and bootstrap results

Parameter Description		Final Model estimate (95% CI)	Bootstrap estimate Median (2.5-97.5%tiles)
Baseline clearance, CL_0 (L/day)	Squamous non-small cell lung cancer	0.204 (0.196 ~ 0.212)	0.204 (0.195 ~ 0.215)
	Hepatocellular carcinoma	0.204 (0.195 ~ 0.214)	0.205 (0.196 ~ 0.216)
	Colorectal cancer	0.182 (0.172 ~ 0.192)	0.182 (0.172 ~ 0.195)
	Non-squamous non-small cell lung cancer	0.184 (0.179 ~ 0.19)	0.185 (0.178 ~ 0.192)
	Small cell lung cancer	0.171 (0.165 ~ 0.177)	0.171 (0.165 ~ 0.179)
	Esophageal squamous cell carcinoma	0.178 (0.171 ~ 0.185)	0.179 (0.172 ~ 0.187)
	Other tumor types	0.211 (0.198 ~ 0.224)	0.211 (0.197 ~ 0.226)
Volume of central compartment, V_c (L)	Squamous non-small cell lung cancer	3.38 (3.31 ~ 3.45)	3.38 (3.31 ~ 3.46)
	Hepatocellular carcinoma	3.2 (3.08 ~ 3.33)	3.21 (3.08 ~ 3.33)
	Colorectal cancer	3.19 (3.09 ~ 3.29)	3.18 (3.08 ~ 3.28)
	Non-squamous non-small cell lung cancer	3.25 (3.18 ~ 3.31)	3.24 (3.18 ~ 3.31)
	Small cell lung cancer	3.45 (3.37 ~ 3.54)	3.45 (3.37 ~ 3.54)
	Esophageal squamous cell carcinoma	3.48 (3.38 ~ 3.59)	3.48 (3.37 ~ 3.59)
	Other tumor types	3.19 (3.09 ~ 3.3)	3.19 (3.08 ~ 3.31)
Inter-compartment clearance, Q (L/day)		0.405 (0.359 ~ 0.456)	0.408 (0.358 ~ 0.474)
Volume of peripheral compartment, V_p (L)		2.98 (2.82 ~ 3.14)	2.96 (2.77 ~ 3.14)
Maximum proportional change in clearance from baseline, T_{max}		0.912 (0.875 ~ 0.95)	0.909 (0.866 ~ 0.952)
Time to half of the maximum change in clearance, TC_{50} (day)		221 (169 ~ 273)	209 (147 ~ 319)
\Impact factor of time-dependent clearance, λ		2.43 (2.13 ~ 2.73)	2.52 (1.92 ~ 3.58)
Influence of body weight on CL		0.514 (0.449 ~ 0.579)	0.514 (0.448 ~ 0.583)
Influence of body weight on V_c		0.47 (0.416 ~ 0.523)	0.468 (0.421 ~ 0.529)
Influence of sex on CL		-0.145 (-0.175 ~ -0.114)	-0.145 (-0.177 ~ -0.112)
Influence of sex on V_c		-0.14 (-0.163 ~ -0.116)	-0.14 (-0.163 ~ -0.114)
Influence of ALB on CL		-0.714 (-0.845 ~ -0.582)	-0.72 (-0.873 ~ -0.579)
Influence of ALB on V_c		-0.32 (-0.409 ~ -0.231)	-0.319 (-0.411 ~ -0.232)
Influence of ALB on V_p		-1.05 (-1.37 ~ -0.732)	-1.03 (-1.42 ~ -0.664)
Influence of ALP on CL		0.0553 (0.0229 ~ 0.0877)	0.0565 (0.0236 ~ 0.0896)
Influence of tumor burden on CL		0.0548 (0.0325 ~ 0.0771)	0.056 (0.0339 ~ 0.0766)
Influence of tumor burden on V_c		0.107 (0.0554 ~ 0.158)	0.106 (0.0492 ~ 0.159)
Covariance (CL, V_c)		0.014 (0.011 ~ 0.017)	0.0141 (0.0111 ~ 0.0171)
Inter-individual variability in CL		24 (22.6 ~ 25.3)	23.9 (22.4 ~ 25.3)
Inter-individual variability in V_c		16.3 (15 ~ 17.5)	16.3 (14.9 ~ 17.5)
Inter-individual variability in Q		54.3 (43.7 ~ 63.1)	53.8 (33.2 ~ 63.1)
Inter-individual variability in V_p		45.9 (41.5 ~ 49.8)	45.6 (40.8 ~ 50)
Inter-individual variability in T_{max}		34.1 (27.3 ~ 39.7)	33 (25.7 ~ 45.2)
Residual errors (%)		17.6 (17 ~ 18.2)	17.6 (17 ~ 18.2)

Prediction-corrected visual predictive check (pcVPC)

The pcVPC evaluated the ability of the model to reproduce the distribution of the data. A total of 1000 replicates of the trials were simulated using the observed covariates for each subject, the final PopPK model parameter estimates, the estimated subject specific random effects, and the residual error. The pcVPC of the serplulimab final model are shown in Figure 3.

Figure 3. pcVPC of serplulimab concentration-time profiles



Points are prediction-corrected concentrations, 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. The left figure includes observed data points, while the right figure excludes observed data points.

Numerical predictive check (NPC)

A total of 1000 replicates of the trials were simulated using the observed covariates for each subject, the final PopPK model parameter estimates, the estimated subject specific random effects, and the residual error. NPC simulations of serplulimab were performed independently to evaluate the final PopPK model, as shown in Table 10.

Table 10. Summary of numerical predictive check

Range	Expected (%)	Observation (%)
Above 95th percentile	5.00	2.08
Above 75th percentile	25.00	24.3
Above 50th percentile	50.00	55.6
Below 50th percentile	50.00	44.4
Below 25th percentile	25.00	18.2
Below 5th percentile	5.00	2.14

Shrinkage

Shrinkage of the final serplulimab model parameters is presented in Table 11. The greater η-shrinkage (>30%) of Q, Vp, and Tmax may be related to the sparse sampling in the dataset and the shorter dosing duration in some subjects.

Table 11. Shrinkage of the final model parameters

Parameters	Description	Shrinkage (%)
ETA1	Inter-individual variability in CL	14.9
ETA2	Inter-individual variability in V_c	27.0
ETA3	Inter-individual variability in Q	67.3
ETA4	Inter-individual variability in V_p	35.8
ETA5	Inter-individual variability in T_{max}	46.7
EPS1	Residual errors	15.7

Absorption

Serplulimab is administered via IV infusion. Absorption is not applicable.

Distribution

In HLX10-001 study, the mean volume of distribution at steady state of serplulimab is in the range from 4.397 L to 7.882 L. In the PopPK analysis, the central volume ranges from 3.19 to 3.48 L, while the peripheral volume is 2.98 L and the volume of distribution of serplulimab in popPK analysis for the typical subject is approximately in the range from 6.17 L to 6.46 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.

In HLX10-001 study, the mean clearance at steady state of serplulimab is in the range from 0.007 L/h to 0.022 L/h. The mean half-life is in the range of 7.7-20.0 days after the first administration and in the range of 7.5 - 27.5 days at steady state.

In popPK analysis, the baseline clearance (CL_0) of serplulimab for the typical subject is in the range from 0.171 L/day to 0.211 L/day. Clearance decreased with the duration of administration, with the lowest value estimated as 0.912 times the baseline clearance which is in the range of 0.156-0.192 L/day (approximately 0.006-0.008 L/h). The time to half-maximum change in CL is 221 days. Model-predicted half-life values of serplulimab at the first dose and steady state for a typical male patient (with body weight of 62 kg, albumin of 41.4 g/L, tumour burden of 73.0 mm and ALP of 94 U/L) were in the range of 23.1- 28.7 days and 25.0-31.2 days, respectively.

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.

The dose-proportionality was analysed with absolute doses for all data (dose ranging from 0.3 mg/Kg to 10 mg/kg, absolute dose: 13.26 mg to 1146 mg) collected from dose escalation part and dose expansion part (study HLX10-001). The results showed that the exposures (Cmax and AUC) of serplulimab had a dose-proportional relationship within the dose range studied both after single and multiple-dose, with a slop ranging from 1.03 to 1.18. The updated dose proportional analysis results are summarized in the following tables and figures.

Table 12. Statistical assessment of dose proportionality for serplulimab (power model - PK data set)

Period	Dose Range	Parameter (Unit)	N/Nx*	Slope Estimate (SE)	90% CI of Slope	P-value
Single dose (Cycle 1 first infusion)	13.26 mg - 1146 mg	C_{max} (μg/mL)	57/58	1.03 (0.05)	(0.94, 1.11)	<0.0001
		$AUC_{0-\infty}$ (h*μg/mL)	57/56	1.13 (0.05)	(1.04, 1.22)	<0.0001
Steady state (Cycle 3 first infusion)	13.26 mg - 1146 mg	$C_{max,ss}$ (μg/mL)	57/35	1.04 (0.05)	(0.95, 1.12)	<0.0001
		$AUC_{0-\infty,ss}$ (h*μg/mL)	57/35	1.18 (0.15)	(0.92, 1.43)	<0.0001

Figure 4. Statistical assessment of dose proportionality for serplulimab after single-dose (power model) (pharmacokinetic data set)

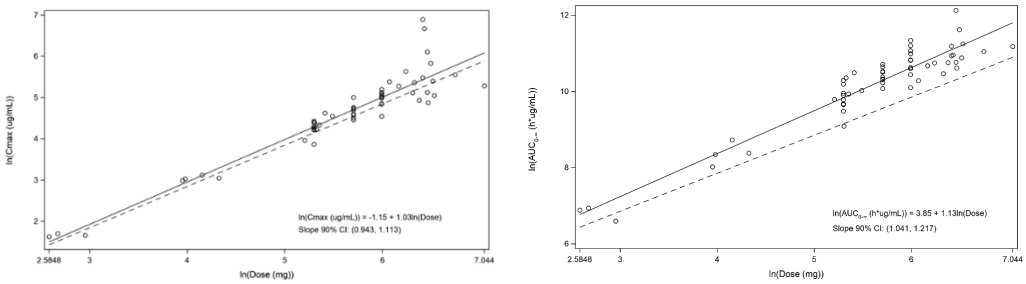
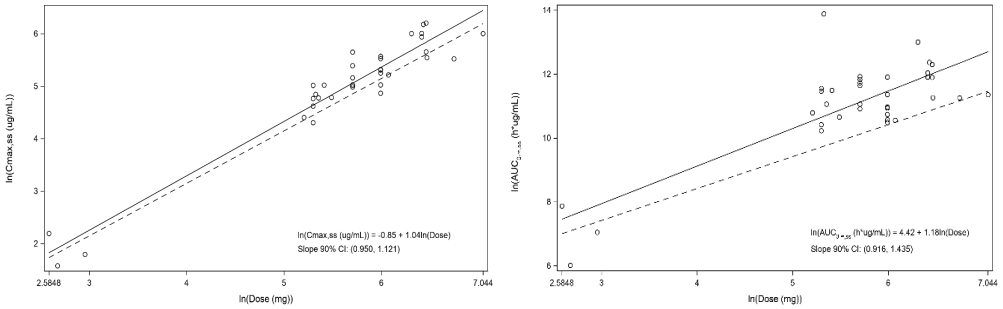


Figure 5. Statistical assessment of dose proportionality for serplulimab after multiple doses (power model) (PK data set)



Target populations

In the pivotal study HLX10-004-NSCLC303 conducted in the target population, 357 patients were in the serplulimab group and 84 patients in the placebo group.

In the serplulimab group following administration of serplulimab at a dose of 4.5 mg/kg, the mean serum serplulimab concentration reached 90.20 μg/mL after 2 h of infusion on day 1 of cycle 1. The mean serum serplulimab concentration reached 137.47 μg/mL after 2 h of infusion on day 1 of cycle 8. The mean serum serplulimab concentration was 16.88 μg/mL prior to infusion on day 1 of cycle 2 and was 46.94 μg/mL prior to infusion on day 1 of cycle 8.

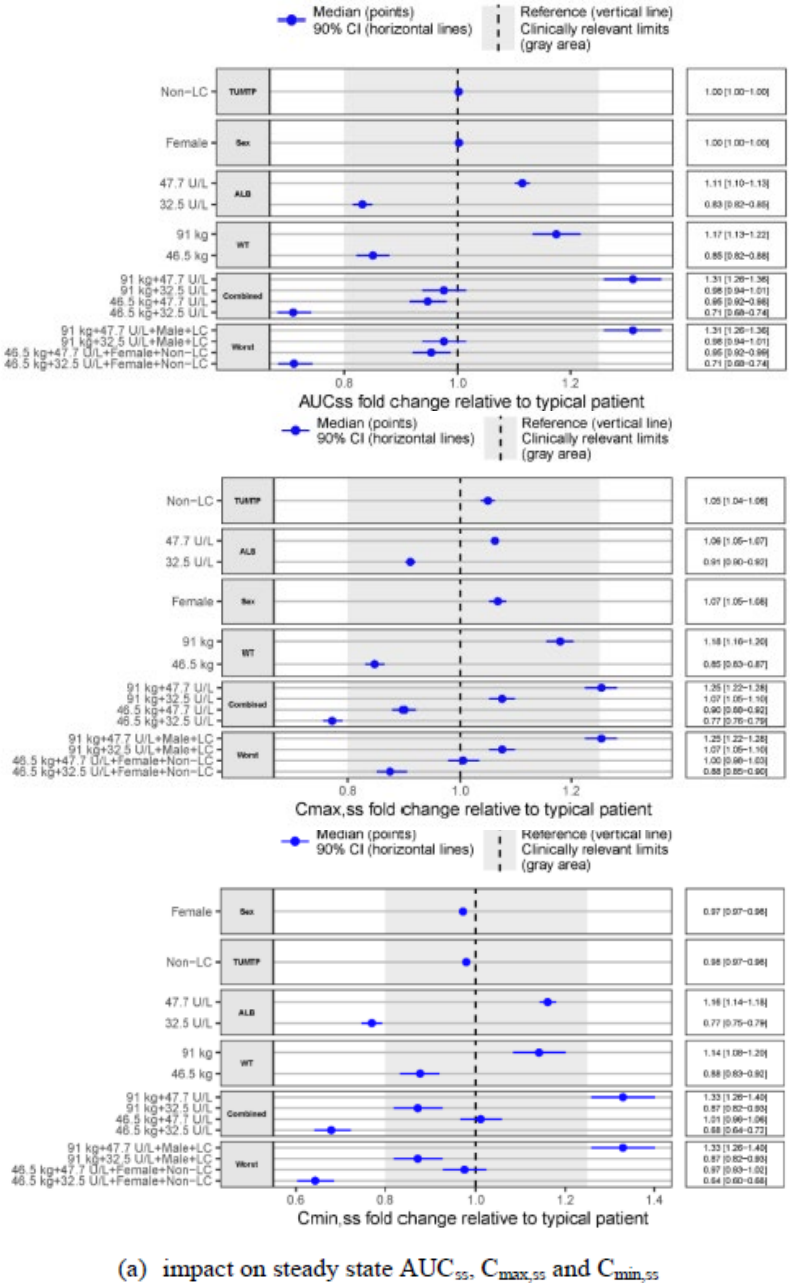
Special populations

No study has been performed in special populations. PK parameters of serplulimab in special populations were evaluated in the popPK analysis.

The results suggest no differences in the total systemic clearance of serplulimab in populations with varied age, race, creatinine, creatinine or creatinine clearance (CRCL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ADA, Eastern Cooperative Oncology Group (ECOG), renal impairment, and hepatic impairment.

Body weight, albumin, sex, and tumour type were significant covariates of PK parameters. The effects of those covariates on serplulimab PK parameter and exposure were small. As Figure 6 showed, model-predicted impact of covariates on both single dose and steady state PK exposure were less than or around 30% and were not considered clinically significant.

Figure 6. Model-predicted impact of covariates on exposures

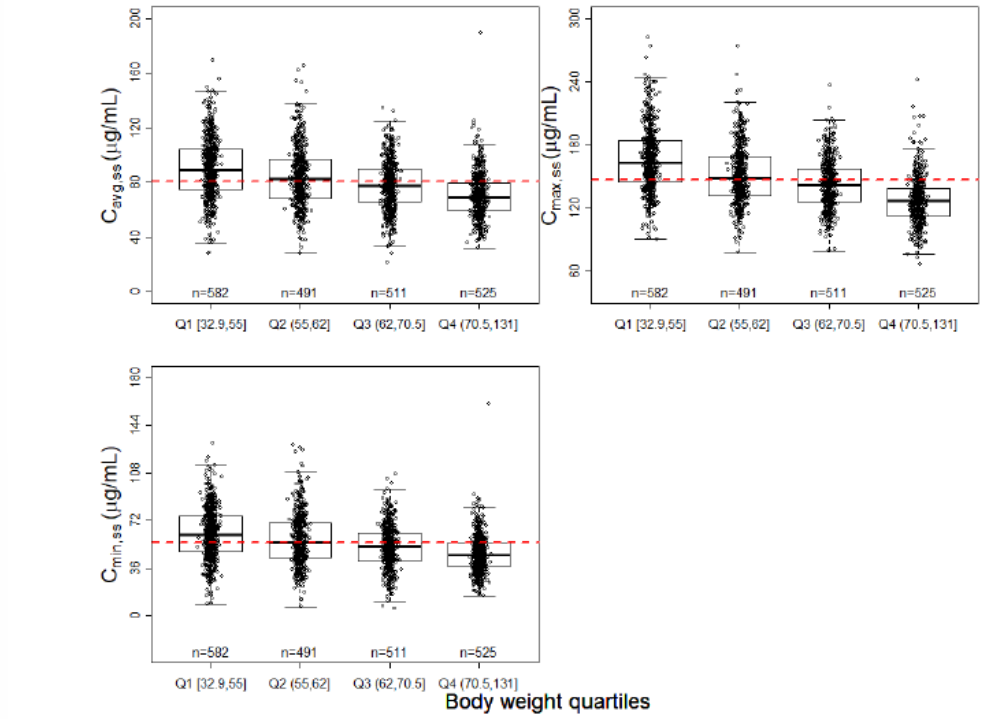


(a) impact on steady state AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$

Body weight

Body weight was identified as a statistically significant covariate influencing the PK parameters CL and Vc in the population PK analysis. To assess the impact of body weight on PK exposure, the final population PK model predicted steady state exposures were compared in body weight stratified by quartiles. Post-hoc estimated exposures (Cavg,ss, Cmax,ss, and Cmin,ss) by quartiles of body weight for patients treated with serplulimab are provided below.

Figure 7 - Impact of body weight on steady state exposure of serplulimab

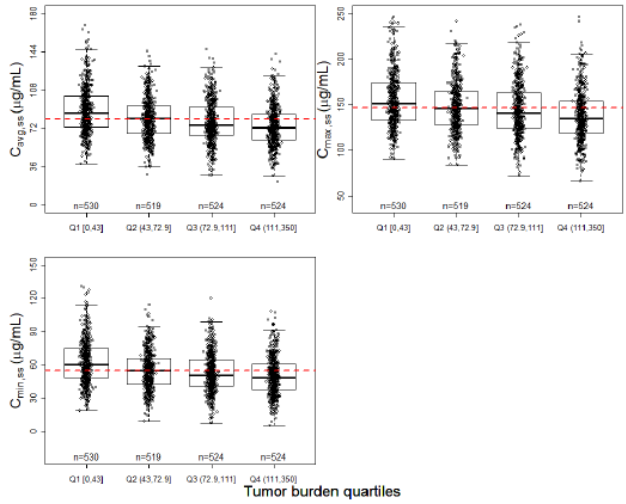


Open points are the model-predicted PK exposures. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents overall geometric mean of post hoc estimates in all subjects.

Impact of tumour burden on exposure

Tumour burden was identified as a statistically significant covariate influencing the PK parameters CL and Vp in the population PK analysis. To assess the impact of tumour burden on PK exposure, the final population PK model predicted steady state exposures were compared in tumour burden stratified by quartiles, as shown in Figure 8.

Figure *8*. Impact of tumour burden on steady state exposure of serplulimab



Open points are the model-predicted PK exposures. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents overall geometric mean of post hoc estimates in all subjects.

Impact of ethnicity on exposure

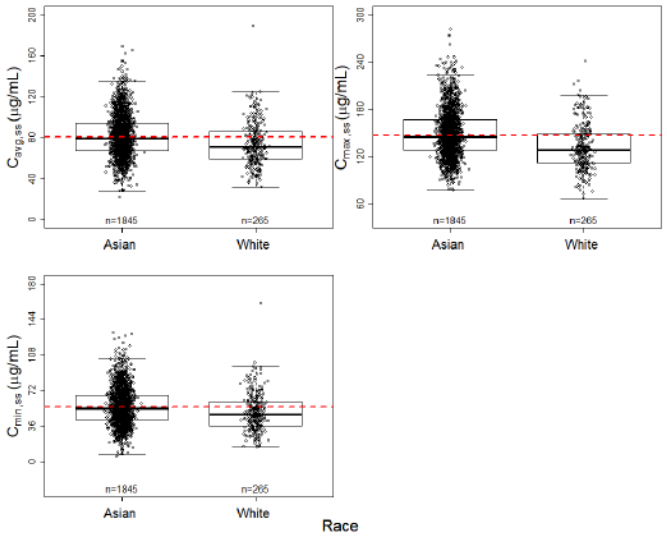
To assess the impact of race on PK exposure, steady state exposures predicted from the final population PK model were compared in subjects of different races. Post-hoc estimated exposures (Cavg,ss, Cmax,ss and Cmin,ss) stratified by race for patients treated with serplulimab are provided in Table 13 and Figure 9.

Table 13. Impact of ethnicity on geometric mean (%CV) steady state exposure of serplulimab

Group		Race	
		Asian	White
No. of subjects (%)		1845 (87.4)	265 (12.6)
$C_{avg,ss}$ (μg/mL)	Geometric mean (%CV)	79.3 (25.3)	71.2 (28.4)
	% Change [a]	—	-10.1
$C_{max,ss}$ (μg/mL)	Geometric mean (%CV)	146 (19.8)	129 (21.9)
	% Change [a]	—	-11.8
$C_{min,ss}$ (μg/mL)	Geometric mean (%CV)	52.5 (33.1)	47.1 (37.5)
	% Change [a]	—	-10.3
Baseline body weight (kg) [min, median, max]		[32.9; 60.6; 115]	[40.1; 76; 131]
ALB (g/L) [min, median, max]		[23.8; 41.7; 67.9]	[25; 40; 50.5]
Baseline tumor burden (mm) [min, median, max]		[0; 68.8; 350]	[5; 99; 324]
ALP (U/L) [min, median, max]		[30; 93; 910]	[10.7; 96; 512]
Sex	Male (%)	1440(78)	235(88.7)
	Female (%)	405(22)	30(11.3)
Tumor type	Hepatocellular carcinoma (%)	125(6.78)	—
	Colorectal cancer (%)	151(8.18)	—
	Squamous non-small cell lung cancer (%)	303(16.4)	138(52.1)
	Non-squamous non-small cell lung cancer (%)	498(27)	—
	Small cell lung cancer (%)	263(14.3)	127(47.9)
	Esophageal squamous cell carcinoma (%)	389(21.1)	—
	Other tumor types (%)	116(6.29)	—

[a] :%change from the geometric mean of Asian subjects.

Figure 9. Impact of ethnicity on steady state exposure of serplulimab

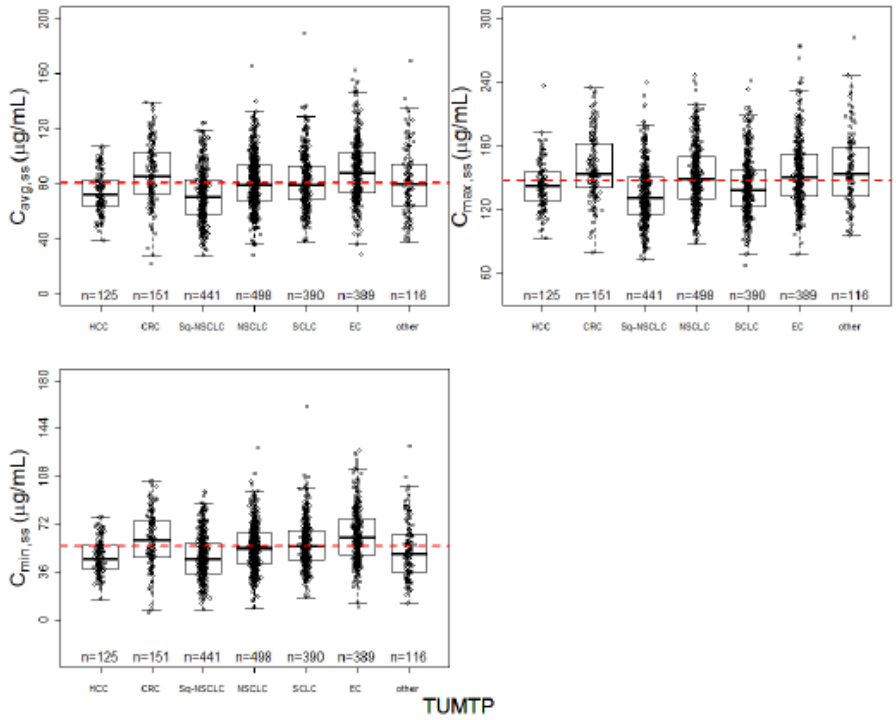


Open points are the model-predicted PK exposures. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents overall geometric mean of post hoc estimates in all subjects.

Impact of tumour type on exposure

Tumour type was identified as a statistically significant covariate influencing the PK parameters CL and Vc in the population PK analysis. To assess the impact of tumour type on PK exposure, steady state exposures predicted from the final population PK model were compared in subjects with various tumour types. Compared to the geometric mean of overall exposures, the exposures in subjects with nsq-NSCLC fluctuated within ± 3.06%.

Figure 10. Impact of tumour type on steady state exposure of serplulimab

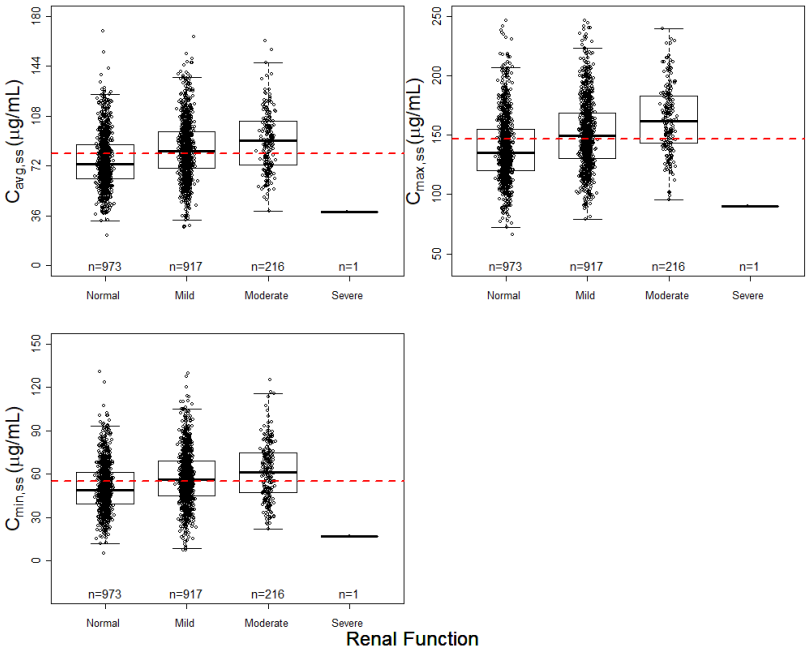


Open points are the model-predicted PK exposures. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents overall geometric mean of post hoc estimates in all subjects.

Impaired renal function

To assess the impact of renal function on PK exposures, steady state exposures predicted from the final population PK model were compared in subjects with different degrees of renal function. Post-hoc estimated exposures ($C_{avg,ss}$, $C_{max,ss}$, and $C_{min,ss}$) by renal function are provided below. The exposures in subjects with mild renal impairment (N=917) increased by 8.92% to 11.9%, the exposures in subjects with moderate renal impairment (N=216) increased by 18.2% to 21.5%.

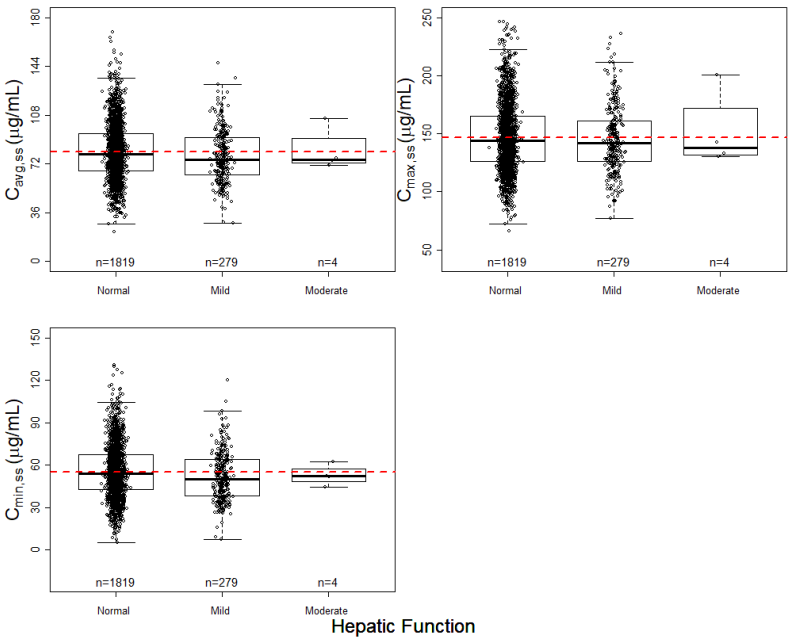
Figure 11. Effect of renal function on steady-state exposure of serplulimab



Impaired hepatic function

To assess the impact of hepatic function on PK exposure, steady state exposures predicted from the final population PK model were compared in subjects with different degrees of hepatic function. Post hoc estimated exposures (Cavg,ss, Cmax,ss and Cmin,ss) by hepatic function for patients treated with serplulimab are provided in **Figure *12***.

Figure 12. Effect of hepatic function on steady-state exposure of serplulimab



Dose - Exposure

The final entire popPK dataset includes 14687 serplulimab serum concentration measurements from 2110 patients.

The individual PK parameters estimated from the final model were used to simulate the exposures in all subjects with body weight records (N = 2109) following multiple dosing regimens (3 mg/kg Q2W, 4.5 mg/kg Q3W, 200 mg Q2W, 300 mg Q3W and 10 mg/kg Q2W).
Comparative exposure analysis across body weight quartiles results showed that in the Q1 subgroup (32.9-55 kg), both 200 mg Q2W vs. 3 mg/kg Q2W and 300 mg Q3W vs. 4.5 mg/kg Q3W demonstrated 33.9% increases in geometric means for Cavg, Cmin, Cmax, and AUC at steady state and post-first dose. See in Figure 13, Table 14, and Table 15.

Figure 13. Concentration-time profiles of different dosing regimens

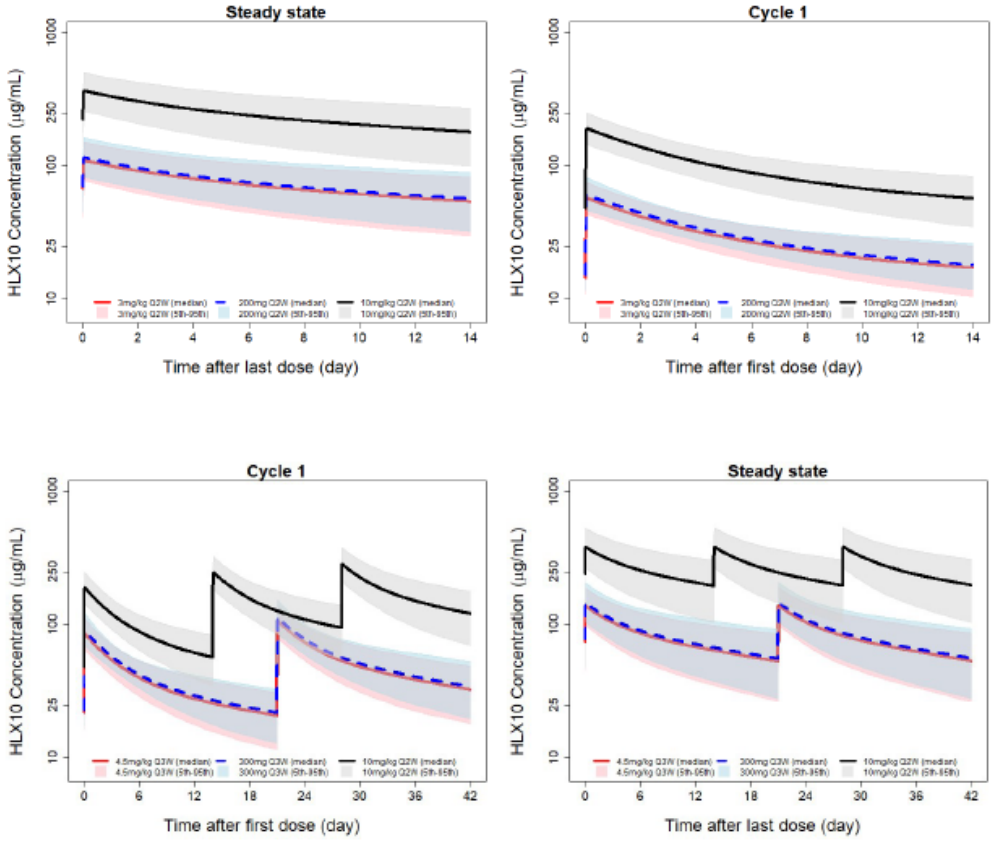


Table 14. Summary of serplulimab exposures following 3 mg/kg Q2W and 200 mg Q2W dosing - stratified by body weight quartiles (geometric mean [CV])

Exposures	Body Weight (kg)											
	Q1 [32.9,55]			Q2 (55,62]			Q3 (62,70.5]			Q4 (70.5,131]		
	3 mg/kg Q2W	200 mg Q2W	Change (%)#	3 mg/kg Q2W	200 mg Q2W	Change (%)#	3 mg/kg Q2W	200 mg Q2W	Change (%)#	3 mg/kg Q2W	200 mg Q2W	Change (%)#
AUC_{ss} (μg*day/mL)	952.71 (26.2)	1275.68 (25.6)	33.9	1051.43 (27.6)	1187.4 (27.5)	12.93	1089.45 (24.8)	1094.56 (24.7)	0.47	1200.08 (23.6)	996.69 (24.3)	-16.95
$C_{max,ss}$ (μg/mL)	103.4 (20.6)	138.45 (20.3)		112.75 (21.3)	127.33 (21.2)		118.36 (19)	118.91 (18.9)		128.51 (18.6)	106.73 (19.3)	
$C_{min,ss}$ (μg/mL)	51.04 (32.1)	68.34 (31.5)		56.29 (34.2)	63.57 (34.1)		57.36 (30.9)	57.63 (31)		63.25 (29.3)	52.53 (30.3)	
$C_{avg,ss}$* (μg/mL)	68.05 (26.2)	91.12 (25.6)		75.1 (27.6)	84.81 (27.5)		77.82 (24.8)	78.18 (24.7)		85.72 (23.6)	71.19 (24.3)	
AUC_1 (μg*day/mL)	339.87 (16.2)	455.08 (15.6)		377.75 (14.4)	426.6 (14.3)		409.87 (13.7)	411.79 (13.4)		456.84 (13.9)	379.42 (13.4)	
C_{max1} (μg/mL)	51.29 (16.2)	68.68 (16.8)		55.29 (15.1)	62.44 (15)		59.75 (14.3)	60.03 (14.1)		64.5 (14.1)	53.57 (14.4)	
C_{min1} (μg/mL)	14.41 (25.6)	19.3 (24.9)		16.17 (23.4)	18.26 (23.4)		17.4 (22.3)	17.48 (22.3)		19.53 (21)	16.22 (21.1)	
C_{avg1}* (μg/mL)	24.28 (16.2)	32.51 (15.6)		26.98 (14.4)	30.47 (14.3)		29.28 (13.7)	29.41 (13.4)		32.63 (13.9)	27.1 (13.4)	

*C_{avg1} and $C_{avg,ss}$ were calculated by dividing AUC_1 and AUC_{ss} by the dosing interval of the corresponding regimen, respectively.

#Change=(200 mg-3 mg/kg)/(3 mg/kg)*100.

Table 15. Summary of serplulimab exposures following 4.5 mg/kg Q3W and 300 mg Q3W dosing - stratified by body weight quartiles (geometric mean [CV])

Exposures	Body Weight (kg)											
	Q1 [32.9,55]			Q2 (55,62]			Q3 (62,70.5]			Q4 (70.5,131]		
	4.5 mg/kg Q3W	300 mg Q3W	Change (%)#	4.5 mg/kg Q3W	300 mg Q3W	Change (%)#	4.5 mg/kg Q3W	300 mg Q3W	Change (%)#	4.5 mg/kg Q3W	300 mg Q3W	Change (%)#
AUC_{ss} (μg*day/mL)	1428.07 (26.1)	1912.19 (25.5)	33.9	1575.92 (27.5)	1779.72 (27.4)	12.93	1633.01 (24.7)	1640.66 (24.7)	0.47	1798.71 (23.5)	1493.87 (24.3)	-16.95
$C_{max,ss}$ (μg/mL)	124.33 (18.9)	166.48 (18.8)		135.07 (19.4)	152.54 (19.3)		142.43 (17.3)	143.1 (17.2)		154.11 (17.1)	127.99 (17.8)	
$C_{min,ss}$ (μg/mL)	46.05 (34)	61.66 (33.4)		50.65 (36.5)	57.2 (36.4)		51.2 (33.1)	51.44 (33.2)		56.37 (31.5)	46.82 (32.6)	
$C_{avg,ss}$* (μg/mL)	68 (26.1)	91.06 (25.5)		75.04 (27.5)	84.75 (27.4)		77.76 (24.7)	78.13 (24.7)		85.65 (23.5)	71.14 (24.3)	
AUC_1 (μg*day/mL)	646.44 (18.2)	865.58 (17.5)		719.33 (16.4)	812.36 (16.3)		777.9 (15.5)	781.54 (15.3)		867.33 (15.4)	720.33 (15.1)	
C_{max1} (μg/mL)	76.93 (16.2)	103.01 (16.8)		82.94 (15.1)	93.66 (15)		89.62 (14.3)	90.04 (14.1)		96.76 (14.1)	80.36 (14.4)	
C_{min1} (μg/mL)	17.31 (28.5)	23.18 (27.9)		19.33 (27.1)	21.83 (27.1)		20.54 (25.7)	20.64 (25.7)		22.94 (24.2)	19.05 (24.7)	
C_{avg1}* (μg/mL)	30.78 (18.2)	41.22 (17.5)		34.25 (16.4)	38.68 (16.3)		37.04 (15.5)	37.22 (15.3)		41.3 (15.4)	34.3 (15.1)	

*C_{avg1} and $C_{avg,ss}$ were calculated by dividing AUC_1 and AUC_{ss} by the dosing interval of the corresponding regimen, respectively.

#Change= (300 mg-4.5 mg/kg)/(4.5 mg/kg)*100.

2.3.3. Pharmacodynamics

The pharmacodynamics was evaluated in the phase I HLX10-001 study. Pharmacodynamic analyses included PD-1 receptor occupancy on peripheral CD3+ T cells and interleukin-2 (IL-2) stimulation ratio, which were used to evaluate the functional regulation of serplulimab on target activity on peripheral T cells.

Across all dose groups from 0.3 to 10 mg/kg, the PD-1 receptor on the peripheral circulating T cells was almost completely occupied at 24 hours after serplulimab administration on Cycle 1 Day 1, and the mean range was 98.13% to 102.4%. The mean PD-1 receptor occupancy remained high through the end of the study. In all dose groups, the changes in the PD-1 receptor occupancy of individual subjects were similar to the trend of change in the mean values.

Despite fluctuations in mean serum serplulimab concentrations across dose groups and cycles, the PD-1 receptor occupancy remained high, indicating that the PD-1 receptor occupancy was unrelated to dose levels. Serplulimab reached saturation within the dose range of 0.3 mg/kg to 10 mg/kg and remained stable over the 28-day treatment cycle of serplulimab administered once every 2 weeks (Q2W). The median PD-1 receptor occupancy of subjects receiving 0.3 mg/kg of serplulimab treatment remained above 88% throughout the study, indicating that the 0.3 mg/kg dose was sufficient to induce target binding. It was concluded that serplulimab had a high affinity to the PD-1 receptor.

Before the first drug administration on Cycle 1 Day 1, the mean IL-2 stimulation ratio was approximately 2 in the 0.3 mg/kg and 3 mg/kg dose groups and 1.5 in the 1 mg/kg and 10 mg/kg dose groups. At 24 hours after the initial dose of serplulimab on Cycle 1 Day 1, the mean IL-2 stimulation ratio decreased to approximately 1 in all dose groups (range: 0.9400–1.167), indicating that serplulimab reached maximum functional blockade of peripheral circulation. IL-2 stimulation ratios remained generally stable at approximately 1 through the end of the study, indicating the maintenance of functional blockade.

2.3.4. Discussion on clinical pharmacology

No dedicated PK studies have been submitted, which is acceptable given that serplulimab is a monoclonal antibody (mAb).

Clinical studies have been conducted exclusively in adult patients, which is endorsed based on safety and pharmacodynamic considerations. The clinical studies submitted are primarily conducted outside the EU.

The use of a popPK approach to characterise PK across eleven studies, including the pivotal trial HLX10-004-NSCLC303 with sparse PK sampling, is considered acceptable.

Pharmacokinetic data supporting the current application are based on these studies in cancer patients with serplulimab administered over the dose range of 0.3-10 mg/kg and were conducted exclusively in adult populations, which is considered appropriate based on the safety and pharmacodynamic profile of the product.

PopPK analysis

Population PK modelling was performed using non-linear mixed effect models.

Sparse PK sampling was performed in pivotal study HLX10-004-NSCLC303, while rich sampling was performed for the FIH dose escalation and expansion study HLX10-001. The database appears overall appropriate for the intended use of the model. In total, 545 out of 15232 (3.58 %) data were excluded from the PopPK analysis and the approach used for data cleaning is considered appropriate.

In general, the popPK model building follows the same approach used in the serplulimab MA with indication for adult patients with extensive-stage small cell lung cancer (ES-SCLC). The model building methodology, rationale for model selection and evaluation are in general considered appropriate for the intended use of the model.

The new PopPK model developed is similar to the previous one (ES-SCLC), and it is based on 14687 serum concentration measurements from 2110 subjects in 11 studies, while the previous model was based on 6677 concentration samples from 1144 subjects in 8 studies.

The PopPK model is based on a structural two compartment model with time-varying CL from the central compartment, similarly to the previous model. The function used to describe the time-dependent clearance (CL(t)) remains the same across both models; however, notable differences are observed in the values of parameters between the updated and previous models.

Specifically, the maximum reduction of the baseline clearance (CL0), represented by exp(Tmax), has increased from 0.695 in the previous model to 0.912 in the updated model. Similarly, the exponent λ, which governs the steepness of the transition in CL(t), has changed from 2.05 to 2.4. Furthermore, T50, the time at which clearance is reduced by 50%, has been extended from 106 days in the earlier model to 221 days in the revised model. The Applicant was requested to provide a detailed explanation for these discrepancies and to justify the selection of the updated parameter values. However, given the relatively small impact of clearance variation over time on AUC (or Cavg), the clinical relevance of this issue is limited.

The covariates tested appear appropriate, even if more significant covariates are present in the new PopPK model. Body weight, tumour burden, and race are covariates of specific interest in the current application.

The regulatory impact of the popPK model is considered low. The model has been used to predict plasma drug exposures, evaluate the impact of covariates on the exposures, and quantify interindividual variability of pharmacokinetic parameters within the target population. Furthermore, it has been utilized to derive exposure metrics for exposure-response (E-R) analyses.

Both the base and final models were evaluated using standard methodologies. Diagnostic plots, such as DV vs (I)PRED and CWRES vs PRED/TIME, show no significant bias, with data points distributed appropriately around the zero line.

Key interindividual variability estimates for pharmacokinetic parameters are as follows: clearance 24.0%, central volume of distribution 16.3%, inter-compartmental clearance 54.3%, peripheral volume of distribution 45.9%, and time to maximum concentration (Tmax) 34.1%. Residual standard errors (RSE) for these estimates remain below 15%, indicating a satisfactory level of precision.

The robustness of the model is further supported by prediction-corrected visual predictive check (pcVPC) plots, which demonstrate adequate alignment with observed data. The median and the majority of the observed data points fall within the 2.5th to 97.5th percentiles, affirming the reliability of the model's predictive performance.

Special populations

Instead of dedicated clinical studies, PK in special populations have been investigated with covariates in the popPK modelling, which is supported. Body weight and tumour burden are covariates of specific interest in the current application.

The initial assessment of body weight based on quartiles was considered unreliable and additional exposure data (AUC, Cavg, Cmax, and Cmin) presented in boxplots stratified by 10 kg weight bands, spanning from 30 kg to 140 kg (data not shown) and a comprehensive table summarizing all exposure data, including minimum and maximum values for each parameter using the appropriate dosing regimen was provided by the MAH. The exposure data stratified by 10 kg body weight bands under the 4.5 mg/kg Q3W Sq-NSCLC dosing regimen demonstrate consistent exposure magnitude and variability between model-derived observed and simulated exposures across all evaluated PK parameters. These results support the adequacy of the final popPK model to characterize exposure under the proposed Sq-NSCLC dosing regimen.

The analysis of the impact of tumour burden on drug exposures indicates only minimal variations in exposure levels.

In the PopPK dataset, 87.44% of patients are Asian, while 12.56% of patients are Caucasian. However, the difference in exposures observed between Caucasian and Asian patients ranges between 10% and 11.8%. For this reason, it can be considered negligible. The analysis of the impact of ethnicity on drug exposures indicates only minimal variations in exposure levels. It is acceptable that the covariate is not clinically significant.

The available data are insufficient to support dosing recommendations for patients with severe renal impairment or moderate and severe hepatic impairment; therefore, the use of serplulimab is not recommended in these populations. No dose adjustment is required in patients with mild hepatic impairment and mild and moderate renal impairment.

The simulation results indicate that the differences in exposure between the 3 mg/kg Q2W and 4.5 mg/kg Q3W dosing regimens are minimal. Given that both regimens exceed the saturation threshold, as demonstrated in the phase 1 study HLX10-001, the use of the 4.5 mg/kg Q3W regimen is considered acceptable from a dose-exposure perspective.

ADME

The absorption, distribution, and elimination of Serplulimab are similar to the characteristics observed in other monoclonal antibodies.

Dose proportionality and time dependencies

The dose proportionality of serplulimab was evaluated for both single-dose and multiple-dose using a power model, which is considered an acceptable approach (guidelines PK of therapeutic proteins CHMP/EWP/89294/2004).

The analysis shows an acceptable dose proportionality in the range considered, even if the 90% CI doesn't include 1 in the single dose case. However, the low value of 1.04 seems acceptable.

Target population

All subjects included in the studies were cancer patients. In the popPK analysis, the difference in exposures between patients with Sq-NSCLC and other type of cancer was considered clinically irrelevant.

ADA

No evidence of ADA impact on pharmacokinetics was observed.

Pharmacodynamics

The pharmacodynamic part has been developed in the serplulimab MA for first-line treatment of adult patients with extensive stage-small cell lung cancer (ES-SCLC). Nothing new has been submitted in support of this extension of indication, which is agreed.

2.3.5. Conclusions on clinical pharmacology

The development of the PopPK model is appropriate for the intended objectives. The clinical pharmacaology data are adequate to support this extension of indication.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

HLX10-001 was a prospective, open-label FIH study of serplulimab in patients with advanced or metastatic solid tumours refractory to standard therapy. Briefly, the study included a dose-finding cohort and a dose expansion cohort. Serplulimab was administered IV at doses from 0.3 to 10 mg/kg once every 2 weeks in dose escalation cohorts and 200 mg Q2W, 300 mg Q3W, 400 mg Q4W and 600 mg Q6W in the dose expansion cohorts. In total 57 subjects received serplulimab as of cut-off date (DCO) Aug-2022.

At the DCO, all subject in the dose escalating cohorts and 93% in the dose expansion cohorts experienced at least one treatment-emergent adverse event. One (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. A saturation of PD effects was observed already at the lowest dose of 0.3 mg/kg.

2.4.2. Main study

Pivotal study: HLX10-004-NSCLC303 (ASTRUM-004)

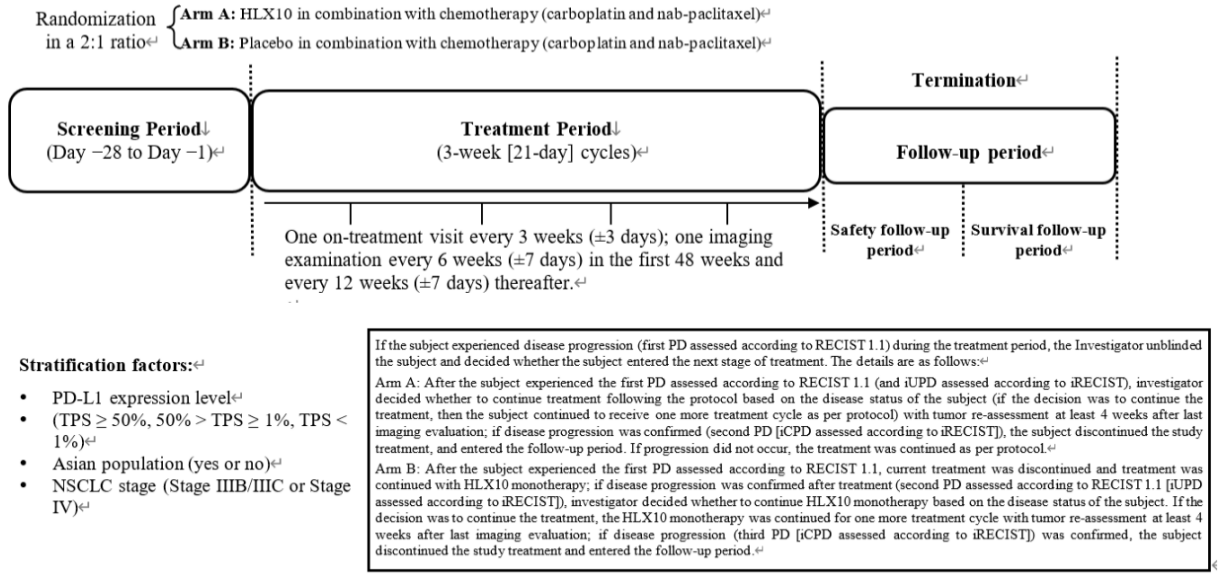
HLX10-004-NSCLC303 is a randomized, double-blind, multi-center, ongoing phase III study to compare the clinical efficacy and safety of serplulimab combined with chemotherapy versus placebo combined with chemotherapy in subjects with locally advanced or metastatic squamous NSCLC.

Eligible subjects in this study were randomized to arm A or arm B at a 2:1 ratio as follows:

- Arm A (serplulimab group): serplulimab + chemotherapy (carboplatin and nab-paclitaxel);
- Arm B (placebo group): placebo + chemotherapy (carboplatin and nab-paclitaxel).

Eligible subjects were enrolled in this study and received treatment the study drug until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent, or other reasons specified in the protocol (whichever occurred first).

Figure 14. Study design of study HLX10-004-NSCLC303



NSCLC = non-small cell lung cancer, PD = progressive disease, TPS = tumor proportion score

Methods

Study participants

Key inclusion and exclusion criteria:

Eligible subjects were aged ≥ 18 years at the time of signing the ICF and had been histologically or cytologically diagnosed with Stage IIIB/IIIC or Stage IV (AJCC Edition 8) squamous NSCLC which were inoperable or not suitable for radiotherapy. Moreover, no known sensitizing EGFR mutations or ALK, ROS1 gene rearrangements were allowed. Subjects had no prior systemic therapy for Stage IIIB/IIIC or Stage IV squamous NSCLC and had at least one measurable target lesion as assessed by IRRC according to RECIST 1.1 within 4 weeks prior to randomization. Patients had to provide tumor tissues, fresh or formalin-fixed, that met the requirements for the **prospective** determination of PD-L1 expression levels through Dako 22C3 assay (PD-L1 IHC 22C3 pharmDx kit). Participants were included regardless of PD-L1-expression level, which was a stratification factor. Furthermore, they were required to have an ECOG PS score of 0 or 1 within 7 days prior to the first dose of study drug, and an expected survival ≥ 12 weeks. Subjects who had received

adjuvant or neoadjuvant therapy had to complete at least 6 months prior to the diagnosis of Stage IIIB/IIIC or Stage IV squamous NSCLC.

Patients with known CNS metastases and/or carcinomatous meningitis during screening period were eligible if the lesions were asymptomatic and had no need for use of glucocorticoids, and without any evidence of new lesions or progression of brain metastases. Stable brain metastases were determined prior to the first dose of study drug.

Patients were excluded if they had active autoimmune disease and if they had been administered systemic immunosuppressive medicinal products within 14 days prior to the first dose.

Major surgery was not allowed within 28 days prior to the first dose. Palliative radiotherapy for bone or cutaneous lesions was allowed if completed two weeks before the first dose of study treatment.

Treatments

Serplulimab was administered at the dose of 4.5 mg/kg via IV infusion on Day 1 of each cycle, once every 3 weeks (21 days), for up to 2 years (up to 35 treatment cycles).

Placebo was administered via IV infusion on Day 1 of each cycle, once every 3 weeks (21 days), for up to 2 years (up to 35 treatment cycles).

Chemotherapy drugs (all subjects):

- Nab-paclitaxel: 100 mg/m^2 via IV infusion on Days 1, 8, and 15 of each cycle, once every 3 weeks (21 days), for 4–6 treatment cycles.
- Carboplatin: AUC = 5, up to a dose of 750 mg, or AUC = 6, up to a dose of 900 mg, IV infusion on Day 1 of each cycle, once every 3 weeks (21 days), for 4-6 treatment cycles. The choice of AUC 5 or 6 was based on local guidance.

Subjects received serplulimab or placebo via intravenous infusion first and then nab-paclitaxel followed by carboplatin via intravenous infusion. Serplulimab or placebo was given by infusion in a blinded state and nab-paclitaxel followed by carboplatin were given by open-label infusion.

Serplulimab, placebo and chemotherapy were given until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent or other protocol-defined reason, whichever occurred first.

Treatment beyond PD:

If a subject experienced disease progression (first PD assessed according to Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) during the treatment period, the Investigator unblinded the subject and decided whether the subject entered the next stage of treatment. The details are as follows:

- Arm A: After the subject experienced the first PD assessed according to RECIST 1.1 (and immune unconfirmed progressive disease [iUPD] assessed according to modified RECIST 1.1 for immune-based therapeutics [iRECIST]), Investigator decided whether to continue the treatment following the protocol based on the disease status of the subject (if the decision was to continue the treatment, then the subject continued to receive one more treatment cycle as per protocol) with tumor re-assessment at least 4 weeks after the last imaging evaluation; if disease progression was confirmed (second PD [iCPD assessed according to iRECIST]), the subject discontinued the study treatment, and entered the

follow-up period. If disease progression did not occur, the treatment continued as per protocol.

- Arm B: After the subject experienced the first PD assessed according to RECIST 1.1, current treatment was discontinued and treatment was continued as serplulimab monotherapy; if disease progression was confirmed after treatment (second PD assessed according to RECIST 1.1 [iUPD assessed according to iRECIST]), Investigator decided whether to continue the serplulimab monotherapy based on the disease status of the subject. If the decision was to continue the treatment, the serplulimab monotherapy was continued for one more treatment cycle, with tumor re-assessment at least 4 weeks from after the last imaging evaluation; if disease progression (third PD [iCPD assessed according to iRECIST]) was confirmed, the subject discontinued the study treatment and entered the follow-up period. If the subject decided to continue serplulimab-containing therapy after the first PD, the subject must meet the following study continuation criteria:

1. No clinical symptoms and signs of significant disease progression (including worsening of laboratory test findings).
2. Stable or improving ECOG performance status (PS) score.
3. No additional localized or systemic treatment for tumor-related symptoms or signs (e.g. emergent radiotherapy for spinal cord compression).
4. The major organ function was stable or improving.
5. Subjects were required to sign the "Informed Consent Form for Treatment after First Disease Progression".

Prohibited concomitant treatment:

Immunosuppressive drugs, including but not limited to: systemic glucocorticoids with a dose of more than 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor (TNF)-inhibitors. Except for the following situations:

- The use of immunosuppressive drugs to treat treatment-related AEs
- Short-term prevention use of prophylaxis in subjects who were expected to receive reactions as required by the prescription information of the drug
- Used in subjects who were allergic to contrast agents
- The use of inhaled, topical, and intranasal glucocorticoids was permitted
- If clinical indications were presented and Investigator considered it was necessary to perform disease management for the subject, the use of short-term glucocorticoids (e.g., to control chronic obstructive pulmonary disease, radiotherapy, nausea, etc.) was permitted

Objectives

Primary Objective:

To compare the clinical efficacy of serplulimab combined with chemotherapy versus placebo combined with chemotherapy as first-line therapy in patients with locally advanced or metastatic squamous NSCLC.

Secondary Objectives:

- To compare the safety of serplulimab combined with chemotherapy versus placebo combined with chemotherapy as first-line therapy in patients with locally advanced or metastatic squamous NSCLC.
- To evaluate the PK, immunogenicity profiles of serplulimab, and to explore the biomarkers.

Outcomes/endpoints

Primary Endpoint

Progression-free survival (PFS) (assessed by IRRC based on RECIST 1.1).

Secondary Endpoints

Secondary Efficacy Endpoints

- Overall survival (OS, key secondary endpoint).
- PFS (assessed by Investigator based on RECIST 1.1).
- PFS (assessed by IRRC and Investigator based on a modified RECIST 1.1 for immune-based therapeutics [iRECIST]).
- Objective response rate (ORR) (assessed by IRRC and Investigator based on RECIST 1.1).
- Duration of response (DOR) (assessed by IRRC and Investigator based on RECIST 1.1).
- Quality of life assessment.

Safety Endpoints

- Adverse events (AEs) (including serious adverse events [SAEs]), laboratory tests (hematology, blood chemistry, coagulation function, urinalysis, thyroid function, cardiac function), 12-lead electrocardiogram (12-lead ECG), vital signs, and physical examination, etc.

PK Endpoint

- The concentration of serplulimab in serum.

Immunogenicity Endpoint

- Anti-drug antibody/neutralizing antibody (ADA/NAb) positive rate of serplulimab.

Biomarker Endpoints

- Relationship between PD-L1 expression, microsatellite instability (MSI), tumor mutation burden (TMB) in tumor tissues and efficacy.

Sample size

The randomization ratio of the trial arm (HLX10 + chemotherapy) and control arm (placebo + chemotherapy) in this study is 2:1. The sample size calculation was based on the assumption that the median PFS, the primary endpoint of the control arm was 6 months, and the hazard ratio (HR) of trial arm compared to the control arm is 0.65. At the overall significance level $\alpha=0.05$ (two-tailed), at least 218 PFS events had to be observed to achieve a power of 85%.

For the key secondary endpoint OS, the median OS of control arm was 12 months and the hazard ratio (HR) of trial arm compared to the control arm was 0.7. The OS analysis had a maximum of three looks with equally spaced information (33%, 66% and 100%). At the same setting of

significance level (α=0.05, two-tailed), at least 299 OS events had to be observed to achieve a power of 80%. Assuming the duration of enrollment was 24 months, the duration of study was approximately 36 months, and the drop-out rate was 10%, the total number of subjects to be enrolled was approximately 516 subjects (approximately 344 subjects in the trial arm and approximately 172 subjects in the control arm) for the two arms.

The primary PFS analysis was performed when at least 218 PFS events were observed and the estimated number of enrollments for PFS was less than 516. Considering the primary endpoint of PFS and the key secondary endpoint of OS simultaneously, the study plans to enroll approximate 516 subjects.

Randomisation

The study employed a 2:1 randomization scheme (serplulimab group: placebo group). Randomization was stratified by PD-L1 expression level (tumor proportion score [TPS] ≥ 50%, 50% > TPS ≥ 1%, TPS < 1%), Asian population (yes or no), and squamous NSCLC stage (Stage IIIB/IIIC or Stage IV).

The analyses of all efficacy endpoints were stratified or corrected by PD-L1 expression level (TPS < 1%, 1% ≤ TPS < 50%, or TPS ≥ 50%), Asian population (yes or no), and squamous NSCLC stage (Stage IIIB/IIIC or Stage IV). If a subject was assigned to a wrong stratification, then the subject was analyzed by the "randomized stratification". Sensitivity analysis of PFS and OS were conducted by "actual stratifications".

Blinding (masking)

The blinding was performed by the Data Management and Statistical Unit during the study treatment. The subjects, Investigators, Sponsor, and designated personnel were blinded for the randomization and treatment allocation. Overall unblinding was performed after the last subject completed the last study visit. Unblinding was performed only in case of emergency (emergency rescue was conducted only if the type of randomized drug received by the subject was known) or as required by regulatory authorities. Otherwise, blinding was maintained. All randomization numbers were unblinded only after all data were entered into the database, all data queries were resolved, and the subjects were included in respective analysis sets.

During the study drug treatment period, if a life-threatening condition determined by Investigator was related to the use of the study drug, or if Investigator considered the known of the subject's drug was helpful for the management of the AE, emergency unblinding was performed. The decision of unblinding in emergency situations was the responsibility of Investigator, and the Sponsor did not delay or reject it. But Investigator contacted the Sponsor or its designated personnel to discuss the unblinding and the most beneficial option for the subject. Investigator ensured that emergency unblinding was performed only under certain circumstances as stipulated in the protocol. Investigator immediately notified the Sponsor of the emergency unblinding and the reason for the unblinding and record these clearly in the subject's source documents. The unblinding process was completed on IWRS/IVRS using the emergency unblinding personal identification number. Unblinding was only performed for the affected subject if required. Subject who was unblinded must discontinue the study drug.

During the treatment period of the investigational products, if a subject developed the first PD, unblinding was performed by Investigator. Subjects who met certain criteria in unblinding proceeded to the next treatment stage.

Statistical methods

The analysis sets for this study were defined as follows:

Intent-to-Treat (ITT) Set: Defined as all randomized subjects of the trial. The ITT population served as the primary analysis population for the efficacy analysis of this study. The ITT set was analyzed based on the randomized treatment groups regardless of the treatment received.

Per Protocol Set (PPS): The per protocol set was a subset of the ITT set. The PPS consisted of all randomized subjects who had at least one post-treatment tumor assessment without major protocol deviations that significantly affected the primary efficacy. PPS-based analysis served as supporting analysis for the ITT-based analysis.

Safety Set (SS): Defined as all subjects who received at least one dose of study drug. The safety analysis population was the primary analysis population for safety endpoints and was analyzed based on the treatment that the subjects actually received.

Pharmacokinetics Set (PKS): All subjects who received at least one dose of serplulimab, had at least one detected concentration measurement after drug administration at the scheduled PK time point, and had no major protocol deviations that significantly impacted PK assessment. PK set was used for PK analysis.

Clinical endpoints of interest:

The primary efficacy endpoint is the PFS assessed by the IRRC based on RECIST 1.1. The PFS were censored based on the following algorithms:

• Subjects alive and progression-free at the end of study or the cut-off date were censored at the day of last effective tumor assessment.

• Subjects who didn’t undergo any tumor assessment during the study and didn’t die at the end of study or the cut-off date were censored on the day of randomization.

• Subjects who had no PD and started anticancer treatment which is not stipulated in the protocol were censored at the day of the last effective tumor assessment before started anticancer treatment.

• Subjects who had a major protocol deviation that was prior to the unblinding and affects the efficacy analysis were censored at the day of the last effective tumor assessment prior to the day of major protocol deviation. The impact of major protocol deviation on efficacy analysis were discussed in the DRM.

• Subjects who had the 1st PD assessed by IRRC after the treatment crossover will be censored at the day of the last effective tumor assessment prior to the day of treatment crossover. This rule only applies to subjects initially assigned to Arm B.

All assessment date were based on the date of scans. In the instance where there are different dates of scans within the same tumor assessment, the response assessment used the last scan date where lesions were defined and an assessment of PD, iCPD or iUPD were dated on the earliest scan date that demonstrates PD.

The comparison of the time-to-event between the two arms was performed by a two-sided stratified log-rank test and the prespecified stratification factors. Time-to-event distributions was estimated using the Kaplan-Meier (KM) product-limit method. If median event time was evaluated, the corresponding two-sided 95% confidence interval (CI) was 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 estimated using Greenwood's formula. The hazard ratio and its 95% CI was estimated by stratified Coxproportional hazards model. Efron's method will be used to handle ties. All CIs were presented to one more decimal place than the point estimate.

For binomial proportions endpoints (e.g., ORR), considering the stratified randomization, the proportion comparison between the two arms was analyzed using the Cochran–Mantel–Haenszel (CMH) statistics. For each single arm, the 95% CI for the proportion was derived using Clopper-Pearson method. The Newcombe approach was used to propose a 95% CI for the proportions difference.

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

Handling of missing data:

For the tumor assessment by Investigator based on iRECIST, if the assessment was missed and prior to the first PD, then the assessment based on iRECIST was imputed with the assessment based on RECIST 1.1. For subjects who withdrew in advance from the study, only the available data were included into the analysis.

The comparison of PFS between the two arms was performed by stratified log-rank test at $\alpha=0.05$ with the stratification factors: PD-L1 expression level (TPS < 1%, 1% ≤ TPS < 50%, TPS ≥50%), Asian population (yes or no), and NSCLC stage (stage IIIB/IIIC or stage IV).

The analysis of primary efficacy endpoint will be using ITT set, and the analysis were repeated on PPS as a supporting analysis.

The OS were censored based on the following algorithms:

• Subjects with no death record will be censored at the last known date of survival.

• Subjects who did not provide any follow-up information will be censored on the date of randomization.

The imputation rules for partial or missing death date:

• If death year and month (yyyymm) are available but day is missing, set death date to the maximum of the first day of the death month or the day after the last date known to be alive .

• If death year is available but month and day are missing, set death date to the maximum of the first day of the death year or the day after the last date known to be alive.

• If death year is totally missing and death is confirmed, set death date to the day after the last date known to be alive.

Statistical methods for OS are the same as those for the primary efficacy endpoint (Analysis set: ITT set).

Since the study will have two interim and one final OS analyses, the significance level will be respectively set as 0.0002, 0.012 and 0.046 for the three OS analyses to control the overall type I error.

On November 1, 2022, a new indication for first-line therapy for Locally Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC), was approved by the National Medical Products Administration of China (NMPA), and the working of maintaining study blinding was completed. In

order to evaluate the robustness of OS results, a sensitivity analysis with Nov 1,2022 as the cutoff date was performed

Interim analyses:

Interim analyses: Two interim analyses and one final analysis for OS were planned to conduct in this study. The first interim analysis of OS was conducted at the final analysis of PFS (at least 218 PFS events were observed), with approximately 99 (33%) OS events were observed.

It was planned that the second interim analysis of OS was conducted after approximately 198 (66%) OS events were observed. The final analysis of OS was conducted after approximately 299 (100%) OS events observed. The first analysis of OS was to take place at the time of PFS final analysis.

If any prior analysis in the order was not statistically significant, then α controlled at 0.05 (two-tailed) was not used for any subsequent analysis. As three analyses for OS were planned, the Lan-DeMets α spending function method with O'Brien-Fleming boundary were used to maintain the total two-tailed type I error at 0.05. The α values for the first and the second interim analysis, and the final analysis for OS were 0.0002, 0.012, and 0.046 (two-tailed).

Quality of Life (QoL) assessment:

QoL of subjects was assessed using EORTC QLQ-LC13 and EORTC QLQ-C30. EORTC QLQ-C30 was used to assess health-related quality of life in subjects with cancer participating in international oncology clinical trials. The instrument with 30 items included a global health status/QoL scale, five functional scales, three symptom scales and six single items. Only two items measured the global health status/QoL ranged from 1 (very poor) to 7 (excellent). The other 28 items were scored on a 4-point scale ranging from 1 (not at all) to 4 (very much). The EORTC QLQ-LC13 included 13 questions assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea and site specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. The module was field tested together with the previous versions of the core questionnaire. A one-week frame was adopted for all items. With the exception of the first item on pain medication, which had dichotomous response categories (no or yes), all items were scored on a 4-point categorical scale ranging from 1 (not at all) to 4 (very much).

Results

Participant flow

Participant flowchart of final analysis as data cutoff January 31, 2023 is shown in Figure 15.

Figure 15. Participant flowchart of final analysis as data cutoff January 31, 2023

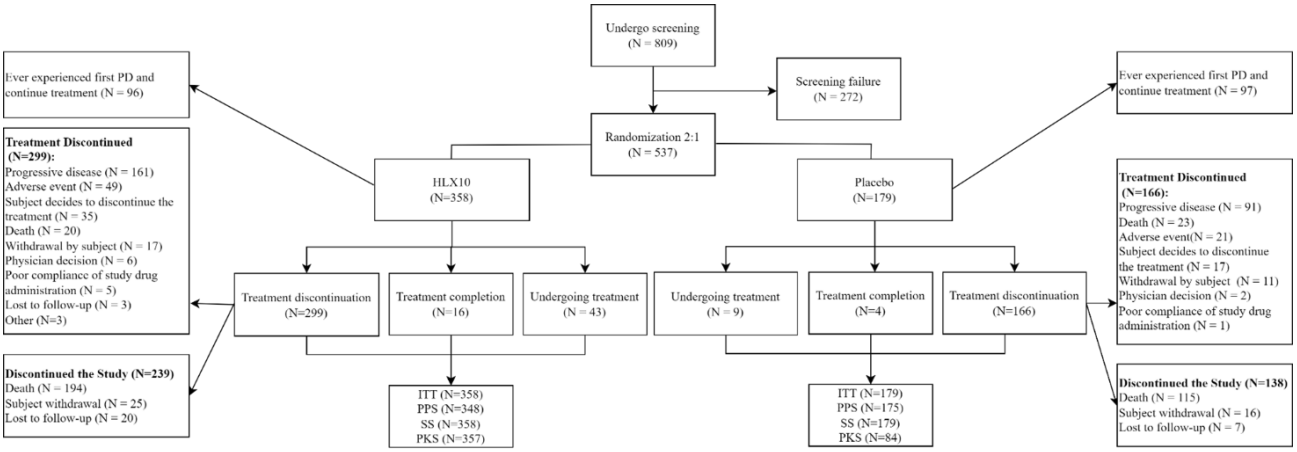


Table 16. Subject disposition (All subjects screened)

	HLX10	Placebo	Total
Screened, n			809
Screen Failed			272
Randomized, n (%)	358 (100.0)	179 (100.0)	537 (100.0)
Did Not Receive Any Treatment, n (%)	0	0	0
Treatment Ongoing, n (%)	43 (12.0)	9 (5.0)	52 (9.7)
Ever Experienced First PD and Continue Treatment, n (%)	96 (26.8)	97 (54.2)	193 (35.9)
Treatment Completed, n (%)	16 (4.5)	4 (2.2)	20 (3.7)

	HLX10	Placebo	Total
Treatment Discontinued, n (%)	299 (83.5)	166 (92.7)	465 (86.6)
Progressive Disease	161 (45.0)	91 (50.8)	252 (46.9)
Poor Compliance of Study Drug Administration	5 (1.4)	1 (0.6)	6 (1.1)
Adverse Event	49 (13.7)	21 (11.7)	70 (13.0)
Death	20 (5.6)	23 (12.8)	43 (8.0)
Protocol Deviation	0	0	0
Withdrawal by Subject	17 (4.7)	11 (6.1)	28 (5.2)
Lost to Follow-Up	3 (0.8)	0	3 (0.6)
Study Terminated by Sponsor	0	0	0
Physician Decision	6 (1.7)	2 (1.1)	8 (1.5)
Pregnancy	0	0	0
Subject Decides to Discontinue the Treatment	35 (9.8)	17 (9.5)	52 (9.7)
Other	3 (0.8)	0	3 (0.6)
Discontinued the Study, n (%)	239 (66.8)	138 (77.1)	377 (70.2)
Death	194 (54.2)	115 (64.2)	309 (57.5)
Lost to Follow-Up	20 (5.6)	7 (3.9)	27 (5.0)
Withdrawal by Subject	25 (7.0)	16 (8.9)	41 (7.6)
Study Terminated by Sponsor	0	0	0
Adverse Event	0	0	0
Other	0	0	0

Note: Percentages were based on the number of subjects randomized.

Table 17. Summary of Reasons for Screen Failure

Screening Failure, n (%)	**272 (100)**
Did not meet eligibility criteria, n (%)	**266 (97.8)**
Unable to provide informed consent or complete all trial procedures	53 (19.5)
Histology or stage of the disease does not meet the protocol	27 (9.9)
Had other factors leading to possible premature discontinuation of the study	24 (8.8)
Did not provide tumor tissue for PD-L1 testing	22 (8.1)
Had an inadequate Eastern Cooperative Oncology Group > 1 score	21 (7.7)
Had inadequate major organ function	17 (6.3)
Had active central nervous system metastases	16 (5.9)
Had an active infection requiring systemic treatment	15 (5.5)
Had hepatitis B infection, hepatitis C infection, or both	13 (4.8)
No measurable target lesion assessed by IRRC according to RECIST1.1	9 (3.3)
NYHA Class III-IV heart failure or LVEF <50%.	8 (2.9)
Not treatment-naive or (neo)adjuvant therapy completed < 6 months prior.	8 (2.9)
Other reasons	33 (12.1)
Exceeded maximum screening period, n (%)	**6 (2.2)**

Recruitment

The study was initiated August 14, 2019 (First Subject Enrolled). Last subject was enrolled February 25, 2021.

A total of 109 study sites were initiated, of which 93 study sites screened subjects. The study recruited patients in Asia, mainly China, and non-Asia. The non-Asian subjects were enrolled at sites in Georgia, Poland, Russia, Turkey, and Ukraine.

Conduct of the study

First interim analysis (final analysis PFS) was conducted at DCO date of March 30, 2021. The final data cut-off date was January 31, 2023, when the final OS analysis was conducted. The final database lock occurred April 12, 2023.

Change in the conduct of the study

The version 1.0 of the protocol was finalized and dated April 4, 2019. The study protocol was revised four times, resulting in a version 2.0 (September 26, 2019), a version 3.0 (April 3, 2020), a version 4.0 (July 8, 2020) and a version 5.0 (December 31, 2021). Major changes in amendments are summarized in the table below.

Table 18. Summary of Protocol Amendments

Version	Date	Key changes
Amendment 01 from Version 1.0 to 2.0	September 26, 2019	• Added evaluation of pharmacokinetics, immunogenicity, and biomarkers as secondary objectives, secondary endpoints including OS, PFS, ORR, DOR, and safety. • Specified a blinded interim analysis, including blinded sample collection/analysis, The role of IDMC for interim analysis was also added. • Defined that PFS will be assessed by both investigators and an IRRC per iRECIST. • Updated the carboplatin dosage to AUC 5 or 6. • Defined study termination/withdrawal criteria and the "end of study." Added procedures for handling subjects lost to follow-up.
Amendment 02 from Version 2.0 to 3.0	April 3, 2020	• Set overall survival (OS) as a key secondary endpoint. Re-estimated the sample size based on OS. Finalized the timing of the interim and final analysis. • Added neutralizing antibody to the immunogenicity assessment. Added EORTC QLQ-C30 to the quality-of-life assessment. • The carboplatin dosage "AUC 5 or 6" has been incorporated as a stratification factor. • Confirmed that the IDMC will evaluate both safety, efficacy and the subjects' benefit and risk.
Amendment 03 from Version 3.0 to 4.0	July 8, 2020	• Removed "Carboplatin AUC (5 or 6)" from stratification factors. • Clarified interim analysis of OS and redefined the end of study. • Updated the risk information reported in Investigator's Brochure. Clarified dose modification for other toxicities. Added guideline for management of myocarditis to Appendix.
Amendment 04 from Version 4.0 to 5.0	December 31, 2021	• The HLX10 treatment duration has been updated from "for up to 2 years" to "until loss of clinical benefit".

Changes in the conduct of the planned analysis

The statistical analysis plan (SAP) version 1.0 was finalized and dated on May 25, 2021. The SAP was revised once, resulting in version 2.0 (April 7, 2023).

Major Changes from Version 1.0 (May 25, 2021) to 2.0 (April 7, 2023) of the SAP:

- Updated the imputation rules for partial or missing death dates.
- Updated the censor rules for iPFS.
- Added sensitivity analysis for OS.

Protocol deviations

Table 19. Major protocol deviations (ITT)

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Subjects with at Least One Major Protocol Deviation, n (%) [1]	311 (86.9)	142 (79.3)	453 (84.4)
AE/SAE [2]	23 (7.4)	8 (5.6)	31 (6.8)
Disallowed Medications [2]	4 (1.3)	6 (4.2)	10 (2.2)
Inc/Excl Criteria [2]	8 (2.6)	2 (1.4)	10 (2.2)
Informed Consent [2]	23 (7.4)	9 (6.3)	32 (7.1)
IP Admin/Study Treat [2]	135 (43.4)	63 (44.4)	198 (43.7)
Other [2]	13 (4.2)	3 (2.1)	16 (3.5)
Procedures/Tests [2]	254 (81.7)	111 (78.2)	365 (80.6)
Visit Schedule [2]	150 (48.2)	52 (36.6)	202 (44.6)
Withdrawal Criteria [2]	1 (0.3)	2 (1.4)	3 (0.7)

[1] All the percentages were calculated with ITT subjects as denominators.
[2] All the percentages were calculated with ITT subjects having any major protocol deviations as denominators.

The details of three most common reasons for major protocol deviations including procedure/test, visit schedule, and IP admin/study treatment are listed in **Table** 20.

Table 20. The most frequent protocol deviations (≥10%) of procedure/test, IP admin/study treatment and visit schedule (ITT, Cutoff on 31Jan2023)

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Number of Subjects with at Least One Major Protocol Deviations, n (%)	311 (86.9)	142 (79.3)	453 (84.4)
PROCEDURES/TESTS	254 (70.9)	111 (62.0)	365 (68.0)
Tumor assessment is not performed after first PD.	52 (14.5)	24 (13.4)	76 (14.2)
Single tumor assessment is not performed before first PD.	47 (13.1)	19 (10.6)	66 (12.3)
Tumor assessment is performed 15-21 days out of window.	42 (11.7)	20 (11.2)	62 (11.5)
12-lead ECG is not performed at scheduled visits.	41 (11.5)	19 (10.6)	60 (11.2)
Endocrine Function Tests are not performed at scheduled visits.	39 (10.9)	19 (10.6)	58 (10.8)
Lab Assessment (Chemistry, Hematology, Urinalysis, Coagulation) is not performed at scheduled visits.	35 (9.8)	22 (12.3)	57 (10.6)
PK Sample Collection is not performed at scheduled visits.	39 (10.9)	16 (8.9)	55 (10.2)
Immunogenicity Sample Collection is not performed at scheduled visits.	37 (10.3)	16 (8.9)	53 (9.9)
Cardias Function is not performed at scheduled visits.	36 (10.1)	17 (9.5)	53 (9.9)
VISIT SCHEDULE	150 (41.9)	52 (29.1)	202 (37.6)
End of treatment visit is not done	79 (22.1)	23 (12.8)	102 (19.0)
Scheduled visit during treatment period is not done.	59 (16.5)	21 (11.7)	80 (14.9)
Safety follow-up visit_30 days is not done	43 (12.0)	13 (7.3)	56 (10.4)
IP admin/study treatment	135 (37.7)	63 (35.2)	198 (36.9)
HLX10/Placebo/Combined chemotherapy skipped.	45 (12.6)	25 (14.0)	70 (13.0)
nab-Paclitaxel on Day 8 and Day 15 is administered out of window following Protocol version 3.0.	37 (10.3)	20 (11.2)	57 (10.6)

Baseline data

Table 21. Demographics (ITT)

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Age at Screening (years)			
n	358	179	537
Mean (SD)	62.5 (7.86)	62.3 (8.08)	62.5 (7.93)
Median (Q1, Q3)	63.0 (57.0, 69.0)	63.0 (57.0, 68.0)	63.0 (57.0, 68.0)
Min, Max	41, 81	35, 86	35, 86
Sex, n (%)			
Male	321 (89.7)	167 (93.3)	488 (90.9)
Female	37 (10.3)	12 (6.7)	49 (9.1)
Fertile [1]	1 (2.7)	3 (25.0)	4 (8.2)
Non-Fertile [1]	36 (97.3)	9 (75.0)	45 (91.8)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	240 (67.0)	119 (66.5)	359 (66.9)
Black or African American	0	0	0
Native Hawaiian or the Pacific Islander	0	0	0
White	118 (33.0)	60 (33.5)	178 (33.1)
Other	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	358 (100.0)	179 (100.0)	537 (100.0)
Other	0	0	0
Height (cm)			
n	354	179	533
Mean (SD)	168.0 (7.84)	168.8 (7.02)	168.3 (7.58)
Median (Q1, Q3)	169.0 (163.0, 173.0)	170.0 (164.0, 174.0)	169.0 (164.0, 173.0)
Min, Max	143, 191	143, 186	143, 191
Weight (kg)			
n	357	179	536
Mean (SD)	66.5 (14.21)	65.7 (14.09)	66.2 (14.16)
Median (Q1, Q3)	65.0 (56.0, 75.4)	64.0 (55.5, 76.0)	64.9 (55.8, 75.8)
Min, Max	38, 131	36, 121	36, 131
BMI (kg/m^2)			
n	353	179	532
Mean (SD)	23.49 (4.199)	22.96 (4.190)	23.31 (4.200)
Median (Q1, Q3)	23.00 (20.50, 25.80)	22.10 (20.00, 25.10)	22.80 (20.40, 25.65)
Min, Max	15.6, 41.3	15.2, 39.6	15.2, 41.3
Baseline ECOG PS, n (%)			
Total	358	179	537
0	65 (18.2)	26 (14.5)	91 (16.9)
1	293 (81.8)	153 (85.5)	446 (83.1)

[1] All the percentages were calculated with ITT female subjects.

Table 22. Baseline characteristics (ITT)

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Time since NSCLC First Diagnosed (month) [1]			
n	354	177	531
Mean (SD)	2.54 (7.43)	1.79 (5.81)	2.29 (6.94)
Median (Q1, Q3)	0.41 (0.16, 1.15)	0.36 (0.20, 0.99)	0.39 (0.16, 1.05)
Min, Max	−0.16, 74.55	0.00, 55.06	−0.16, 74.55
< 6 months	323 (90.2)	167 (93.3)	490 (91.2)
≥ 6 months	31 (8.7)	10 (5.6)	41 (7.6)
Type of Initial Diagnosis, n (%)			
Squamous cell carcinoma	353 (98.6)	175 (97.8)	528 (98.3)
Large cell carcinoma	0	0	0
Adenocarcinoma	2 (0.6)	0	2 (0.4)
Adenosquamous	1 (0.3)	1 (0.6)	2 (0.4)
Other	2 (0.6)	3 (1.7)	5 (0.9)
Echocardiogram, n (%)			
Normal	140 (39.1)	60 (33.5)	200 (37.2)
Abnormal, Clinically Significant	17 (4.7)	12 (6.7)	29 (5.4)
Abnormal, Not Clinically Significant	201 (56.1)	107 (59.8)	308 (57.4)
LVEF			
n	358	179	537
Mean (SD)	62.9 (5.89)	62.6 (5.38)	62.8 (5.72)
Median (Q1, Q3)	62.3 (59.0, 66.1)	62.0 (60.0, 66.0)	62.0 (59.0, 66.0)
Min, Max	50, 85	50, 77	50, 85
EGFR, n (%)			
ND	324 (90.5)	159 (88.8)	483 (89.9)
Positive	0	0	0
Negative	29 (8.1)	19 (10.6)	48 (8.9)
Not Assessable	5 (1.4)	1 (0.6)	6 (1.1)
ALK, n (%)			
ND	324 (90.5)	159 (88.8)	483 (89.9)
Positive	0	0	0
Negative	26 (7.3)	18 (10.1)	44 (8.2)
Not Assessable	8 (2.2)	2 (1.1)	10 (1.9)
ROS1, n (%)			
ND	324 (90.5)	159 (88.8)	483 (89.9)
Positive	0	0	0
Negative	26 (7.3)	18 (10.1)	44 (8.2)
Not Assessable	8 (2.2)	2 (1.1)	10 (1.9)
MSI Biomarker, n (%)			
MSS	199 (55.6)	98 (54.7)	297 (55.3)
MSI-L	12 (3.4)	4 (2.2)	16 (3.0)
MSI-H	5 (1.4)	1 (0.6)	6 (1.1)
TMB Biomarker			
n	216	103	319

Table 23. Randomization strata (All randomized subjects)

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
PD-L1 Expression Level, n (%)			
TPS ≥ 50%	104 (29.1)	53 (29.6)	157 (29.2)
50% > TPS ≥ 1%	119 (33.2)	58 (32.4)	177 (33.0)
TPS < 1%	135 (37.7)	68 (38.0)	203 (37.8)
Asian Population, n (%)			
Yes	240 (67.0)	119 (66.5)	359 (66.9)
No	118 (33.0)	60 (33.5)	178 (33.1)
NSCLC Stage, n (%)			
Stage IIIB/IIIC	103 (28.8)	49 (27.4)	152 (28.3)
Stage IV	255 (71.2)	130 (72.6)	385 (71.7)

Note: Percentages were based on the number of subjects randomized

Table *24*. Country by Race (All randomized subjects)

Race Country	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Asian			
China	240 (67.0)	119 (66.5)	359 (66.9)
White			
Georgia	40 (11.2)	20 (11.2)	60 (11.2)
Poland	1 (0.3)	1 (0.6)	2 (0.4)
Russian Federation	14 (3.9)	10 (5.6)	24 (4.5)
Turkey	32 (8.9)	20 (11.2)	52 (9.7)
Ukraine	31 (8.7)	9 (5.0)	40 (7.4)

Source: Listing 16.2.3.3
Note: Percentages were based on the number of subjects randomized.
[SOURCE: E:\sasserver\projects\hlx10nsclc303\interim\prog\tables\en\t_adsl_race.sas] (EDC Date: 12APR2023, Output

The proportion of patients with brain metastases at baseline was 5.6% and 10.1% in the serplulimab and placebo arm, respectively.

The proportion of patients in different age groups in each treatment arm is presented in Table 25.

The proportion of patients who received carboplatin dose of AUC5 and AUC6 was 87.9% and 12.1%, respectively.

Table *25*. Proportion of Patients in Different Age Groups (ITT)

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
<65 years, n(%)	204 (57.0)	106 (59.2)	310 (57.7)
≥65 years, n(%)	154 (43.0)	73 (40.8)	227 (42.3)
<75 years, n(%)	336 (93.9)	173 (96.6)	509 (94.8)
≥75 years, n(%)	22 (6.1)	6 (3.4)	28 (5.2)

Treatment

The extent of exposure to serplulimab/placebo, carboplatin and nab-paclitaxel for each arm is shown in Table 26, Table 27 and Table 28, respectively.

Table 26. Extent of exposure – serplulimab/placebo

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Cumulative Total Number of Treatment Cycles			
n	358	179	537
Mean (SD)	14.0 (12.14)	7.8 (6.61)	12.0 (11.01)
Median	9.0	6.0	8.0
Q1, Q3	4.0, 23.0	4.0, 9.0	4.0, 16.0
Min, Max	1, 46	1, 35	1, 46
Actual Cumulative Total Dose Received (mg) [1]			
n	358	179	537
Mean (SD)	4252.229 (3886.2006)	2367.284 (2162.9877)	3623.914 (3521.8882)
Median	2833.500	1758.000	2259.200
Q1, Q3	1237.500, 6120.000	936.000, 2808.000	1080.000, 5040.000
Min, Max	211.50, 18018.00	162.00, 11895.00	162.00, 18018.00
Planned Cumulative Total Dose (mg) [2]			
n	358	179	537
Mean (SD)	4259.261 (3895.2474)	2371.814 (2163.4729)	3630.112 (3528.9351)
Median	2833.500	1764.000	2277.450
Q1, Q3	1237.500, 6120.000	936.000, 2848.500	1080.000, 5040.000
Min, Max	211.50, 18018.00	162.00, 11900.00	162.00, 18018.00
Actual Duration of Exposure (Weeks) [3]			
n	358	179	537
Mean (SD)	45.11 (43.157)	22.77 (22.034)	37.67 (38.896)
Median	28.29	18.14	23.14
Q1, Q3	11.43, 70.14	9.14, 27.71	10.14, 51.14
Min, Max	0.1, 168.4	0.1, 139.3	0.1, 168.4
Planned Duration of Exposure (Weeks) [4]			
n	358	179	537
Mean (SD)	39.41 (36.467)	20.67 (19.856)	33.17 (33.088)
Median	24.14	15.14	21.14
Q1, Q3	9.14, 66.14	9.14, 24.14	9.14, 45.14
Min, Max	0.1, 135.1	0.1, 102.1	0.1, 135.1
Actual Dose Intensity (mg/week) [5]			
n	358	179	537
Mean (SD)	244.14 (520.019)	254.35 (536.762)	247.55 (525.180)
Median	100.55	109.13	103.67
Q1, Q3	84.16, 124.35	90.88, 136.08	85.75, 129.94
Min, Max	34.8, 3118.5	44.3, 3811.5	34.8, 3811.5
Planned Dose Intensity (mg/week) [6]			
n	358	179	537
Mean (SD)	256.57 (516.692)	265.55 (533.690)	259.57 (521.938)
Median	115.06	119.19	116.94
Q1, Q3	97.62, 140.12	100.65, 147.66	98.44, 143.33
Min, Max	37.3, 3118.5	68.1, 3811.5	37.3, 3811.5
Relative Dose Intensity (%) [7]			
n	358	179	537
Mean (SD)	89.52 (11.601)	91.06 (10.925)	90.04 (11.393)
Median	93.57	94.87	93.81
Q1, Q3	84.07, 98.79	86.00, 99.84	84.80, 99.28
Min, Max	45.0, 115.8	43.4, 104.9	43.4, 115.8

Table 27. Extent of exposure - carboplatin

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Cumulative Total Number of Treatment Cycles			
n	358	179	537
Mean (SD)	4.1 (1.47)	3.9 (1.43)	4.1 (1.46)
Median	4.0	4.0	4.0
Q1, Q3	4.0, 5.0	3.0, 5.0	3.0, 5.0
Min, Max	0, 6	1, 7	0, 7
Actual Cumulative Total Dose Received (mg) [1]			
n	358	179	537
Mean (SD)	2346.804 (1042.9447)	2223.854 (1032.7511)	2305.821 (1040.2131)
Median	2264.000	2107.000	2206.900
Q1, Q3	1685.000, 2968.700	1500.000, 2839.900	1605.000, 2922.100
Min, Max	0.00, 5400.00	400.00, 5250.00	0.00, 5400.00
Planned Cumulative Total Dose (mg) [2]			
n	358	179	537
Mean (SD)	2350.494 (1039.4150)	2224.911 (1032.7611)	2308.633 (1037.9307)
Median	2263.580	2107.000	2206.900
Q1, Q3	1685.000, 2968.700	1500.000, 2839.900	1605.000, 2922.100
Min, Max	315.00, 5400.00	400.00, 5250.00	315.00, 5400.00
Actual Duration of Exposure (Weeks) [3]			
n	358	179	537
Mean (SD)	11.61 (5.696)	10.70 (5.249)	11.31 (5.563)
Median	11.36	10.71	11.29
Q1, Q3	9.14, 15.57	8.43, 15.14	9.14, 15.29
Min, Max	0.1, 31.3	0.1, 23.0	0.1, 31.3
Planned Duration of Exposure (Weeks) [4]			
n	358	179	537
Mean (SD)	9.97 (4.688)	9.38 (4.635)	9.77 (4.674)
Median	9.14	9.14	9.14
Q1, Q3	9.14, 15.14	6.14, 12.14	9.14, 15.14
Min, Max	0.1, 30.1	0.1, 21.1	0.1, 30.1
Actual Dose Intensity (mg/week) [5]			
n	358	179	537
Mean (SD)	478.88 (978.681)	531.57 (1117.202)	496.44 (1026.187)
Median	213.71	215.28	214.34
Q1, Q3	167.51, 274.03	168.04, 280.35	168.04, 274.23
Min, Max	0.0, 5250.0	67.7, 6069.7	0.0, 6069.7
Planned Dose Intensity (mg/week) [6]			
n	358	179	537
Mean (SD)	518.92 (997.976)	556.97 (1110.240)	531.60 (1035.866)
Median	243.87	246.04	244.19
Q1, Q3	201.61, 296.95	196.98, 302.56	199.85, 297.17
Min, Max	67.3, 5250.0	73.6, 6069.7	67.3, 6069.7
Relative Dose Intensity (%) [7]			
n	358	179	537
Mean (SD)	88.47 (13.424)	89.61 (11.993)	88.85 (12.965)
Median	92.75	92.75	92.75
Q1, Q3	81.73, 99.54	84.13, 100.00	82.05, 99.79
Min, Max	0.0, 115.8	43.9, 104.8	0.0, 115.8

Table 28. Extent of exposure – nab-paclitaxel

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Cumulative Total Number of Treatment Cycles			
n	358	179	537
Mean (SD)	4.3 (1.49)	4.1 (1.53)	4.2 (1.50)
Median	4.0	4.0	4.0
Q1, Q3	4.0, 6.0	3.0, 5.0	4.0, 6.0
Min, Max	1, 7	1, 8	1, 8

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Actual Cumulative Total Dose Received (mg) [1]			
n	358	179	537
Mean (SD)	1815.121 (845.2018)	1768.327 (864.2870)	1799.523 (851.0908)
Median	1739.100	1705.000	1734.000
Q1, Q3	1294.000, 2296.000	1217.000, 2295.500	1265.000, 2295.500
Min, Max	146.00, 4273.00	147.00, 4600.00	146.00, 4600.00
Planned Cumulative Total Dose (mg) [2]			
n	358	179	537
Mean (SD)	1816.436 (845.7644)	1768.822 (864.7101)	1800.565 (851.6157)
Median	1741.500	1705.000	1735.000
Q1, Q3	1294.000, 2296.000	1217.830, 2295.500	1265.000, 2295.500
Min, Max	146.00, 4273.00	147.00, 4600.00	146.00, 4600.00
Actual Duration of Exposure (Weeks) [3]			
n	358	179	537
Mean (SD)	13.07 (5.854)	12.37 (5.454)	12.84 (5.729)
Median	12.71	12.86	12.71
Q1, Q3	10.29, 17.29	9.57, 16.71	10.29, 17.14
Min, Max	0.1, 33.3	0.1, 25.1	0.1, 33.3
Planned Duration of Exposure (Weeks) [4]			
n	358	179	537
Mean (SD)	11.38 (4.896)	11.01 (4.897)	11.26 (4.895)
Median	11.14	11.14	11.14
Q1, Q3	9.14, 16.14	9.14, 15.14	9.14, 15.14
Min, Max	0.1, 32.1	0.1, 23.1	0.1, 32.1
Actual Dose Intensity (mg/week) [5]			
n	358	179	537
Mean (SD)	172.66 (163.539)	175.19 (164.856)	173.50 (163.830)
Median	142.59	148.03	145.23
Q1, Q3	114.24, 181.68	117.21, 181.65	115.91, 181.65
Min, Max	43.3, 1435.0	44.8, 1393.0	43.3, 1435.0
Planned Dose Intensity (mg/week) [6]			
n	358	179	537

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Mean (SD)	189.10 (159.721)	190.68 (161.817)	189.63 (160.273)
Median	163.30	164.40	163.57
Q1, Q3	140.16, 195.34	139.60, 197.46	140.16, 195.34
Min, Max	48.5, 1435.0	48.6, 1390.0	48.5, 1435.0
Relative Dose Intensity (%) [7]			
n	358	179	537
Mean (SD)	89.43 (11.839)	90.36 (10.835)	89.74 (11.512)
Median	93.36	93.42	93.42
Q1, Q3	82.61, 99.17	84.33, 99.26	83.46, 99.17
Min, Max	42.8, 109.1	50.9, 104.8	42.8, 109.1

[1] Actual cumulative total dose received = summation of all actual dose administrated from the first dosing date to the last dosing date.

[2] Planned cumulative total dose received = summation of all planned dose from the first dosing date to the planned dosing date.

[3] Actual Duration of Exposure (weeks) = (date of last dose – date of first dose + 1) / 7

[4] Planned Duration of Exposure (weeks) = ((the number of cycles-1)*21+days) / 7

[5] Actual Dose Intensity= (Actual cumulative total dose received) / (Actual duration of exposure)

[6] Planned Dose Intensity = (Planned cumulative total dose received) / (Planned duration of exposure)

[7] Relative Dose Intensity = 100 * (Average Dose Intensity) / (Planned Dose Intensity)

Numbers analysed

The analysis sets are summarized in Table 29.

Table 29. Analysis sets by treatment group (all randomized subjects)

	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Subjects Randomized, n	358	179	537
Intent-to-Treat Set (ITT), n (%)	358 (100.0)	179 (100.0)	537 (100.0)
Per Protocol Set (PPS), n (%)	348 (97.2)	175 (97.8)	523 (97.4)
Reason for Exclusion from PPS, n (%)			
Not Treated	0	0	0
No Post-Treatment Tumor Assessment	8 (2.2)	4 (2.2)	12 (2.2)
Major Protocol Deviation affecting analysis [1]	2 (0.6)	0	2 (0.4)
Inc/Excl Criteria	2 (0.6)	0	2 (0.4)
Safety Set (SS), n (%)	358 (100.0)	179 (100.0)	537 (100.0)
Reason for Exclusion from SS, n (%)			
Not Treated	0	0	0
Pharmacokinetic Set (PKS), n (%)	357 (99.7)	84 (46.9)	441 (82.1)
Reason for Exclusion from PKS, n (%)			
Not Treated by HLX10	0	82 (45.8)	82 (15.3)
No Post-Treatment Detected Concentration	1 (0.3)	13 (7.3)	14 (2.6)

Note: Percentages were based on the number of subjects randomized.

[1] Major protocol deviations that significantly affect evaluation of primary efficacy were defined in Data Review Meeting.

Outcomes and estimation

Primary endpoint - PFS assessed by IRRC based on RECIST 1.1

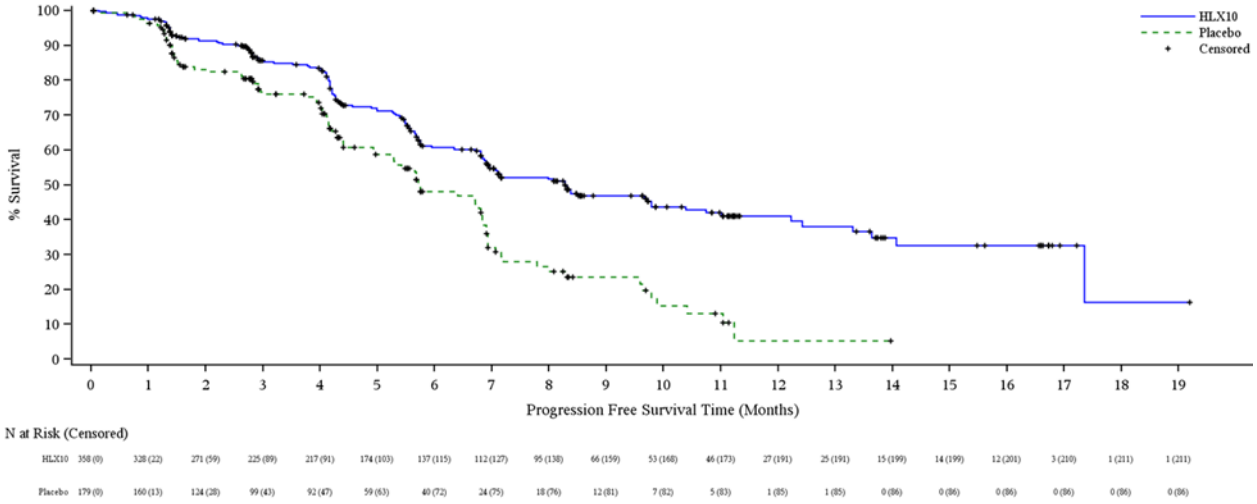
The first interim analysis (final analysis of PFS) was conducted when at least 218 PFS events were observed (actual 239 PFS events) at the data cut-off date of March 30, 2021. PFS assessed by IRRC based on RECIST 1.1 in the ITT is shown in Table 30. The corresponding Kaplan-Meier (KM) curve is shown in Figure 16.

Table 30. Analysis of PFS (RECIST 1.1) by IRRC (ITT Set) at the final PFS analysis (DCO March 30, 2021)

Characteristics	Serplulimab (N=358)	Placebo (N=179)	Total (N=537)
Number of Event (PD/Deaths), n (%)	146 (40.8)	93 (52.0)	239 (44.5)
Progression	114 (31.8)	73 (40.8)	187 (34.8)
Deaths	32 (8.9)	20 (11.2)	52 (9.7)
Number of Censor, n (%)	212 (59.2)	86 (48.0)	298 (55.5)
No Baseline or Post Baseline	20 (5.6)	12 (6.7)	32 (6.0)
No Progression and No Death	170 (47.5)	37 (20.7)	207 (38.5)
New Anti-cancer Treatment Started Prior to Documented Disease Progression or Death on Study	22 (6.1)	10 (5.6)	32 (6.0)
Major Protocol Deviation Occurred Prior to Unblinding	0	0	0
Treatment Switched from Placebo to Serplulimab		27 (15.1)	27 (5.0)
Progression Free Survival (Months)			
Median (95% CI) [1]	8.28 (6.90, 10.38)	5.72 (5.22, 6.83)	6.93 (6.77, 7.98)
Min, Max	0.0, 19.2	0.0, 14.0	0.0, 19.2
Stratified [2]			
Hazard Ratio (95% CI) [3]	0.55 (0.42, 0.73)		
p-Value [4]	< 0.001		
PFS Rate (95% CI) at [5]			
3 Months	0.857 (0.812, 0.892)	0.760 (0.683, 0.820)	0.825 (0.786, 0.857)
6 Months	0.607 (0.544, 0.663)	0.482 (0.387, 0.570)	0.567 (0.515, 0.615)
9 Months	0.469 (0.402, 0.532)	0.236 (0.152, 0.331)	0.401 (0.347, 0.455)
12 Months	0.411 (0.341, 0.480)	0.052 (0.006, 0.179)	0.315 (0.258, 0.375)
15 Months	0.326 (0.240, 0.414)	- (-, -)	0.251 (0.185, 0.323)

[1] The Brookmeyer-Crowley method was used to construct the 95% CI for the median PFS.
[2] Stratification factor: PD-L1 expression level (TPS < 1%, 1% ≤ TPS < 50% or TPS ≥ 50%), Asian population (yes or no) and NSCLC stage (Stage IIIB/IIIC or Stage IV).
[3] The hazard ratio and its 95% CI were estimated by (stratified) Cox proportional hazards model. Efron's method was used to handle ties.
[4] The comparison of PFS between the two arms was performed by a two-tailed stratified log-rank test with significant level at 0.05.
[5] The standard error of the PFS rate was calculated using Greenwood's formula.

Figure 16. Kaplan-Meier Curve of PFS (RECIST 1.1) by IRRC (ITT Set) at the final PFS analysis (DCO March 30, 2021)



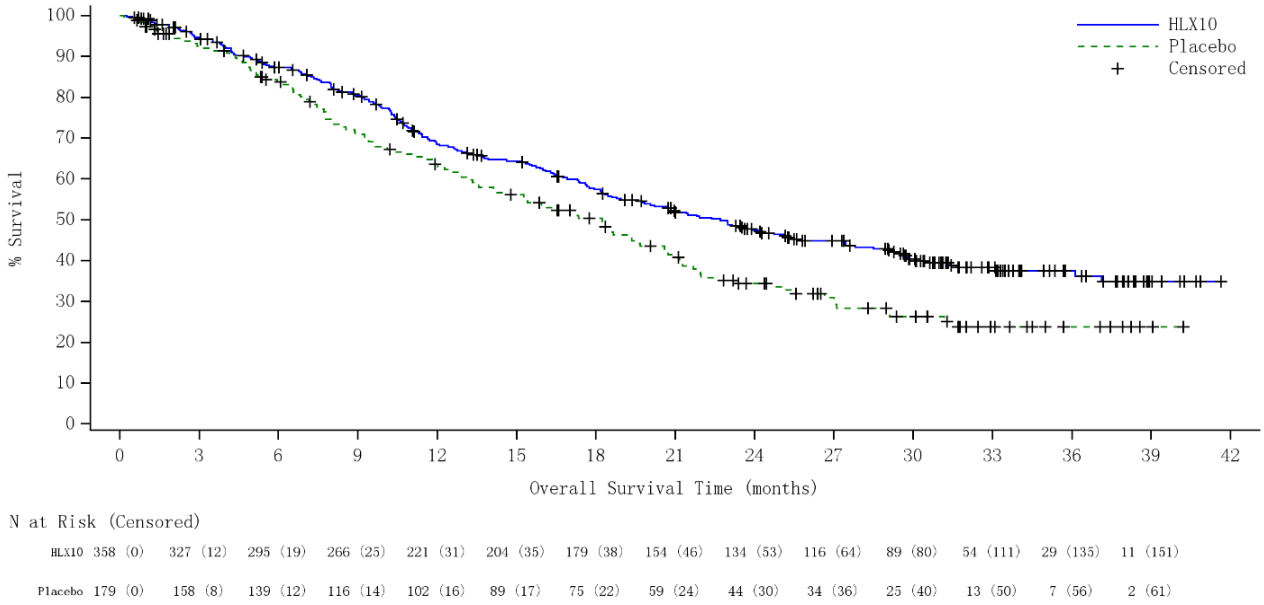
Secondary endpoint – OS

The final analysis of OS was conducted when 100% (approximately 299) of OS events were observed (actual 312 OS events) at the data cut-off date of January 31, 2023. Analysis of OS (ITT set) is presented in Table 31 and the corresponding KM curve is shown in figure 17.

Table 31. Analysis of OS (ITT set) from final OS analysis (DCO January 31, 2023)

Characteristics	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Number of Event (Deaths), n (%)	196 (54.7)	116 (64.8)	312 (58.1)
Number of Censor, n (%)	162 (45.3)	63 (35.2)	225 (41.9)
Alive	111 (31.0)	36 (20.1)	147 (27.4)
Lost to Follow-up	51 (14.2)	27 (15.1)	78 (14.5)
Overall Survival (Months)			
Median (95% CI) [1]	22.70 (18.60, 27.40)	18.23 (14.13, 20.60)	20.24 (18.23, 22.37)
Min, Max	0.3, 41.6	0.2, 40.2	0.2, 41.6
Stratified [2]			
Hazard Ratio (95% CI) [3]	0.73 (0.58, 0.93)		
p-Value [4]	0.010		
Survival Rate at [5]			
3 Months	0.946 (0.916, 0.965)	0.926 (0.875, 0.956)	0.939 (0.915, 0.956)
6 Months	0.873 (0.833, 0.904)	0.837 (0.773, 0.884)	0.861 (0.828, 0.888)
9 Months	0.804 (0.757, 0.842)	0.709 (0.634, 0.772)	0.772 (0.734, 0.807)
12 Months	0.684 (0.632, 0.731)	0.635 (0.557, 0.703)	0.668 (0.625, 0.708)
15 Months	0.644 (0.590, 0.693)	0.561 (0.481, 0.632)	0.616 (0.572, 0.657)
18 Months	0.574 (0.518, 0.625)	0.503 (0.424, 0.577)	0.550 (0.505, 0.593)
21 Months	0.518 (0.462, 0.571)	0.407 (0.330, 0.483)	0.482 (0.437, 0.526)
24 Months	0.474 (0.418, 0.528)	0.344 (0.270, 0.419)	0.432 (0.386, 0.476)
27 Months	0.449 (0.393, 0.503)	0.310 (0.237, 0.386)	0.404 (0.359, 0.448)
30 Months	0.403 (0.348, 0.459)	0.263 (0.192, 0.339)	0.358 (0.314, 0.403)
33 Months	0.382 (0.326, 0.438)	0.237 (0.167, 0.315)	0.336 (0.291, 0.382)

Figure 17. KM curve of OS (ITT set) from final OS analysis (DCO January 31, 2023)



Other secondary endpoints

PFS assessed by investigator based on RECIST 1.1, PFS assessed by IRRC based on iRECIST and PFS assessed by investigator based on iRECIST are shown in Table 32.

Table 32: Other secondary efficacy endpoints

Endpoint	Statistics	Serplulimab (N=358)	Placebo (N=179)
PFS Based on RECIST 1.1 (months)			
By Investigator Assessment	Median (95% CI)	8.28 (7.10, 9.53)	5.55 (4.40, 5.75)
	Stratified HR (95% CI)	0.47 (0.37, 0.60)	
	P value	< 0.001	
PFS Based on iRECIST (months)			
By IRRC Assessment	Median (95% CI)	12.42 (9.69, -)	5.72 (5.22, 6.83)
	Stratified HR (95% CI)	0.41 (0.31, 0.55)	
	P value	< 0.001	
By Investigator Assessment	Median (95% CI)	17.35 (11.93, -)	5.55 (4.40, 5.75)
	Stratified HR (95% CI)	0.22 (0.16, 0.30)	
	P value	< 0.001	

Abbreviations: CI=confidence interval, CR=complete response, DOR=duration of response, HR=hazard ratio, iRECIST=modified RECIST 1.1 for immune-based therapeutics, IRRC=Independent Radiology Review Committee, ORR=objective response rate, OS=overall survival, PFS=progression-free survival, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors.

The confirmed best overall response assessed by IRRC based on RECIST 1.1 in the ITT set is shown in Table 33. The confirmed DOR assessed by IRRC based on RECIST 1.1 in the ITT set is shown in Table 34.

Table 33: Confirmed Best Overall Response (RECIST 1.1) by IRRC (ITT set) at DCO January 31, 2023.

Characteristics	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Best Overall Response, n (%)			
CR	12 (3.4)	1 (0.6)	13 (2.4)
PR	203 (56.7)	72 (40.2)	275 (51.2)
SD	85 (23.7)	62 (34.6)	147 (27.4)
PD	26 (7.3)	23 (12.8)	49 (9.1)
NE or NA	32 (8.9)	21 (11.7)	53 (9.9)
Objective Response Rate (CR+PR), n (%) [1]	215 (60.1)	73 (40.8)	288 (53.6)
95% CI (%) [2]	(54.8, 65.2)	(33.5, 48.4)	(49.3, 57.9)
Odds Ratio (95% CI) [3]	2.24 (1.54, 3.26)		
Stratified difference and 95% CI [4]	19.07 (10.11, 27.60)		
CMH Test P-value [4]	< 0.001		

Note: CR= Complete Response; PR= Partial Response; SD= Stable Disease; PD= Progressive Disease; NA= Not Applicable; NE= Not Evaluable.
[1] Stratification factor: PD-L1 expression level (TPS < 1%, 1% ≤ TPS < 50% or TPS ≥ 50%), Asian population (yes or no) and NSCLC stage (Stage IIIB/IIIC or Stage IV).
[2] Clopper-Pearson method.
[3] The odds ratio of ORR and its 95% CI were estimated by the Cochran-Mantel-Heanszel statistics.
[4] Stratified difference, its 95% CI and p-value are calculated from a stratified CMH with stratification factors.

Table 34: Analysis of Confirmed Duration of Response (RECIST 1.1) by IRRC (ITT set) at DCO January 31, 2023.

Characteristics	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Subjects with CR or PR	215	73	288
Number of Event (PD/Deaths), n (%)	127 (59.1)	46 (63.0)	173 (60.1)
Progression	111 (51.6)	42 (57.5)	153 (53.1)
Deaths	16 (7.4)	4 (5.5)	20 (6.9)
Number of Censor, n (%)	88 (40.9)	27 (37.0)	115 (39.9)
No Progression and No Death	65 (30.2)	6 (8.2)	71 (24.7)
New Anti-cancer Treatment Started Prior to Documented Disease Progression or Death on Study	23 (10.7)	4 (5.5)	27 (9.4)
Major Protocol Deviation Occurred Prior to Unblinding	0	0	0
Treatment Switched from Placebo to HLX10		17 (23.3)	17 (5.9)
Duration of Response (Months)			

Characteristics	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Median (95% CI) [1]	11.07 (8.31, 15.44)	5.52 (5.29, 7.06)	8.48 (7.00, 10.15)
Min, Max	1.0, 39.9	1.4, 30.0	1.0, 39.9
Stratified [2]			
Hazard Ratio (95% CI) [3]	0.45 (0.32, 0.65)		
p-Value [4]	< 0.001		
DOR Rate (95% CI) at [5]			
3 Months	0.899 (0.849, 0.933)	0.854 (0.738, 0.921)	0.888 (0.844, 0.921)
6 Months	0.665 (0.595, 0.725)	0.416 (0.285, 0.541)	0.611 (0.549, 0.668)
9 Months	0.552 (0.480, 0.619)	0.228 (0.124, 0.351)	0.484 (0.421, 0.545)
12 Months	0.478 (0.406, 0.547)	0.152 (0.066, 0.271)	0.411 (0.348, 0.472)
15 Months	0.449 (0.377, 0.518)	0.122 (0.045, 0.239)	0.382 (0.320, 0.444)
18 Months	0.393 (0.322, 0.463)	0.122 (0.045, 0.239)	0.336 (0.276, 0.398)
21 Months	0.359 (0.289, 0.430)	0.122 (0.045, 0.239)	0.309 (0.249, 0.370)
24 Months	0.336 (0.266, 0.407)	0.122 (0.045, 0.239)	0.290 (0.231, 0.352)
27 Months	0.327 (0.257, 0.398)	0.122 (0.045, 0.239)	0.282 (0.223, 0.344)
30 Months	0.327 (0.257, 0.398)	- (-, -)	0.282 (0.223, 0.344)

Note: Percentages were based on number of subjects with CR or PR.
[1] The Brookmeyer-Crowley method was used to construct the 95% CI for the median DOR.
[2] Stratification factor: PD-L1 expression level (TPS < 1%, 1% ≤ TPS < 50% or TPS ≥ 50%), Asian population (yes or no) and NSCLC stage (Stage IIIB/IIIC or Stage IV).
[3] The hazard ratio and its 95% CI were estimated by (stratified) Cox proportional hazards model. Efron's method was used to handle ties.
[4] The comparison of DOR between the two arms was performed by a two-tailed stratified log-rank test with significant level at 0.05.
[5] The standard error of the DOR rate was calculated using Greenwood's formula.

Secondary endpoint – Quality of Life

Subjects were assessed for quality of life using the EORTC QLQ-C30 and EORTC QLQ-LC13.

Figure 18 : Forest Plot of EORTC QLQ-LC13 Standardized Score (ITT, Cutoff on 31Jan2023)

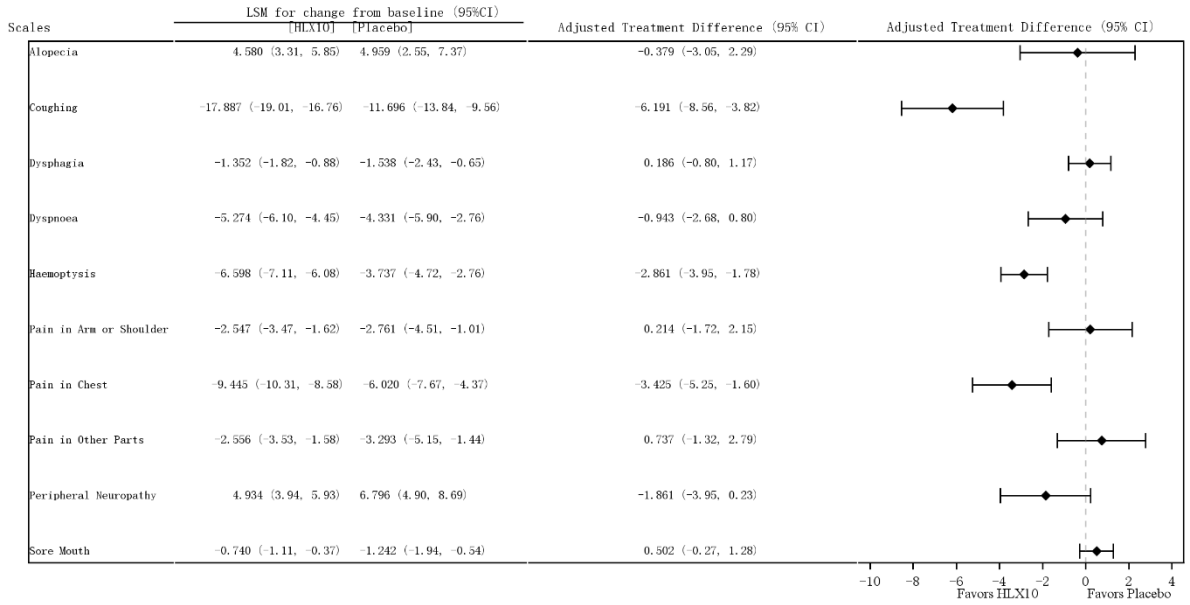


Figure *19*: Forest Plot of Function Domains of EORTC QLQ-C30 Standardized Score (ITT, Cutoff on 31Jan2023)

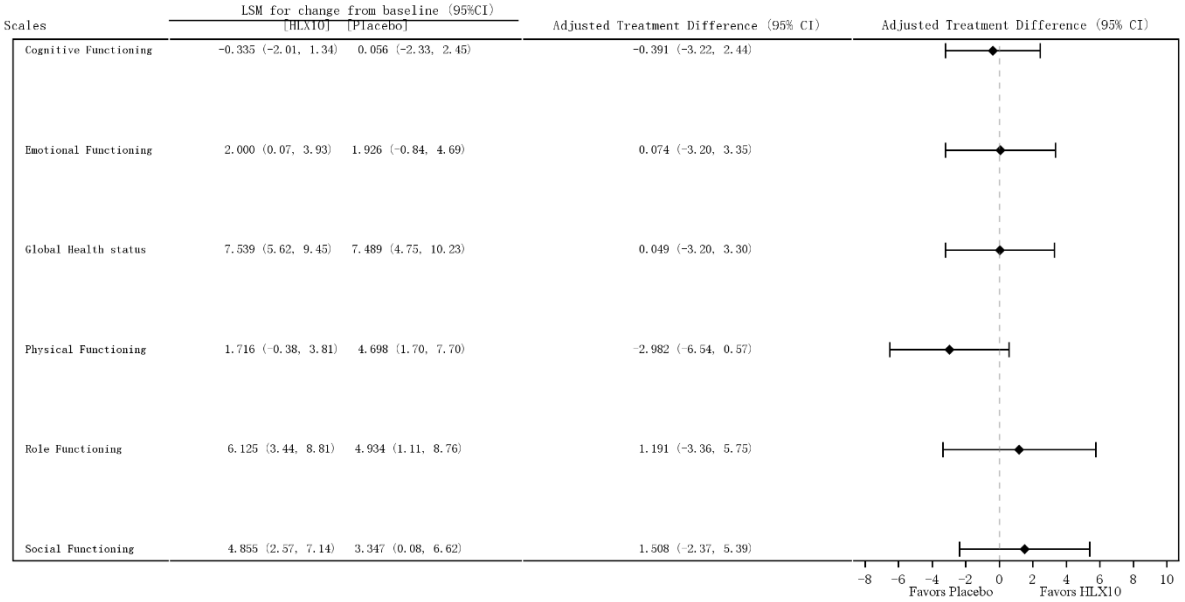
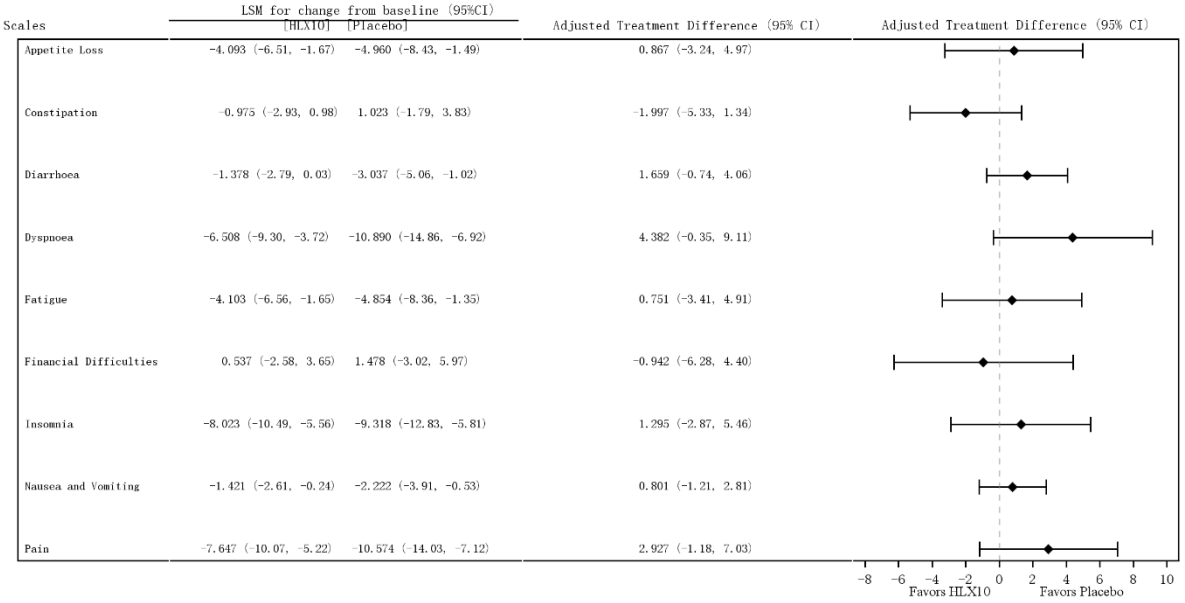


Figure 20: Forest Plot of Symptom Domains of EORTC QLQ-C30 Standardized Score (ITT, Cutoff on 31Jan2023)



Ancillary analyses

Sensitivity analyses

The PFS assessed by IRRC as per RECIST 1.1 based on the actual stratifications in the ITT set is presented below.

Table 35. Analysis of PFS (RECIST 1.1) Based on Actual Stratum by IRRC (ITT Set) at the final PFS analysis (DCO March 30, 2021)

Characteristics	Serplulimab (N=358)	Placebo (N=179)	Total (N=537)

Number of Event (PD/Deaths), n (%)	146 (40.8)	93 (52.0)	239 (44.5)
Progression	114 (31.8)	73 (40.8)	187 (34.8)
Deaths	32 (8.9)	20 (11.2)	52 (9.7)
Number of Censor, n (%)	212 (59.2)	86 (48.0)	298 (55.5)
No Baseline or Post Baseline	20 (5.6)	12 (6.7)	32 (6.0)
No Progression and No Death	170 (47.5)	37 (20.7)	207 (38.5)
New Anti-cancer Treatment Started Prior to Documented Disease Progression or Death on Study	22 (6.1)	10 (5.6)	32 (6.0)
Major Protocol Deviation Occurred Prior to Unblinding	0	0	0
Treatment Switched from Placebo to Serplulimab		27 (15.1)	27 (5.0)
Progression Free Survival (Months)			
Median (95% CI) [1]	8.28 (6.90, 10.38)	5.72 (5.22, 6.83)	6.93 (6.77, 7.98)
Min, Max	0.0, 19.2	0.0, 14.0	0.0, 19.2
Stratified [2]			
Hazard Ratio (95% CI) [3]	0.55 (0.42, 0.72)		
p-Value [4]	< 0.001		
PFS Rate (95% CI) at [5]			
3 Months	0.857 (0.812, 0.892)	0.760 (0.683, 0.820)	0.825 (0.786, 0.857)
6 Months	0.607 (0.544, 0.663)	0.482 (0.387, 0.570)	0.567 (0.515, 0.615)
9 Months	0.469 (0.402, 0.532)	0.236 (0.152, 0.331)	0.401 (0.347, 0.455)
12 Months	0.411 (0.341, 0.480)	0.052 (0.006, 0.179)	0.315 (0.258, 0.375)
15 Months	0.326 (0.240, 0.414)	- (-, -)	0.251 (0.185, 0.323)

[1] The Brookmeyer-Crowley method was used to construct the 95% CI for the median PFS.

[2] Stratification factor: PD-L1 expression level (TPS < 1%, 1% ≤ TPS < 50% or TPS ≥ 50%), Asian population (yes or no) and NSCLC stage (Stage IIIB/IIIC or Stage IV).

[3] The hazard ratio and its 95% CI were estimated by (stratified) Cox proportional hazards model. Efron's method was used to handle ties.

[4] The comparison of PFS between the two arms was performed by a two-tailed stratified log-rank test with significant level at 0.05.

[5] The standard error of the PFS rate was calculated using Greenwood's formula

Table 36. Analysis of PFS (RECIST 1.1) regardless of new anti-cancer treatment by IRRC ITT Set at the final PFS analysis (DCO March 30, 2021)

Characteristics	HLX10 (N=358)	Placebo (N=179)	Total (N=537)
Number of Event (PD/ Deaths), n(%)	153 (42.7)	98 (54.7)	251 (46.7)
Progression	114 (31.8)	73 (40.8)	187 (34.8)
Deaths	39 (10.9)	25 (14.0)	64 (11.9)
Number of Censor, n(%)	205 (57.3)	81 (45.3)	286 (53.3)
No Baseline or Post Baseline	20 (5.6)	12 (6.7)	32 (6.0)
No Progression and No Death	185 (51.7)	42 (23.5)	227 (42.3)
Major Protocol Deviation Occurred Prior to Unblinding	0	0	0
Progression or Death after Treatment Switched from Placebo to HLX10		27 (15.1)	27 (5.0)
Progression Free Survival (Months)			
Median (95% CI) [1]	8.28 (6.90, 9.72)	5.72 (5.22, 6.83)	6.90 (6.67, 7.16)
Min, Max	0.0, 19.2	0.0, 14.0	0.0, 19.2
Stratified [2]			
Hazard Ratio (95% CI) [3]	0.54 (0.42, 0.71)		
p-Value [4]	<0.001		
PFS Rate (95% CI) at [5]			
3 Months	0.859 (0.814, 0.893)	0.762 (0.686, 0.822)	0.826 (0.789, 0.858)
6 Months	0.604 (0.543, 0.660)	0.488 (0.396, 0.574)	0.567 (0.516, 0.615)
9 Months	0.453 (0.387, 0.517)	0.215 (0.137, 0.305)	0.383 (0.329, 0.436)
12 Months	0.392 (0.323, 0.460)	0.048 (0.006, 0.166)	0.297 (0.242, 0.355)
15 Months	0.310 (0.228, 0.397)	- (-, -)	0.237 (0.174, 0.306)

Subgroup analysis of PFS

Figure 21. Forest Plot of IRRC-Assessed PFS (ITT, Cutoff on March 30, 2021)

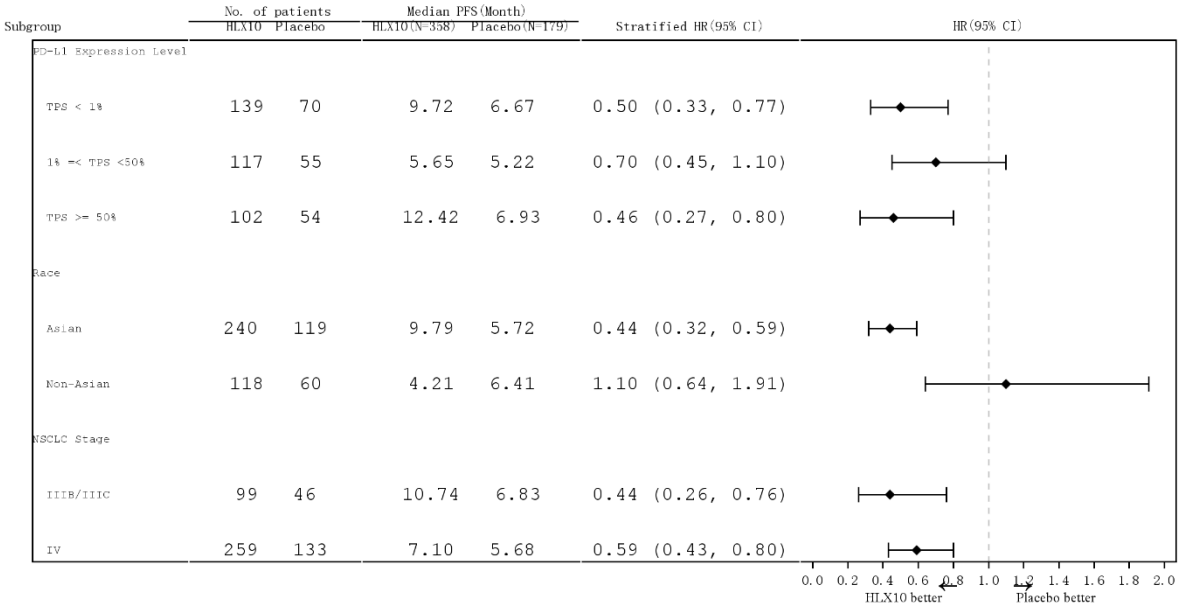
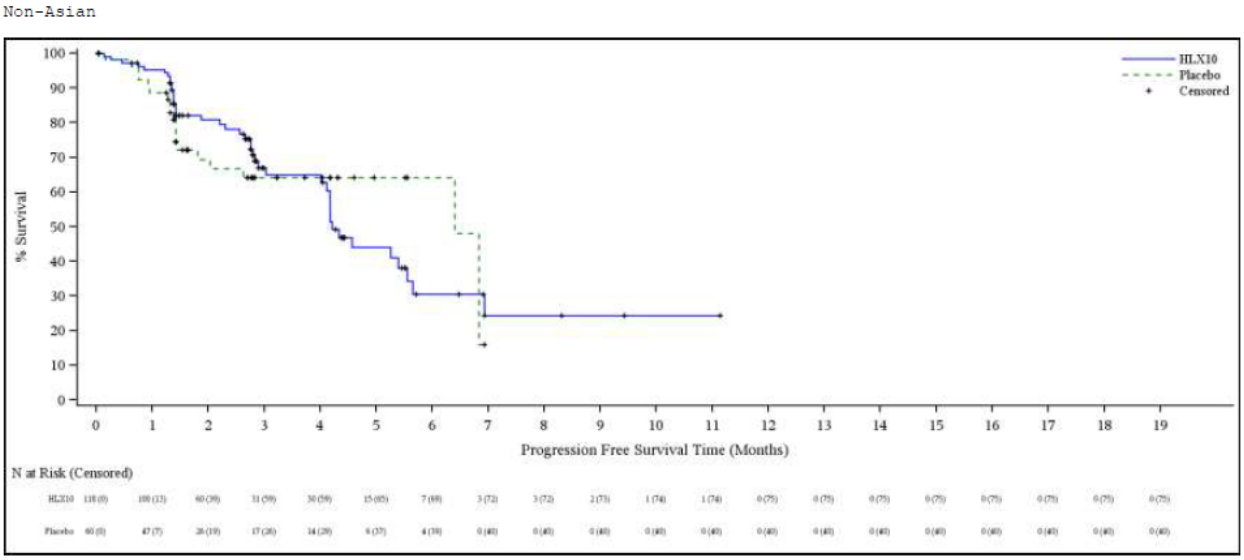


Table 37. Subgroup analysis of PFS (RECIST 1.1) by IRCC for non-Asian population (ITT set) at the final PFS analysis (DCO March 30, 2021)

Non-Asian

Characteristics	HLX10 (N=118)	Placebo (N=60)	Total (N=178)
Number of Event (PD/ Deaths), n(%)	43 (36.4)	20 (33.3)	63 (35.4)
Progression	30 (25.4)	12 (20.0)	42 (23.6)
Deaths	13 (11.0)	8 (13.3)	21 (11.8)
Number of Censor, n(%)	75 (63.6)	40 (66.7)	115 (64.6)
No Baseline or Post Baseline	11 (9.3)	7 (11.7)	18 (10.1)
No Progression and No Death	63 (53.4)	25 (41.7)	88 (49.4)
New Anticancer Treatment Started Prior to Documented Disease Progression or Death on Study	1 (0.8)	2 (3.3)	3 (1.7)
Major Protocol Deviation Occurred Prior to Unblinding	0	0	0
Progression or Death after Treatment Switched from Placebo to HLX10		6 (10.0)	6 (3.4)
Progression Free Survival (Months)			
Median (95% CI) [1]	4.21 (4.11, 5.55)	6.41 (6.41, 6.83)	4.57 (4.17, 6.41)
Min, Max	0.0, 11.1	0.0, 6.9	0.0, 11.1
Stratified [2]			
Hazard Ratio (95% CI) [3]	1.10 (0.64, 1.91)		
p-Value [4]	0.698		
PFS Rate (95% CI) at [5]			
3 Months	0.670 (0.552, 0.763)	0.641 (0.483, 0.762)	0.660 (0.568, 0.737)
6 Months	0.305 (0.169, 0.453)	0.641 (0.483, 0.762)	0.388 (0.260, 0.514)
9 Months	0.244 (0.107, 0.411)	- (-, -)	0.229 (0.104, 0.382)

Figure 22. KM curve of PFS in the non-Asian population (ITT set) at the final PFS analysis (DCO March 30, 2021)



Data from a later DCO (DCO January 31, 2023), for the non-Asian patients, the median PFS (IRRC assessed) was 5.62 months (95% CI: 4.34, 7.23) for patients receiving serplulimab versus 5.55 months (95% CI: 4.14, 7.26) for patients receiving placebo. with a stratified HR of 0.81 (95% CI: 0.55, 1.19). The median OS was 16.30 months (95% CI: 10.64, 19.78) in the serplulimab arm vs 15.41 months (95% CI: 9.56, 23.29) in the placebo arm, with a stratified HR of 1.04 (95% CI: 0.68, 1.60).

In Asian patients, the median PFS was 9.89 months (95% CI: 8.31, 13.80) in the serplulimab arm vs 5.75 months (95% CI: 5.22, 6.93) in the placebo arm, with a stratified HR of 0.43 (95% CI: 0.32, 0.58).

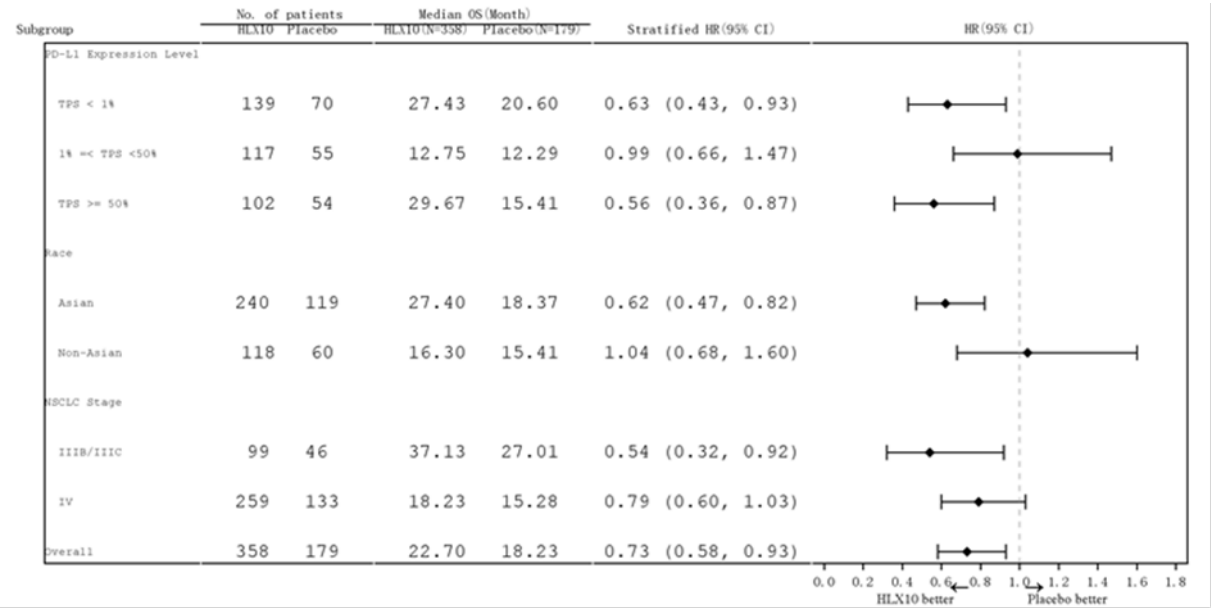
Table 38. Subgroup Analyses of PFS by IRRC Based on Baseline PD-L1 Expression (ITT, Cutoff on 31Jan2023)

	Median (95%CI), Months		Stratified HR (95%CI)	p value
	HLX10	Placebo		
ITT	N=358	N=179	0.55 (0.43, 0.69)	<0.001
	8.31 (7.00, 9.79)	5.72 (5.13, 6.83)		
TPS<1%	N=139	N=70	0.48 (0.33, 0.70)	<0.001
	9.20 (7.00, 11.47)	6.21 (4.96, 6.90)		
1%≤TPS<50%	N=117	N=55	0.72 (0.48, 1.09)	0.119
	6.70 (5.26, 8.02)	5.32 (4.30, 6.83)		
TPS≥50%	N=102	N=54	0.46 (0.30, 0.71)	<0.001
	11.47 (7.16, 16.76)	6.93 (4.37, 8.31)		

Subgroup analysis of OS

A forest plot of OS (DCO January 31, 2023) for the main subgoups is shown in Figure 23.

Figure 23. Forest Plot of OS (ITT, Cutoff on January 31, 2023)



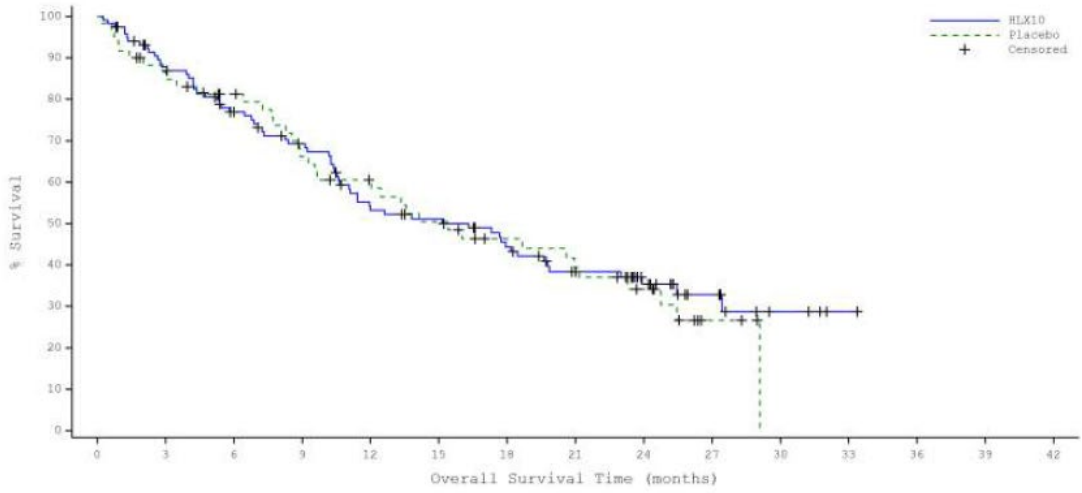
Subgroup analysis of OS for non-Asian population (ITT set) is shown in Table 39 and the corresponding KM curve is shown in figure 24.

Table 39: Subgroup analysis of OS for non-Asian population (ITT set) from final OS analysis (DCO January 31, 2023)

Non-Asian

Characteristics	HLX10 (N=118)	Placebo (N=60)	Total (N=178)
Number of Event (Deaths), n(%)	67 (56.8)	37 (61.7)	104 (58.4)
Number of Censor, n(%)	51 (43.2)	23 (38.3)	74 (41.6)
Alive	24 (20.3)	12 (20.0)	36 (20.2)
Lost to Follow-up	27 (22.9)	11 (18.3)	38 (21.3)
Overall Survival (Months)			
Median (95% CI) [1]	16.30 (10.64, 19.78)	15.41 (9.56, 23.29)	15.41 (11.43, 19.61)
Min, Max	0.3, 33.4	0.2, 29.1	0.2, 33.4
Stratified [2]			
Hazard Ratio (95% CI) [3]	1.04 (0.68, 1.60)		
p-Value [4]	0.853		
Survival Rate at [5]			
3 Months	0.878 (0.803, 0.926)	0.865 (0.749, 0.930)	0.874 (0.815, 0.915)
6 Months	0.770 (0.680, 0.837)	0.813 (0.688, 0.892)	0.784 (0.715, 0.839)
9 Months	0.693 (0.597, 0.770)	0.662 (0.521, 0.770)	0.682 (0.605, 0.747)
12 Months	0.532 (0.432, 0.622)	0.605 (0.463, 0.720)	0.556 (0.476, 0.630)
15 Months	0.511 (0.411, 0.602)	0.504 (0.364, 0.629)	0.508 (0.428, 0.584)
18 Months	0.444 (0.345, 0.538)	0.463 (0.325, 0.590)	0.450 (0.369, 0.527)
21 Months	0.384 (0.287, 0.480)	0.394 (0.259, 0.525)	0.386 (0.307, 0.465)
24 Months	0.353 (0.256, 0.451)	0.342 (0.211, 0.477)	0.349 (0.270, 0.429)
27 Months	0.328 (0.228, 0.432)	0.266 (0.139, 0.411)	0.305 (0.224, 0.390)
30 Months	0.287 (0.177, 0.407)	- (-, -)	0.231 (0.129, 0.350)
33 Months	0.287 (0.177, 0.407)	- (-, -)	0.231 (0.129, 0.350)

Figure 24. KM curve of OS in the non-Asian population (ITT set) from final OS analysis (DCO January 31, 2023)



Source: Listing 16.2.6.2 and Table 14.2.2.5.1
[SOURCE: E:\sasserver\projects\hlx10nsclc303\interim\prog\figures\en\f adtte km.sas] (EDC Date: 12APR2023, Output Date: 01JUN2025 22:07)

Summary of main study(ies)

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

Table 40: Summary of Efficacy for trial HLX10-004-NSCLC303

Title: A Randomized, Double-blind, Multi-center, Phase III Clinical Study of HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin and Nanoparticle Albumin-bound Paclitaxel) versus Chemotherapy (Carboplatin and Nanoparticle Albumin-bound Paclitaxel) as First-line Treatment for Locally Advanced or Metastatic Squamous Non-small Cell Lung Cancer (NSCLC)		
Study identifier	ClinicalTrial.gov: NCT04033354 EudraCT Number: 2019-003064-50	
Design	Randomized, double-blind, multi-center, phase III clinical study aimed to compare the efficacy and safety of HLX10 combined with chemotherapy versus placebo combined with chemotherapy in subjects with locally advanced or metastatic squamous NSCLC who had not previously received systemic treatment.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	August 14, 2019-May 30, 2025 not applicable not applicable
Hypothesis	Superiority	

Treatments groups	HLX10 group		HLX10 + chemotherapy (carboplatin + nab-paclitaxel) N = 358 Subjects received HLX10 for up to 2 years (up to 35 treatment cycles) or until loss of clinical benefit. Subjects received chemotherapy for 4-6 treatment cycles. Subjects were treated with HLX10 in combination with chemotherapy once every 3 weeks, until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent or other reasons specified in the protocol (whichever occurred first).
	Placebo group		Placebo + chemotherapy (carboplatin + nab-paclitaxel) N = 179 Subjects received placebo for up to 2 years (up to 35 treatment cycles) or until loss of clinical benefit. Subjects received chemotherapy for 4-6 treatment cycles. Subjects were treated with placebo in combination with chemotherapy once every 3 weeks, until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent or other reasons specified in the protocol (whichever occurred first).
Endpoints and definitions	Primary endpoint	PFS by IRRC	PFS assessed by IRRC based on RECIST v1.1.
	Key secondary endpoint	OS	Defined as the time from randomization to death due to any cause.
	Secondary endpoint	PFS by IRRC	PFS assessed by IRRC based on iRECIST.
	Secondary endpoint	PFS by Investigator	PFS assessed by Investigator based on RECIST 1.1 and iRECIST.
	Secondary endpoint	ORR by IRRC	ORR assessed by IRRC based on RECIST 1.1.
	Secondary endpoint	ORR by Investigator	ORR assessed by Investigator based on RECIST 1.1.
	Secondary endpoint	DOR by IRRC	DOR assessed by IRRC based on RECIST 1.1.
	Secondary endpoint	DOR by Investigator	DOR assessed by Investigator based on RECIST 1.1.
<u>Results and Analysis</u>			
Analysis description	**First Interim Analysis**		
Database lock	June 18, 2021		

Analysis population and time point description	Intent-to-treat set: Defined as all randomized subjects of the trial. Results from the first interim analysis.		
Descriptive statistics and estimate variability	Treatment group	HLX10 group	Placebo group
	Number of subjects	358	179
	PFS by IRRC based on RECIST 1.1 (Median)	8.28	5.72
	95% confidence interval	6.90, 10.38	5.22, 6.83
	OS (Median)	-	-
	95% confidence interval	17.35, -	13.11, -
	PFS by Investigator based on RECIST 1.1 (Median)	8.28	5.55
	95% confidence interval	7.10, 9.53	4.40, 5.75
	PFS by IRRC based on iRECIST (Median)	12.42	5.72
	95% confidence interval	9.69, -	5.22, 6.83
	PFS by Investigator based on iRECIST (Median)	17.35	5.55
	95% confidence interval	11.93, -	4.40, 5.75
	Unconfirmed ORR by IRRC based on RECIST 1.1 (%)	64.2%	44.7%
	95% confidence interval (%)	59.0%, 69.2%	37.3%, 52.3%
	Unconfirmed ORR by Investigator based on RECIST 1.1 (%)	61.2%	40.2%
	95% confidence interval (%)	55.9%, 66.3%	33.0%, 47.8%
	Unconfirmed DOR by IRRC based on RECIST 1.1 (Median)	9.43	5.36
	95% confidence interval	6.97, -	4.14, 5.59
	Unconfirmed DOR by Investigator based on RECIST 1.1 (Median)	8.48	4.50
	95% confidence interval	7.00, 12.88	4.14, 5.55
Effect estimates per comparison	PFS by IRRC based on RECIST 1.1	Comparison groups	HLX10 group vs Placebo group
		Stratified hazard ratio	0.55
		95% confidence interval	0.42, 0.73

		P-value (By a two-tailed stratified log-rank test)	< 0.001
	OS	Comparison groups	HLX10 group vs Placebo group
		Stratified hazard ratio	0.75
		95% confidence interval	0.52, 1.10
		P-value (By a two-tailed stratified log-rank test)	0.138
	PFS by Investigator based on RECIST 1.1	Comparison groups	HLX10 group vs Placebo group
		Stratified hazard ratio	0.47
		95% confidence interval	0.37, 0.60
		P-value (By a two-tailed stratified log-rank test)	< 0.001
	PFS by IRRC based on iRECIST	Comparison groups	HLX10 group vs Placebo group
		Stratified hazard ratio	0.41
		95% confidence interval	0.31, 0.55
		P-value (By a two-tailed stratified log-rank test)	< 0.001
	PFS by Investigator based on iRECIST	Comparison groups	HLX10 group vs Placebo group
		Stratified hazard ratio	0.22
		95% confidence interval	0.16, 0.30
		P-value (By a two-tailed stratified log-rank test)	< 0.001
	Unconfirmed ORR by IRRC based on RECIST 1.1 (%)	Comparison groups	HLX10 group vs Placebo group
		Odds ratio	2.44
		95% confidence interval	1.65, 3.61
		P-value	-
	Unconfirmed ORR by Investigator based on RECIST 1.1 (%)	Comparison groups	HLX10 group vs Placebo group
		Odds ratio	2.52
		95% confidence	1.71, 3.72

		interval	
		P-value	-
	Unconfirmed DOR by IRRC based on RECIST 1.1	Comparison groups	HLX10 group vs Placebo group
		Stratified hazard ratio	0.48
		95% confidence interval	0.33, 0.71
		P-value (By a two-tailed stratified log-rank test)	< 0.001
	Unconfirmed DOR by Investigator based on RECIST 1.1	Comparison groups	HLX10 group vs Placebo group
		Stratified hazard ratio	0.37
		95% confidence interval	0.26, 0.54
		P-value (By a two-tailed stratified log-rank test)	< 0.001
Notes	The first interim analysis (final analysis of PFS) results demonstrated that HLX10 in combination with carboplatin and nab-paclitaxel significantly reduced the risk of progressive disease or death in patients with squamous NSCLC (median PFS: 8.28 months versus 5.72 months, HR = 0.55, 95% CI: 0.42–0.73, $p < 0.001$), meeting the prespecified primary endpoint with statistical significance.		
Analysis description	**Final Analysis**		
Database lock	April 12, 2023		
Analysis population and time point description	Intent-to-treat set: Defined as all randomized subjects of the trial. Results from the final analysis.		
Descriptive statistics and estimate variability	Treatment group	HLX10 group	Placebo group
	Number of subjects	358	179
	PFS by IRRC based on RECIST 1.1 (Median)	8.31	5.72
	95% confidence interval	7.00, 9.79	5.13, 6.83
	OS (Median)	22.70	18.23
	95% confidence interval	18.60, 27.40	14.13, 20.60
	PFS by Investigator based on RECIST 1.1 (Median)	8.31	5.59
	95% confidence interval	7.16, 9.53	4.96, 5.75
	PFS by IRRC based on iRECIST (Median)	8.38	5.72
	95% confidence interval	7.16, 10.38	5.13, 6.83

	PFS by Investigator based on iRECIST (Median)	8.77	5.59
	95% confidence interval	8.05, 10.74	4.96, 5.75
	Confirmed ORR by IRRC based on RECIST 1.1 (%)	60.1%	40.8%
	95% confidence interval (%)	54.8%, 65.2%	33.5%, 48.4%
	Confirmed ORR by Investigator based on RECIST 1.1 (%)	57.5%	36.3%
	95% confidence interval (%)	52.2%, 62.7%	29.3%, 43.8%
	Confirmed DOR by IRRC based on RECIST 1.1 (Median)	11.07	5.52
	95% confidence interval	8.31, 15.44	5.29, 7.06
	Confirmed DOR by Investigator based on RECIST 1.1 (Median)	11.53	5.16
	95% confidence interval	8.08, 14.06	4.21, 5.65
Effect estimates per comparison	PFS by IRRC based on RECIST 1.1	Comparison groups	HLX10 group vs Placebo group
		Stratified hazard ratio	0.55
		95% confidence interval	0.43, 0.69
		P-value (By a two-tailed stratified log-rank test)	< 0.001
	OS	Comparison groups	HLX10 group vs Placebo group
		Stratified hazard ratio	0.73
		95% confidence interval	0.58, 0.93
		P-value (By a two-tailed stratified log-rank test)	0.010
	PFS by Investigator based on RECIST 1.1	Comparison groups	HLX10 group vs Placebo group
		Stratified hazard ratio	0.50
		95% confidence interval	0.40, 0.61
		P-value (By a two-tailed stratified log-rank test)	< 0.001

PFS by IRRC based on iRECIST	Comparison groups	HLX10 group vs Placebo group
	Stratified hazard ratio	0.53
	95% confidence interval	0.42, 0.66
	P-value (By a two-tailed stratified log-rank test)	< 0.001
PFS by Investigator based on iRECIST	Comparison groups	HLX10 group vs Placebo group
	Stratified hazard ratio	0.45
	95% confidence interval	0.37, 0.56
	P-value (By a two-tailed stratified log-rank test)	< 0.001
Confirmed ORR by IRRC based on RECIST 1.1 (%)	Comparison groups	HLX10 group vs Placebo group
	Odds ratio	2.24
	95% confidence interval	1.54, 3.26
	P-value	< 0.001
Confirmed ORR by Investigator based on RECIST 1.1 (%)	Comparison groups	HLX10 group vs Placebo group
	Odds ratio	2.45
	95% confidence interval	1.68, 3.58
	P-value	< 0.001
Confirmed DOR by IRRC based on RECIST 1.1	Comparison groups	HLX10 group vs Placebo group
	Stratified hazard ratio	0.45
	95% confidence interval	0.32, 0.65
	P-value (By a two-tailed stratified log-rank test)	< 0.001
Confirmed DOR by Investigator based on RECIST 1.1	Comparison groups	HLX10 group vs Placebo group
	Stratified hazard ratio	0.36
	95% confidence interval	0.26, 0.50
	P-value (By a two-tailed stratified log-rank test)	< 0.001

Notes	The final analysis (final analysis of OS) results demonstrated that HLX10 in combination with carboplatin and nab-paclitaxel significantly prolonged OS (median OS: 22.70 months versus 18.23 months, HR = 0.73, 95% CI: 0.58–0.93, p = 0.010), meeting the prespecified key secondary endpoint with statistical significance. Consistent with the first interim analysis.

2.4.3. Discussion on clinical efficacy

HLX10-004-NSCLC303 is a randomized, double-blind, multi-center, ongoing phase III study to compare the clinical efficacy and safety of serplulimab combined with chemotherapy versus placebo combined with chemotherapy in subjects with locally advanced or metastatic squamous NSCLC. A total of 537 subjects were randomized 2:1 to arm A (serplulimab + chemotherapy (carboplatin and nab-paclitaxel)) or arm B (placebo + chemotherapy (carboplatin and nab-paclitaxel)). Randomization was stratified by PD-L1 expression level (tumor proportion score [TPS] ≥ 50%, 50% > TPS ≥ 1%, TPS < 1%) measured by PD-L1 IHC 22C3 pharmDx kit, Asian population (yes or no), and squamous NSCLC stage (Stage IIIB/IIIC or Stage IV).

The overall study design is considered adequate, including the chosen stratification factors.

Design and conduct of clinical studies

Comparator

The choice of comparator (chemotherapy only) is justified based on limited availability of pembrolizumab in Asia and some regions in Europe. The scientific advice given by the CHMP in 2019, questioned the choice of chemotherapy only, as pembrolizumab was granted the same indication (based on the phase 3 KEYNOTE-407 trial) in EU in 2019. Furthermore, the combination of pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel was implemented as a SOC in patients with metastatic squamous NSCLC in ESMO clinical treatment guideline (updated September 2019). CHMP recommended a randomized comparison to pembrolizumab plus chemotherapy to be relevant to the EU treatment setting. The Applicant chose, however, to keep chemotherapy only as comparator. The choice of chemotherapy plus placebo in the control arm is considered suboptimal, both currently and at study initiation, in the European population. However, the chosen comparator of chemotherapy only is in line with previous approvals for products in the same class and in the same setting and, therefore, is considered acceptable.

Study population

Overall, the inclusion and exclusion criteria are considered clinically relevant and in line with clinical practice.

No known sensitizing EGFR mutations or ALK, ROS1 gene rearrangements were allowed. If EGFR, ALK, and ROS1 status were unknown, testing of mutations such as EGFR were considered if there were high risk factors (e.g. non-smoking female patients). As testing for driver mutations was not an inclusion criteria, there is a risk of inclusion of patients with (unknown) EGFR mutations and ALK/ROS1 rearrangements. However, the strategy is acceptable as in line with testing recommendations in ESMO clinical treatment guidelines.

Patients had to provide tumour tissues for the prospective determination of PD-L1 expression levels. Participants were included regardless of PD-L1-expression level. Since PD-L1 expression level was decided before randomization and a stratification factor, this is acceptable.

Eligible subjects were required to have an ECOG PS score of 0 or 1. More than 30% of NSCLC have poor (ECOG ≥ 2) at baseline which is associated with worse survival outcomes than those with favorable (0-1) ECOG PS (Passaro et al 2021, Meyers et al 2023).

Patients with known CNS metastases and/or carcinomatous meningitis during screening period were eligible if the lesions were asymptomatic and had no need for use of glucocorticoids, and without any evidence of new lesions or progression of brain metastases. Since approximately 20% of patients with NSCLC have brain metastases at baseline (Schmid et al 2024), inclusion of these patients is endorsed.

The study was mainly conducted in Asia, however non-Asian patients were recruited from Georgia, Poland, Russia, Turkey and Ukraine. As discussed, CHMP highlighted in its SA the importance of recruiting a sufficient number of Caucasian (European) patients to be able to show consistency of efficacy across regions. Literature suggests that Chinese patients with NSCLC may have more driver gene mutations, different gene profiles, better clinical responses to chemotherapy, and different toxicity profiles (Liu et al. J Hematol Oncol. 2017). A meta-analysis (11000 patients from 19 RCTs) comparing responses of Asian versus non-Asian cancer patients to PD-1 and PD-L1 inhibitor-based therapy indicates that Asian cancer patients might have improved survival benefit compared to non-Asian patients (OS HR 0.69 [95%CI: 0.61-0.77] in Asian versus 0.82 [95%CI: 0.77-0.88] in non-Asian) (Peng et al, 2020). There is however, no consensus in the literature regarding this issue. The chosen stratification factor Asian vs non-Asian is therefore endorsed.

Treatments:

Serplulimab was administered at the dose of 4.5 mg/kg via IV infusion on Day 1 of each cycle, once every 3 weeks (21 days), for up to 2 years (up to 35 treatment cycles). Placebo was administered via IV infusion on Day 1 of each cycle, once every 3 weeks (21 days), for up to 2 years (up to 35 treatment cycles). Serplulimab or placebo was given by infusion in a blinded state and nab-paclitaxel followed by carboplatin were given by open-label infusion.

If a subject experienced disease progression (first PD assessed according to Response Evaluation Criteria in Solid Tumours [RECIST] 1.1) during the treatment period, the Investigator unblinded the subject and decided whether the subject could continue study treatment according to prespecified protocol criteria and requirement of new informed consent. Continuation of serplulimab monotherapy (Arm B) was allowed up to the third PD (according to RECIST 1.1). This approach is acceptable as the first recorded PD is used in the registration of PFS by protocol.

Endpoints:

The primary endpoint was PFS assessed by IRRC based on RECIST 1.1, while OS was a secondary endpoint. This is considered acceptable, provided that PFS data is supported by sufficiently mature OS data showing no detrimental effect. The CHMP SA provided in 2019 recommended the use of OS as an additional primary endpoint, either as co-primary endpoint (meaning that both PFS and OS need to be significant at the 5% two-sided significance level) or second primary endpoint with some alpha-splitting, however the applicant didn’t follow this advice.

Efficacy data and additional analyses

Study conduct

The version 1.0 of the protocol was finalized and dated April 4, 2019. The study protocol was revised four times, resulting in a version 2.0 (September 26, 2019), a version 3.0 (April 3, 2020),

a version 4.0 (July 8, 2020) and a version 5.0 (December 31, 2021).. The protocol changes are considered not to influence the balance of benefits and risks.

84.4% of the study subjects had at least one major protocol deviation, which is extensive. The proportion was higher in the serplulimab-arm compared to the placebo-arm (86.9% vs 79.3%). The most common reasons were procedure/test (80.6%), IP admin/study treatment (43.7%) and visit schedule (44.6%). However, the deviations did not raise a concern.

Baseline and disease characteristics

Overall, the demographic and baseline characteristics seem well balanced between treatment arms. The majority of included patients were Asians (66.9%, 359 patients), whilst 33.1%, 178 patients were non-Asian/white.

The white population was recruited form Georgia, Poland, Russia, Turkey and Ukraine. 33% of the study population is in principle considered an acceptable proportion to reflect efficacy and safety in a Caucasian population. However, only two participants were recruited from EU (Poland). Low recruitment at European sites may be understood from the outdated choice of comparator (chemotherapy without addition of pembrolizumab). As discussed above, some literature data have reported better clinical responses, overall survival and different toxicity profile to chemotherapy and PD-1/PD-L1-inhibitor based therapy in Asian versus non-Asian patients, although no consensus has been reached on this observation.

None of the included patients had *known* driver mutations (ALK, EGFR, ROS1) at baseline, which is in line with inclusion/exclusion criteria. However, only 54 (10.1%) of the patients underwent EGFS/ALK/ROS1 genetic testing. All the tested patients were EGFR/ALK/ROS1 negative. Limitation of testing for oncogenic driver mutations to a selected patient population with high-risk factors (e.g. non-smoking female patients) is according to ESMO treatment guideline, and thus acceptable.

The PD-L1 expression level subgroups (TPS ≥ 50%, 1-49% and < 1%) were of similar size; 29%, 33% and 38%, respectively. This is of relevance in the evaluation of efficacy by PD-L1-expresssion level.

The small proportion of females (9,1%; expected around 35-50%) and low median age (63 years; expected around 70 years) are not considered representative for a European patient population. It is reasonable to believe that the efficacy and toxicity profile of a relatively younger patient population could differ from that of an older population. The fraction of never-smokers was relatively high (14% serplulimab-arm, 11.2% placebo-arm) compared to what is expected in the European population (5-10%). The fraction of never-smokers is, however, expected to be even lower when patients with driver mutations are excluded, as in this trial. In general, never-smokers have less comorbidities typically caused by smoking.

Exclusion of patients with ECOG PS ≥ 2 raises concern about the external validity of the trial due to selection of a healthier patient population than expected in clinical practice. The population represents a rather selected population accounting for the fact that there is evidence from literature that > 30% of NSCLC patients have ECOG PS ≥ 2 (Passaro et al 2021). Furthermore, it is shown, retrospectively, that patients with poor ECOG PS treated with immune check-point inhibitors (ICI) had a significantly worse survival outcome than those with favourable ECOG PS (ECOG 0-1) (Meyers et al, 2023). Uncertainty remains regarding how the selected patient population will have implications to the outcome of efficacy and safety compared to a representative European population.

A carboplatin dose of AUC 5 or 6 was allowed. In Europe, the recommended dose of carboplatin in combination with nab-paclitaxel is AUC 6. It is understood that the lower dose is added due to

safety reasons in the Asian population. However, it is noted that only 12.1% of the patients received carboplatin of AUC6 in the study, while 33.1% of the patients were white.

Statistics and methodology

The sample size is deemed adequate and the methodology used is considered standard and appropriate, despite the fact the estimand framework has not been used to define how intercurrent events were handled.

Efficacy outcomes

The HLX10-004-NSCLC303 study met its primary endpoint at the DCO of March 30, 2021 (final PFS analysis), demonstrating a statistically significant difference in PFS (assessed by IRRC based on RECIST 1.1) in favour of serplulimab [stratified HR = 0.55 (95% CI: 0.42, 0.73, p < 0.001)]. At the DCO (March 30, 2021) of the final PFS analysis, 146 (40.8%) patients in the serplulimab arm and 93 (52.0%) patients in the placebo arm had experienced an PFS event. The median PFS was 8.28 months (95% CI: 6.90, 10.38) for patients receiving serplulimab versus 5.72 months (95% CI: 5.22, 6.83) for patients receiving placebo. Sensitivity analyses showed results consistent with the primary analysis.

Consistency of treatment effect has not been demonstrated in all prespecified subgroups. A lower efficacy was observed in the non-Asian/Caucasian population, in which the median PFS was 4.21 months (95% CI: 4.11, 5.55) for patients receiving serplulimab versus 6.41 months (95% CI: 6.41, 6.83) for patients receiving placebo (DCO March 30, 2021). At a later DCO (DCO January 31, 2023), the median PFS (IRRC assessed) was 5.62 months (95% CI: 4.34, 7.23) for patients receiving serplulimab versus 5.55 months (95% CI: 4.14, 7.26) for patients receiving placebo, for the non-Asian patients. Stratified HR for PFS (IRRC assessed) was 0.43 (0.32, 0.58) for Asians, whereas 0.81 (0.55, 1.19) for non-Asians (DCO January 31, 2023). The limited overlap of the confidence intervals for PFS HR for Asian vs non-Asian patients, reinforces the differential treatment effect between the two subgroups.

The final analysis of OS was conducted when 312 OS events were observed, 196 (54.7%) in the serplulimab arm and 116 (64.8%) in the placebo arm at the DCO of January 31, 2023. At the final OS analysis, the median OS was 22.7 months (95% CI: 18.6, 27.4) and 18.2 months (95% CI: 14.1, 20.6) in the serplulimab group and the placebo group, respectively. The median OS in the serplulimab group was significantly longer than in the placebo group (HR = 0.73, 95% CI: 0.58–0.93, p = 0.010), meeting the prespecified significance boundary (p = 0.046). However, stratified HR for OS was 1.04 (95% CI: 0.68, 1.60) in the non-Asian subgroup, whereas 0.62 (95% CI: 0.47, 0.82) in the Asian subgroup at DCO: January 31, 2023. Thus, subgroup analysis of OS (HR=1.04 and crossing KM curves) also indicates a lower efficacy in the non-Asian population.

In conclusion, there is an uncertainty regarding the magnitude of the effect in the subgroup of non-Asian patients based on the results in the primary endpoint of PFS and in the secondary endpoint of OS. However, the mechanism of action for PD-1 inhibitors is well known, and other PD-1 inhibitors have been approved for the same indication in the non-Asian population. Although efficacy was lower in non-Asian NSCLC patients compared to Asian patients in the pivotal study supporting this application, there is no biological rationale justifying that this specific PD-1 inhibitor would have a differential effect compared to other PD-1 inhibitors. Results in the non-Asian sub-group have been included in section 5.1 of the SmPC.

Of note, 54% of patients in the placebo arm received serplulimab monotherapy after disease progression at the DCO of the final OS analysis, thus OS data are confounded by extensive cross-over between the two treatment arms, and interpretation of OS data is difficult.

The confirmed ORR assessed by IRRC based on RECIST 1.1 was 52.8% (95% CI: (47.5, 58.1)) and 34.6% (95% CI: 27.7, 42.1) in the serplulimab and control arm, respectively (data cutoff of 30 March 2021). The median confirmed DOR was 11.07 months (95% CI: 8.31, 15.44) for the serplulimab arm versus 5.52 months (95% CI: 5.29, 7.06) for the control arm.

2.4.4. Conclusions on the clinical efficacy

The primary endpoint was met in the pivotal phase 3 randomized trial HLX10-004-NSCLC303, demonstrating a superiority of chemotherapy plus serplulimab over chemotherapy alone in terms of PFS (by IRRC) in advanced squamous NSCLC. This was supported by OS, which was significantly longer in the serplulimab arm compared to the placebo arm.

Consistency of treatment effect was not demonstrated in all prespecified subgroups. There is an uncertainty regarding the magnitude of the effect in the subgroup of non-Asian patients based on the results in the primary endpoint of PFS and in the secondary endpoint of OS. Nevertheless, the mechanism of action for PD-1 inhibitors is well known, and other PD-1 inhibitors have been approved for the same indication in the non-Asian population. Although efficacy was lower in non-Asian NSCLC patients compared to Asian patients in the pivotal study supporting this application, there is no biological rationale justifying that this specific PD-1 inhibitor would have a differential effect compared to other PD-1 inhibitors.

2.5. Clinical safety

Introduction

The safety analyses of serplulimab were based primarily on the pivotal phase III study HLX10-004-NSCLC303 (NCT04033354), N=537, which evaluated serplulimab versus placebo in combination with chemotherapy (carboplatin and nanoparticle-albumin-bound (nab) paclitaxcel).

Adverse drug reactions were to be handled by treatment interruption or discontinuation, and/or symptomatic treatment (e.g., glucocorticoids) could be given.

In order to fully evaluate the safety of serplulimab, safety data collected from a total of ten clinical studies (including the pivotal study HLX10-004-NSCLC303) in subjects with various types of solid tumors were pooled for analyses. The pooled safety population included all subjects in these studies who received at least one dose of serplulimab (N=2086), regardless of the amount of treatment administered. Cut-off for safety for the individual studies included in the pooled safety population was 1-4 years ago. Details of the ten studies included in the pooled safety dataset are listed in the table below.

Table 41. Overview of the Ten Clinical Studies Pooled in Safety Evaluations for Serplulimab

Study No.	Title	Study Treatment	Control	Serplulimab Dose	Number of Subjects in Analysis [a]	Study Status	Cut-off Date for Safety Data
HLX10-004-NSCLC303 (Pivotal study for target indication)	A randomized, double-blind, multicenter, phase III clinical study of HLX10 + chemotherapy (carboplatin and nab-paclitaxel) vs placebo + chemotherapy (carboplatin and nab-paclitaxel) as first-line therapy for locally advanced or metastatic squamous NSCLC	Serplulimab with carboplatin and nab-paclitaxel combination therapy	Placebo with carboplatin and nab-paclitaxel	4.5 mg/kg, Q3W	Serplulimab: 358/455 [b]	Completed	January 31, 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, 600 mg Q6W.	3 4 6 16 9 9 10 9 Total: 66	Completed	January 05, 2024
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	October 11, 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	September 16, 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	Completed	July 10, 2021
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	September 22, 2022
HLX10-008-HCC201	A single-arm, open, multicenter, phase II clinical study evaluating	Serplulimab monotherapy or	None	3 mg/kg, Q2W	Monotherapy: 21 Combination therapy:	Completed	February 07, 2023

Study No.	Title	Study Treatment	Control	Serplulimab Dose	Number of Subjects in Analysis [a]	Study Status	Cut-off Date for Safety Data
	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			102 Total: 123		
HLX10-005-SCLC301	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 and etoposide combination therapy	Placebo with carboplatin and etoposide	4.5 mg/kg, Q3W	Serplulimab: 389	Completed	May 07, 2024
HLX10-002-NSCLC301	A three-arm, randomized, double-blind, multicenter, phase III clinical study to evaluate HLX10 (recombinant humanized anti-PD-1 monoclonal antibody injection) in combination with chemotherapy (carboplatin-pemetrexed) versus HLX10 + HLX04 (recombinant anti-VEGF humanized monoclonal antibody injection) in combination with chemotherapy (carboplatin-pemetrexed) versus chemotherapy (carboplatin-pemetrexed) as first-line treatment of advanced non-squamous non-small cell lung cancer (NSCLC)	Serplulimab with carboplatin and pemetrexed or serplulimab plus HLX04 with carboplatin and pemetrexed	Placebo with carboplatin and pemetrexed	4.5 mg/kg, Q3W	Stage I: Serplulimab + HLX04+chemotherapy: 6. Stage II: Serplulimab + chemotherapy: 214; Serplulimab + HLX04 + chemotherapy: 211; Placebo + chemotherapy switching to serplulimab + HLX04: 72. Total: 503	Ongoing	June 15, 2023
HLX10-007-EC301	A randomized, double-blind, multicenter, phase III clinical study to evaluate HLX10 (recombinant humanized anti-PD-1 monoclonal antibody injection) versus placebo in combination with chemotherapy (cisplatin + 5-FU) as first-line therapy in patients with locally advanced/metastatic esophageal squamous cell carcinoma (ESCC)	Serplulimab with cisplatin and 5-FU combination therapy	Placebo with cisplatin and 5-FU	3 mg/kg, Q2W	Serplulimab: 382	Completed	January 09, 2023

Abbreviations: NSCLC=non-small cell lung cancer, Q2W=once every 2 weeks, Q3W=once every 3 weeks, Q4W=once every 4 weeks, Q6W=once every 6 weeks. [a] Data Source: Table 2.7.4.1.1. [b] In the HLX10-004-NSCLC303 study, subjects randomized to the placebo group either ended treatment or were allowed to crossover to receive serplulimab after the first progressive disease. As of the cut-off date, 97 subjects in the placebo group crossed over to receive serplulimab monotherapy. Therefore, 455 subjects received serplulimab (serplulimab + chemotherapy: 358 subjects, serplulimab monotherapy: 97 subjects).

Patient exposure

Pivotal study

As of January 31, 2023, 537 subjects were included in the safety set. The summary of exposure for the pivotal trial can be in the table below.

Table *42*. PIVOTAL STUDY: SUMMARY OF EXPOSURE TO SERPLULIMAB

	Serplulimab (N=358)	Placebo (N=179)	Total (N=537)
Cumulative Number of Treatment Cycles			
n	358	179	537
Mean (SD)	14.0 (12.14)	7.8 (6.61)	12.0 (11.01)
Median	9.0	6.0	8.0
Q1, Q3	4.0, 23.0	4.0, 9.0	4.0, 16.0
Min, Max	1, 46	1, 35	1, 46
Actual Cumulative Dose Received (mg) [1]			
n	358	179	537
Mean (SD)	4252.229 (3886.2006)	2367.284 (2162.9877)	3623.914 (3521.8882)
Median	2833.500	1758.000	2259.200
Q1, Q3	1237.500, 6120.000	936.000, 2808.000	1080.000, 5040.000
Min, Max	211.50, 18018.00	162.00, 11895.00	162.00, 18018.00
Planned Cumulative Dose (mg) [2]			
n	358	179	537
Mean (SD)	4259.261 (3895.2474)	2371.814 (2163.4729)	3630.112 (3528.9351)
Median	2833.500	1764.000	2277.450
Q1, Q3	1237.500, 6120.000	936.000, 2848.500	1080.000, 5040.000
Min, Max	211.50, 18018.00	162.00, 11900.00	162.00, 18018.00
Actual Duration of Exposure (Weeks) [3]			
n	358	179	537
Mean (SD)	45.11 (43.157)	22.77 (22.034)	37.67 (38.896)
Median	28.29	18.14	23.14
Q1, Q3	11.43, 70.14	9.14, 27.71	10.14, 51.14
Min, Max	0.1, 168.4	0.1, 139.3	0.1, 168.4
Planned Duration of Exposure (Weeks) [4]			
n	358	179	537
Mean (SD)	39.41 (36.467)	20.67 (19.856)	33.17 (33.088)
Median	24.14	15.14	21.14
Q1, Q3	9.14, 66.14	9.14, 24.14	9.14, 45.14
Min, Max	0.1, 135.1	0.1, 102.1	0.1, 135.1
Actual Dose Intensity (mg/week) [5]			
n	358	179	537
Mean (SD)	244.14 (520.019)	254.35 (536.762)	247.55 (525.180)
Median	100.55	109.13	103.67
Q1, Q3	84.16, 124.35	90.88, 136.08	85.75, 129.94
Min, Max	34.8, 3118.5	44.3, 3811.5	34.8, 3811.5
Planned Dose Intensity (mg/week) [6]			
n	358	179	537
Mean (SD)	256.57 (516.692)	265.55 (533.690)	259.57 (521.938)
Median	115.06	119.19	116.94
Q1, Q3	97.62, 140.12	100.65, 147.66	98.44, 143.33
Min, Max	37.3, 3118.5	68.1, 3811.5	37.3, 3811.5
Relative Dose Intensity (%) [7]			
n	358	179	537
Mean (SD)	89.52 (11.601)	91.06 (10.925)	90.04 (11.393)
Median	93.57	94.87	93.81
Q1, Q3	84.07, 98.79	86.00, 99.84	84.80, 99.28
Min, Max	45.0, 115.8	43.4, 104.9	43.4, 115.8

[1] Actual cumulative dose received = summation of all actual dose administrated from the first dosing date to the last dosing date.
[2] Planned cumulative dose received = summation of all planned dose from the first dosing date to the planned dosing date.
[3] Actual Duration of Exposure (weeks) = (date of last dose – date of first dose + 1) / 7
[4] Planned Duration of Exposure (weeks) = ((the number of cycles-1)*21+days) / 7
[5] Actual Dose Intensity = (Actual cumulative dose received) / (Actual duration of exposure)
[6] Planned Dose Intensity = (Planned cumulative dose received) / (Planned duration of exposure)
[7] Relative Dose Intensity = 100 * (Average Dose Intensity) / (Planned Dose Intensity)

Pooled safety population

The pooled safety population was presented according to different dosing regimens with:

- <RP2D/3D: Doses of serplulimab included 0.3 mg/kg/2 week and 1 mg/kg/2 week.
- -≥RP2D/3D: Doses of 3 mg/kg/2 week, 4.5 mg/kg/3 week, 10 mg/kg/2 week, 200 mg/2 week, 300 mg/3 week, 400 mg/4 week and 600 mg/6 week.

Total subjects included all the subjects treated at least one dose with serplulimab; other combination included all other kinds of combinations with serplulimab except chemotherapy combination with serplulimab.

Table 43. Pooled safety population: summary of exposure to serplulimab

	<RP2D/3D			≥RP2D/3D				
	Monotherapy (N=7)	Other Combination (N=3)	Total (N=10)	Monotherapy (N=285)	Chemotherapy Combination (N=1364)	Other Combination (N=427)	Total (N=2076)	Total population (N=2086)
Treated subjects	7	3	10	285	1364	427	2076	2086
Duration of treatment (Month)								
N	7	3	10	285	1364	427	2076	2086
Mean (SD)	2.05 (1.867)	8.47 (2.957)	3.97 (3.726)	5.73 (6.736)	9.34 (9.498)	8.63 (7.851)	8.70 (8.922)	8.68 (8.910)
Median	1.41	9.69	3.06	2.79	6.00	6.28	5.55	5.55
Q1, Q3	0.49, 3.25	5.09, 10.61	0.95, 5.32	0.99, 8.28	3.27, 12.68	2.10, 13.17	2.45, 12.45	2.43, 12.42
Min, Max	0.0, 5.3	5.1, 10.6	0.0, 10.6	0.0, 30.2	0.0, 52.7	0.0, 34.1	0.0, 52.7	0.0, 52.7
≥3 months	2 (28.6%)	3 (100%)	5 (50.0%)	133 (46.7%)	1043 (76.5%)	294 (68.9%)	1470 (70.8%)	1475 (70.7%)
≥ 6 months	0	2 (66.7%)	2 (20.0%)	90 (31.6%)	682 (50.0%)	220 (51.5%)	992 (47.8%)	994 (47.7%)
≥ 9 months	0	2 (66.7%)	2 (20.0%)	66 (23.2%)	464 (34.0%)	162 (37.9%)	692 (33.3%)	694 (33.3%)
Number of administrations								
N	7	3	10	285	1364	427	2076	2086
Mean (SD)	5.1 (3.80)	19.0 (6.08)	9.3 (7.92)	10.6 (11.64)	14.0 (13.00)	13.4 (12.03)	13.4 (12.68)	13.4 (12.66)
Median	4.0	22.0	7.0	6.0	9.0	9.0	9.0	9.0
Q1, Q3	2.0, 7.0	12.0, 23.0	3.0, 12.0	3.0, 12.0	5.0, 19.0	4.0, 19.0	4.0, 19.0	4.0, 19.0
Min, Max	1, 12	12, 23	1, 23	1, 47	1, 73	1, 53	1, 73	1, 73
Cumulative dose (mg)								
N	7	3	10	285	1364	427	2076	2086
Mean (SD)	147.49 (79.566)	1551.20 (411.524)	568.60 (708.250)	2631.99 (3022.934)	3792.39 (4041.754)	3498.33 (3409.802)	3572.61 (3810.846)	3558.21 (3807.642)
Median	130.00	1733.60	165.00	1400.00	2346.00	2450.00	2250.00	2244.00
Q1, Q3	91.00, 173.00	1080.00, 1840.00	126.40, 1080.00	600.00, 3600.00	1203.00, 5016.00	1051.00, 5096.00	1050.00, 4821.75	1043.00, 4800.00
Min, Max	52.0, 303.0	1080.0, 1840.0	52.0, 1840.0	135.0, 26994.3	129.0, 33561.0	135.0, 29818.0	129.0, 33561.0	52.0, 33561.0
Drug Compliance (%)								
N	7	3	10	285	1364	427	2076	2086
Mean (SD)	100.66 (3.987)	100.00 (0.000)	100.46 (3.271)	99.94 (0.859)	99.92 (0.800)	99.88 (0.678)	99.91 (0.785)	99.91 (0.813)
Median	101.12	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Q1, Q3	96.11, 104.00	100.00, 100.00	100.00, 104.00	100.00, 100.00	100.00, 100.00	99.93, 100.00	100.00, 100.00	100.00, 100.00
Min, Max	94.7, 104.7	100.0, 100.0	94.7, 104.7	86.5, 102.6	89.2, 109.1	92.9, 102.1	86.5, 109.1	86.5, 109.1
Relative Dose Intensity (%)								
N	7	3	10	285	1364	427	2076	2086
Mean (SD)	99.81 (4.664)	100.00 (0.000)	99.87 (3.809)	98.66 (3.563)	97.54 (4.365)	98.35 (3.559)	97.86 (4.130)	97.87 (4.130)
Median	101.12	100.00	100.00	100.00	99.75	99.88	99.92	99.93
Q1, Q3	94.69, 104.00	100.00, 100.00	100.00, 101.92	98.25, 100.00	96.42, 100.00	98.13, 100.00	96.92, 100.00	96.92, 100.00
Min, Max	92.3, 104.7	100.0, 100.0	92.3, 104.7	73.7, 113.5	67.7, 109.1	70.0, 103.7	67.7, 113.5	67.7, 113.5

< RP2D/3D: Doses of serplulimab included 0.3 mg/kg/2 week and 1 mg/kg/2 week. ≥RP2D/3D: Doses of 3 mg/kg/2 week, 4.5 mg/kg/3 week, 10 mg/kg/2 week, 200 mg/2 week, 300 mg/3 week, 400 mg/4 week and 600 mg/6 week. Data source: Table 2.7.4.1.2

Demographic and other characteristics

Pivotal study

A summary of the demographic characteristics is included in **Table** 21**. Demographics (ITT).**

Pooled safety population

Table 44. Pooled safety population- Summary of demographic characteristics

	<RP2D/3D			≥RP2D/3D				
	Monotherapy (N=7)	Other Combination (N=3)	Total (N=10)	Monotherapy (N=285)	Chemotherapy Combination (N=1364)	Other Combination (N=427)	Total (N=2076)	Total population (N=2086)
Treated subjects	7	3	10	285	1364	427	2076	2086
Age (year)								
n	7	3	10	285	1364	427	2076	2086
Mean (SD)	60.3 (2.69)	46.3 (13.28)	56.1 (9.46)	57.4 (11.24)	61.4 (8.42)	58.6 (9.70)	60.3 (9.26)	60.3 (9.27)
Median	60.0	54.0	58.5	58.0	63.0	59.0	62.0	61.5
Q1, Q3	57, 63	31, 54	54, 61	52, 65	56, 68	53, 66	55, 67	55, 67
Age Group								
<65	7 (100)	3 (100)	10 (100)	210 (73.7)	794 (58.2)	298 (69.8)	1302 (62.7)	1312 (62.9)
≥65	0	0	0	75 (26.3)	570 (41.8)	129 (30.2)	774 (37.3)	774 (37.1)
Sex								
Male	4 (57.1)	1 (33.3)	5 (50.0)	205 (71.9)	1123 (82.3)	328 (76.8)	1656 (79.8)	1661 (79.6)
Female	3 (42.9)	2 (66.7)	5 (50.0)	80 (28.1)	241 (17.7)	99 (23.2)	420 (20.2)	425 (20.4)
Height (cm)								
n	7	3	10	284	1359	426	2069	2079
Mean (SD)	158.50 (6.817)	164.00 (8.544)	160.15 (7.366)	165.12 (7.868)	166.66 (8.070)	165.91 (7.532)	166.29 (7.950)	166.26 (7.957)
Median	160.00	163.00	160.50	165.50	168.00	167.00	167.00	167.00
Q1, Q3	150.0, 164.0	156.0, 173.0	156.0, 164.0	160.0, 170.0	161.0, 172.0	160.0, 171.0	160.0, 172.0	160.0, 172.0
Missing	0	0	0	1	5	1	7	7
Weight (kg)								
n	7	3	10	285	1363	427	2075	2085
Mean (SD)	57.34 (10.951)	85.20 (5.897)	65.70 (16.393)	62.21 (12.613)	64.14 (13.480)	62.84 (10.229)	63.61 (12.774)	63.62 (12.790)
Median	53.50	82.90	63.85	61.00	62.00	62.00	62.00	62.00
Q1, Q3	48.3, 64.0	80.8, 91.9	52.0, 80.8	54.0, 68.5	55.0, 71.0	55.0, 69.0	55.0, 70.0	55.0, 70.0
Missing	0	0	0	0	1	0	1	1
BMI (kg/m^2)								
n	7	3	10	284	1358	426	2068	2078
Mean (SD)	22.99 (5.337)	31.70 (1.321)	25.61 (6.089)	22.73 (3.833)	23.01 (4.034)	22.79 (3.082)	22.93 (3.829)	22.94 (3.845)
Median	22.84	31.20	23.87	22.37	22.49	22.87	22.54	22.55
Q1, Q3	19.3, 24.1	30.7, 33.2	20.3, 31.2	20.2, 24.8	20.1, 25.2	20.5, 24.8	20.2, 25.1	20.2, 25.1
Missing	0	0	0	1	6	1	8	8
ECOG at Baseline								
0	3 (42.9)	1 (33.3)	4 (40.0)	104 (36.5)	301 (22.1)	143 (33.5)	548 (26.4)	552 (26.5)
1	3 (42.9)	2 (66.7)	5 (50.0)	179 (62.8)	1063 (77.9)	283 (66.3)	1525 (73.5)	1530 (73.3)
2	1 (14.3)	0	1 (10.0)	2 (0.7)	0	0	2 (0.1)	3 (0.1)
Missing	0	0	0	0	0	1 (0.2)	1 (<0.1)	1 (<0.1)
Disease Stage								
I	0	0	0	1 (0.4)	1 (0.1)	1 (0.2)	3 (0.1)	3 (0.1)
II	0	0	0	1 (0.4)	4 (0.3)	8 (1.9)	13 (0.6)	13 (0.6)
III	0	0	0	33 (11.6)	205 (15.0)	74 (17.3)	312 (15.0)	312 (15.0)
IV	7 (100)	3 (100)	10 (100)	249 (87.4)	1100 (80.6)	330 (77.3)	1679 (80.9)	1689 (81.0)
Missing	0	0	0	1 (0.4)	54 (4.0)	14 (3.3)	69 (3.3)	69 (3.3)

Adverse events

Overall safety evaluation plan

Pivotal study

This is the only phase III clinical study of serplulimab conducted in subjects with squamous NSCLC.. All adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system version 25.0. AEs were recorded starting from the signing of ICF until 90 days after the final study treatment. If a subject initiated a new anti-tumor treatment during the AE collection period, only SAEs related to study treatment were collected after the start of the new anti-tumor treatment, after that only study treatment-related SAE were collected. Adverse events of special interest (AESIs) included infusion-related adverse reactions (IRRs) and immune-related adverse events (irAEs). The severity of AEs was classified in accordance with CTCAE 5.0. For the

placebo arm safety data from all subjects treated with placebo who did not switch to serplulimab monotherapy or data only before switching were included. Correspondingly, safety data for the group who switched from placebo to serplulimab monotherapy included only data after switching (SAP 4.10.2).

Pooled Safety Population

Table 45. Grouping Structure of the Pooled Safety Dataset

Dose Category	Treatment
< RP2D/3D [a]: • 0.3 mg/kg Q2W • 1 mg/kg Q2W	Monotherapy
	Other Combination
≥ RP2D/3D: • 3 mg/kg Q2W • 4.5 mg/kg Q3W • 10 mg/kg Q2W • 200 mg Q2W • 300 mg Q3W • 400 mg Q4W • 600 mg Q6W	Monotherapy
	Chemotherapy Combination
	Other Combination

Abbreviations: RP2D/3D = recommended phase II/III dose, Q2W = once every 2 weeks, Q3W = once every 3 weeks, Q4W = once every 4 weeks, Q6W = once every 6 weeks. a In the < RP2D/3D group, no subjects received serplulimab in combination with chemotherapy

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used in HLX10-001, HLX10HLX04-001 and HLX10-007-EC301 studies, CTCAE version 5.0 was used in the other studies. MedDRA version 27.0 was used in all ten pooled studies.

All safety variables were summarized using descriptive statistics. In tables summarizing TEAEs, certain common MedDRA preferred terms (PTs) were grouped together based on medical experiences. For example, "Hypoalbuminaemia", "Hypoproteinaemia", and "Blood albumin decreased" were grouped into "Hypoproteinaemia". The ungrouped AEs were presented by the original MedDRA SOC and PT.

Adverse events of special interest (AESIs), including Investigator-reported immune-related adverse events (irAEs) and infusion-related reactions (IRRs), were grouped. In addition, Standardized MedDRA Queries (SMQs) were also used for the presentation of AESIs.

Overview of adverse events

Pooled safety population

Table 46. Pooled safety population: overview of adverse events

	< RP2D/3D			≥ RP2D/3D				
	Monotherapy (N=7)	Other Combination (N=3)	Total (N=10)	Monotherapy (N=285)	Chemotherapy Combination (N=1364)	Other Combination (N=427)	Total (N=2076)	Total population (N=2086)
All adverse events	7 (100%)	3 (100%)	10 (100%)	272 (95.4%)	1347 (98.8%)	415 (97.2%)	2034 (98.0%)	2044 (98.0%)
TEAEs	7 (100%)	3 (100%)	10 (100%)	270 (94.7%)	1342 (98.4%)	415 (97.2%)	2027 (97.6%)	2037 (97.7%)
CTCAE Grade ≥ 3	5 (71.4%)	2 (66.7%)	7 (70.0%)	127 (44.6%)	1059 (77.6%)	273 (63.9%)	1459 (70.3%)	1466 (70.3%)
Serplulimab-related TEAEs	6 (85.7%)	3 (100%)	9 (90.0%)	199 (69.8%)	1073 (78.7%)	369 (86.4%)	1641 (79.0%)	1650 (79.1%)
CTCAE Grade ≥ 3	2 (28.6%)	1 (33.3%)	3 (30.0%)	58 (20.4%)	496 (36.4%)	159 (37.2%)	713 (34.3%)	716 (34.3%)
Drug-related TEAEs	6 (85.7%)	3 (100%)	9 (90.0%)	206 (72.3%)	1321 (96.8%)	399 (93.4%)	1926 (92.8%)	1935 (92.8%)
CTCAE Grade ≥ 3	2 (28.6%)	2 (66.7%)	4 (40.0%)	58 (20.4%)	928 (68.0%)	233 (54.6%)	1219 (58.7%)	1223 (58.6%)
TESAEs	5 (71.4%)	0	5 (50.0%)	92 (32.3%)	601 (44.1%)	173 (40.5%)	866 (41.7%)	871 (41.8%)
CTCAE Grade ≥ 3	4 (57.1%)	0	4 (40.0%)	74 (26.0%)	500 (36.7%)	145 (34.0%)	719 (34.6%)	723 (34.7%)
Serplulimab-related TESAEs	2 (28.6%)	0	2 (20.0%)	35 (12.3%)	298 (21.8%)	96 (22.5%)	429 (20.7%)	431 (20.7%)
CTCAE Grade ≥ 3	1 (14.3%)	0	1 (10.0%)	30 (10.5%)	229 (16.8%)	77 (18.0%)	336 (16.2%)	337 (16.2%)
TEAEs leading to serplulimab discontinuation	3 (42.9%)	0	3 (30.0%)	32 (11.2%)	150 (11.0%)	57 (13.3%)	239 (11.5%)	242 (11.6%)
CTCAE Grade ≥ 3	3 (42.9%)	0	3 (30.0%)	26 (9.1%)	104 (7.6%)	45 (10.5%)	175 (8.4%)	178 (8.5%)
Serplulimab-related	1 (14.3%)	0	1 (10.0%)	14 (4.9%)	94 (6.9%)	41 (9.6%)	149 (7.2%)	150 (7.2%)
TEAEs leading to serplulimab interruption	5 (71.4%)	2 (66.7%)	7 (70.0%)	86 (30.2%)	732 (53.7%)	227 (53.2%)	1045 (50.3%)	1052 (50.4%)
CTCAE Grade ≥ 3	3 (42.9%)	0	3 (30.0%)	39 (13.7%)	436 (32.0%)	123 (28.8%)	598 (28.8%)	601 (28.8%)
Serplulimab-related	3 (42.9%)	0	3 (30.0%)	54 (18.9%)	433 (31.7%)	161 (37.7%)	648 (31.2%)	651 (31.2%)
TEAEs leading to death	2 (28.6%)	0	2 (20.0%)	38 (13.3%)	155 (11.4%)	51 (11.9%)	244 (11.8%)	246 (11.8%)
CTCAE Grade ≥ 3	2 (28.6%)	0	2 (20.0%)	38 (13.3%)	155 (11.4%)	51 (11.9%)	244 (11.8%)	246 (11.8%)
Serplulimab-related	1 (14.3%)	0	1 (10.0%)	9 (3.2%)	28 (2.1%)	12 (2.8%)	49 (2.4%)	50 (2.4%)
All serious adverse events	5 (71.4%)	0	5 (50.0%)	92 (32.3%)	603 (44.2%)	174 (40.7%)	869 (41.9%)	874 (41.9%)
AESIs	1 (14.3%)	3 (100%)	4 (40.0%)	93 (32.6%)	487 (35.7%)	151 (35.4%)	731 (35.2%)	735 (35.2%)
CTCAE Grade ≥ 3	0	1 (33.3%)	1 (10.0%)	24 (8.4%)	127 (9.3%)	38 (8.9%)	189 (9.1%)	190 (9.1%)
IRRs	0	0	0	3 (1.1%)	25 (1.8%)	7 (1.6%)	35 (1.7%)	35 (1.7%)
CTCAE Grade ≥ 3	0	0	0	0	5 (0.4%)	0	5 (0.2%)	5 (0.2%)
irAEs	1 (14.3%)	3 (100%)	4 (40.0%)	91 (31.9%)	473 (34.7%)	146 (34.2%)	710 (34.2%)	714 (34.2%)
CTCAE Grade ≥ 3	0	1 (33.3%)	1 (10.0%)	24 (8.4%)	122 (8.9%)	38 (8.9%)	184 (8.9%)	185 (8.9%)

CTCAE: Common Terminology Criteria for Adverse Events. < RP2D/3D: Doses of serplulimab included 0.3 mg/kg/2 week and 1 mg/kg/2 week. ≥ RP2D/3D: Doses of 3 mg/kg/2 week, 4.5 mg/kg/3 week, 10 mg/kg/2 week, 200 mg/2 week, 300 mg/3 week, 400 mg/4 week and 600 mg/6 week. Total patients included all the patients treated at least one dose with serplulimab; other combinations included all other kinds of combinations with serplulimab except chemotherapy combination with serplulimab. Percentage was based on the safety population as denominator. TEAEs were AEs that developed or worsened during the on-treatment period. CTCAE 4.03 version was used in HLX10-001, HLX10HLX04-001 and HLX10-007-EC301, CTCAE 5.0 version was used in other studies.

Treatment emergent adverse events (TEAEs)

Pivotal trial

Table *47*. Overview of treatment-emergent adverse events (TEAEs) (safety set)

	HLX10 (N=358)	Placebo (N=179)	Placebo Switched to HLX10 (N=97)	Total (N=537)
	n (%) E	n (%) E	n (%) E	n (%) E
Any Treatment-emergent adverse events (TEAEs)	354 (98.9) 13175	176 (98.3) 4976	88 (90.7) 851	531 (98.9) 19002
TEAEs by Grade	354 (98.9) 1031	176 (98.3) 542	88 (90.7) 175	531 (98.9) 1551
Grade 1	7 (2.0) 15	1 (0.6) 1	17 (17.5) 53	9 (1.7) 17
Grade 2	42 (11.7) 206	33 (18.4) 151	36 (37.1) 72	65 (12.1) 322
Grade 3	150 (41.9) 561	83 (46.4) 290	20 (20.6) 33	232 (43.2) 852
Grade 4	106 (29.6) 196	40 (22.3) 73	3 (3.1) 4	145 (27.0) 267
Grade 5	49 (13.7) 53	19 (10.6) 27	12 (12.4) 13	80 (14.9) 93
≥ Grade 3	305 (85.2) 810	142 (79.3) 390	35 (36.1) 50	457 (85.1) 1212
TEAEs related to HLX10/Placebo by Grade	262 (73.2) 664	112 (62.6) 296	62 (63.9) 167	388 (72.3) 989
Grade 1	51 (14.2) 174	24 (13.4) 75	28 (28.9) 107	74 (13.8) 254
Grade 2	84 (23.5) 181	31 (17.3) 90	21 (21.6) 44	124 (23.1) 291
Grade 3	80 (22.3) 214	37 (20.7) 94	9 (9.3)12	119 (22.2) 308
Grade 4	43 (12.0) 90	18 (10.1) 35	2 (2.1)2	63 (11.7) 127
Grade 5	4 (1.1) 5	2 (1.1) 2	2 (2.1)2	8 (1.5) 9
≥ Grade 3	127 (35.5) 309	57 (31.8) 131	13 (13.4)16	190 (35.4) 444
TEAEs Related to Any Study Drug	345 (96.4) 10013	170 (95.0) 3900	69 (71.1) 389	516 (96.1) 14302
Related to HLX10/Placebo	262 (73.2) 4791	112 (62.6) 1571	62 (63.9) 351	388 (72.3) 6713
Related to Carboplatin or Nab-Paclitaxel	345 (96.4) 8904	170 (95.0) 3697	35 (36.1) 111	515 (95.9) 12712
TESAEs	186 (52.0) 565	76 (42.5) 187	21 (21.6) 44	274 (51.0) 796
TESAEs by Grade	186 (52.0) 245	76 (42.5) 107	21 (21.6) 25	274 (51.0) 368
Grade 1	6 (1.7) 6	3 (1.7) 3	0	9 (1.7) 9
Grade 2	26 (7.3) 34	11 (6.1) 15	3 (3.1) 5	38 (7.1) 52
Grade 3	68 (19.0) 89	30 (16.8) 41	4 (4.1) 4	97 (18.1) 130
Grade 4	37 (10.3) 63	13 (7.3) 21	2 (2.1) 3	50 (9.3) 84
Grade 5	49 (13.7) 53	19 (10.6) 27	12 (12.4) 13	80 (14.9) 93
≥ Grade 3	154 (43.0) 205	62 (34.6) 89	18 (18.6) 20	227 (42.3) 307
TESAEs Related to HLX10/Placebo by Grade	81 (22.6) 116	28 (15.6) 36	7 (7.2) 7	116 (21.6) 159
Grade 1	2 (0.6) 2	1 (0.6) 1	0	3 (0.6) 3
Grade 2	18 (5.0) 27	8 (4.5) 11	1 (1.0) 1	27 (5.0) 39
Grade 3	39 (10.9) 50	12 (6.7) 12	2 (2.1) 2	53 (9.9) 64
Grade 4	18 (5.0) 32	5 (2.8) 10	2 (2.1) 2	25 (4.7) 44
Grade 5	4 (1.1) 5	2 (1.1) 2	2 (2.1) 2	8 (1.5) 9

≥ Grade 3	61 (17.0) 87	19 (10.6) 24	6 (6.2) 6	86 (16.0) 117
TESAEs Related to Any Study Drug	119 (33.2) 383	49 (27.4) 120	8 (8.2) 15	174 (32.4) 518
Related to HLX10/Placebo	81 (22.6) 258	28(15.6) 59	7 (7.2) 14	116 (21.6) 331
Related to Carboplatin or Nab-Paclitaxel	101 (28.2) 309	44 (24.6) 108	2 (2.1) 2	146 (27.2) 419
TEAEs Leading to Any Study Drug Interruption	284 (79.3) 2146	140 (78.2) 794	23 (23.7) 51	425 (79.1) 2991
HLX10/Placebo	226 (63.1) 1184	92 (51.4) 346	23 (23.7) 51	326 (60.7) 1581
Carboplatin or Nab-Paclitaxel	277 (77.4) 1749	139 (77.7) 699	0	416 (77.5) 2448
TEAEs Related to HLX10/Placebo Leading to Any Study Drug Interruption	153 (42.7) 1013	68 (38.0) 322	13 (13.4) 34	230 (42.8) 1369
HLX10/Placebo	134 (37.4)660	45 (25.1) 173	13 (13.4) 34	188 (35.0) 867
Carboplatin or Nab-Paclitaxel	121 (33.8)781	65 (36.3) 267	0	186 (34.6) 1048
TEAEs Leading to Any Study Drug Discontinuation	80 (22.3) 160	27 (15.1) 51	12 (12.4) 17	118 (22.0) 228
HLX10/Placebo	60 (16.8) 106	23 (12.8) 36	12 (12.4) 17	95 (17.7) 159
Carboplatin or Nab-Paclitaxel	54 (15.1) 109	18 (10.1) 36	0	72 (13.4)145
TEAEs Related to HLX10/Placebo Leading to Any Study Drug Discontinuation	37 (10.3) 60	9 (5.0) 13	5 (5.2) 7	51 (9.5) 80
HLX10/Placebo	31 (8.7) 51	8 (4.5) 11	5 (5.2) 7	44 (8.2) 69
Carboplatin or Nab-Paclitaxel	23 (6.4) 32	5 (2.8) 9	0	28 (5.2) 41
Treatment-Emergent Injection Reaction (IRR)	4 (1.1) 4	0	0	4 (0.7) 4
TEAE of Special Interest (AESI)	109 (30.4) 523	31 (17.3) 88	21 (21.6) 63	155 (28.9) 674
Immune Related Adverse Event	106 (29.6) 519	31 (17.3) 88	21 (21.6) 63	152 (28.3) 670
TEAEs Leading to Death	49 (13.7) 53	19 (10.6) 28	12 (12.4) 13	80 (14.9) 94
TEAEs Leading to Death and Related to Any Study Drug	4 (1.1) 5	5 (2.8) 5	2 (2.1) 2	11 (2.0) 12
Related to HLX10/Placebo	4 (1.1) 5	2 (1.1) 2	2 (2.1) 2	8 (1.5) 9
Related to Carboplatin or Nab-Paclitaxel	1 (0.3) 1	5 (2.8) 5	0	6 (1.1) 6

Note: E= Frequency of specified adverse events. 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. 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. Subjects had one or more than one AESI applied. When summarizing AE events (E), only AEs with the maximum CTCAE grade for a subject were counted. Missing Causality was imputed as 'related'.

Table 48. Most common TEAEs (≥5%) summarized by SOC and PT

System Organ Class (SOC) Preferred Term (PT)	HLX10 (N=358)	Placebo (N=179)	Placebo Switched to HLX10 (N=97)	Total (N=537)
Any TEAE with an incidence ≥ 5%, n (%)	350 (97.8)	174 (97.2)	77 (79.4)	525 (97.8)
Blood and lymphatic system disorders, n (%)	321 (89.7)	158 (88.3)	34 (35.1)	479 (89.2)
Anaemia	302 (84.4)	144 (80.4)	31 (32.0)	446 (83.1)
Neutropenia	107 (29.9)	59 (33.0)	3 (3.1)	167 (31.1)
Leukopenia	89 (24.9)	38 (21.2)	2 (2.1)	128 (23.8)
Thrombocytopenia	81 (22.6)	33 (18.4)	4 (4.1)	114 (21.2)
Investigations, n (%)	279 (77.9)	130 (72.6)	48 (49.5)	413 (76.9)
White blood cell count decreased	212 (59.2)	101 (56.4)	9 (9.3)	313 (58.3)
Neutrophil count decreased	211 (58.9)	95 (53.1)	4 (4.1)	306 (57.0)
Platelet count decreased	176 (49.2)	87 (48.6)	9 (9.3)	264 (49.2)
Alanine aminotransferase increased	84 (23.5)	28 (15.6)	19 (19.6)	127 (23.6)
Aspartate aminotransferase increased	76 (21.2)	20 (11.2)	20 (20.6)	113 (21.0)
Weight decreased	45 (12.6)	17 (9.5)	9 (9.3)	69 (12.8)
Weight increased	46 (12.8)	20 (11.2)	6 (6.2)	68 (12.7)
Lymphocyte count decreased	41 (11.5)	20 (11.2)	6 (6.2)	64 (11.9)
Blood alkaline phosphatase increased	33 (9.2)	17 (9.5)	7 (7.2)	55 (10.2)
Blood lactate dehydrogenase increased	30 (8.4)	11 (6.1)	9 (9.3)	47 (8.8)
Gamma-glutamyltransferase increased	26 (7.3)	15 (8.4)	7 (7.2)	45 (8.4)
Blood creatinine increased	26 (7.3)	5 (2.8)	5 (5.2)	35 (6.5)
Blood bilirubin increased	18 (5.0)	9 (5.0)	0	27 (5.0)
Metabolism and nutrition disorders, n (%)	241 (67.3)	112 (62.6)	40 (41.2)	361 (67.2)
Decreased appetite	124 (34.6)	59 (33.0)	13 (13.4)	188 (35.0)
Hypoalbuminaemia	74 (20.7)	41 (22.9)	8 (8.2)	117 (21.8)
Hyponatraemia	60 (16.8)	27 (15.1)	8 (8.2)	88 (16.4)
Hypokalaemia	63 (17.6)	19 (10.6)	4 (4.1)	85 (15.8)
Hypocalcaemia	40 (11.2)	17 (9.5)	5 (5.2)	61 (11.4)
Hypomagnesaemia	40 (11.2)	16 (8.9)	7 (7.2)	61 (11.4)
Hyperglycaemia	33 (9.2)	10 (5.6)	6 (6.2)	48 (8.9)
Hypercholesterolaemia	19 (5.3)	12 (6.7)	10 (10.3)	37 (6.9)
Hyperuricaemia	23 (6.4)	8 (4.5)	5 (5.2)	34 (6.3)
Hypoproteinaemia	21 (5.9)	11 (6.1)	2 (2.1)	33 (6.1)
Hypertriglyceridaemia	21 (5.9)	8 (4.5)	7 (7.2)	33 (6.1)
Hypochloraemia	25 (7.0)	7 (3.9)	2 (2.1)	32 (6.0)
Hyperlipidaemia	22 (6.1)	6 (3.4)	3 (3.1)	29 (5.4)
Hypophosphataemia	21 (5.9)	7 (3.9)	3 (3.1)	29 (5.4)

Skin and subcutaneous tissue disorders, n (%)	235 (65.6)	105 (58.7)	8 (8.2)	341 (63.5)
Alopecia	218 (60.9)	99 (55.3)	1 (1.0)	318 (59.2)
Rash	47 (13.1)	11 (6.1)	3 (3.1)	60 (11.2)
Pruritus	24 (6.7)	9 (5.0)	4 (4.1)	37 (6.9)
General disorders and administration site conditions, n (%)	196 (54.7)	87 (48.6)	22 (22.7)	288 (53.6)
Pyrexia	75 (20.9)	31 (17.3)	8 (8.2)	110 (20.5)
Fatigue	65 (18.2)	23 (12.8)	6 (6.2)	92 (17.1)
Asthenia	64 (17.9)	22 (12.3)	4 (4.1)	89 (16.6)
Non-cardiac chest pain	29 (8.1)	16 (8.9)	5 (5.2)	49 (9.1)
Oedema peripheral	35 (9.8)	12 (6.7)	0	47 (8.8)
Malaise	24 (6.7)	13 (7.3)	0	37 (6.9)
Chest discomfort	18 (5.0)	12 (6.7)	2 (2.1)	32 (6.0)
Gastrointestinal disorders, n (%)	193 (53.9)	83 (46.4)	13 (13.4)	280 (52.1)
Nausea	118 (33.0)	45 (25.1)	4 (4.1)	165 (30.7)
Constipation	81 (22.6)	25 (14.0)	3 (3.1)	108 (20.1)
Vomiting	72 (20.1)	24 (13.4)	5 (5.2)	101 (18.8)
Diarrhoea	61 (17.0)	31 (17.3)	4 (4.1)	95 (17.7)
Respiratory, thoracic and mediastinal disorders, n (%)	134 (37.4)	75 (41.9)	30 (30.9)	218 (40.6)
Dyspnoea	61 (17.0)	31 (17.3)	12 (12.4)	101 (18.8)
Cough	60 (16.8)	33 (18.4)	10 (10.3)	100 (18.6)
Haemoptysis	54 (15.1)	43 (24.0)	13 (13.4)	100 (18.6)
Productive cough	28 (7.8)	9 (5.0)	5 (5.2)	41 (7.6)
Musculoskeletal and connective tissue disorders, n (%)	113 (31.6)	41 (22.9)	14 (14.4)	161 (30.0)
Pain in extremity	54 (15.1)	17 (9.5)	4 (4.1)	74 (13.8)
Arthralgia	51 (14.2)	20 (11.2)	6 (6.2)	73 (13.6)
Back pain	39 (10.9)	14 (7.8)	7 (7.2)	60 (11.2)
Infections and infestations, n (%)	105 (29.3)	42 (23.5)	8 (8.2)	153 (28.5)

Pooled Safety Population

Table 49. Pooled Safety Population: Summary of Adverse Events

	< RP2D/3D			**≥ RP2D/3D**			
	Monotherapy (N=7)	**Other Combination (N=3)**	**Total (N=10)**	**Monotherapy (N=285)**	**Chemotherapy Combination (N=1364)**	**Other Combination (N=427)**	**Total (N=2076)**	**Total population (N=2086)**
All adverse events	7 (100%)	3 (100%)	10 (100%)	272 (95.4%)	1347 (98.8%)	415 (97.2%)	2034 (98.0%)	2044 (98.0%)
TEAEs	7 (100%)	3 (100%)	10 (100%)	270 (94.7%)	1342 (98.4%)	415 (97.2%)	2027 (97.6%)	2037 (97.7%)

	< RP2D/3D			≥ RP2D/3D				
	Monotherapy (N=7)	**Other Combination (N=3)**	**Total (N=10)**	**Monotherapy (N=285)**	**Chemotherapy Combination (N=1364)**	**Other Combination (N=427)**	**Total (N=2076)**	**Total population (N=2086)**
CTCAE Grade ≥ 3	5 (71.4%)	2 (66.7%)	7 (70.0%)	127 (44.6%)	1059 (77.6%)	273 (63.9%)	1459 (70.3%)	1466 (70.3%)
Serplulimab-related TEAEs	6 (85.7%)	3 (100%)	9 (90.0%)	199 (69.8%)	1073 (78.7%)	369 (86.4%)	1641 (79.0%)	1650 (79.1%)
CTCAE Grade ≥ 3	2 (28.6%)	1 (33.3%)	3 (30.0%)	58 (20.4%)	496 (36.4%)	159 (37.2%)	713 (34.3%)	716 (34.3%)
Drug-related TEAEs	6 (85.7%)	3 (100%)	9 (90.0%)	206 (72.3%)	1321 (96.8%)	399 (93.4%)	1926 (92.8%)	1935 (92.8%)
CTCAE Grade ≥ 3	2 (28.6%)	2 (66.7%)	4 (40.0%)	58 (20.4%)	928 (68.0%)	233 (54.6%)	1219 (58.7%)	1223 (58.6%)
TESAEs	5 (71.4%)	0	5 (50.0%)	92 (32.3%)	601 (44.1%)	173 (40.5%)	866 (41.7%)	871 (41.8%)
CTCAE Grade ≥ 3	4 (57.1%)	0	4 (40.0%)	74 (26.0%)	500 (36.7%)	145 (34.0%)	719 (34.6%)	723 (34.7%)
Serplulimab-related TESAEs	2 (28.6%)	0	2 (20.0%)	35 (12.3%)	298 (21.8%)	96 (22.5%)	429 (20.7%)	431 (20.7%)
CTCAE Grade ≥ 3	1 (14.3%)	0	1 (10.0%)	30 (10.5%)	229 (16.8%)	77 (18.0%)	336 (16.2%)	337 (16.2%)
TEAEs leading to serplulimab discontinuation	3 (42.9%)	0	3 (30.0%)	32 (11.2%)	150 (11.0%)	57 (13.3%)	239 (11.5%)	242 (11.6%)
CTCAE Grade ≥ 3	3 (42.9%)	0	3 (30.0%)	26 (9.1%)	104 (7.6%)	45 (10.5%)	175 (8.4%)	178 (8.5%)

	< RP2D/3D			≥ RP2D/3D				
	Monotherapy (N=7)	**Other Combination (N=3)**	**Total (N=10)**	**Monotherapy (N=285)**	**Chemotherapy Combination (N=1364)**	**Other Combination (N=427)**	**Total (N=2076)**	**Total population (N=2086)**
Serplulimab-related	1 (14.3%)	0	1 (10.0%)	14 (4.9%)	94 (6.9%)	41 (9.6%)	149 (7.2%)	150 (7.2%)
TEAEs leading to serplulimab interruption	5 (71.4%)	2 (66.7%)	7 (70.0%)	86 (30.2%)	732 (53.7%)	227 (53.2%)	1045 (50.3%)	1052 (50.4%)
CTCAE Grade ≥ 3	3 (42.9%)	0	3 (30.0%)	39 (13.7%)	436 (32.0%)	123 (28.8%)	598 (28.8%)	601 (28.8%)
Serplulimab-related	3 (42.9%)	0	3 (30.0%)	54 (18.9%)	433 (31.7%)	161 (37.7%)	648 (31.2%)	651 (31.2%)
TEAEs leading to death	2 (28.6%)	0	2 (20.0%)	38 (13.3%)	155 (11.4%)	51 (11.9%)	244 (11.8%)	246 (11.8%)
CTCAE Grade ≥ 3	2 (28.6%)	0	2 (20.0%)	38 (13.3%)	155 (11.4%)	51 (11.9%)	244 (11.8%)	246 (11.8%)
Serplulimab-related	1 (14.3%)	0	1 (10.0%)	9 (3.2%)	28 (2.1%)	12 (2.8%)	49 (2.4%)	50 (2.4%)
All serious adverse events	5 (71.4%)	0	5 (50.0%)	92 (32.3%)	603 (44.2%)	174 (40.7%)	869 (41.9%)	874 (41.9%)
AESIs	1 (14.3%)	3 (100%)	4 (40.0%)	93 (32.6%)	487 (35.7%)	151 (35.4%)	731 (35.2%)	735 (35.2%)

	< RP2D/3D			≥ RP2D/3D				
	Monotherapy (N=7)	**Other Combination (N=3)**	**Total (N=10)**	**Monotherapy (N=285)**	**Chemotherapy Combination (N=1364)**	**Other Combination (N=427)**	**Total (N=2076)**	**Total population (N=2086)**
CTCAE Grade ≥ 3	0	1 (33.3%)	1 (10.0%)	24 (8.4%)	127 (9.3%)	38 (8.9%)	189 (9.1%)	190 (9.1%)
IRRs	0	0	0	3 (1.1%)	25 (1.8%)	7 (1.6%)	35 (1.7%)	35 (1.7%)
CTCAE Grade ≥ 3	0	0	0	0	5 (0.4%)	0	5 (0.2%)	5 (0.2%)
irAEs	1 (14.3%)	3 (100%)	4 (40.0%)	91 (31.9%)	473 (34.7%)	146 (34.2%)	710 (34.2%)	714 (34.2%)
CTCAE Grade ≥ 3	0	1 (33.3%)	1 (10.0%)	24 (8.4%)	122 (8.9%)	38 (8.9%)	184 (8.9%)	185 (8.9%)

CTCAE: Common Terminology Criteria for Adverse Events.
< RP2D/3D: Doses of serplulimab included 0.3 mg/kg/2 week and 1 mg/kg/2 week.
≥ RP2D/3D: Doses of 3 mg/kg/2 week, 4.5 mg/kg/3 week, 10 mg/kg/2 week, 200 mg/2 week, 300 mg/3 week, 400 mg/4 week and 600 mg/6 week.
Total patients included all the patients treated at least one dose with serplulimab; other combinations included all other kinds of combinations with serplulimab except chemotherapy combination with serplulimab.
Percentage was based on the safety population as denominator.
TEAEs were AEs that developed or worsened during the on-treatment period.
CTCAE 4.03 version was used in HLX10-001, HLX10HLX04-001 and HLX10-007-EC301, CTCAE 5.0 version was used in other studies.

Treatment related TEAEs

Pivotal study

Table 50. Summary of most frequent TEAEs (>1%) related to hlx10/placebo by soc and pt (safety set)

System Organ Class (SOC) Preferred Term (PT)	HLX10 (N=358)	Placebo (N=179)	Placebo Switched to HLX10 (N=97)	Total (N=537)
Any HLX10/placebo-related TEAE with an incidence ≥ 1%, n (%)	248 (69.3)	106 (59.2)	57 (58.8)	367 (68.3)
Investigations, n (%)	161 (45.0)	69 (38.5)	33 (34.0)	242 (45.1)
White blood cell count decreased	79 (22.1)	40 (22.3)	7 (7.2)	119 (22.2)
Neutrophil count decreased	80 (22.3)	38 (21.2)	2 (2.1)	118 (22.0)
Platelet count decreased	70 (19.6)	34 (19.0)	6 (6.2)	107 (19.9)
Alanine aminotransferase increased	50 (14.0)	13 (7.3)	14 (14.4)	75 (14.0)
Aspartate aminotransferase increased	49 (13.7)	9 (5.0)	13 (13.4)	70 (13.0)
Blood alkaline phosphatase increased	14 (3.9)	8 (4.5)	4 (4.1)	25 (4.7)
Gamma-glutamyltransferase increased	13 (3.6)	8 (4.5)	5 (5.2)	25 (4.7)
Blood bilirubin increased	14 (3.9)	6 (3.4)	0	20 (3.7)
Blood creatinine increased	13 (3.6)	2 (1.1)	5 (5.2)	19 (3.5)
Blood lactate dehydrogenase increased	11 (3.1)	2 (1.1)	5 (5.2)	17 (3.2)
Blood creatine phosphokinase increased	12 (3.4)	3 (1.7)	2 (2.1)	16 (3.0)
Blood thyroid stimulating hormone increased	10 (2.8)	3 (1.7)	2 (2.1)	15 (2.8)
Lymphocyte count decreased	10 (2.8)	3 (1.7)	2 (2.1)	15 (2.8)
Bilirubin conjugated increased	8 (2.2)	5 (2.8)	1 (1.0)	14 (2.6)
Protein urine present	8 (2.2)	2 (1.1)	5 (5.2)	14 (2.6)
Neutrophil percentage decreased	8 (2.2)	5 (2.8)	1 (1.0)	13 (2.4)
Weight increased	7 (2.0)	5 (2.8)	1 (1.0)	12 (2.2)
Blood glucose increased	7 (2.0)	5 (2.8)	0	12 (2.2)
Blood cholesterol increased	8 (2.2)	3 (1.7)	1 (1.0)	11 (2.0)
Brain natriuretic peptide increased	6 (1.7)	3 (1.7)	1 (1.0)	10 (1.9)
Blood urea increased	5 (1.4)	4 (2.2)	2 (2.1)	10 (1.9)
Weight decreased	7 (2.0)	1 (0.6)	1 (1.0)	9 (1.7)
Electrocardiogram QT prolonged	6 (1.7)	0	2 (2.1)	8 (1.5)
Blood thyroid stimulating hormone decreased	5 (1.4)	1 (0.6)	0	6 (1.1)
Blood and lymphatic system disorders, n (%)	134 (37.4)	66 (36.9)	16 (16.5)	204 (38.0)
Anaemia	118 (33.0)	51 (28.5)	14 (14.4)	172 (32.0)
Neutropenia	36 (10.1)	23 (12.8)	2 (2.1)	61 (11.4)
Thrombocytopenia	36 (10.1)	17 (9.5)	1 (1.0)	54 (10.1)
Leukopenia	33 (9.2)	17 (9.5)	1 (1.0)	51 (9.5)
Metabolism and nutrition disorders, n (%)	101 (28.2)	39 (21.8)	12 (12.4)	149 (27.7)
Decreased appetite	52 (14.5)	27 (15.1)	4 (4.1)	81 (15.1)
Hyperglycaemia	15 (4.2)	2 (1.1)	4 (4.1)	21 (3.9)

Hypomagnesaemia	15 (4.2)	2 (1.1)	1 (1.0)	18 (3.4)
Hyponatraemia	15 (4.2)	1 (0.6)	1 (1.0)	17 (3.2)
Hypokalaemia	13 (3.6)	2 (1.1)	1 (1.0)	16 (3.0)
Hypoalbuminaemia	12 (3.4)	3 (1.7)	2 (2.1)	16 (3.0)
Hyperlipidaemia	9 (2.5)	2 (1.1)	0	11 (2.0)
Hypoproteinaemia	7 (2.0)	4 (2.2)	0	11 (2.0)
Hypercholesterolaemia	5 (1.4)	4 (2.2)	1 (1.0)	10 (1.9)
Hypocalcaemia	5 (1.4)	2 (1.1)	1 (1.0)	8 (1.5)
Hypophosphataemia	5 (1.4)	2 (1.1)	0	7 (1.3)
Hyperuricaemia	4 (1.1)	3 (1.7)	0	7 (1.3)
Hypochloraemia	5 (1.4)	0	1 (1.0)	6 (1.1)
General disorders and administration site conditions, n (%)	93 (26.0)	35 (19.6)	3 (3.1)	129 (24.0)
Asthenia	34 (9.5)	6 (3.4)	2 (2.1)	42 (7.8)
Pyrexia	32 (8.9)	8 (4.5)	0	40 (7.4)
Fatigue	28 (7.8)	6 (3.4)	0	34 (6.3)
Malaise	18 (5.0)	8 (4.5)	0	26 (4.8)
Oedema peripheral	11 (3.1)	6 (3.4)	0	17 (3.2)
Non-cardiac chest pain	5 (1.4)	4 (2.2)	1 (1.0)	9 (1.7)
Chest discomfort	5 (1.4)	3 (1.7)	0	8 (1.5)
Chills	6 (1.7)	1 (0.6)	0	7 (1.3)
Gastrointestinal disorders, n (%)	76 (21.2)	31 (17.3)	7 (7.2)	113 (21.0)
Nausea	38 (10.6)	15 (8.4)	2 (2.1)	55 (10.2)
Diarrhoea	24 (6.7)	13 (7.3)	4 (4.1)	40 (7.4)
Vomiting	20 (5.6)	10 (5.6)	2 (2.1)	32 (6.0)
Constipation	21 (5.9)	2 (1.1)	1 (1.0)	24 (4.5)
Abdominal distension	8 (2.2)	1 (0.6)	0	9 (1.7)
Abdominal pain upper	4 (1.1)	3 (1.7)	0	7 (1.3)
Dysphagia	4 (1.1)	2 (1.1)	0	6 (1.1)
Skin and subcutaneous tissue disorders, n (%)	83 (23.2)	24 (13.4)	6 (6.2)	111 (20.7)
Rash	38 (10.6)	8 (4.5)	3 (3.1)	48 (8.9)
Alopecia	33 (9.2)	8 (4.5)	0	41 (7.6)
Pruritus	16 (4.5)	8 (4.5)	3 (3.1)	27 (5.0)
Rash pruritic	10 (2.8)	1 (0.6)	0	11 (2.0)
Rash maculo-papular	4 (1.1)	2 (1.1)	0	6 (1.1)
Endocrine disorders, n (%)	46 (12.8)	7 (3.9)	15 (15.5)	67 (12.5)
Hypothyroidism	37 (10.3)	4 (2.2)	12 (12.4)	52 (9.7)
Hyperthyroidism	13 (3.6)	3 (1.7)	4 (4.1)	20 (3.7)
Respiratory, thoracic and mediastinal disorders, n (%)	35 (9.8)	13 (7.3)	4 (4.1)	51 (9.5)
Dyspnoea	11 (3.1)	9 (5.0)	1 (1.0)	21 (3.9)
Immune-mediated lung disease	15 (4.2)	1 (0.6)	3 (3.1)	19 (3.5)
Haemoptysis	8 (2.2)	1 (0.6)	1 (1.0)	10 (1.9)
Cough	5 (1.4)	5 (2.8)	1 (1.0)	10 (1.9)
Musculoskeletal and connective tissue disorders, n (%)	36 (10.1)	8 (4.5)	4 (4.1)	48 (8.9)

Arthralgia	18 (5.0)	6 (3.4)	2 (2.1)	26 (4.8)
Pain in extremity	20 (5.6)	3 (1.7)	2 (2.1)	25 (4.7)
Back pain	6 (1.7)	0	0	6 (1.1)
Muscular weakness	4 (1.1)	1 (0.6)	1 (1.0)	6 (1.1)
Nervous system disorders, n (%)	32 (8.9)	10 (5.6)	3 (3.1)	44 (8.2)
Hypoaesthesia	21 (5.9)	8 (4.5)	1 (1.0)	29 (5.4)
Dizziness	13 (3.6)	2 (1.1)	2 (2.1)	17 (3.2)
Headache	6 (1.7)	1 (0.6)	1 (1.0)	8 (1.5)
Cardiac disorders, n (%)	25 (7.0)	8 (4.5)	6 (6.2)	37 (6.9)
Supraventricular extrasystoles	8 (2.2)	3 (1.7)	2 (2.1)	11 (2.0)
Sinus bradycardia	8 (2.2)	0	2 (2.1)	10 (1.9)
Sinus tachycardia	6 (1.7)	4 (2.2)	0	10 (1.9)
Ventricular extrasystoles	5 (1.4)	3 (1.7)	1 (1.0)	8 (1.5)
Arrhythmia	2 (0.6)	2 (1.1)	2 (2.1)	6 (1.1)
Infections and infestations, n (%)	19 (5.3)	9 (5.0)	2 (2.1)	30 (5.6)
Pneumonia	19 (5.3)	9 (5.0)	2 (2.1)	30 (5.6)
Renal and urinary disorders, n (%)	22 (6.1)	1 (0.6)	2 (2.1)	25 (4.7)
Proteinuria	19 (5.3)	1 (0.6)	2 (2.1)	22 (4.1)
Haematuria	7 (2.0)	0	0	7 (1.3)
Hepatobiliary disorders, n (%)	11 (3.1)	4 (2.2)	1 (1.0)	16 (3.0)
Hepatic function abnormal	11 (3.1)	4 (2.2)	1 (1.0)	16 (3.0)
Psychiatric disorders, n (%)	8 (2.2)	1 (0.6)	0	9 (1.7)
Insomnia	8 (2.2)	1 (0.6)	0	9 (1.7)

Note: E= Frequency of specified adverse events.
Adverse events (AEs) were coded using MedDRA Version 25.0
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.
When summarizing AE incidence, a subject was counted only once for each SOC or PT according to the highest CTCAE grade.
When summarizing AE events (E), only AEs with the maximum CTCAE grade for a subject for each SOC or PT were counted.
Missing Causality was imputed as 'related'.

Pooled Safety Population

A total of 1650 (79.1%) subjects experienced serplulimab-related TEAEs.
For the grouped categories, serplulimab-related TEAEs with incidence ≥ 10% in the total population were anaemia (27.9%), leukopenia (24.8%), neutropenia (24.7%), thrombocytopenia (21.0%), hypothyroidism (18.7%), decreased appetite (13.4%), asthenia (12.4%), rash (11.4%), protein urine present (11.1%), hyperthyroidism (10.1%), and hyperlipidaemia (10.1%).

For the ungrouped PTs, serplulimab-related TEAEs with an incidence ≥ 10% in the total population were aspartate aminotransferase increased (18.6%), alanine aminotransferase increased (18.0%), and nausea (13.1%).

Adverse events by severity

Pivotal trial

A total of 457 (85.1%) subjects experienced Grade ≥ 3 TEAEs (serplulimab group: 85.2%, placebo group: 79.3%.

The most common grade ≥ 3 TEAEs (with an incidence ≥ 5%) in any group by PT were neutrophil count decreased (serplulimab group vs placebo group: 43.0% vs 37.4%), anaemia (37.4% vs 38.5%), white blood cell count decreased (31.3% vs 30.7%), neutropenia (17.3% vs 17.3%),

platelet count decreased (17.0% vs 8.9%), leukopenia (10.6% vs 8.4%), pneumonia (8.1% vs 7.3%), hyponatraemia (5.6% vs 5.0%), and lymphocyte count decreased (5.6% vs 2.2%).

A total of 190 (35.4%) subjects experienced serplulimab/placebo-**related** grade ≥ 3 TEAEs (serplulimab group: 35.5%, placebo 31.8%).

Serplulimab/placebo-related Grade ≥ 3 TEAEs with an incidence ≥ 5% in any group by PT were neutrophil count decreased (serplulimab group vs placebo group: 14.8% vs 14.5%), anaemia (12.0% vs 10.6%), white blood cell count decreased (10.1% vs 11.2%), platelet count decreased (6.7% vs 2.8%), and neutropenia (4.7% vs 7.3%).

Pooled safety population

A total of 1466 (70.3%) subjects experienced severe (grade ≥ 3) TEAEs. In the ≥ RP2D/3D dose group, the incidence of Grade ≥ 3 TEAEs was 44.6% with serplulimab monotherapy, 77.6% with serplulimab plus chemotherapy, and 63.9% with serplulimab combined with other drugs.

For the grouped categories, grade ≥ 3 TEAEs with an incidence ≥ 5% in the total population were neutropenia (35.7%), leukopenia (20.9%), anaemia (19.9%), thrombocytopenia (12.5%), and hyponatraemia (5.4%).

No Grade ≥ 3 TEAEs had an incidence ≥ 5% by ungrouped PT.

A total of 716 (34.3%) subjects experienced serplulimab-**related** grade ≥ 3 TEAEs in the pooled safety population. In the ≥ RP2D/3D dose group, the incidence of serplulimab-related Grade ≥ 3 TEAEs was 20.4% with serplulimab monotherapy, 36.4% with serplulimab plus chemotherapy, and 37.2% with serplulimab combined with other drugs.

For the grouped categories, serplulimab-related Grade ≥ 3 TEAEs with an incidence ≥ 5% in the total population were neutropenia (12.3%), leukopenia (7.6%), anaemia (7.2%), and thrombocytopenia (5.6%).

No serplulimab-related Grade ≥ 3 TEAEs had an incidence ≥ 5% by ungrouped PT.

Adverse Events of Special Interest (AESIs)

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, and toxins.

Pivotal study

Infusion-related Reactions (IRRs)

In total, 4 (0.7%) subjects experienced IRRs, and all of them were from the serplulimab group.

Immune-related Adverse Events (irAEs)

In total, 29.6% of subjects in the serplulimab group and 17.3% in the placebo group experienced irAEs.

irAEs with an incidence ≥ 2% in any group by PT were hypothyroidism (serplulimab group vs placebo group: 6.4% vs 0.6%), rash (5.0% vs 1.1%), immune-mediated lung disease (4.2% vs 0.6%), pneumonia (2.8% vs 1.7%), blood thyroid stimulating hormone increased (2.5% vs

1.7%), aspartate aminotransferase increased (2.0% vs 1.1%), hyperthyroidism (1.7% vs 0.6%), diarrhoea (0.8% vs 1.7%), sinus bradycardia (0.6% vs 0), and thyroiditis (0.3% vs 0).

Regarding serious AESIs, 11.5% of subjects in the serplulimab group and 5.6% of subject in the placebo group experienced such reactions with only immune-mediated lung disease (serplulimab group vs. placebo group: 3.1% vs 0.6%) reported with an incidence ≥ 2% in any group by PT.

Pooled safety population

A total of 735 (35.2%) subjects experienced at least one AESI, including 190 (9.1%) subjects who experienced Grade ≥ 3 AESIs. AESIs leading to serplulimab discontinuation occurred in 97 (4.7%) subjects. AESIs leading to serplulimab interruption occurred in 237 (11.4%) subjects.

For the 735 subjects with at least one AESI, the median (range) time to AESI onset was 2.6283 (0.0329, 34.5298) months, the median (range) duration of AESI was 1.5770 (0.0329, 29.8316), months, and the median (range) time to AESI resolution was 1.1335 (0.0329, 20.9281) months.

For the grouped categories, AESIs with an incidence ≥ 2.0% in the total population were hypothyroidism (11.7%), immune-mediated skin adverse reactions (7.8%), hyperthyroidism (6.7%), immune-mediated lung disease (4.9%), abnormal liver function (3.7%), immune-mediated nephritis and renal dysfunction (3.0%), and immune-mediated colitis (2.0%).

1) Analysis of AESI by SOC and PT

Immune-related TEAEs

A total of 714 (34.2%) subjects experienced at least one irAE. In the ≥ RP2D/3D dose group, 31.9% of the subjects who received serplulimab monotherapy experienced irAEs, compared to 34.7% of the subjects who received serplulimab in combination with chemotherapy, and 34.2% of the subjects who received serplulimab in combination with other drugs.

Among the subjects who experienced irAEs, 154 (7.4%) subjects received high dose corticosteroids. The median (range) dose of initial corticosteroid dose was 65.00 (5.0, 666.7) mg prednisone or equivalent. The median (range) duration of use was 1.1828 (0.0329, 35.1211) months.

Infusion-related Reactions

IRRs were reported in 35 (1.7%) subjects. Most of the events were Grade 1 or Grade 2 in severity. Five (0.2%) subjects experienced Grade ≥ 3 IRRs, including 3 (0.1%) subjects with Grade 3 IRRs and 2 (0.1%) subjects with Grade 4 IRRs.

2) Analysis of AESI by SMQ and PT

Immune-related TEAEs

Immune-mediated Lung Disease

Immune-mediated lung disease occurred in 4.9% of subjects, including Grade 3, 4 or 5 in 1.2%, 0.2%, and 0.3% of subjects, respectively. The median time to onset was 4.40 months (range: 0.03, 34.53 months). The median duration was 1.76 months (range: 0.10, 13.34 months). 2.5% of subjects received high-dose corticosteroid treatment. Immune-mediated lung disease led to discontinuation in 1.3% of subjects.

Immune-mediated Colitis

Immune-mediated colitis occurred in 2.0% of subjects, including Grade 3 in 0.6% of subjects and Grade 5 in < 0.1% of subjects. The median time to onset was 3.35 months (range: 0.03, 30.55

months). The median duration was 0.43 months (range: 0.03, 8.94 months). 0.7% of subjects received high-dose corticosteroid treatment. Immune-mediated colitis led to discontinuation in 0.2% of subjects.

Immune-mediated Hepatitis

Hepatitis occurred in 0.8% of subjects, including Grade 3 in 0.3% of subjects, Grade 4 in 0.1% of subjects, and Grade 5 in 0.1% of subjects. The median time to onset was 2.48 months (range: 0.36, 26.78 months). The median duration was 0.95 months (range: 0.10, 8.48 months). 0.4% of subjects received high-dose corticosteroid treatment. Hepatitis led to discontinuation in 0.3% of subjects. Abnormal liver function occurred in 3.7% of subjects, including Grade 3 in 0.8% of subjects, and Grade 4 in 0.1% of subjects. The median time to onset was 2.30 months (range: 0.07, 45.31 months). The median duration was 1.31 months (range: 0.26, 17.54 months). 0.5% of subjects received high-dose corticosteroid treatment. Abnormal liver function led to discontinuation in 0.2% of subjects.

Immune-mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis and renal dysfunction occurred in 3.0% of subjects, including Grade 3 in 0.3% of subjects and Grade 4 in < 0.1% of subjects. The median time to onset was 2.83 months (range: 0.23, 17.77 months). The median duration was 1.48 months (range: 0.13, 17.94 months). 0.4% of subjects received high-dose corticosteroid treatment. Immune-mediated nephritis and renal dysfunction led to discontinuation in 0.2% of subjects.

Immune-mediated Endocrinopathies

Hypothyroidism

Hypothyroidism occurred in 11.7% of subjects, including Grade 3 in 0.2% of subjects. The median time to onset was 3.83 months (range: 0.46, 34.10 months). The median duration was 2.73 months (range: 0.13, 29.08 months). 6.7% of subjects received thyroid hormone replacement therapy. < 0.1% subjects discontinued serplulimab due to hypothyroidism.

Hyperthyroidism

Hyperthyroidism occurred in 6.7% of subjects, and there were no Grade ≥ 3 hyperthyroidism. The median time to onset was 2.73 months (range: 0.62, 31.18 months). The median duration was 1.45 months (range: 0.07, 17.77 months). No subjects discontinued serplulimab due to hyperthyroidism.

Thyroiditis

Thyroiditis occurred in 0.7% of subjects, and there were no Grade ≥ 3 thyroiditis. The median time to onset was 6.64 months (range: 0.99, 13.50 months). The median duration was 1.30 months (range: 0.56, 11.30 months). 0.2% of subjects received thyroid hormone replacement therapy. No subjects discontinued serplulimab due to thyroiditis.

Adrenal Gland Disorders

Adrenal gland disorders occurred in 0.5% of subjects, including Grade 3 in 0.1% of subjects. The median time to onset was 6.24 months (range: 3.55, 21.45 months). The median duration was 4.60 months. < 0.1% of patients received high dose corticosteroid treatment. No subjects discontinued serplulimab due to adrenal gland disorders.

Pituitary Disorders

Pituitary disorders occurred in 0.8% of subjects, including Grade 3 in 0.1% of subjects. The median time to onset was 6.72 months (range: 1.41, 20.53 months). The median duration was 3.25 months. 0.2% of subjects received high-dose corticosteroid treatment. Pituitary disorders led to discontinuation in 0.1% of subjects.

Diabetes Mellitus/Hyperglycaemia

Diabetes mellitus/hyperglycaemia occurred in 0.9% of subjects, including Grade 3 in 0.4% of subjects and Grade 4 in 0.1% of subjects. The median time to onset was 4.34 months (range: 0.69, 40.28 months). The median duration was 3.48 months (range: 0.53, 10.68). 0.5% of subjects received insulin replacement therapy. Diabetes mellitus/hyperglycaemia led to discontinuation in < 0.1% of subjects

Immune-mediated Skin Adverse Reactions

Immune-mediated skin adverse reactions occurred in 7.8% of subjects, including Grade 3 in 0.8% of subjects, Grade 4 in < 0.1% of subjects, and Grade 5 in < 0.1% of subjects. The median time to onset was 2.96 months (range: 0.03, 30.52months). The median duration was 1.56 months (range: 0.07, 19.06 months). 1.2% of subjects received high-dose corticosteroid treatment. Immune-mediated skin adverse reactions led to discontinuation in 0.5% of subject

Immune-mediated Pancreatitis

Immune-mediated pancreatitis occurred in 1.0% of subjects, including Grade 3 in 0.3% of subjects, Grade 4 in 0.1% of subjects and Grade 5 in < 0.1% of subjects. The median time to onset was 2.86 months (range: 0.23, 13.67 months). The median duration was 0.76 months (range: 0.16, 10.12 months). 0.1% of subjects received high-dose corticosteroid treatment. Immune-mediated pancreatitis led to discontinuation in 0.2% of subjects.

Immune-mediated Myocarditis

Immune-mediated myocarditis occurred in 0.7% of subjects, including Grade 3 in 0.1% of subjects, Grade 4 in < 0.1% of subjects and Grade 5 in 0.2% of subjects. The median time to onset was 1.71 months (range: 0.26, 20.70 months). The median duration was 0.79 months (range: 0.30, 5.72 months). 0.5% of subjects received high-dose corticosteroid treatment. Immune-mediated myocarditis led to discontinuation in 0.3% of subjects

Immune-mediated Uveitis

Immune-mediated uveitis occurred in < 0.1% of subjects, which was Grade 1. The time to onset was 6.90 months. The duration of immune-mediated uveitis was 1.35 months. The event resolved for the subjects.

Other Immune-mediated Adverse Reactions

Other clinically significant immune-mediated adverse reactions were reported in the following SOCs:

Blood and lymphatic system, Nervous system, Eye disorders

Cardiac/vascular,

Respiratory, thoracic and mediastinal,

Gastrointestinal and

General disorders and administration site conditions.

Infusion-related Reactions

Infusion-related reactions occurred in 1.7% of subjects, including Grade 3 in 0.1% of subjects and Grade 4 in 0.1% of subjects. The median time to onset was 1.74 months (range: 0.03, 34.04 months). The median duration was 0.07 months (range: 0.03, 6.70 months). No subjects discontinued serplulimab due to infusion-related reactions.

Laboratory Abnormalities

The proportions of subjects who experienced a shift from baseline to a Grade ≥ 3 laboratory abnormality were as follows: 0.5% for platelet count decreased, 0.3% for neutrophil count decreased, 0.2% for blood creatine phosphokinase increased, 0.1% for white blood cell count decreased, 0.1% for troponin I increased, < 0.1% for blood alkaline phosphatase increased, < 0.1% for blood lactate dehydrogenase increased, < 0.1% for N-terminal prohormone brain natriuretic peptide increased, and < 0.1% for blood cholesterol increased.

Adverse drug reactions (ADRs)

ADRs including frequency estimation are based on a database including 1343 subjects from the study HLX10-005-SCLC301, HLX10-007-EC301, HLX10-002-NSCLC301 and HLX10-004-NSCLC303. ADR frequencies presented in the SmPC were estimated based on all-cause AE frequencies.

Table 51. Adverse reactions in patients treated with serplulimab

	Serplulimab in combination with chemotherapy
Infections and infestations	
Very common	pneumonia [a]
Common	urinary tract infection [b], respiratory tract infection [c], skin infection
Uncommon	septic shock
Rare	gastrointestinal infection, meningoencephalitis herpetic
Blood and lymphatic system disorders	
Very common	neutropenia, leukopenia, anaemia, thrombocytopenia, lymphopenia
Common	coagulation function test abnormal [d], granulocytopenia, febrile neutropenia
Rare	lymphadenitis
Immune system disorders	
Common	infusion-related reaction [e]
Uncommon	anaphylactic reaction
Endocrine disorders	
Very common	hypothyroidism [f], hyperthyroidism [g], hyperglycaemia or type 1 diabetes mellitus [h]
Common	thyroiditis [i]

Uncommon	adrenal insufficiency [j], other thyroid disorder [k], hypophysitis, thyroid function test abnormal [l], hypoparathyroidism
Rare	hyperadrenocorticism
Metabolism and nutrition disorders	
Very common	hyperlipidaemia, decreased appetite, hypoproteinaemia, hyperuricaemia, electrolyte imbalance [m], weight decreased
Common	hypoglycaemia
Uncommon	lipoprotein abnormal
Psychiatric disorders	
Very common	insomnia
Nervous system disorders	
Common	paraesthesia, headache, dizziness, neuropathy peripheral [n]
Uncommon	vertigo, immune-mediated encephalitis [o], neurotoxicity, cerebral infarction, taste disorder, memory impairment
Rare	motor dysfunction, myasthenia gravis, myasthenic syndrome
Eye disorders	
Uncommon	vision blurred, keratitis, conjunctivitis
Cardiac disorders	
Very common	arrhythmia [p]
Common	sinus tachycardia, conduction defects [q], sinus bradycardia, cardiac failure [r], troponin increased, myocardial injury
Uncommon	myocardial ischaemia, pericardial effusion, myocarditis
Rare	cardiomyopathy
Vascular disorders	
Common	hypertension, vasculitis, hypotension
Uncommon	venous thrombosis
Respiratory, thoracic and mediastinal disorders	
Very common	cough, chest pain
Common	pneumonitis [s], dyspnoea, dysphonia, pulmonary embolism
Uncommon	respiratory failure
Gastrointestinal disorders	
Very common	nausea, constipation, diarrhoea, vomiting

Common	dysphagia, abdominal pain, flatulence, gastrointestinal disorder [t], stomatitis, dyspepsia, dry mouth, gastritis
Uncommon	enteritis [u], immune-mediated pancreatitis, gingival bleeding, oesophagitis, gastric ulcer
Hepatobiliary disorders	
Very common	alanine aminotransferase increased, aspartate aminotransferase increased
Common	gamma-glutamyltransferase increased, hyperbilirubinaemia, liver injury [v]
Skin and subcutaneous tissue disorders	
Very common	rash [w], alopecia
Common	pruritus, dermatitis [x]
Uncommon	pigmentation disorder, psoriasis, dry skin, hyperhidrosis
Rare	toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain
Common	arthritis
Rare	myositis [y]
Renal and urinary disorders	
Very common	protein urine present, blood creatinine increased
Common	blood urea increased, haematuria, renal injury [z]
Uncommon	dysuria, pollakiuria
General disorders and administration site conditions	
Very common	pyrexia, asthenia
Common	malaise, oedema
Uncommon	chills
Investigations	
Common	blood alkaline phosphatase increased, myoglobin blood increased, blood creatine phosphokinase increased, amylase increased
Uncommon	lipase increased

Serious adverse event/deaths/other significant events

Deaths

Pivotal study

There were 13.7% of TEAEs that were fatal in the serplulimab arm vs 10.6% in the placebo arm.

Table 52. Summary of fatal TEAEs by SOC and PT (safety set)

System Organ Class (SOC) Preferred Term (PT)	Serplulimab (N=358)	Placebo (N=179)	Placebo Switched to Serplulimab (N=97)	Total (N=537)
Any TEAE leading to death, n (%)	49 (13.7)	19 (10.6)	12 (12.4)	80 (14.9)
General disorders and administration site conditions, n (%)	22 (6.1)	9 (5.0)	4 (4.1)	35 (6.5)
Disease progression	14 (3.9)	6 (3.4)	3 (3.1)	23 (4.3)
Death	7 (2.0)	2 (1.1)	1 (1.0)	10 (1.9)
Sudden death	1 (0.3)	0	0	1 (0.2)
Multiple organ dysfunction syndrome	0	1 (0.6)	0	1 (0.2)
Infections and infestations, n (%)	10 (2.8)	5 (2.8)	2 (2.1)	17 (3.2)
Pneumonia	5 (1.4)	4 (2.2)	2 (2.1)	11 (2.0)
COVID-19	4 (1.1)	0	0	4 (0.7)
Sepsis	1 (0.3)	1 (0.6)	0	2 (0.4)
Septic shock	0	2 (1.1)	0	2 (0.4)
Respiratory, thoracic and mediastinal disorders, n (%)	8 (2.2)	3 (1.7)	5 (5.2)	16 (3.0)
Respiratory failure	3 (0.8)	1 (0.6)	2 (2.1)	6 (1.1)
Pulmonary haemorrhage	2 (0.6)	0	1 (1.0)	3 (0.6)
Haemoptysis	1 (0.3)	1 (0.6)	1 (1.0)	3 (0.6)
Immune-mediated lung disease	2 (0.6)	0	0	2 (0.4)
Pulmonary embolism	1 (0.3)	0	1 (1.0)	2 (0.4)
Acute respiratory distress syndrome	0	1 (0.6)	0	1 (0.2)
Dyspnoea	0	1 (0.6)	0	1 (0.2)
Cardiac disorders, n (%)	5 (1.4)	4 (2.2)	1 (1.0)	10 (1.9)
Myocardial infarction	3 (0.8)	1 (0.6)	1 (1.0)	5 (0.9)
Cardiac failure	1 (0.3)	0	0	1 (0.2)
Myocardial ischaemia	1 (0.3)	0	0	1 (0.2)
Myocarditis	1 (0.3)	0	0	1 (0.2)
Acute myocardial infarction	0	1 (0.6)	0	1 (0.2)
Cardiac arrest	0	1 (0.6)	0	1 (0.2)
Cardiac failure acute	0	1 (0.6)	0	1 (0.2)

Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	3 (0.8)	0	1 (1.0)	4 (0.7)
Malignant neoplasm progression	2 (0.6)	0	1 (1.0)	3 (0.6)
Leukaemia	1 (0.3)	0	0	1 (0.2)
Nervous system disorders, n (%)	1 (0.3)	1 (0.6)	0	2 (0.4)
Syncope	1 (0.3)	0	0	1 (0.2)
Loss of consciousness	0	1 (0.6)	0	1 (0.2)
Gastrointestinal disorders, n (%)	1 (0.3)	0	0	1 (0.2)
Immune-mediated enterocolitis	1 (0.3)	0	0	1 (0.2)
Vascular disorders, n (%)	1 (0.3)	0	0	1 (0.2)
Haemorrhage	1 (0.3)	0	0	1 (0.2)
Hepatobiliary disorders, n (%)	0	1 (0.6)	0	1 (0.2)
Hepatic failure	0	1 (0.6)	0	1 (0.2)
Renal and urinary disorders, n (%)	0	1 (0.6)	0	1 (0.2)
Renal failure	0	1 (0.6)	0	1 (0.2)

Note: Adverse events (AEs) were coded using MedDRA Version 25.0
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.

Deaths considered treatment related

A total of 4 (1.1%) subjects experienced serplulimab/placebo-related TEAEs leading to death in the serplulimab arm compared to 2 (1.1%) subjects in the placebo arm.

Table 53. Summary of Serplulimab/Placebo-related TEAEs Leading to Death by SOC and PT (Safety Set)

System Organ Class (SOC) Preferred Term (PT)	Serplulimab (N=358)	Placebo (N=179)	Placebo Switched to Serplulimab (N=97)	Total (N=537)
Any serplulimab/placebo-related TEAE leading to death, n (%)	4 (1.1)	2 (1.1)	2 (2.1)	8 (1.5)
Respiratory, thoracic and mediastinal disorders, n (%)	3 (0.8)	0	0	3 (0.6)
Immune-mediated lung disease	2 (0.6)	0	0	2 (0.4)
Pulmonary haemorrhage	1 (0.3)	0	0	1 (0.2)
Respiratory failure	1 (0.3)	0	0	1 (0.2)
Infections and infestations, n (%)	0	1 (0.6)	1 (1.0)	2 (0.4)
Pneumonia	0	1 (0.6)	1 (1.0)	2 (0.4)
Gastrointestinal disorders, n (%)	1 (0.3)	0	0	1 (0.2)
Immune-mediated enterocolitis	1 (0.3)	0	0	1 (0.2)
Hepatobiliary disorders, n (%)	0	1 (0.6)	0	1 (0.2)
Hepatic failure	0	1 (0.6)	0	1 (0.2)
Cardiac disorders, n (%)	0	0	1 (1.0)	1 (0.2)
Myocardial infarction	0	0	1 (1.0)	1 (0.2)

Note: Adverse events (AEs) were coded using MedDRA Version 25.0
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.
Missing Causality was imputed as 'related'.

Pooled safety population

Adverse Events Leading to Death

TEAEs that resulted in death occurred in 246 (11.8%) subjects in the pooled safety population. Of these subjects, 89 (4.3%) experienced the event of disease progression, 33 (1.6%) experienced the event of death and 6 (0.3%) experienced the event of sudden death.

Among the grouped categories TEAEs leading to death that occurred in ≥ 3 subjects in the total population were respiratory failure (17 (0.8%) subjects), pneumonia (14 (0.7%) subjects), pneumonitis (9 (0.4%) subjects), COVID-19 (8 (0.4%) subjects), myocardial infarction (7 (0.3%) subjects), cardiac failure (5 (0.2%) subjects), myocarditis (5 (0.2%) subjects), septic shock (5 (0.2%) subjects), sepsis (5 (0.2%) subjects), gastrointestinal disorder (4 (0.2%) subjects), liver injury (3 (0.1%) subjects), pulmonary haemorrhage (3 (0.1%) subjects), and thrombocytopenia (3 (0.1%) subjects). No clear trends were observed in these events that led to death.

For the ungrouped PTs, TEAEs leading to death that occurred in ≥ 3 subjects in the total population were disease progression (89 (4.3%) subjects), death (33 (1.6%) subjects), sudden death (6 (0.3%) subjects), malignant neoplasm progression (8 (0.4%) subjects), multiple organ dysfunction syndrome (3 (0.1%) subjects), sudden cardiac death (3 (0.1%) subjects), pulmonary embolism (3 (0.1%) subjects), and haemoptysis (3 (0.1%) subjects).

Deaths considered treatment related

A total of 50 (2.4%) subjects experienced serplulimab-related TEAEs leading to death (Table 2.7.4-14).

For the grouped categories, serplulimab-related TEAEs leading to death that occurred in ≥ 3 subjects in the total population were pneumonitis (9 (0.4%) subjects), respiratory failure (9 (0.4%) subjects), septic shock (5 (0.2%) subjects), myocarditis (4 (0.2%) subjects), pneumonia (4 (0.2%) subjects), liver injury (3 (0.1%) subjects), myocardial infarction (3 (0.1%) subjects), and thrombocytopenia (3 (0.1%) subjects). No clear trends or patterns were observed in these events.

For the ungrouped PTs, serplulimab-related TEAE leading to death that occurred in ≥ 3 subjects in the total population was death (4 (0.2%) subjects), and disease progression (3 (0.1%) subjects)

A total of 50 (2.4%) subjects experienced serplulimab-related TEAEs leading to death.

Table 54. Pooled Safety Population: Summary of Serplulimab-related TEAEs Leading to Death (part of table 2.5-19)

	< RP2D/3D			≥ RP2D/3D				
SOC PT	Monotherapy (N=7)	Other Combination (N=3)	Total (N=10)	Monotherapy (N=285)	Chemotherapy Combination (N=1364)	Other Combination (N=427)	Total (N=2076)	Total population (N=2086)
At least one serplulimab-related TEAE leading to death	1 (14.3%)	0	1 (10.0%)	9 (3.2%)	28 (2.1%)	12 (2.8%)	49 (2.4%)	50 (2.4%)
Combined TEAE	1 (14.3%)	0	1 (10.0%)	7 (2.5%)	23 (1.7%)	11 (2.6%)	41 (2.0%)	42 (2.0%)

Treatment emergent serious adverse events (TESAEs)

Pivotal trial

In total, 51.0% of subjects experienced TESAEs (serplulimab group: 52.0% of subjects; placebo group: 42.5% of subjects.

TESAEs with an incidence ≥ 2% in any group by PT were pneumonia (10.9% in the serplulimab group vs 10.1% in the placebo group), platelet count decreased (7.3% vs 5.0%), anaemia (5.9% vs 5.0%) , neutrophil count decreased (5.6% vs 6.7%), white blood cell count decreased (5.3% vs 5.0%), disease progression (3.9% vs 3.4%), immune-mediated lung disease (3.1% vs 0.6%), pyrexia (2.8% vs 0.6%), death (2.0% vs 1.1%), febrile neutropenia (2.0% vs 0), haemoptysis (1.1% vs 3.4%), thrombocytopenia (1.1% vs 2.2%), and respiratory failure (0.8% vs 0.6%).

TESAEs considered treatment related

21.6% of subjects experienced serplulimab/placebo-related TESAEs (serplulimab group: 22.6% vs placebo group: 15.6%.

Serplulimab/placebo-related TESAEs with an incidence ≥ 2% in any group by PT were platelet count decreased (4.5% in the serplulimab group vs 2.8% in the placebo group, anaemia (3.1% vs 2.8%), immune-mediated lung disease (3.1% vs 0.6%), pneumonia (2.8% vs 2.2%), and white blood cell count decreased (2.0% vs 1.1%).

Pooled safety population

In total, 41.8% of subjects in the pooled safety population experienced TESAEs, with 20.7% related to serplulimab and 34.7% of subjects reported Grade ≥ 3 TESAEs, with 16.2% related to serplulimab.

In the ≥ RP2D/3D dose group, 32.3% of the subjects who received serplulimab monotherapy experienced TESAEs, compared to 44.1% of the subjects who received serplulimab in combination

with chemotherapy, and 40.5% of the subjects who received serplulimab in combination with other drugs.

For the grouped AE categories, TESAEs with an incidence ≥ 2% in the total population were thrombocytopenia (6.9%), pneumonia (5.2%), neutropenia (4.6%), leukopenia (4.5%), anaemia (3.5%), and pneumonitis (3.0%).

For the ungrouped PTs, TESAE with an incidence ≥ 2% in the total population was disease progression (4.3%).

Serplulimab-related TESAEs were reported in 431 (20.7%) subjects in the pooled safety population (Table 2.7.4.2.2.3.2). In the ≥ RP2D/3D dose group, 12.3% of the subjects who received serplulimab monotherapy experienced serplulimab-related TESAEs, compared to 21.8% of the subjects who received serplulimab in combination with chemotherapy, and 22.5% of the subjects who received serplulimab in combination with other drugs.

For the grouped categories, serplulimab-related TESAEs with an incidence ≥ 2% in the total population were thrombocytopenia (4.1%), pneumonitis (2.4%), leukopenia (2.3%), and neutropenia (2.1%).

No serplulimab-related TESAEs had an incidence ≥ 2% by ungrouped PT

Laboratory findings

Haematology

Pivotal study

TEAEs with incidence ≥ 5% in any group in haematology variables by PT were white blood cell count decreased (serplulimab + chemotherapy group vs. placebo + chemotherapy group vs. 59.2% vs. 56.4%), neutrophil count decreased (79.4% vs. 73.2%), platelet count decreased (49.2% vs. 48.6%), lymphocyte count decreased (11.5% vs 11.2).

Pooled Safety Population

Haematology parameters with shifts from normal or abnormal with no clinical significance at baseline to clinically significant post-baseline observed in > 10% of subjects included: neutrophils (64.8%), leukocytes (62.5%), haemoglobin (55.5%), platelets (46.9%), erythrocytes (45.8%), neutrophils/leukocytes (22.7%), and lymphocytes (14.8%).

Blood chemistry

Pivotal Study

TEAEs with incidence ≥ 5% were alanine aminotransferase increased (serplulimab + chemotherapy group vs. placebo + chemotherapy group 23.5% vs 15.6%), aspartate aminotransferase increased (21.2% vs. 11.2%), blood alkaline phosphatase increased (9.5% vs 7.2%), blood lactate dehydrogenase increased (8.6% vs 6.1%), gamma-glutamyltransferase increased (7.3% vs 8.4%), blood creatinine increased (7.3% vs 2.8%) and blood bilirubin increased (5.0% vs 5.0%).

Pooled Safety Population

Blood chemistry parameters with shifts from normal or abnormal with no clinical significance at baseline to clinically significant post-baseline observed in > 10% of subjects included: aspartate aminotransferase (27.3%), alanine aminotransferase (26.5%), albumin (23.3%), potassium

(19.8%), sodium (17.4%), cholesterol (15.5%), glucose (14.9%), creatinine (13.6%), protein (10.6%), and calcium (10.3%).

Coagulation Function

Pivotal study

TEAEs with incidence ≥ 1% were activated partial thromboplastin time prolonged (serplulimab + chemotherapy group vs. placebo + chemotherapy group: 4.2% vs 2.2%), fibrin D dimer increased (3.1% vs 1.1%), blood fibrinogen increased (1.4% vs 1.1%) and INR increased (1.4% vs 0.6%).

Pooled Safety Population

Coagulation function parameters with shifts from normal or abnormal with no clinical significance at baseline to clinically significant post-baseline were observed in less than 5% of subjects.

Urinalysis

Pivotal study

TEAEs with incidence ≥ 1% in any group in urinalysis variables under the SOC of Investigations by PT were protein urine present (serplulimab + chemotherapy group vs. placebo + chemotherapy group: 3.4% vs. 3.9%), white blood cells urine positive (2.0% vs 1.1%), urinary occult blood positive (1.7% vs 1.7%), glucose urine present (1.1% vs 0.6%) and urine ketone body present (0.6% vs 1.1%).

Pooled Safety Population

Urinalysis parameter with shifts from normal or abnormal with no clinical significance at baseline to clinically significant post-baseline observed in > 10% of subjects was urine protein (14.7%).

Endocrine function

Pivotal study

TEAEs with incidence ≥ 1% in any group in endocrine function variables under the SOC of Investigations by PT were blood thyroid stimulating hormone increased (serplulimab + chemotherapy group vs. placebo + chemotherapy group: 3.1% vs 1.7%), blood thyroid stimulating hormone decreased (1.7% vs. 0.6%), tri-iodothyronine decreased (0,8% vs 1.7%) and thyroxine free increased (0% vs 1.1%).

Pooled Safety Population (Thyroid Function)

Thyroid function parameters with shifts from normal or abnormal with no clinical significance at baseline to clinically significant post-baseline observed in > 10% of subjects included: thyrotropin (19.4%), free triiodothyronine (13.1%) and free thyroxine (12.8%).

Cardiac function:

Pivotal study

TEAEs with an incidence ≥ 1% in any group in cardiac function variables under the SOC of Investigations by PT were N-terminal prohormone brain natriuretic peptide increased (serplulimab group vs placebo group: 2.2% vs 1.7%), brain natriuretic peptide increased (1.7% vs 2.8%), troponin I increased (0.6% vs 1.7%), and troponin T increased (0.3% vs 0.6%)

Pooled safety population

No data was provided with this submission.

Vital signs and physical findings

Pivotal study

TEAEs with an incidence ≥ 1% in any group in vital sign variables under the SOC of Investigations by PT were weight increased (serplulimab group vs placebo group: 12.8% vs 11.2%), weight decreased (12.6% vs 9.5%), and blood pressure increased (0.8% vs 1.1%)

Pooled Safety Population

Serplulimab did not have any notable effects on body temperature, respiration, blood pressure or heart rate.

Electrocardiogram

Pivotal study

The mean (SD) worst change (largest increase) from baseline in QTcF interval was 28.4 (40.51) msec in the serplulimab group and 26.9 (45.48) msec in the placebo group. The proportion of subjects with the worst QTcF > 500 msec was 1.4% in the serplulimab group and 3.4% in the placebo group. The proportion of subjects with the largest QTcF increases between >30 and ≤60 msec was 28.5% in the serplulimab group and 21.2% in the placebo group. The proportion of subjects with the largest QTcF increase of > 60 msec was 8.1% in the serplulimab group and 9.5% in the placebo group.

TEAEs with an incidence ≥ 1% in any group in 12-lead ECG variables under the SOC of Investigations by PT were electrocardiogram QT prolonged (serplulimab group vs placebo group vs placebo switched to serplulimab group: 2.0% vs 1.7% vs 3.1%), electrocardiogram repolarisation abnormality (0.3% vs 0.6% vs 1.0%), and electrocardiogram PR shortened (0 vs 0.6% vs 1.0%).

Pooled Safety Population

In the pooled safety population, the mean (SD) worst change (largest increase) in QTcF interval on treatment was 28.84 (34.704) msec. The proportion of subjects with the worst QTcF > 500 msec was 2.5%. The proportion of subjects with the largest QTcF increases between > 30 and ≤ 60 msec was 26.2%. The proportion of subjects with the largest QTcF increase of > 60 msec was 10.6%.

ECOG Performance status

Pivotal study

At baseline, all subjects in the serplulimab group and the placebo group had ECOG scores of 0 or 1, and the scores were balanced between the two groups. At the end-of-treatment visit, only 16 (4.5%) subjects and 10 (5.6%) subjects in the two groups experienced worsening of ECOG scores to 2 or 3, respectively

Pooled safety population

In the total population, at baseline, 1403 (73.2%) subjects' ECOG PS score were ≥ 1, and 513 (26.8%) subjects' ECOG PS score were < 1. At the end-of-treatment visit, 810 (42.3%) subjects' ECOG PS score were ≥ 1, and 184 (9.6%) subjects' ECOG PS score were < 1.

Safety in special populations

No separate analysis was provided for the pivotal study and only data from the pooled safety population were analysed.

Intrinsic Factors

Geriatric Use

Table 55. Safety profile by age group

MedDRA Terms	Age < 65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
Total TEAEs	1284 (97.9%)	715 (97.5%)	37 (92.5%)	1 (100%)
TESAEs – Total	489 (37.3%)	365 (49.8%)	16 (40.0%)	1 (100%)
-Fatal	132 (10.1%)	108 (14.7%)	5 (12.5%)	1 (100%)
-Hospitalization/prolong existing hospitalization	414 (31.6%)	313 (42.7%)	13 (32.5%)	1 (100%)
-Life-threatening	56 (4.3%)	52 (7.1%)	4 (10.0%)	1 (100%)
-Disability/incapacity	5 (0.4%)	1 (0.1%)	0	0
-Other (medically significant)	19 (1.4%)	9 (1.2%)	0	0
MedDRA Terms	Age < 65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
AE leading to drop-out	135 (10.3%)	103 (14.1%)	3 (7.5%)	1 (100%)
Psychiatric disorders	154 (11.7%)	102 (13.9%)	4 (10.0%)	0
Nervous system disorders	265 (20.2%)	168 (22.9%)	10 (25.0%)	0
Accidents and injuries	47 (3.6%)	39 (5.3%)	2 (5.0%)	1 (100%)
Cardiac disorders	277 (21.1%)	196 (26.7%)	7 (17.5%)	1 (100%)
Vascular disorders	177 (13.5%)	106 (14.5%)	7 (17.5%)	1 (100%)
Cerebrovascular disorders	26 (2.0%)	16 (2.2%)	1 (2.5%)	0
Infections and infestations	455 (34.7%)	280 (38.2%)	12 (30.0%)	1 (100%)
Anticholinergic syndrome	319 (24.3%)	215 (29.3%)	9 (22.5%)	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	83 (6.3%)	77 (10.5%)	2 (5.0%)	0
Other AE appearing more frequently in older patients	1161 (88.5%)	678 (92.5%)	37 (92.5%)	1 (100%)
Decreased appetite	362 (27.6%)	286 (39.0%)	12 (30.0%)	1 (100%)
Anaemia	813 (62.0%)	539 (73.5%)	26 (65.0%)	0
White blood cell count decreased	638 (48.6%)	429 (58.5%)	14 (35.0%)	0
Neutrophil count decreased	629 (47.9%)	421 (57.4%)	14 (35.0%)	0
Platelet count decreased	468 (35.7%)	358 (48.8%)	12 (30.0%)	0
Nausea	429 (32.7%)	292 (39.8%)	12 (30.0%)	0
Alanine aminotransferase increased	395 (30.1%)	139 (19.0%)	10 (25.0%)	0
Dyspnoea	89 (6.8%)	52 (7.1%)	10 (25.0%)	0
Asthenia	253 (19.3%)	183 (25.0%)	8 (20.0%)	0
Cough	156 (11.9%)	102 (13.9%)	8 (20.0%)	0
Neutropenia	125 (9.5%)	96 (13.1%)	7 (17.5%)	0
Leukopenia	106 (8.1%)	75 (10.2%)	6 (15.0%)	0
Fatigue	84 (6.4%)	49 (6.7%)	6 (15.0%)	0
Constipation	290 (22.1%)	208 (28.4%)	5 (12.5%)	0
Pruritus	76 (5.8%)	59 (8.0%)	5 (12.5%)	0
Protein urine present	44 (3.4%)	18 (2.5%)	3 (7.5%)	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" included 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.

Renal impairment

No effect of CRCL (Cockcroft-Gault) was found on serplulimab CL based on a popPK analysis in patients with mild (CRCL=60-89 mL/min; n=917), moderate (CRCL=30-59 mL/min; n=216), and severe (CRCL=15-29 mL/min; n=1) renal impairment, and normal renal function (CRCL ≥ 90 mL/min, n=973). There is insufficient data in patients with severe renal impairment for dosing recommendations.

Hepatic impairment

No effect of ALT, AST or total BIL was found on serplulimab CL based on a popPK analysis in patients with mild (BIL ≤ ULN and AST > ULN or BIL > 1 to 1.5 × ULN and any AST; n=279) and moderate (BIL > 1.5 to 3 × ULN and any AST; n=4) hepatic impairment, and normal (BIL ≤ ULN and AST ≤ ULN; n=1819) hepatic function. There is insufficient data in patients with moderate hepatic impairment for dosing recommendations. Serplulimab has not been studied in patients with severe (BIL > 3 × ULN and any AST) hepatic impairment.

Extrinsic Factors

No specific safety analyses based on factors associated with patient environment (medical environment, use of other drugs, use of tobacco, use of alcohol, and food habits) were conducted in the pivotal study HLX10-002-NSCLC301 and the pooled ten studies.

Immmunological events

The immunogenicity of serplulimab has been assessed in 10 clinical studies, which are presented in an integrated summary of immunogenicity (ISI). The presence of anti-serplulimab antibodies (ADA) in serum was evaluated with a 3-tier approach composed of screening, confirmation, and titre determination. In 7 of the studies, ELISA and electrochemiluminescence immunoassays were employed to detect NAb against serplulimab.

Table 56: Overview of studies included in the Integrated Summary of Immunogenicity

Study	serplulimab dose regimen	Planned sampling schedules	Detection method#	Cut-off date
HLX10-001 Phase 1, dose escalation and expansion, safety and tolerance in advanced solid tumor subjects.	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 600 mg Q6W	0.3~10 mg/kg, 200 mg, 300 mg: pre-dose cycle 1 and before first infusion in cycle 2-6 or up to 24 weeks, follow-up visit. 400 mg: pre-dose in cycle 1 to cycle 6, and on the 28-day follow-up visit. 600 mg: pre-dose in cycle 1 to cycle 6 and every 2 cycles thereafter, and on the 28-day follow-up visit.	***ADA***: electrochemiluminescence (ECL) immunoassay (Method ID: BTM-2497) ***NAb:*** ELISA(AP-HLX10NAb-01)	5-Jan-2024*
HLX10HLX04-001 Phase 1, dose escalation and expansion, safety and tolerance combined with HLX04 in advanced solid tumor subjects.	1 mg/kg Q2W 3 mg/kg Q2W 10 mg/kg Q2W	C1D1 pre-dose, C1D15 pre-dose, C3D1 pre-dose, C6D1 pre-dose, thereafter, pre-dose every 3 cycles before dosing.	***ADA***: ECL immunoassay (Method ID: 19BASM038)	11-Oct-2022*
HLX10HLX07-001 Phase 2, efficacy and safety of combined with HLX07 in patients with advanced head and neck tumors	3 mg/kg Q2W	C1D1 pre-dose, C1D15 pre-dose, every even cycle (2, 4, 6, etc.) before HLX10 first infusion and at follow-up visit 1 or exit visit.	***ADA***: ECL immunoassay (Method ID: SHBTM-1863)	16-Sep-2022
HLX10-008-HCC201 Phase 2, efficacy and safety of combined with HLX04 in patients with hepatocellular carcinoma	3 mg/kg Q2W	pre-dose, pre-dose in cycle 1, 2, 4, 6, 8, and every 4 weeks thereafter, as well as at the time of termination visits and safety follow-up.	***ADA***:Automatic chemiluminescent (ACL)immunoassay(Method ID: AP-HLX10ADA02) ***NAb:*** ECL·immunoassay(AP-HLX10NAb01)	7-Feb-2023
HLX10-010-MSI201 Phase 2, efficacy and safety in patients with Unresectable or MSI-H or dMMR solid tumors that have failed standard treatment	3 mg/kg Q2W	pre-dose in cycle 1, 2, 4, 6, 8, and every 4 weeks thereafter, as well as at the time of termination visits and safety follow-up.	***ADA***: ECL immunoassay (Method ID: 19BASM038) ***NAb:*** ECL immunoassay (Method ID: 20BASM164)	10-Jul-2021
HLX10-011-CC201 Phase 2, Combined with albumin-paclitaxel for the treatment of advanced cervical cancer with disease progression or intolerable toxic reactions after treatment with first-line standard chemotherapy	3 mg/kg Q2W	pre-dose in cycle 1, 2, 4, 6, 8, and every 4 weeks thereafter, as well as at the time of termination visits and safety follow-up.	***ADA***: ACL immunoassay (Method ID: AP-HLX10ADA02)	22-Sep-2022
HLX10-004-NSCLC303 Phase 3, First-line treatment for locally advanced or metastatic squamous non-small cell lung cancer (NSCLC)	4.5 mg/kg Q3W	pre-dose in cycle 1, 2, 4, 6, 8, and every 4 weeks thereafter, as well as at the time of termination visits and safety follow-up.	***ADA***: ACL immunoassay (Method ID: AP-HLX10ADA02) ***NAb:*** ELISA (Method ID: AP-HLX10NAb01)	31-Jan-2023
HLX10-005-SCLC301 Phase 3, combination with chemotherapy (carboplatin-etoposide) in previously untreated patients with extensive stage small cell lung cancer	4.5 mg/kg Q3W	pre-dose in cycle 1, 2, 4, 6, 8, and every 4 weeks thereafter, as well as at the time of termination visits and safety follow-up.	***ADA***: ACL immunoassay (Method ID: AP-HLX10ADA02) ***NAb:*** ELISA (Method ID: AP-HLX10NAb01)	07-May-2024
HLX10-002-NSCLC301 Phase 3, First-line treatment for advanced non-squamous non-small1cell lung cancer	4.5 mg/kg Q3W	Within 7 days before dosing in Cycle 1, within 3 days before dosing in Cycles 2, 4, 6, 8, and every 4 cycles thereafter, at the termination visit and/or during the safety follow-up.	***ADA***: ACL immunoassay (Method ID: AP-HLX10ADA02) ***NAb:*** ELISA (Method ID: AP-HLX10NAb01)	15-Jun-2023
HLX10-007-EC301 in combination with chemotherapy (cisplatin plus 5-FU) as first-line treatment in patients with locally advanced/metastatic esophageal squamous cell carcinoma	3 mg/kg Q2W	Within 24 hr before dosing in Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter, at the termination visit and during the safety follow-up.	***ADA***: ECL immunoassay (Method ID: 19BASM038) ***NAb:*** ECL immunoassay (Method ID: 20BASM164)	09-Jan-2023

Table *57*: Summary of immunogenicity results for serplulimab by study

ADA category	HLX10-001 (N=66)	HLX10 HLX04-001 (N=26)	HLX10-010-MSI201 (N=108)	HLX10-008-HCC201 (N=123)	HLX10-011-CC201 (N=21)	HLX10 HLX07-001 (N=13)	HLX10-004-NSCLC303 (N=455)	HLX10-005-SCLC301 (N=389)	HLX10-002-NSCLC301 (N=503)	HLX10-007-EC301 (N=382)	Total (N=2086)
ADA positive at baseline only	2 (3.0%)	0	2 (1.9%)	1 (0.8%)	0	0	2 (0.4%)	1 (0.3%)	5 (1.0%)	2 (0.5%)	15 (0.7%)
ADA positive at any visit	13 (19.7%)	1 (3.8%)	7 (6.5%)	3 (2.4%)	0	1 (7.7%)	15 (3.3%)	8 (2.1%)	22 (4.4%)	24 (6.3%)	94 (4.5%)
Treatment-emergent ADA positive	11 (16.7%)	1 (3.8%)	5 (4.6%)	2 (1.6%)	0	1 (7.7%)	13 (2.9%)	7 (1.8%)	17 (3.4%)	22 (5.8%)	79 (3.8%)
Treatment-boosted ADA	0	0	0	0	0	0	0	0	0	0	0
Treatment-induced ADA	8 (12.1%)	1 (3.8%)	3 (2.8%)	2 (1.6%)	0	0	12 (2.6%)	6 (1.5%)	15 (3.0%)	15 (3.9%)	62 (3.0%)
Persistent positive ADA	6 (9.1%)	0	2 (1.9%)	1 (0.8%)	0	1 (7.7%)	3 (0.7%)	2 (0.5%)	4 (0.8%)	8 (2.1%)	27 (1.3%)
Transient positive ADA	5 (7.6%)	1 (3.8%)	3 (2.8%)	1 (0.8%)	0	0	10 (2.2%)	5 (1.3%)	14 (2.8%)	14 (3.7%)	53 (2.5%)
NAb positive at any visit	0	NA	0	0	NA	NA	0	0	2 (0.4%)	1 (0.3%)	3 (0.1%)

Note: NA: not applicable. NAb testing was not performed in this study.Definitions for the different categories of ADA-positive patients are as follows:
☐ Treatment-emergent ADA positive is defined as at least one post-baseline ADA positive.
☐ Treatment-induced ADA is defined as baseline negative ADA, post-baseline ADA positive.
☐ Treatment-boosted ADA is defined as baseline positive ADA titer that was boosted to ≥4 fold during the study period. If the titer test value is less than 10, it will be calculated as 10.
☐ Persistently positive is defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks between the first and last positive measurements, or an ADA positive result at the last available assessment, including patients meeting these criteria who are ADA positive at baseline.
☐ Transiently positive is defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive, including patients meeting these criteria who are ADA positive at baseline.
☐ For subjects who switched from placebo to serplulimab, baseline is defined as the last observation before serplulimab treated.

Table 58: Summary of immunogenicity results for serplulimab by dose and combination

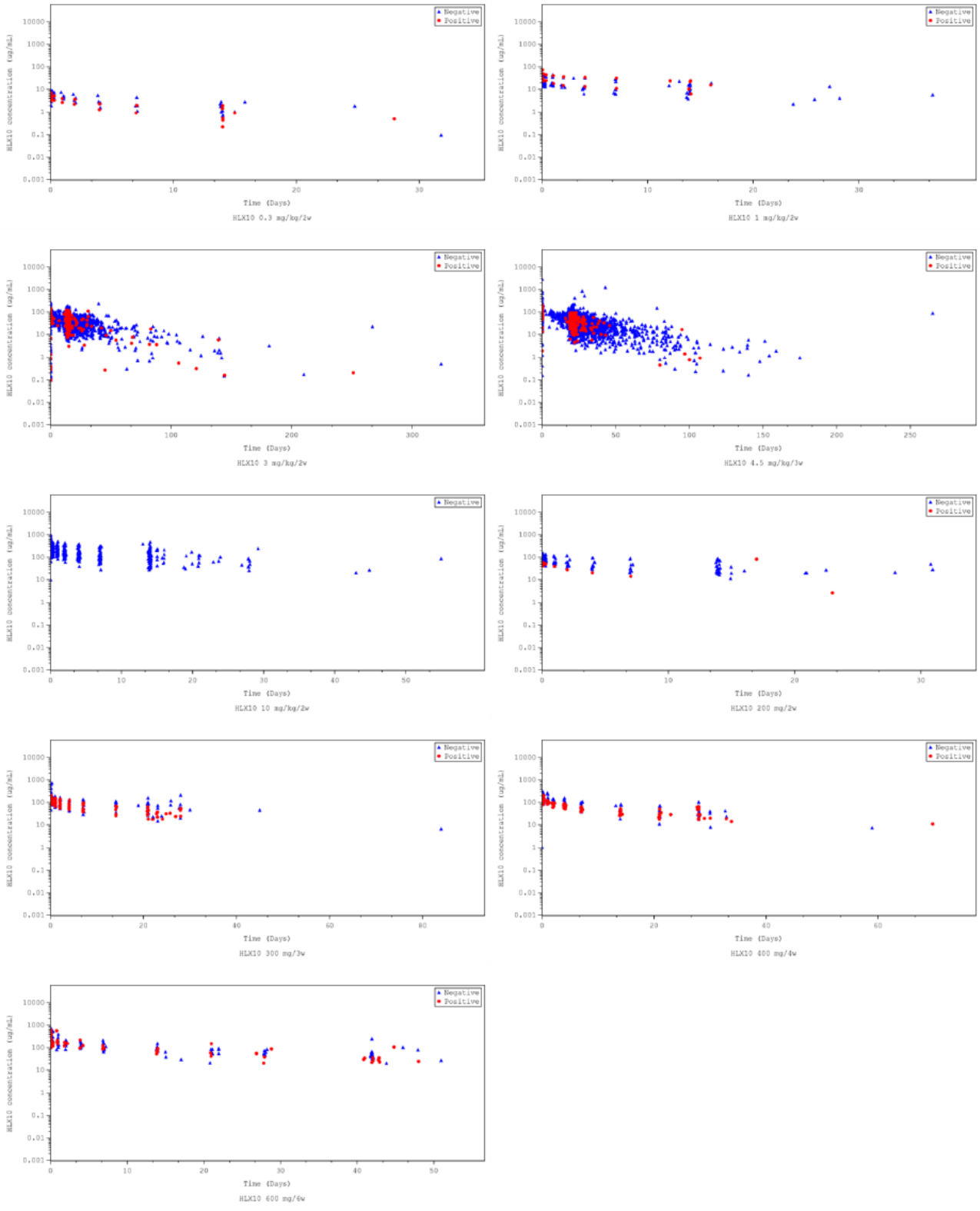
ADA category	<RP2D/3D			≥RP2D/3D				Total population (N=2086)
	Monotherapy (N=7)	Other Combination (N=3)	Total (N=10)	Monotherapy (N=285)	Chemotherapy Combination (N=1364)	Other Combination (N=427)	Total (N=2076)	
ADA positive at baseline only	0	0	0	4 (1.4%)	8 (0.6%)	3 (0.7%)	15 (0.7%)	15 (0.7%)
ADA positive at any visit	1 (14.3%)	1 (33.3%)	2 (20.0%)	21 (7.4%)	55 (4.0%)	16 (3.7%)	92 (4.4%)	94 (4.5%)
Treatment-emergent ADA positive	1 (14.3%)	1 (33.3%)	2 (20.0%)	17 (6.0%)	47 (3.4%)	13 (3.0%)	77 (3.7%)	79 (3.8%)
Treatment-boosted ADA	0	0	0	0	0	0	0	0
Treatment-induced ADA	1 (14.3%)	1 (33.3%)	2 (20.0%)	12 (4.2%)	37 (2.7%)	11 (2.6%)	60 (2.9%)	62 (3.0%)
Persistent positive ADA	0	0	0	8 (2.8%)	15 (1.1%)	4 (0.9%)	27 (1.3%)	27 (1.3%)
Transient positive ADA	1 (14.3%)	1 (33.3%)	2 (20.0%)	9 (3.2%)	32 (2.3%)	10 (2.3%)	51 (2.5%)	53 (2.5%)
NAb positive at any visit	0	0	0	0	2 (0.1%)	1 (0.2%)	3 (0.1%)	3 (0.1%)

Note: Definitions for the different categories of ADA-positive patients are as follow.
☐ Treatment-emergent ADA positive is defined as at least one post-baseline ADA positive.
☐ Treatment-induced ADA is defined as baseline negative ADA, post-baseline ADA positive.
☐ Treatment-boosted ADA is defined as baseline positive ADA titer that was boosted to ≥4 fold during the study period. If the titer test value is less than 10, it will be calculated as 10.
☐ Persistently positive is defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks between the first and last positive measurements, or an ADA positive result at the last available assessment, including patients meeting these criteria who are ADA positive at baseline.
☐ Transiently positive is defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive, including patients meeting these criteria who are ADA positive at baseline.
☐ For subjects who switched from placebo to serplulimab, baseline is defined as the last observation before serplulimab treated.

Relationship of ADA with PK, safety and efficacy

PK concentrations by ADA status were presented for the pooled safety population and per dose level.

Figure 25: PK concentrations plot by ADA and dose level



Note: -Positive will be defined as at least one positive result regardless of baseline or post-baseline. Individual serplulimab concentration for ADA positive subjects (red circles), ADA negative subjects (blue triangles). Time for x-axis is relative time from last dose to PK sampling.

For the three patients with positive neutralizing antibodies, two patients were from study HLX10-

002-NSCLC301 and one patient from study HLX10-007-EC301. In the two patients from study HLX10-002-NSCLC301, one was from the serplulimab + chemotherapy group (subject ID 027006), the other was from placebo + chemotherapy switching to serplulimab + HLX04 after PD group (subject ID 030032). One patient from study HLX10-007-EC301 (subject ID 153004) was in the serplulimab + chemotherapy group. PK exposures for these three patients with Nabs are shown below.

Table 59: PK exposure comparison for the three patients with Nabs.

	C1-C_{max} (μg/mL)	C2-Ct_{rough} (μg/mL)
Study HLX10-002-NSCLC301		
serplulimab + chemotherapy group (overall)*	93.381±48.816	19.423±7.263
subject ID 027006	77.699	NA
Placebo + chemotherapy switching to serplulimab + HLX04 group (overall)*	88.035±25.021	18.908±7.719
subject ID 030032	NA	10.238
Study HLX10-007-EC301		
serplulimab + chemotherapy group (overall)*	54.030±20.263	16.776±7.118
subject ID 153004	39.7	8.955

Note:*the mean±SD, NA : not applicable.

Table 60: Overview of AEs by ADA

Number of subjects experiencing	Subjects with at least one positive ADA (n=94)	Subjects without positive ADA (n=1992)	Total (n=2086)
At least one adverse event	90 (95.7%)	1947 (97.7%)	2037 (97.7%)
At least one adverse event with CTCAE Grade >=3	55 (58.5%)	1411 (70.8%)	1466 (70.3%)
At least one serplulimab related adverse event with CTCAE Grade >=3	31 (33.0%)	685 (34.4%)	716 (34.3%)
At least one serious adverse event	34 (36.2%)	837 (42.0%)	871 (41.8%)
At least one irAE	30 (31.9%)	684 (34.3%)	714 (34.2%)
At least one AESI	30 (31.9%)	705 (35.4%)	735 (35.2%)

Safety related to drug-drug interactions and other interactions

Serplulimab is a humanised monoclonal antibody and thus has not been investigated for PK interactions with other drugs. Monoclonal antibodies are not metabolised by Cytochrome P450 enzymes or other drug metabolic enzymes. The inhibitory effect or induction of the concomitant drugs on these enzymes is not expected to affect the PK profile of serplulimab.

Before treatment with serplulimab is started, systemic corticosteroids or other immunosuppressants should be avoided, as they may interfere with the pharmacodynamic activity of serplulimab. Systemic corticosteroids and other immunosuppressants can be used for treatment of immune-related adverse reactions after the treatment with this product is started.

Discontinuation due to adverse events

Adverse Events Leading to Treatment Discontinuation

Pivotal study

TEAEs leading to the discontinuation of serplulimab/placebo occurred in 16.8 % of subjects in the serplulimab + chemotherapy group and 12.8% of subjects in the placebo + chemotherapy group.

TEAEs leading to the discontinuation of serplulimab/placebo with incidence ≥ 1% by PT (in descending order of incidence) included pneumonia (3.1% vs 3.4% of subjects in the serplulimab + chemotherapy group, platelet count decreased (1.7% vs 0.6%) , immune-mediated lung disease (1.7% vs 0), COVID-19 (1.1% vs 0), disease progression (0.8% vs 1.1%), pulmonary haemorrhage (0.6% vs 0), myocardial infarction (0.3% vs 1.1%), death (0,3% vs 0.6%9, pulmonary embolism (0.3% vs 0), arrhythmia (0.3% vs 0).

In total, 8.7% subjects in the serplulimab + chemotherapy group and 4.5% subjects in the placebo + chemotherapy group experienced serplulimab/placebo-related TEAEs leading to the discontinuation of serplulimab/placebo.

Serplulimab/placebo-related TEAEs leading to the discontinuation of serplulimab/placebo with incidence ≥ 1% by PT (in descending order of incidence) included immune-mediated lung disease (1.7% vs 0), pneumonia (1.1% vs 1.7%), platelet count decreased (1.1% vs 0.6%), arrhythmia (0.3% vs 0), diarrhea (0 vs 0.6%), myocardial infarction (0 vs 0.6%).

Pooled safety population

TEAEs leading to serplulimab discontinuation occurred in 242 (11.6%) subjects. In the ≥ RP2D/3D dose group, 11.2% of the subjects who received serplulimab monotherapy discontinued serplulimab due to TEAEs, compared to 11.0% of the subjects who received serplulimab in combination with chemotherapy, and 13.3% of the subjects who received serplulimab in combination with other drugs.

For the grouped categories, TEAEs leading to serplulimab discontinuation with an incidence ≥ 0.5% in the total population were pneumonitis (1.3%), pneumonia (1.0%), thrombocytopenia (0.6%), liver injury (0.6%), and renal injury (0.5%).

For the ungrouped PTs, TEAEs leading to serplulimab discontinuation with incidence ≥ 0.5% in the total population was disease progression (0.7%).

A total of 150 (7.2%) subjects experienced serplulimab-related TEAEs leading to serplulimab discontinuation. In the ≥ RP2D/3D dose group, 4.9% of the subjects who received serplulimab monotherapy discontinued serplulimab due to serplulimab-related TEAEs, compared to 6.9% of the subjects who received serplulimab in combination with chemotherapy, and 9.6% of the subjects who received serplulimab in combination with other drugs.

For the grouped categories, serplulimab-related TEAE leading to serplulimab discontinuation with an incidence ≥ 0.5% in the total population was pneumonitis (1.3%). No serplulimab-related TEAEs leading to serplulimab discontinuation had an incidence ≥ 0.5% by ungrouped PT.

TEAEs Leading to Dose Modification

Dose modification of serplulimab/placebo was not allowed as per study protocol.

TEAEs leading to serplulimab/placebo interruption

Pivotal study

In total, 63.1% of subjects in the serplulimab + chemotherapy group and 51.4% of subjects in the placebo + chemotherapy group experienced a TEAE leading to the interruption of serplulimab/placebo, respectively.

TEAEs leading to serplulimab/placebo interruption with an incidence ≥ 5% in any group by PT were neutrophil count decreased (serplulimab group vs placebo group: 23.2% vs 12.8%), platelet count decreased (21.2% vs 12.8%), white blood cell count decreased (20.4% vs 14.5%), anaemia (19.8% vs 16.2%), neutropenia (10.1% vs 11.7%), pneumonia (8.9% vs 7.3%), thrombocytopenia (8.7% vs 6.7%), and leukopenia (5.9% vs 5.0%)

Overall, serplulimab/placebo-related TEAEs leading to serplulimab/placebo interruption were experienced by 37.4% of subjects in the serplulimab- and 25.1% of subjects in the placebo arm. Related TEAEs leading to serplulimab/placebo interruption with an incidence ≥ 5% in any group by PT were neutrophil count decreased (serplulimab group vs placebo group: 11.2% vs 6.1%), anaemia (10.6% vs 8.4%), white blood cell count decreased (10.6% vs 6.7%), platelet count decreased (8.7% vs 5.6%), neutropenia (4.5% vs 6.7%), and thrombocytopenia (4.2% vs 5.0%)

Pooled safety population

TEAEs leading to serplulimab interruption occurred in 1052 (50.4%) subjects. In the ≥ RP2D/3D dose group, 30.2% of the subjects who received serplulimab monotherapy reported serplulimab interruption due to TEAEs, compared to 53.7% of the subjects who received serplulimab in combination with chemotherapy, and 53.2% of the subjects who received serplulimab in combination with other drugs.

For the grouped categories, TEAEs leading to serplulimab interruption with an incidence ≥ 5% in the total population were neutropenia (15.2%), thrombocytopenia (13.8%), leukopenia (10.8%), anaemia (8.1%), and COVID-19 (5.1%).

No TEAEs leading to serplulimab interruption had an incidence ≥ 5% by ungrouped PT.

A total of 651 (31.2%) subjects experienced serplulimab-related TEAEs leading to the serplulimab interruption. In the ≥ RP2D/3D dose group, 18.9% of the subjects who received serplulimab monotherapy interrupted serplulimab due to serplulimab-related TEAEs, compared to 31.7% of the subjects who received serplulimab in combination with chemotherapy, and 37.7% of the subjects who received serplulimab in combination with other drugs.

For the grouped categories, serplulimab-related TEAEs leading to the serplulimab interruption with an incidence ≥ 5% in the total population were thrombocytopenia (7.4%), neutropenia (6.4%), and leukopenia (5.1%).

No serplulimab-related TEAEs leading to serplulimab interruption had an incidence ≥ 5% by ungrouped PT.

Post marketing experience

Serplulimab was approved by National Medical Products Administration (NMPA) of China with the trade name Hansizhuang on March 22, 2022 and marketed in China on March 30, 2022 and is authorized for indications in NSCLC, SCLC and ESCC combined with chemotherapy. Serplulimab (the brand name is Hetronifly) has been approved in the EU for ES-SCLC in combination with carboplatin and etoposide on February 3, 2025. This indication is also approved in Indonesia, Cambodia and Thailand.

As of March 21, 2025, about 1521171 vials (100 mg/vial) of serplulimab injection, totalling 152117100 mg, were sold. Cumulatively, it was estimated that 93 899 patients were treated with serplulimab injection.

Adverse Events from Marketing Experience

As of March 21, 2025, 1554 valid individual case safety reports (ICSRs) were collected which included 2712 AEs (2641 ADRs). 1500 ICSRs were collected from spontaneous reports, which included 2593 AEs (2528 ADRs). And the rest of 54 ICSRs were collected from solicited source, which included 119 AEs (113 ADRs).

No new significant safety risks have been identified so far. Neither regulatory authorities nor Henlius have taken any actions for safety issues of serplulimab.

2.5.1. Discussion on clinical safety

Safety database

The safety profile of serplulimab in the targeted indication is based primarily on interim results from the pivotal study HLX10-004-NSCLC303 with the data cut off January 31, 2023. The safety database includes 358 subjects treated with serplulimab and 179 subjects in the placebo arm, whereof 97 subjects crossed over to serplulimab monotherapy after disease progression.

Supportive pooled safety data from a total of 10 clinical trials with serplulimab in subjects with various types of solid tumours is available including a total of 2086 serplulimab treated patients. Of these, only 268 patients are non-Asian.

Overall, the safety database from the pivotal study together with supporting safety data from the pooled safety population is considered large enough to sufficiently describe the safety profile of serplulimab in the sought indication.

Exposure

The median duration of exposure to serplulimab or placebo was substantially higher in the serplulimab arm (28.3 weeks) compared to the placebo arm (18.1 weeks), which is also reflected in the median treatment cycles (9 vs. 6 cycles) and the median cumulative dose (2834 vs. 1758 mg). However, no difference in exposure between the serplulimab and placebo arm was seen for carboplatin and Nab-paclitaxel. The relative dose intensity was similar (>90%) between the two arms. No data on the exposure to serplulimab was provided for subjects in the placebo arm who crossed over to serplulimab monotherapy.

As of the cut-off of 9 January 2023, 70.7%, 47.7%, and 33.3% of subjects in the pooled safety population had serplulimab exposure for at least 3 months, 6 months, and 9 months, respectively. Data on exposure for at least 12 months was not provided.

The exposure is considered sufficient to characterise a reliable safety profile for serplulimab.

Demographics and disease baseline characteristics were already discussed in section 2.4.3.

The study population is considered acceptable in terms of characterization of the safety profile of serplulimab.

Adverse events

In the pivotal study, almost all (98.9% in the serplulimab arm and 98.3% in the placebo arm) reported at least one **TEAE**, of which the majority were considered by the investigator as

serplulimab/placebo-related (serplulimab: 73.2% vs placebo: 62.6%). The rates of **≥Grade 3 TEAEs** were 85.2% and 79.3% (serplulimab/placebo-related: 35.5% and 31.8%), respectively. The large proportion of TEAEs reported as related to serplulimab in the placebo arm (62.6%) indicates that the safety profile of the combination treatment regimen is likely driven by the chemotherapy backbone with serplulimab increasing treatment toxicity only moderately.

The most common TEAEs that occurred in at least 20% in the serplulimab group were related to haematology (i.e. neutrophil count decreased, white blood cell count decreased, platelet count decreased and anaemia), hepatic function (i.e. alanine aminotransferase increased, aspartate aminotransferase increased and gamma-glutamyltransferase increased), metabolism/nutrition (i.e. weight decreased, weight increased, decreased appetite, hypoalbuminemia, hypercholesterolaemia and hypokalaemia), gastrointestinal disorders (i.e. nausea, constipation and vomiting) as well as asthenia.

Similarly, the most common grade ≥ 3 TEAEs, both all-cause and serplulimab related, were within the haematology SOC (e.g. anaemia, neutropenia and white blood cell -, platelet- and neutrophil count decreased), and related to respiratory function, (e.g. pneumonia). On PT level, grade ≥ 3 TEAEs were generally comparable in the serplulimab and placebo arm with the exceptions of 'platelet count decreased' (43.0% in the serplulimab vs. 37.4% in the placebo arm; 6.7% vs. 2.8% serplulimab/placebo related) and 'immune-mediated lung disease' (2.2% vs. 0% both all-cause and related AEs).

There is a higher incidence of SAEs in the serplulimab arm compared to the placebo arm (52.0 % vs 42.5%, of which 22.6% vs 15.6% were considered related).

The higher incidence of TEAEs, ≥Grade 3 TEAEs and SAEs is not unexpected, given the additive effect of serplulimab on the overall toxicity of the chemotherapy backbone.

The incidence of -PTs related to haematology and respiratory function are slightly higher in the serplulimab arm, which is consistent with the imbalances seen for adverse events overall.

Overall, the pattern of all-cause and related TEAEs, grade ≥ 3 TEAEs and TESAEs in the pivotal study is consistent with the pooled safety population. The safety profile of the combination treatment is mainly driven by the chemotherapy backbone and the increase in toxicity by adding serplulimab to the treatment regimen is moderate. Imbalances seen between the arms were predominantly reported for listed ADRs of serplulimab. In conclusion, the safety data submitted for the current application is consistent with the known safety profile of serplulimab and no new safety concerns have been identified.

Frequency estimation for ADRs, as presented in the SmPC, is based on the all-cause AE frequency, which is in line with EMA guidance.

Toxic Epidermal Necrolysis, was included as a new ADR with the frequency 'Rare'. One case occurred in the ASTRUM-004 study, and occurrences have also been reported in post-marketing safety data. The ADRs have been evaluated and are grouped under existing terms to the greatest extent possible, in accordance with the SmPC Guideline. Furthermore, the frequencies of some ADRs have changed due to the inclusion of ADR from the ASTRUM-004 study into the existing ASTRUM-005 safety dataset, which affected the overall incidence rates.

TEAEs leading to death

In total, 13.7% in the serplulimab arm and 10.6% in the placebo arm experienced TEAEs leading to death, however, this also includes 'disease progression', which accounts for 14 out of 49 deaths in the serplulimab arm and 6 out of 19 deaths in the placebo arm. Per protocol, disease progression

of lung cancer was not to be reported as an adverse event. Serplulimab/placebo-related TEAEs leading to death occurred in 4 subjects in the serplulimab group ('immune-mediated lung disease' in 2 subjects and 'pulmonary haemorrhage', 'respiratory failure', and 'immune-mediated enterocolitis' in one subject each). In the placebo group, the reported related TEAEs leading to death were 'pneumonia' and 'hepatic failure' in one subject each and in the placebo switched to serplulimab-group 'myocardial infarction' and 'pneumonia' in one subject each.

Most deaths due to serplulimab-related AEs were related to the respiratory system. Both 'immune-mediated lung disease', 'respiratory failure' and 'pneumonia' are listed as adverse reactions of serplulimab in the amended SmPC submitted with the current application and are addressed in the section "Description of selected adverse reactions". However, considering the nature of the treated disease, disease-related complications may be difficult to exclude as potential contributing factors to the deaths.

AESIs

Immune-related adverse events (irAEs) and **infusion related reactions (IRRs)** were defined as adverse events of special interest (AESI) for serplulimab. In the pivotal study, irAEs occurred in 29.6% of the patients in the serplulimab and 17.3 % in the placebo arm. Few subjects, 4 subjects (0.7%) in the serplulimab arm, reported IRRs. The majority of the reported AESIs were non-serious in both arms (serious irAESIs: 11.5% vs 5.6%). This is in line with the overall results in the pooled safety population (AESIs: 35.2% with grade ≥ 3 AESIs 9.1%).

The most common irAEs by PT were 'hypothyroidism', 'rash', 'immune-mediated lung disease' and 'pneumonia', which all were reported more frequently in the serplulimab arm. These irAEs are well known adverse reactions for the class of PD1-inhibitors and are also in line with the known safety profile of serplulimab.

In the pooled safety population, 7.4% received high-dose corticosteroids to treat irAEs. In the pivotal study, 34 out of 358 participants (9.5%) in the serplulimab arm and 9 out of 179 participants (5.0%) in the placebo arm received high-dose corticosteroid treatment. The difference between treatment arms (9.5% vs. 5.0%) is mainly driven by immune-mediated lung disease (5.0% vs. 1.7%) and immune-mediated skin adverse reactions (1.7% vs 0). The median duration of high-dose corticosteroid treatment was 1.64 months vs. 0.23 months in the serplulimab and placebo arms, respectively, with a wide range especially for the serplulimab arm (0.0329, 19.1869 months).

Adequate description of how to manage immune-mediated adverse reactions are already included in the product information and were adequately updated by the MAH.

Laboratory findings and vital signs

Apart from some serum chemistry parameters (AST, ALT and blood creatinine increased) and thyroid function parameters, there are no notable differences between the serplulimab arm and the placebo arm in laboratory findings or vital signs. This indicates that most events are likely related to the chemotherapy backbone, while toxic effects on liver and thyroid function are well-known adverse reactions to serplulimab and other PD1 inhibitors.

TEAEs leading to serplulimab/placebo discontinuation or interruption

In total, 16.8 % of subjects in the serplulimab arm experienced TEAEs leading to the discontinuation of serplulimab/placebo vs. 12.8% of subjects in the placebo arm. Serplulimab/placebo-related TEAEs leading to **serplulimab/placebo discontinuation** were twice as frequent in subjects in the serplulimab arm (8.7%) compared to the placebo arm (4.5%).

Similarly, all-cause as well as serplulimab/placebo-related TEAEs leading to **drug interruptions** were reported more frequently in the serplulimab arm than in the placebo arm (63.1% vs. 51.4% and 37.4% vs 25.1%, respectively). Addition of serplulimab to the chemotherapy regimen resulted in a slight increase in discontinuation of Carboplatin or Nab-Paclitaxel but did not affect the incidence of Carboplatin or Nab-Paclitaxel treatment interruptions. Overall, this is considered acceptable.

Safety in special populations

No separate analysis by race, age or gender was provided for the pivotal study and only data for the pooled safety population were included in the dossier.

Only a few subjects in the pooled safety population were non-Asian (all White: 268 subjects). Frequencies of the TEAEs were generally lower in the non-Asian population, however, the conclusion in the initial MAA procedure that the safety profile of serplulimab in the Asian and non-Asian subsets were overall comparable is considered to be still valid.

In the pooled safety set, 37% of the patients were ≥ 65 years old, generally reporting more Grade ≥3 TEAEs, TESAEs and deaths than patients <65 years of age, which is as expected. TEAEs reported more frequently in older subjects were anaemia, leukopenia, neutropenia, platelet count decreased, and decreased appetite, which are likely driven by the chemotherapy backbone.

In contrast, younger patients (<65 years) had a numerically higher incidence of irAEs (35.4% vs 32.2%), which is not unexpected. 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. In total, 425 females vs. 1661 males are included in the pooled safety population, whereof 37 females originate from the pivotal study for the current application. In addition, separate safety data were provided for Caucasian women (N=31). Overall, the safety profile seems slightly worse in men than in women with Caucasian women tolerating the treatment better than Asian women. This is consistent with the findings in the initial MAA procedure (see EPAR), and no further analysis is deemed necessary.

Immunogenicity

The MAH has provided an integrated summary of immunogenicity (ISI) including results from the ten studies where the immunogenicity of serplulimab was studied. At the time of the MAA, the lack of crossvalidation of the four ADA methods used in the different studies was raised. In the absence of any crossvalidation, direct comparison of immunogenicity results across studies is not possible.

Bearing this uncertainty in mind, the overall rate of ADA incidence appears low. From the 2086 evaluable subjects, 94 (4.5%) were ADA positive at any visit and 62 (3.0%) had treatment-induced ADAs, defined as baseline negative ADA, post-baseline ADA positive. 27 patients (1.3%) were persistently positive for ADA, defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks between the first and last positive measurements, or an ADA positive result at the last available assessment, including patients meeting these criteria who are ADA positive at baseline. Three patients (0.1%) had neutralising antibodies (Nabs). It should be noted that Nabs were only tested in 7 of the 10 studies included in the ISI. Overall, the ISI did not show any evidence for ADA impact on PK, safety or efficacy in these ten studies.

Overall, the immunogenicity in the pivotal study in SQ NSCLC was in line with that observed in the pivotal study for the MAA, HLX10-005-SCLC301 and in the overall safety population. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. This is reflected in section 5.1

of the SmPC.

Immunogenicity in dose-finding study HLX10-001 was presented and assessed in the original application and no further data has been provided in this submission. No patients were found to be Nab positive. Though data was very limited, no evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

2.5.2. Conclusions on clinical safety

The dossier for serplulimab in this extension of indication application on squamous-NSCLC provides data from a population large enough to assess the safety profile of serplulimab in the sought indication and to identify the most common adverse reactions. The reported safety profile is overall consistent with the known safety profile of serplulimab and comparable to the other anti-PD1/PD-L1 antibodies qualitatively. There is an increased incidence of TESAEs, grade ≥3 AEs, TEAEs leading to drug discontinuation and drug interruption compared to a standard of care regimen but the increase is modest and indicative of an additive effect indicating that toxicity is mainly driven by the chemotherapy SOC components. No new safety concerns were identified and the safety profile of serplulimab in combination with carboplatin and pemetrexed is considered acceptable.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 3.0 with the following content:

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

The list of safety concerns remains unchanged.

Pharmacovigilance plan

There are no additional pharmacovigilance activities for this product.

Risk minimisation measures

Table 61. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Immune-mediated adverse reactions	**Routine risk minimisation measures:** Routine risk communication: 1. Immune-mediated adverse reactions added in SmPC section 4.4. 2. 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: 3. Guidance for withholding or permanently discontinuing serplulimab based on the severity of adverse reactions provided in SmPC section 4.2. 4. Warning to monitor for signs and symptoms of immune-mediated adverse reactions and treatment advice based on severity included in SmPC section 4.4. 5. Warning for the patient to talk to their doctor if they have inflammation provided in Package leaflet. Other routine risk minimisation measures: **6.** Legal status: subject to restricted medical prescription. **Additional risk minimisation measures:** Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Severe infusion reactions	**Routine risk minimisation measures:** Routine risk communication:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

	7. Description of the infusion-related reactions observed in clinical trials provided in SmPC section 4.4. 8. Infusion-related reaction listed as adverse reaction in SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: 9. Guidance for withholding or discontinuing serplulimab based on the severity of the infusion-related reaction provided in SmPC section 4.2. 10. Warning to monitor for signs and symptoms of infusion-related reactions and treatment advice based on severity included in SmPC section 4.4. 11. Warning for the patient to talk to their doctor if they have infusion-related reactions provided in Package leaflet. Other routine risk minimisation measures: **12.** Legal status: subject to restricted medical prescription. **Additional risk minimisation measures:** Patient Card	None **Additional pharmacovigilance activities:** None
Long-term safety in immunocompromised patients	**Routine risk minimisation measures:** Routine risk communication: 13. 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: 14. Guidance for the patient to check with their doctor before receiving serplulimab	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

	if they have an autoimmune disease in Package leaflet. Other routine risk minimisation measures: **15.** Legal status: subject to restricted medical prescription. **Additional risk minimisation measures:** None	

The risk minimisations activities remain unchanged.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8., 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The variation is intended to extend the already existing marketing authorisation of Hetronifly (serplulimab). The changes to the package leaflet are minimal and do not require user consultation with target patient groups. They do not affect key messages for the safe use of the medicinal product. Thus, the justification for not performing a full user testing is considered acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The final indication is: *HETRONIFLY in combination with carboplatin and nab-paclitaxel is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic squamous non-small cell lung carcinoma.*

3.1.1. Disease or condition

Non-small-cell lung cancer (NSCLC) accounts for 80%-90% of all lung cancers (Torre LA et al, 2012). The main histological subtypes are adenocarcinoma (40%), squamous cell carcinoma (25%), and large cell carcinoma (10%) (National Cancer Institute 2025).

Lung cancer is often diagnosed at an advanced stage, resulting in a poor prognosis; the 5-year OS rate for patients with advanced NSCLC (2010-2016) ranges from 6% in patients with distant metastases to 17% in patients with stage IIIB (Ganti et al, 2021, JAMA Oncology). However, treatment has changed markedly during the past decade with wider lung cancer screening, improved radiation techniques, and treatment advances. These changes have likely resulted in the reported decline in NSCLC mortality.

3.1.2. Available therapies and unmet medical need

Over the past decade, there have been considerable advances in the management of NSCLC.

For patients with metastatic NSCLC with no actionable oncogenic driver, the development of immune checkpoint inhibitors (ICIs) has transformed the care, providing a survival benefit when administered as monotherapy following disease progression on platinum-based chemotherapy (Rittmeyer et al 2017) or when administered with or without chemotherapy in the first-line setting (Jotte et al 2020, West et al 2019, Wang et al 2023). These changes to the treatment landscape applies to both squamous and non-squamous NSCLC.

In the first-line squamous NSCLC setting, pembrolizumab is approved as first-line treatment therapy for squamous NSCLC, either as monotherapy for the "PD-L1 high" (≥50%) population or in combination with platinum-based chemotherapy. More recently, nivolumab/ipilimumab with platinum-doublet chemotherapy was approved as first-line treatment for NSCLC irrespective of histology, and nivolumab/ipilimumab combination therapy alone was approved in tumours expressing PD-L1 ≥1% (Opdivo SmPC 2021). Other ICIs approved for treatment in the first-line setting include atezolizumab and cemiplimab as monotherapy for first-line treatment of NSCLC whose tumours have high PD-L1 expression irrespective of histology. However, there is still a medical need for more treatment options.

3.1.3. Main clinical studies

Data from a phase 3 study (HLX10-004-NSCLC303) were provided to support the current application.

HLX10-004-NSCLC303 is a randomized, double-blind, multi-center, ongoing phase III study to compare the clinical efficacy and safety of serplulimab combined with chemotherapy versus placebo combined with chemotherapy in subjects with locally advanced or metastatic squamous NSCLC.

Patients were randomized (2:1) to arm A: serplulimab combined with chemotherapy (carboplatin and nab-paclitaxel) and arm B: placebo combined with chemotherapy (carboplatin and nab-paclitaxel). Stratification factors were PD-L1 expression level (TPS < 1%, 1% ≤ TPS < 50%, TPS ≥ 50%), Asian population (yes or no), and squamous NSCLC stage (Stage IIIB/IIIC or Stage IV).

Out of total 537 patients (358 subjects in the serplulimab group and 179 subjects in the placebo group) 359 (66.9%) subjects were Asian and 178 (33.1%) were non-Asian (White). The non-Asian subjects were enrolled in Georgia, Poland, Russia, Turkey, and Ukraine.

The serplulimab treatment was 4.5 mg/kg every 3 weeks until disease progression or unacceptable toxicity, for up to two years.

The primary endpoint was PFS assessed by IRRC based on RECIST 1.1. Secondary endpoints included OS, PFS (assessed by investigator based on RECIST 1.1), PFS (assessed by IRRC and investigator based on iRECIST), ORR, DOR and quality of life.

3.2. Favourable effects

The primary endpoint was met, showing a statistically significant difference in PFS (assessed by IRRC based on RECIST 1.1) in favour of serplulimab [stratified HR = 0.55 (95% CI: 0.42, 0.73, p < 0.001)]. The median PFS was 8.28 months (95% CI: 6.90, 10.38) for patients receiving serplulimab versus 5.72 months (95% CI: 5.22, 6.83) for patients receiving placebo. Sensitivity analyses showed results consistent with the primary analysis.

At the final OS analysis (DCO: January 31, 2023) the median OS was 22.70 months (95% CI: 18.60, 27.40) and 18.23 months (95% CI: 14.13, 20.60) in the serplulimab group and the placebo group, respectively. The median OS in the serplulimab group was significantly longer than in the placebo group (HR = 0.73, 95% CI: 0.58–0.93, p = 0.010), meeting the prespecified significance boundary (p = 0.046).

The confirmed ORR assessed by IRRC based on RECIST 1.1 was 60.1% (95% CI: 54.8, 65.2) and 40.8% (95% CI: 33.5, 48.4) in the serplulimab and control arm, respectively. The median confirmed DOR was 11.07 months (95% CI: 8.31, 15.44) for the serplulimab arm versus 5.52 months (95% CI: 5.29, 7.06) for the control arm.

3.3. Uncertainties and limitations about favourable effects

A subgroup analysis based on race showed a lower efficacy of the investigational arm in non-Asian patients compared to Asian patients both on PFS and OS. Existing literature data (Peng et all, 2020) have reported a trend towards improved OS benefit in Asian population compared to non-Asian patients when treated with anti-PD-1/PD-L1-based therapy, although no consensus on such observation has been reached. Although efficacy was lower in non-Asian NSCLC patients in the pivotal study supporting this application, no biological rationale justifying that this specific PD-1 inhibitor would have a differential effect compared to other PD-1 inhibitors. The subgroup results in Asian and non-Asian patients have been reflected in section 5.1 of the SmPC.

3.4. Unfavourable effects

Pivotal study

As of the cut-off date, January 31, 2023, almost all (98.9% in the serplulimab arm and 98.3% in the placebo arm) reported at least one **TEAE**, of which the majority were considered serplulimab/placebo-related (serplulimab: 73.2% vs. placebo: 62.6%). The rates of **≥Grade 3 TEAEs** were 85.2% and 79.3% (serplulimab/placebo-related: 35.5% and 31.8%), respectively. The large proportion of TEAEs reported as related to serplulimab in the placebo arm (62.6%) indicates that many of the TEAEs are not related to the study drug, or they are caused by the chemotherapy backbone in both study arms.

As expected, TESAEs were reported in highest frequency in the serplulimab-containing arm and were observed in 52% (22.6 % considered related) in the serplulimab arm vs 42.5% (15.6 % considered related) in the placebo arm.

Serplulimab/placebo-related TEAEs led to serplulimab/placebo discontinuation twice as frequent in subjects in the serplulimab arm (8.7%) compared to the placebo arm (4.5%). The rate of TEAEs leading to discontinuation of serplulimab/placebo was 16.8% in the serplulimab arm vs.12.8% in the placebo arm.

The rate of TEAEs leading to drug interruption was 63.1% in the serplulimab arm vs 51.4% in the placebo-arm. For 37.4% of subjects in the serplulimab arm and 25.1% of subjects in the placebo + chemotherapy arm these TEAEs were considered related to serplulimab/placebo

The majority of the most common TEAEs (≥20%) were typical of chemotherapy treatment.

In the pivotal study, the most common TEAEs (≥10%) reported as related to serplulimab/placebo were anaemia, neutrophil count decreased, white blood cell count decreased, platelet count decreased, decreased appetite, alanine aminotransferase increased, aspartate aminotransferase increased, nausea, rash, hypothyroidism, neutropenia and thrombocytopenia.

irAEs were observed in 29.6% and 17.3% in the serplulimab + chemotherapy arm and placebo + chemotherapy arm, respectively.

The most common irAEs (incidence ≥ 2% by PT) observed in any of the arms included hypothyroidism, rash, immune-mediated lung disease, pneumonia, blood thyroid stimulating hormone increased, aspartate aminotransferase increased, hyperthyroidism, diarrhea, sinus bradycardia and thyroiditis.

Pooled safety analysis

In the pooled safety population (N=2086), 97.7% experienced TEAEs, of which 79.1% related to serplulimab. In total, 70.3% of subjects experienced Grade ≥ 3 TEAEs, of which 34.3% related to serplulimab. In total, 41.8% of subjects experienced TESAEs, of which 20.7% related to serplulimab and 34.7% of subjects experienced Grade ≥ 3 TESAEs, of which 16.2% related to serplulimab.

34.2% of subjects experienced immune-related AEs (irAEs), and 1.7% experienced infusion-related reactions (IRRs).

In total in the pooled population, 11.8% of subjects experienced TEAEs leading to death, of which 2.4% related to serplulimab.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 62: Effects Table for HETRONIFLY in combination with carboplatin and nab-paclitaxel for the first-line treatment of adult patients with unresectable, locally advanced or metastatic squamous non-small cell lung carcinoma (DCO of March 30, 2021 for PFS and DCO of January 31, 2023 for OS).

Effect	Short description	Unit	Treatment Serplulimab n=358	Control Pbo n=179	Uncertainties / Strength of evidence	Ref
Favourable Effects						
PFS by IRRC	PFS assessed by IRRC based on RECIST v1.1. PFS was defined as the time from randomization to the time of the first recorded PD or death due to any cause (whichever occurred first).	Months (95% CI)	8.28 (6.90, 10.38)	5.72 (5.22, 6.83)	HR = 0.55 (95% CI: 0.42–0.73) p < 0.001 Lower efficacy was observed in the non-Asian/Caucasian population.	

Effect	Short description	Unit	Treatment Serplulimab n=358	Control Pbo n=179	Uncertainties / Strength of evidence	Ref
OS	Defined as the time from randomization to death due to any cause.	Months (95% CI)	22.70 (18.60, 27.40)	18.23 (14.13, 20.60)	HR = 0.73 (95% CI: 0.58–0.93) p = 0.010 Lower efficacy was observed in the non-Asian/Caucasian population.	
Unfavourable Effects						
Anaemia		%	84.4	80.4		
Nausea		%	33.0	25.1		
WBC count decreased		%	59.5	53.1		
TEAEs (related)		%	98.9 (73.2)	98.3 (62.6)		
TESAEs (related)		%	52 (22.6)	42.5 (15.6)		
Grade ≥ 3 TEAEs (related)		%	85.2 (35.5)	79.3 (31.8)		
TEAEs leading to serp/placebo discontinuation (related)		%	16.8 (8.7)	12.8 (4.5)		
Immune-related AEs		%	29.6	17.3		
TEAEs leading to death (related)		%	13.7 (1.1)	10.6 (1.1)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the pivotal phase 3 randomized trial HLX10-004-NSCLC303, median PFS was significantly prolonged for advanced squamous NSCLC patients receiving chemotherapy plus serplulimab (8.3 months) compared to chemotherapy alone (5.7 months). This was supported by OS, which was significantly longer in the serplulimab arm (22.7 months) compared to the placebo arm (18.2 months).

However, consistency of treatment effect has not been demonstrated in all prespecified subgroups. Efficacy appears lower in the subgroup of non-Asian patients compared to Asian patients, on the primary endpoint of PFS (similar median PFS for serplulimab and placebo, and confidence interval for PFS HR covering 1), and on the secondary endpoint of OS. Nevertheless, the mechanism of action for PD-1 inhibitors is well known, and other PD-1 inhibitors have been approved for the same indication in the non-Asian population. Although efficacy was lower in non-Asian NSCLC patients in the pivotal study supporting this application compared to Asian patients, there is no biological rationale justifying that this specific PD-1 inhibitor would have a differential effect compared to other PD-1 inhibitors.

Serplulimab moderately increases the toxicity of chemotherapy, and the safety profile is consistent with other PD1-inhibitors. No new safety concerns were identified.

3.7.2. Balance of benefits and risks

The delay of disease progression observed in the pivotal study, supported by OS data, indicates a clinical benefit of Hetronifly in combination with chemotherapy compared to placebo with chemotherapy in advanced squamous NSCLC. Although efficacy was lower in non-Asian patients compared to Asian patients, there is no biological rationale justifying that this specific PD-1 inhibitor would have a differential effect compared to other PD-1 inhibitors . The safety profile is consistent with the known safety profile of serplulimab and other PD1-inhibitors and is considered acceptable in the sought indication. The balance of benefits and risks is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Hetronifly in advanced squamous NSCLC is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication to include HETRONIFLY in combination with carboplatin and nab-paclitaxel for the first-line treatment of adult patients with unresectable, locally advanced or metastatic squamous non-small cell lung carcinoma based on final results from study HLX10-004-NSCLC303; this is a randomized, double-blind, multi-center, phase III pivotal study, to compare the clinical efficacy and safety of serplulimab combined with chemotherapy (carboplatin and nab-paclitaxel) versus placebo combined with chemotherapy (carboplatin and nab-paclitaxel). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP Version 3.0 is agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

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

- **Risk management plan (RMP)**

The 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.

In addition, 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-mediated 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.