



Safety Data Cutoff Date: 13 May 2025

Trastuzumab Rezetecan (SHR-A1811)

INVESTIGATOR'S BROCHURE

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Summary of Key Changes

Version Number/Date	Version 6.0, 04 Jul 2025
Version Superseded/Date	Version 5.0, 05 Jul 2024

IB Section	Revision Description
Section 2 Summary	Updated the pharmaceutical properties, nonclinical study results and clinical trial data of SHR-A1811.
Section 3 Introduction	Added the approval information of other HER-2 targeted drugs and updated the proposed indications for the clinical development of SHR-A1811.
Section 5.2.1 Primary Pharmacodynamics	- Added the data showing that 9106-IM-2 inhibited topoisomerase I activity and induced cell cycle arrest. - Added the effect of SHR-A1811 on the human breast cancer BT-474/T721 xenograft model.
Section 5.3.1 Analytical Methods and Validation	Add the methods and validation of total antibody, ADC and 9106-IM-2 in SD rat serum.
Section 5.3.2 Absorption and Pharmacokinetics	- Added Caco-2 cell permeability study of 9106-IM-2. - Added pharmacokinetic study of a single intravenous injection of [³H]-9106-IM-2 in SD rats.
Section 5.3.3 Distribution	Added tissue distribution of 125I-SHR-A1811 in Xenograft Model in Nude Mice.
Section 5.3.6 Pharmacokinetic Drug-Drug Interactions	- Added direct and time-dependent inhibitory effects of 9106-IM-2 on major CYP enzymes. - Updated <i>In Vitro</i> effects of 9106-IM-2 on transporter results.
Section 5.4.2 Repeat-Dose Toxicity	Added 13-week repeat-dose toxicity study in SD Rats.
Section 5.4.5 Reproductive and Developmental Toxicity	Added embryo-fetal developmental toxicity study of 9106-IM-2 and SHR-A1811 via intravenous injection in SD rats.
Section 5.4.7 Formulation Toxicity Studies	Added phototoxicity Studies of 9106-IM-2.
Section 6.1.1 Pharmacokinetic Studies	Updated the pharmacokinetic results of Study SHR-A1811-I-101, Study SHR-A1811-I-102 and Study SHR-A1811-I-103.
Section 6.2.1 Safety	- Updated the pooled safety data of SHR-A1811 clinical study results as of 13 May 2025. - Updated the safety results of Study SHR-A1811-III-301,

IB Section	Revision Description
	Study SHR-A1811-305, Study SHR-A1811-III-306, Study SHR-A1811-307, Study SHR-A1811-308 and Study SHR-A1811-309 and added the safety results of Study SHR-A1811-310 and Study SHR-A1811-315 as of 13 May 2025.
Section 6.2.2 Efficacy	Added the efficacy results of Study SHR-A1811-I-101, Study SHR-A1811-102, Study SHR-A1811-I-103 and Study SHR-A1811-II-202 publicly posted in academic conferences and journals.
Section 7.4 Special Warnings and Precautions for Use	Updated the special warnings and precautions for use of SHR-A1811.
Section 7.8.1 Adverse Drug Reaction	Updated the pooled safety analysis of adverse drug reactions in SHR-A1811 clinical studies as of 13 May 2025.
Section 7.8.2 Reference Safety Information (RSI) for Expectedness Assessment of SAR	Based on the cumulative safety data as of 13 May 2025 and after thorough assessment by sponsor on individual case reports, added 4 new expected serious adverse reactions (SARs) of SHR-A1811 that have been previously reported more than once in the RSI, which were "Gastroenteritis", "Gamma-glutamyltransferase increased", "Aspartate aminotransferase increased", "Hypersensitivity".

Signature Page**Compound Name:** Trastuzumab Rezetecan (SHR-A1811)**Formulation:** Injection (lyophilized powder)**Current Version and Date:** 6.0, 04 Jul 2025**SPONSOR STATEMENT**

This Investigator's Brochure (IB) was subject to critical review and has been approved by the following person:

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ABBREVIATIONS

Abbreviations	Definitions
ADA	Anti-drug antibody
ADC	Antibody-Drug-Conjugate
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
CHL	Classic Hodgkin lymphoma
CIC	Circulation immunity compound
CRC	Clinical research coordinator
DAR	Drug to Antibody Ratio
DLT	Dose Limiting Toxicity
DMSO	Dimethyl sulfoxide
EGFR	Epidermal Growth Factor Receptor
FDA	Food and Drug Administration
FOB	Functional observation battery
GEJ	Gastroesophageal junction
HNSTD	Highest Non-Severely Toxic Dose
IB	Investigator's Brochure
IC ₅₀	Half maximal inhibitory concentration
ILD	Interstitial Lung Disease
IV	Intravenous
LLOQ	Lower Limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NMPA	National Medical Products Administration
NSCLC	Non-small cell lung cancer
PBMC	Peripheral blood mononuclear cell
PDX	Patient-Derived Xenograft
P-gp	P-glycoprotein
PPB	Plasma protein binding
PT	Preferred term
Q3W	Once Every 3 Weeks
RED	Rapid Equilibrium Dialysis
RP2D	Recommended Phase II Dose
RP-UPLC	Reverse Phase Ultra Performance Liquid Chromatography
RSI	Reference safety information
SAE	Serious adverse event
SAR	Serious adverse reaction
SARs	Severe acute respiratory syndrome
SD	Standard deviation
TCA	Trichloroacetic Acid
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TK	Toxicokinetics

Abbreviations	Definitions
US	United States
WFI	Water for Injection

2. SUMMARY

2.1. Pharmaceutical Properties

SHR-A1811 is a sterile, single use, preservative free lyophilized white to off- white powder. Each vial of SHR-A1811 drug product contains 100 mg SHR-A1811 active ingredient. The drug product is intended for reconstitution with 5 mL sterile water for injection (WFI) and subsequent dilution in 0.9% NaCl or 5% dextrose for intravenous infusion.

SHR-A1811 is identified by hydrophobic interaction chromatography (HIC-HPLC) as a mixture of antibody conjugates with different drug to antibody ratios (DAR). The average DAR value of SHR-A1811 is about 6.0 ± 0.5 .

2.2. Nonclinical Pharmacology

Pharmacology studies showed that SHR-A1811 retained similar binding affinity to both human and Cynomolgus monkey HER2 as the naked antibody SHR-1805 without cross-reactivity with rat HER2. SHR-A1811 had strong inhibition on proliferation of HER2 overexpression cancer cell lines. Binding of SHR-A1811 to HER2 overexpressing cells resulted in internalization into the lysosomes, leading to decreased level of extracellular HER2 and inhibition of HER2 downstream signaling. SHR-A1811 can also induce DNA damage and apoptosis in HER2 overexpressing cells. Additionally, SHR-A1811 could induce cell death in adjacent HER2-negative cells through its bystander-killing effect.

Furthermore, SHR-A1811 showed significant anti-tumor efficacy in multiple xenografts models as well as breast cancer patient-derived xenograft (PDX) models with high expression of HER2. Compared to naked antibody SHR-1805 or toxin 9106-IM-2 alone, SHR-A1811 demonstrated superior anti-tumor potency in *in vivo* settings, which was attributed to dual mechanisms of blocking HER2 signaling transduction and inhibiting DNA topoisomerase I.

2.3. Nonclinical Pharmacokinetics

Pharmacokinetics studies indicated that SHR-A1811 at 0.6-6 mg/kg had a non-linear pharmacokinetic property with half-life of 1.96-5.96 days in Cynomolgus monkeys via single-dose intravenous administration, which might support a once every 3 weeks (Q3W) dosing paradigm in clinical use. 9106-IM-2 at 0.06-0.24 mg/kg also showed a non-linear pharmacokinetic property with half-life of 0.67-0.77 hrs in SD rats via single-dose intravenous administration. SHR-A1811 was predominantly distributed in blood, tumor and vascular tissues in ^{125}I -SHR-A1811- or ^3H -SHR-A1811-treated xenograft mouse models. The metabolism of 9106-IM-2 in human liver microsomes included CYP enzymes independent hydrolysis, and oxidation by CYP2D6 or CYP3A4. 9106-IM-2 was quite stable in both microsomes and hepatocytes from different species. 9106-IM-2 was neither an inhibitor nor an inducer for the main CYP450 enzymes, 9106-IM-2 was a substrate of P-gp but not BCRP. It was not an inhibitor of them. To evaluate the inhibitory effects of 9106-IM-2 on solute carrier transporters (SLC) OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1 and MATE2-K, OAT1 in HEK293 cells overexpressing SLC transporters. The results showed that: at the test concentration of

9106-IM-2 at 1 μM , the inhibition rate on OAT3 was 6.53%, the inhibition rate on OCT1 was -4.50%. There was 10.8% inhibition rate on OCT2, 27.9% inhibition rate on OATP1B1, 3.64% inhibition rate on OATP1B3, 17.1% inhibition rate on MATE1, and 8.94% inhibition rate on MATE2-K. 9106-IM-2 had inhibitory effect on transporter OAT1 in the test concentration range of 0.005-1.5 μM , with an IC_{50} value of 0.627 μM . 9106-IM-2 was neither a substrate of BSEP nor its inhibitor.

2.4. Toxicology

Single- and repeat-dose toxicology studies in Cynomolgus monkeys with SHR-A1811 or 9106-IM-2 resulted in similar toxicities, suggesting toxicities were mediated primarily by 9106-IM-2. In 6-week and 13-week repeat-dose toxicity studies, the Highest Non-Severely Toxic Dose (HNSTD) in both studies were established at 40 mg/kg in Cynomolgus monkeys. In addition, during the repeat-dose toxicity study, no adverse effects on cardiovascular systems or irritation at the injection site were noted. No genotoxicity was observed with 9106-IM-2 in the *in vitro* bacterial reverse mutation (Ames) assay. The results of the CHL cell test and *in vivo* micronucleus test were positive, which was considered related to the mechanism of action of the DNA topoisomerase I inhibitor.

2.5. Clinical Experience

As of 13 May 2025, twenty-five clinical studies of SHR-A1811 for malignant tumor population were conducted by the sponsor. All the studies were ongoing, one of them was a clinical study associated with SHR-A1811 in the HRS-8080 research and development project (HRS-8080-202). Except for one international multi-center study (SHR-A1811-I-101), the remaining 24 studies were conducted in China, with trial indications including breast cancer, gastric cancer or gastroesophageal junction adenocarcinoma, colorectal cancer, non-small cell lung cancer, biliary cancer, and ovarian cancer, etc.

So far, a total of approximately 2971 subjects have received SHR-A1811 (monotherapy or combination therapy) for the treatment of advanced malignant tumors, in all the clinical trials that have been conducted.

2.5.1. Clinical Pharmacology

As of 29 Feb 2024, preliminary PK data of Study SHR-A1811-I-101 shows that in the dose range of 1.0-8.0 mg/kg SHR-A1811, the exposure of ADC and total antibody were similar at each dose level, and increased with the increasing dose. The average elimination half-life of ADC after single administration was about 2.8-7.8 days, and increased with the increasing dose. The exposure of released 9106-IM-2 after single administrations of SHR-A1811 was low. The geometric mean C_{max} of released 9106-IM-2 in the highest dose group of 8.0 mg/kg was 3.89 ng/mL. The half-life of released 9106-IM-2 averaged about 3.3-5.8 day after single administrations of SHR-A1811. After multiple intravenous infusions of SHR-A1811, mild accumulation of total antibody and ADC was observed with every 3 weeks dosing. No significant accumulation of released 9106-IM-2 was observed after multiple intravenous infusions of SHR-A1811.

2.5.2. Clinical Safety

As of 13 May 2025, except for eight ongoing pivotal, randomized, open-label with treatment-masked studies (SHR-A1811-III-301, SHR-A1811-305, SHR-A1811-III-306, SHR-A1811-307, SHR-A1811-308, SHR-A1811-309, SHR-A1811-310 and SHR-A1811-315), a pooled safety analysis was carried out for the remaining 17 SHR-A1811 clinical studies, including 1429 cancer patients treated with SHR-A1811 monotherapy or in combination with other drugs.

Overall, the incidence of treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs) and SHR-A1811 related adverse events (AEs) were 98.7% (1410/1429), 98.0% (1401/1429) and 98.0% (1400/1429), respectively.

A total of 1410 (98.7%) subjects had TEAEs, and TEAEs with an incidence of $\geq 10\%$ were neutrophil count decreased (81.2%), anaemia (79.8%), white blood cell count decreased (77.1%), nausea (61.0%), platelet count decreased (46.2%), vomiting (44.4%), aspartate aminotransferase increased (42.6%), decreased appetite (42.1%), alanine aminotransferase increased (39.1%), alopecia (37.6%), hypoalbuminaemia (33.9%), weight decreased (32.8%), gamma-glutamyltransferase increased (26.5%), hypertriglyceridaemia (25.8%), lymphocyte count decreased (25.5%), diarrhoea (25.4%), blood alkaline phosphatase increased, proteinuria (24.1% each), urinary tract infection (23.2%), hypokalaemia (22.4%), blood lactate dehydrogenase increased (20.7%), hyponatraemia (20.4%), hyperglycaemia (20.2%), constipation (19.0%), hyperuricaemia, fatigue (17.1% each), asthenia (15.3%), stomatitis, upper respiratory tract infection (14.8% each), pyrexia (14.3%), COVID-19 (13.6%), hypercholesterolaemia, hypocalcaemia (13.4% each), cough (12.7%), blood creatinine increased, blood bilirubin increased (12.0% each), malaise (10.8%), and dizziness (10.6%).

Based on the cumulative safety data as of 13 May 2025 and after thorough assessment by sponsor on individual case reports, compared to the previous version of the report, 4 new expected serious adverse reactions (SARs) of SHR-A1811 that have been previously reported more than once were added in the Reference Safety Information (RSI), which were “gastroenteritis”, “gamma-glutamyltransferase increased”, “aspartate aminotransferase increased”, “hypersensitivity”.

2.5.3. Clinical Efficacy

Several clinical studies are currently underway to evaluate the anti-tumor activities of SHR-A1811.

3. INTRODUCTION

Epidermal growth factor receptor (EGFR) is a class of cell-surface transmembrane receptors, including human epidermal growth factor receptor (HER) 1 (erbB1, EGFR), HER2 (erbB2, NEU), HER3 (erbB3) and HER4 (erbB4) that have tyrosine kinase activities. Among them, the HER2 gene, in particular, has shown gene amplification/over-expression in more than 30% of all human cancers, including breast cancer, ovarian cancer, and endometrial cancer. In the clinical diagnosis and treatment of breast cancer, HER2 is an important prognostic indicator in addition to tumor size, lymph node invasion and hormone receptors. It is also an independent prognostic marker for recurrence and survival duration in breast cancer patients. About 20 to 30% of primary invasive breast cancers present HER2 gene amplification/over-expression. Before HER2-targeted drugs became available, the mean survival of the HER2-positive patients was 50% less when compared to HER2 negative patients^[1].

Genentech's trastuzumab (Herceptin[®]) gained market approval in 1998, and significantly improved the clinical remission rate and survival rate of HER2-positive patients. A decade later, after obtaining approvals from the United States (US) Food and Drug Administration (FDA) in 2012 and 2013 respectively, Genentech's pertuzumab (Perjeta[®]) and ado-trastuzumab emtansine (T-DM1, Kadcyla[®]) entered the market consecutively, being used either as the first-line treatment in combination with trastuzumab or as a second-line treatment. Apart from the rapid development of HER2 antibody macromolecules, the small-molecule inhibitors targeting the HER2 receptor, like lapatinib (Tykerb[®]) developed by GlaxoSmithKline, neratinib (Puma Biotechnology, US), tucatinib developed by Seagen and margetuximab-cmkb (MARGENZA) developed by MacroGenics were approved by the FDA. Pyrotinib, a pan-HER inhibitor developed by Hengrui was approved by the Chinese National Medical Products Administration (NMPA) in 2018.

The advent of HER2-targeting therapies has achieved significant clinical benefit. However, resistance towards HER2-targeting therapies is common in patients, occurring as either intrinsic or acquired resistance. Studies to understand resistance mechanisms have shown that HER2-positive tumors escape HER2 inhibition by 1) activation of downstream signaling pathways, 2) upregulation of other receptor tyrosine kinases, or 3) intratumoral heterogeneity^[2]. HER2-ADC drugs, at least to some degree, can overcome such resistance mechanisms. Since the approval of T-DM1, the Japanese pharmaceutical company Daiichi-Sankyo developed the second generation HER2-ADC, comprising of a topoisomerase I inhibitor conjugated to trastuzumab. This drug releases toxins by protease cleavage in the lysosomes of tumor cells. The released toxins have potent cytotoxic effect and can penetrate cell membrane to exert bystander killing effect of cells nearby. The toxin of DS-8201a is exatecan analog DXd, structurally similar to SN-38, an active metabolite of irinotecan, but with higher potency. A phase 2 trial has shown that Grade 3/4 AE of exatecan are mostly hematological toxicity, including anemia, leukopenia, neutropenia, and thrombocytopenia. Non-hematological AEs are relatively mild, mainly Grade 1/2, including fatigue and nausea. Similarly,

Grade 3/4 AEs of DS-8201a in a phase I trials are mostly hematological toxicity, including anemia, neutropenia, thrombocytopenia, and leukopenia. Non-hematological side effects include nausea and vomiting, most of which are Grade 1/2^[3]. Of note, Grade 5 AE of pneumonitis occurred in 2 breast cancer patients (2%) treated with DS-8201a. DS-8201a (trastuzumab deruxtecan, Enhertu[®]) has so far been approved by the NMPA as a monotherapy for the treatment of 1) adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens; 2) adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy; 3) adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received two or more prior treatment regimens; 4) adult patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations and who have received a prior systemic therapy.

Disitamab vedotin (RC48, Aidixi[®]) is a newly developed ADC drug targeting HER2 that is comprised of hertuzumab coupling monomethyl auristatin E (MMAE) via a cleavable linker, which has gained approval by the NMPA in 2021, 2022 and 2025 for the following indications: HER2-overexpressing locally advanced or metastatic gastric cancer and urothelial carcinoma, HER2-positive advanced breast cancer with liver metastasis.

SHR-A1811 for Injection (hereafter referred to as SHR-A1811) is an ADC with HER2 as the target and developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd (hereafter referred to as Hengrui) independently. SHR-A1811 is currently under investigation for the treatment of 1) HER2 expressing/mutated advanced solid tumor; 2) HER2 expressing advanced gastric cancer, gastroesophageal junction (GEJ) adenocarcinoma, and colorectal cancer; 3) advanced non-small cell lung cancer (NSCLC) with HER2 overexpression, amplification or mutation; 4) HER2-positive or HER2-low breast cancer; and 5) HER2-expressing advanced gynecological cancer.

3.1. References

- [1] Fan L, Strasser-Weippl K, Li JJ, et al. Breast cancer in China. *Lancet Oncol.* 2014 Jun;15 (7): e279-289.
- [2] Rimawi MF, Schiff R, Osborne CK. Targeting HER2 for the treatment of breast cancer. *Annu Rev Med.* 2015; 66: 111-28.
- [3] Tamura K, Tsurutani J, Takahashi S, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. *Lancet Oncol.* 2019; 20: 816-26.

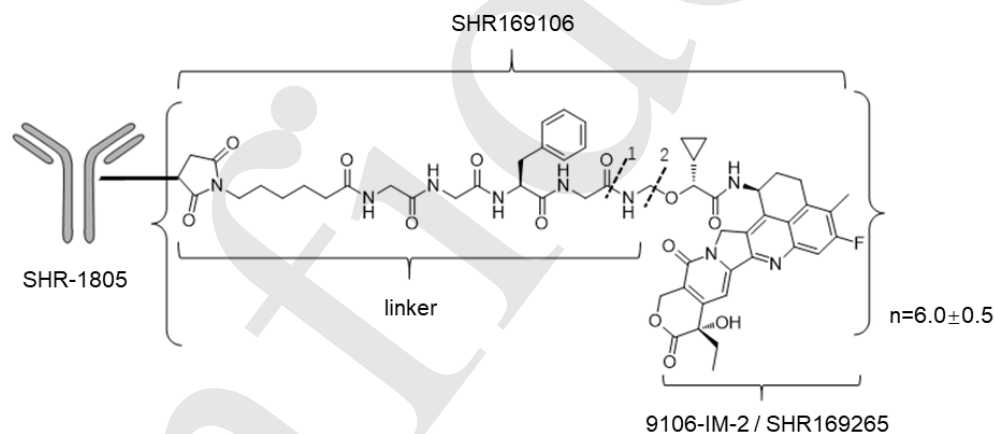
4. PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION

4.1. Structure and Molecular Weight of Investigational Product(s)

Compound Name:	SHR-A1811 for Injection
Research Number:	SHR-A1811
CAS Number:	2647845-11-0
Molecular Weight:	~ 154.5 kDa (calculated based on an antibody conjugated with 6.0 ± 0.5 SHR169106)

As illustrated in [Figure 1](#), SHR-A1811 is an antibody-drug conjugate (ADC) consisting of a humanized anti-HER2 IgG₁ monoclonal antibody (SHR-1805) linked with SHR169106. The position 1 is the intracellular enzymatic cleavage site of the linker. After enzymatic hydrolysis, a hydrolysis reaction occurs at position 2 to form a free active toxin component 9106-IM-2 (Research number: SHR169265).

Figure 1 Structure of SHR-A1811 ADC Molecule



4.2. Dosage Form and Strength

Dosage Form: Lyophilized powder for solution for intravenous infusion

Strength: 100 mg/Vial

4.3. Physicochemical Properties

SHR-A1811 is a white to off-white lump or powder.

4.4. Formulation

SHR-A1811 is a sterile, single use, preservative free lyophilized white to off-white

powder. Each vial of SHR-A1811 drug product contains 100 mg deliverable SHR-A1811 antibody-drug-conjugate (ADC) active ingredient.

The excipients include sucrose, polylobate 80, succinic acid, sodium hydroxide, and water for injection (removed during lyophilization).

4.5. Storage and Handling

This product should be protected from light and stored and shipped in the original packaging at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The drug product should be reconstituted with 5 mL of sterile water for injection then diluted with 0.9% sodium chloride solution or 5% dextrose for intravenous administration. According to the compatibility study between SHR-A1811 and the diluent, the final concentration of the diluted investigational product solution should be between 0.4 and 10 mg/mL.

Store the reconstituted and diluted solution of SHR-A1811 ADC drug product either:

- Protected from light at room temperature for no more than 4 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Protected from light under refrigeration at 2°C to 8°C for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

5. NONCLINICAL STUDIES

5.1. Nonclinical Test Material

SHR-A1811 is an antibody-drug conjugate (ADC) consisting of a humanized anti-HER2 IgG₁ monoclonal antibody (SHR-1805) linked with a DNA topoisomerase inhibitor 9106-IM-2 via the cleavable linker. The lot of SHR-A1811 (P1919) used in the preclinical studies was similar, in impurity profile and purity, to the lot to be used in the first clinical trial.

5.2. Nonclinical Pharmacology

A range of *in vitro* and *in vivo* studies have been performed to characterize the pharmacodynamics of SHR-A1811. The results of SPR showed that SHR-A1811 showed high affinity with human and cynomolgus monkey HER2 antigens, with K_D values of 2.67 nM and 29.2 nM, respectively, which were similar to that of naked antibody SHR-1805. There was no binding difference between them. The affinity of SHR-A1811 with FcγRI, FcγRIII and C1q was strong, similar to SHR-1805, suggesting that SHR-A1811 retained strong ADCC, CDC and ADCP activities.

SHR-A1811 has a strong inhibitory activity on the proliferation of HER2 expressing gastric cancer and breast cancer, while it has no inhibitory activity on HER2 non-expressing three negative breast cancer cells, with IC_{50} above 10 μg/mL. The IC_{50} of 9106-IM-2 was between 0.3 and 8.7 nM, and there was no significant cell selectivity.

SHR-A1811 can bind to the membrane surface of HER2 positive N87 gastric cancer cells, and then internalize into the cells to reach the lysosome. Through cathepsin B, 9106-IM-2 was released and can cause cell cycle arrest by inhibiting DNA topoisomerase I, thus inducing tumor cell apoptosis. Additionally, SHR-A1811 could induce cell death in neighboring HER2-negative tumor cells through its bystander killing effect.

After single administration of 1 and 5 mg/kg SHR-A1811 to xenograft (human gastric cancer NCI-N87) model in nude mice, the expression of HER2 in tumor was decreased and maintained for more than 168 hours. SHR-A1811 showed significant dose-dependent tumor suppressive activity in a variety of HER2 expressing cell lines or patient derived mouse models, including human gastric cancer and breast cancer models. In some models, partial or complete tumor regression was observed. The antitumor activity of SHR-A1811 was significantly higher than that of naked antibody SHR-1805 and 9106-IM-2. The mice in each group were well tolerated.

The IC_{50} of 9106-IM-2 was more than 20 μM for the inhibition of ERG current.

The single intravenous (IV) administration of 3, 10 and 30 mg/kg SHR-A1811 in GLP did not affect the neuro-behavioral activities of SD rats.

Three times of IV administration of SHR-A1811 of 3, 10 and 40 mg/kg was repeated once every 3 weeks under GLP condition in conscious macaque eating monkeys. There was no significant effect on ECG, blood pressure and respiratory frequency of lead II in cynomolgus monkeys.

5.2.1. Primary Pharmacodynamics

Table 1 Overview of Primary Pharmacodynamics for SHR-A1811

Project	Main result
Binding affinity study of SHR-A1811 with HER2, human Fc and C1q receptors	SHR-A1811 had high binding affinity with human and Cynomolgus monkey HER2, but no cross-reactivity with rat HER2. SHR-A1811 showed high binding affinity with FcγRI, FcγRIII, FcRn and C1q, which was similar to SHR-1805.
<i>In vitro</i> inhibitory activity of SHR-A1811 on cell proliferation	SHR-A1811 had a strong inhibitory activity on HER2 high-expression cells, such as gastric cancer and breast cancer (IC ₅₀ was 0.052-1 μg/mL), while it showed low inhibitory activity on HER2 low or no expression cells (IC ₅₀ >10 μg/mL), the activity was better than SHR-1805. 9106-IM-2 had significant inhibitory activity on these cells, but showed no significant selectivity.
Mechanism of action	SHR-A1811 could bind to the membrane surface of HER2 positive cells, and could be internalized into cells and mostly located on the lysosome, then released 9106-IM-2. Cell cycle arrest was induced by inhibition of HER2 downstream signaling pathway and topoisomerase I.
The PK/PD study	SHR-A1811 at 1 mg/kg and 5 mg/kg could decrease the expression level of HER2, the effect could last for more than 168 hours in tumor tissues, with ADC concentrations of 3.6 ± 0.40 and 78.9 ± 2.34 μg/mL, respectively.
<i>In vivo</i> anti-tumor efficacy	SHR-A1811 reduced the tumor size significantly in a dose-dependent manner in NCI-N87 human gastric and breast cancer xenograft model in nude mice, and showed superior anti-tumor efficacy compared to T-DM1, SHR-1805 and 9106-IM-2. In NCI-N87/16-8 (T-DM1 resistant) human gastric cancer cell xenograft model, SHR-A1811 at 2 mg/kg had tumor growth inhibition rate over 90%, at 5 mg/kg dosage group, tumor regression was observed. In T-DM1 sensitive or resistant breast cancer model, 2 mg/kg SHR-A1811 had tumor growth inhibition rate over 90%.

5.2.1.1. Binding Affinity of SHR-A1811

The purpose of this study was to determine the binding affinity of SHR-A1811 with HER2 from different species, human C1q and Fc receptors. This Non-GLP study was conducted by Shanghai ChemPartner Co., Ltd in 2019.

By using SPR technology, it was demonstrated that SHR-A1811 had high binding affinity with human and Cynomolgus monkey HER2, but no cross-reactivity with rat HER2. As an IgG1 isotype, the affinity of SHR-A1811 with FcγRI, FcγRIII and C1q was strong, similar to SHR-1805, suggesting that SHR-A1811 retained strong ADCC, CDC and ADCP activities. (Table 2).

Table 2 Affinity of SHR-A1811

Immobilized phase	Mobile phase	K _D , M
SHR-A1811	Human HER2	2.67×10 ⁻⁹
SHR-1805		1.58×10 ⁻⁹
SHR-A1811	Cynomolgus monkey HER2	2.92×10 ⁻⁸
SHR-1805		2.99×10 ⁻⁸
SHR-A1811	Rat HER2	No binding
SHR-1805		
Human FcRn	SHR-A1811	3.66×10 ⁻⁸
Monkey FcRn	SHR-A1811	1.04×10 ⁻⁷
Human FcγR I/CD64	SHR-A1811	7.56×10 ⁻¹⁰
Human FcγRIIA/CD32a	SHR-A1811	1.66×10 ⁻⁶
Human FcγRIIB/C/CD32b	SHR-A1811	5.33×10 ⁻⁶
Human FcγR III/CD16a	SHR-A1811	1.28×10 ⁻⁸
SHR-A1811	C1Q	1.57×10 ⁻⁹

Note: SHR-1805 is the naked antibody of SHR-A1811, which was synthesized by Shanghai Hengrui Pharmaceutical Co. Ltd. according to Trastuzumab.

5.2.1.2. *In vitro* Inhibitory Activity of SHR-A1811 on Cell Proliferation and HER2 Expression in Various Cancer Cell Lines

The purpose of this study was to evaluate the *in vitro* inhibitory activity of SHR-A1811 or 9106-IM-2 on proliferation of various cancer cell lines. This Non-GLP study was conducted by Shanghai Institute of *Materia Medica*, Chinese Academy of Science in 2019.

Exponentially growing cells were seeded in 96-well plates and cultured for 24 hrs. Cells were then treated with different compounds at various concentrations (0.3-10000 ng/mL for SHR-A1811, SHR-1805 and SHR-A1201, and 0.3-3000 nM for 9106-IM-2) for 72 hrs. SHR-A1201 is produced in house with reference to the amino acid sequence of T-DM1, which is investigated in Phase 1 clinical trial in China. Cell growth was detected using SRB and CCK-8 kits and the inhibition rate was calculated as follows:

$$\text{Inhibition rate} = (\text{OD value in control} - \text{OD value in treated cells}) / \text{OD value in control} \times 100\%$$

From the inhibition rate at each concentration, 50% inhibition concentration (IC₅₀) of each compound was calculated (Table 3).

The results showed that SHR-A1811 had a strong inhibitory activity on HER2 expression cells, such as gastric cancer NCI-N87 cell line and breast cancer BT-474 cell line, which was higher than SHR-1805. While SHR-A1811 had low inhibitory activity on HER2 no-expression cells (triple-negative breast cancer MDA-MB-231). 9106-IM-2 had significant inhibitory activity on all these cells, but with no significant selectivity.

Table 3 The *In Vitro* Inhibitory Activity of Test Compounds on the Proliferation of Cancer**Cell Lines (IC₅₀, Mean $\pm$ SD, n=2)**

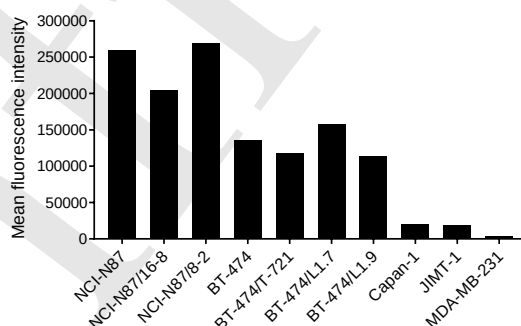
Cell line	Cancer Types	IC ₅₀ (Mean $\pm$ SD, n=2)			
		SHR-A1811 (ng/mL)	SHR-1805 (ng/mL)	SHR-A1201 (ng/mL)	9106-IM-2 (nM)
NCI-N87	Gastric	71.4 $\pm$ 4.6	>10,000	20.1 $\pm$ 3.4	0.8 $\pm$ 0.1
NCI-N87/16-8	Gastric	52.2 $\pm$ 14.3	>10,000	2,879 $\pm$ 1174	0.5 $\pm$ 0.1
NCI-N87/8-2	Gastric	111.1 $\pm$ 37	>10,000	1,502.5 $\pm$ 238.5	0.7 $\pm$ 0.2
BT-474	Breast	$\approx$ 1,000	838 $\pm$ 470.1	38.3 $\pm$ 4.9	8.7 $\pm$ 2.5
BT-474/T-721	Breast	584.2 $\pm$ 426.9	>10,000	48.5 $\pm$ 8	1.1 $\pm$ 0.6
Capan-1	Pancreas	$\approx$ 10,000	>10,000	8482 $\pm$ 707	0.3 $\pm$ 0.0
JIMT-1	Breast	>10,000	>10,000	1,030.4 $\pm$ 67.6	2.6 $\pm$ 0.9
MDA-MB-231	Breast	>10,000	>10,000	>10,000	4.4 $\pm$ 1.1

Note: SHR-1805 is the naked antibody of SHR-A1811 (ADC); and SHR-A1201 is produced in house with reference to the amino acid sequence of T-DM1; and 9106-IM-2 is the free toxin released from SHR-A1811.

5.2.1.3. Mechanism of Action

5.2.1.3.1. Expression Level of HER2

To explore whether cell proliferation inhibitory activities of SHR-A1811 were correlated with HER2 expression levels, Dylight 488 NHS Ester dye-labeled SHR-A1811 was used to assess the expression of extracellular HER2. The fluorescence intensity on cells indirectly reflected the expression levels of extracellular HER2. Results are shown in [Figure 2](#).

**Figure 2 Expression Levels of HER2 in Different Cancer Cell Lines**

The results indicated that MDA-MB-231 cells showed very low level of HER2 expression, while N87 and BT-474 showed high levels of HER2 expression, and Capan-1 cells also showed visible HER2 expression. These results suggested positive association between the HER2 expression levels and the inhibitory activities of SHR-A1811 on cancer cell proliferation.

5.2.1.3.2. The Binding Activity of SHR-A1811 to HER2 Positive N87 Cell

The purpose of this study was to explore whether SHR-A1811 would be internalized and transported into lysosome after binding to HER2 positive cells. This Non-GLP study was conducted by Shanghai Institute of *Materia Medica*, Chinese Academy of Science in 2019.

In the cell binding assay, DyLight™ 488 NHS Ester dye-labeled SHR-A1811 and SHR-1805 (1-10000 ng/ml) was incubated with N87 cell at 4°C for 1 hour. After discarding the supernatant, the cells were resuspended in PBS buffer and washed for 3 times. The cell binding fluorescence intensity was detected by flow cytometer. As shown in [Figure 3](#), SHR-A1811 could bind to HER2 positive NCI-N87 cells, and the binding activity of SHR-A1811 was comparable to that of SHR-1805 with the EC₅₀ of 184.9 and 183.4 ng/ml, respectively.

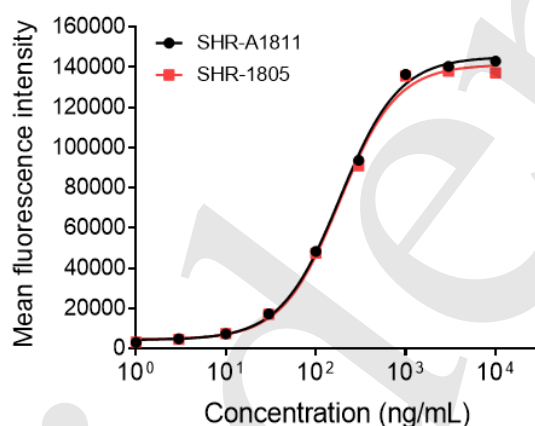


Figure 3 The Binding Activity of SHR-A1811 and SHR-1805 to HER2 Positive N87 Cell

5.2.1.3.3. Internalization and Transportation to Lysosome of SHR-A1811 upon Binding to HER2 Positive Cells

In the flow cytometry assay, DyLight™ 488 NHS Ester dye-labeled SHR-A1811 was incubated with N87 cells on ice for 10 min. Cells were then cultured in fresh 10% FBS cell culture media at 37°C for 0.5 to 48 hours. At those designated time points, cells were immediately placed on ice to terminate the internalization, centrifuged, and resuspended in the strip buffer (ddH₂O, 0.05 M glycine, pH 2.45 + 0.1 M NaCl), then kept at room temperature for 7 min. The cells were centrifuged and washed once with FACS buffer followed by FACS analysis.

As shown in [Figure 4](#), with the increase of the incubation duration at 37°C, the fluorescence intensity of SHR-A1811 in N87 cells was significantly increased, indicating an obvious time-dependent effect. Overall, the internalization rate of SHR-A1811 was comparable to SHR-1805.

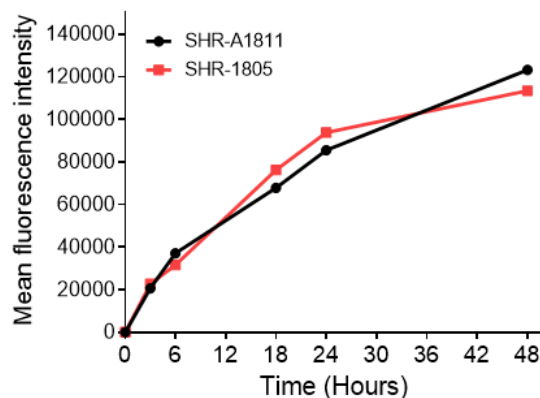


Figure 4 Internalization Rate of SHR-A1811 and SHR-1805 Upon Binding to N87

In the immunofluorescent assay, MKN-45 cells were seeded in 6-well plates. Dylight™ 488 NHS Ester dye-labeled SHR-A1811 or SHR-1805 (1 µg/mL) was incubated with N87 cells at 37°C for 24 hrs. Lysosome red fluorescence probe (LysoTracker Deep Red) was then added and incubated with the cells at 37°C for 1 hr. As a control, N87 cells were incubated with LysoTracker Deep Red at 37°C for 1 hr, followed by addition of Dylight™ 488 NHS Ester dye-labeled SHR-A1811 or SHR-1805 and incubated at 4°C for 1 hr. At the end of reaction, the supernatant was discarded, and cells were washed in PBS for 3 times followed by laser scanning confocal microscopic examination.

As shown in [Figure 5](#), after incubation with N87 cells at 4°C for 1 hr, 1 µg/mL Dylight 488 NHS Ester-labeled SHR-A1811 or SHR-1805 were detected on the cell membrane. After incubation at 37°C for 24 hrs, both SHR-A1811 and SHR-1805 were detected on lysosome, which indicated that they could be internalized into the cells and mostly located on the lysosome. SHR-A1811 and SHR-1805 showed similar fluorescent staining profiles.

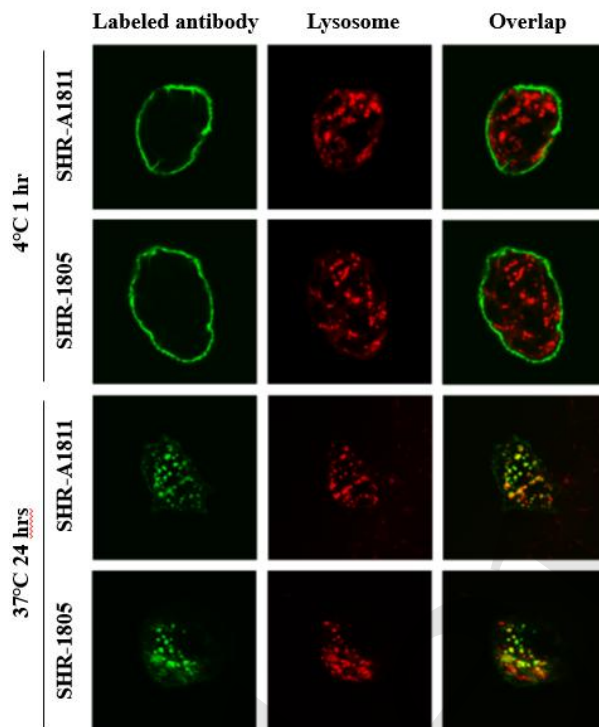


Figure 5 SHR-A1811 Binding and Internalization into Lysosome of N87 Cells

5.2.1.3.4. Inhibition of HER2, DNA Damage and Apoptosis Signaling

The purpose of this study was to investigate the inhibitory effects of SHR-A1811 on HER2 signaling pathway, and induction on DNA damage and cell apoptosis signaling pathway in N87 cells. This Non-GLP study was conducted by Shanghai Institute of *Materia Medica*, Chinese Academy of Science in 2019.

Figure 6 showed that SHR-A1811 and SHR-1805 in the range of 0.01-10 $\mu\text{g/mL}$, and 10 $\mu\text{g/mL}$ SHR-A1201 can reduce the levels of phosphorylated HER2 (p-her2), HER2, phosphorylated Akt (p-Akt) and phosphorylated ERK (p-ERK) to a certain extent in a concentration dependent manner, but have no significant effect on the protein expression levels of Akt and ERK. The effect of SHR-A1811 on HER2 signal pathway is similar to that of SHR-1805 and SHR-A1201. 1 and 10 $\mu\text{g/mL}$ SHR-A1811 significantly induced DNA damage (up-regulated by p- γ -h2ax), which was similar to that of 100 nM 9106-IM-2.

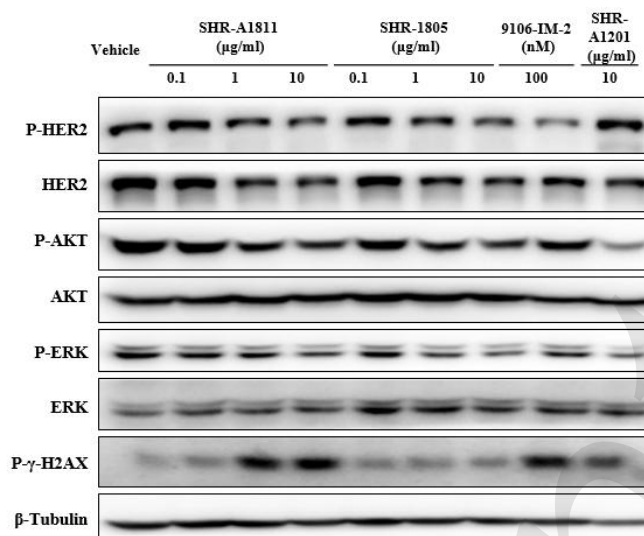


Figure 6 Inhibition of SHR-A1811 on HER2 Signaling and Induction on DNA Damage

Inhibition of the activity of topoisomerase I by 9106-IM-2: 9106-IM-2, pHOT1 DNA, and topoisomerase I were incubated at 37 °C for 30 min to determine the effect of 9106-IM-2 on the activity of topoisomerase I. As shown in [Figure 7](#), super coiled DNA was converted to relaxed DNA by topoisomerase I catalysis, which was manifested as a slowing down of motility during DNA gel electrophoresis. 9106-IM-2 inhibited the conversion of super coiled DNA to relaxed DNA in a concentration-dependent manner. The inhibitory effect was obvious at 30 μM and more significant at 100 μM, indicating that 9106-IM-2 is a topoisomerase I inhibitor.

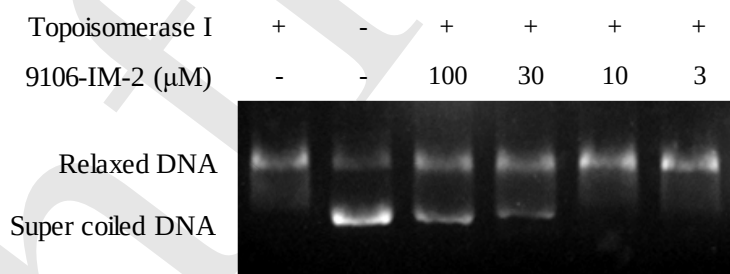


Figure 7 9106-IM-2 inhibited the activity of topoisomerase I

Since the inhibition of topoisomerase I activity by 9106-IM-2, the payload of SHR-A1811, may lead to S phase arrest, the effect of SHR-A1811 on the cell cycle of NCI-N87 cells was further examined. The flow cytometry analysis results are shown in [Figure 8](#). The percentage of cells in S phase in the vehicle control group was 19.71%; after 48 h of SHR-A1811 treatment at 1 μg/mL and 10 μg/mL, the percentage of cells in S phase was 40.38% and 41.50%, respectively, indicating that S phase arrest was induced. The percentage of cells in S phase in the SHR-1805 (10 μg/mL) treatment group was 19.51%, indicating that S phase arrest was not induced. The percentage of

cells in S phase in the 9106-IM-2 (100 nM) treatment group was 60.96%, indicating that S phase arrest was induced. The above results indicated that SHR-A1811 induced cell cycle arrest at the S phase, and the mechanism was mainly completed by the small molecule 9106-IM-2.

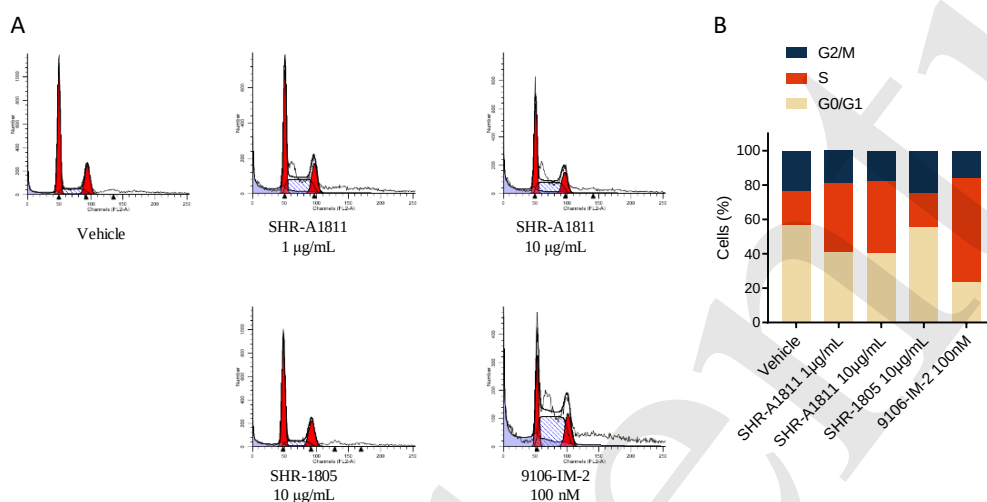


Figure 8 Induction of cell cycle arrest at S phase by SHR-A1811. A: histograms for cell cycle analysis; B: cell cycle distribution

Figure 9 showed that SHR-A1811 and SHR-1805 in the range of 0.01-10 µg/mL as well as 100 nM 9106-IM-2 could activate PARP and Caspase 3 signaling pathway, inducing cell apoptosis. However, the induction of cell apoptosis was not obvious upon the treatment of SHR-1805.

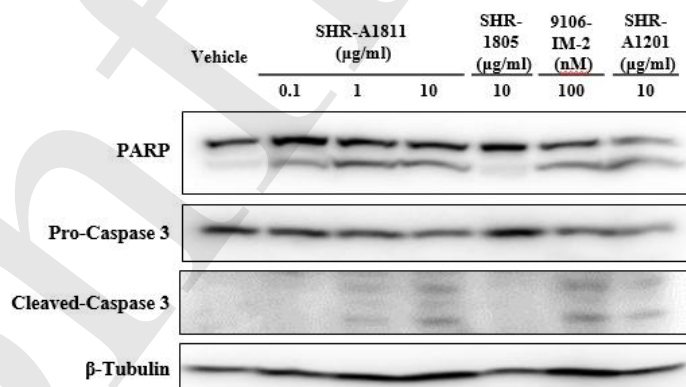


Figure 9 SHR-A1811 Induced Cell Apoptosis

5.2.1.3.5. Antibody-dependent Cell-mediated Cytotoxicity (ADCC)

The ADCC of SHR-A1811 and SHR-1805 on NCI-N87 cells was detected. As shown in Figure 10 and Table 4, NCI-N87 was used as target cell and human peripheral blood

mononuclear cell (PBMC) as effector cell, SHR-A1811 and SHR-1805 both have significant ADCC on NCI-N87 cells with the maximum lysis rate of 90.8% and 82.4%, and the EC₅₀ of 28.1 ng/mL and 12.8 ng/mL, respectively.

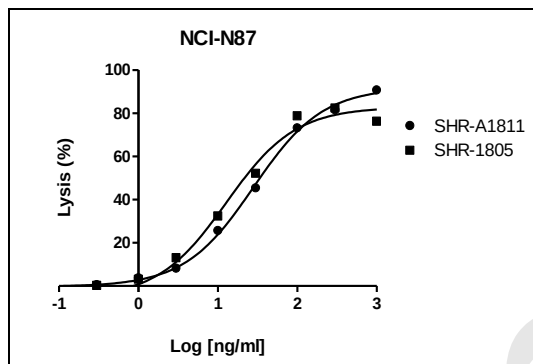


Figure 10 ADCC Effect of SHR-A1811 and SHR-1805 on NCI-N87 Cells

Table 4 ADCC activity of SHR-A1811 and SHR-1805 on NCI-N87 cells

Cell Line	Maximum Lysis Rate (%)		EC ₅₀ (ng/ml)	
	SHR-A1811	SHR-1805	SHR-A1811	SHR-1805
NCI-N87	90.8	82.4	28.1	12.8

5.2.1.3.6. Bystander Effect

KPL-4, a HER2 positive breast cancer cell, and MDA-MB-468, a non HER2 expressing breast cancer cell were mixed and co-cultured for 24 hours (37°C, 5% CO₂). 0.1 or 1 µg/mL SHR-A1811 or SHR-A1201 was added to incubate with cells for 5 days (37°C, 5% CO₂). The signal intensity of HER2 was detected by flow cytometry, and the number of HER2 positive cells and negative cells were analyzed and calculated. Results in [Figure 11](#) showed that SHR-A1811 and SHR-A1201 significantly inhibited the proliferation of HER2 positive cells, and the inhibitory activity was dose-dependent. SHR-A1811 had the same killing effect on HER2 negative cells when co-culturing with HER2 positive cells, but SHR-A1201 has no such effect on HER2 negative cells. SHR-A1811 and SHR-A1201 did not inhibit MDA-MB-468 cells when cultured alone, which were HER2 negative breast cancer cells. The above results show that SHR-A1811 can significantly inhibit the growth of HER2 positive tumor cells, and exhibit bystander effect on the HER2 negative cells bypass, but SHR-A1201 had no bystander effect.

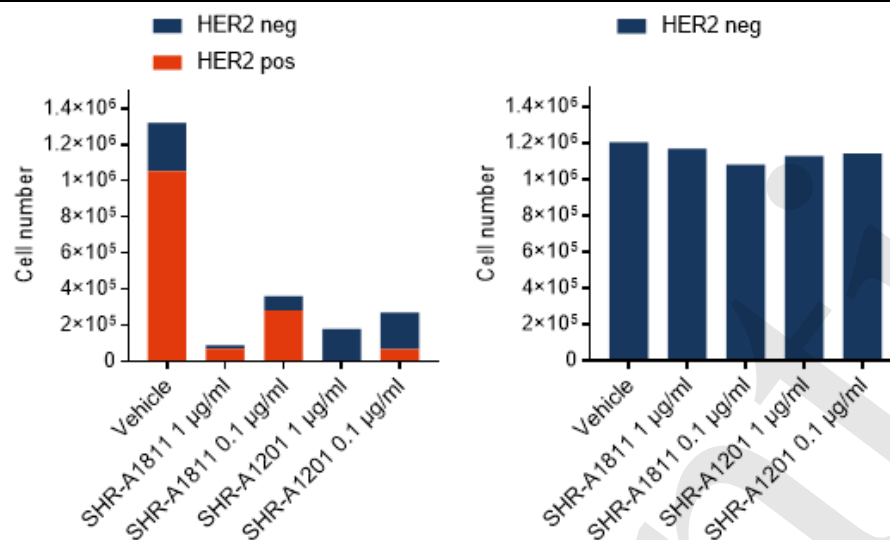


Figure 11 Bystander Effect of SHR-A1811

5.2.1.4. *In vivo* Pharmacological Studies

5.2.1.4.1. The PK/PD Study of SHR-A1811 in NCI-N87 Xenograft Model

The purpose of this study was to investigate the serum concentrations of SHR-A1811 in NCI-N87 xenograft model in nude mice, the HER2 expression and DNA damage in tumor tissues and to explore the PK/PD correlation of SHR-A1811 in NCI-N87 xenograft model. This Non-GLP study was conducted by Shanghai Institute of *Materia Medica*, Chinese Academy of Science in 2019.

The nude mice were implanted with NCI-N87 cells subcutaneously. After single IV injection of 1 or 5 mg/kg SHR-A1811, blood and tumor tissues were collected at predose and at 5 min, 4, 24, 48, 96 and 168 hrs postdose (3 mice/time point). The concentration of SHR-A1811 in serum was determined and partial tumor tissues (collected at predose and at 24, 48, 96 and 168 hrs postdose) were lysed in RIPA for detecting HER2 and γ H2A protein expression by Western Blot. The pharmacokinetic parameters are shown in Table 5 and Table 6 and the effect of SHR-A1811 on HER2 signaling is shown in Figure 12.

Following a single IV injection of SHR-A1811 at 1 or 5 mg/kg, the HER2 protein level in tumor tissues began to decrease at 24 hrs post-dose under different SHR-A1811 dose levels. This effect could last for at least 168 hrs in tumor tissues. The level of P- γ -H2A was induced by 5 mg/kg SHR-A1811 at 48 hrs post-dose. It suggested that single injection of SHR-A1811 could induce DNA damage for a long time, in a dose-dependent manner. Following the IV injection of SHR-A1811 to xenograft model in mice, SHR-A1811 distributed rapidly and eliminated slowly. The mean concentrations of SHR-A1811 in mice serum was 0.1 and 2.6 μ g/mL for 1 and 5 mg/kg doses, respectively at 168 hrs post-dose. The AUC_{0-168h} was 14.4 and 91.9 μ g·day/mL for 1 and 5 mg/kg doses. The serum C_{max} of small molecule 9106-IM-2 was 5.5×10^{-5} ng/mL and 23.6×10^{-5} ng/mL, respectively, and the AUC_{last} was 1.1 h·ng/mL and 12.0 h·ng/mL, respectively. The C_{max} of 9106-IM-2 in tumor tissue was 4.0×10^{-3} ng/g and 21.3×10^{-3} ng/g, and the AUC_{last} was 371.0 h·ng/g and 2260.0 h·ng/g, respectively. The results

showed that a single intravenous injection of SHR-A1811, 9106-IM-2 was mainly exposed in tumor tissues, about 188 to 334 times of that in serum. The exposure and clearance rates of total antibodies and SHR-A1811 were comparable, and the exposure levels of 9106-IM-2 and SHR-A1811 increased with increasing doses, and the clearance rate decreased with increasing doses. As the TGI% at 1 and 5 mg/kg was 65% and 133%, respectively, the PK/PD results indicated that the target exposure should be reached to 91.9 $\mu\text{g}\cdot\text{day}/\text{mL}$.

Table 5 The PK Parameters of SHR-A1811 Following Single IV Injection in Nude Mice

Group	Components	C _{max} ($\mu\text{g}/\text{mL}$)	AUC _{0-168h} ($\mu\text{g}\cdot\text{day}/\text{mL}$)	C _{168h} (Mean $\pm$ SD, $\mu\text{g}/\text{mL}$)
1 mg/kg	Total antibody	15.9	15.5	0.2 $\pm$ 0.2
	ADC	13.6	14.4	0.1 $\pm$ 0.1
5 mg/kg	Total antibody	75.1	105	4.2 $\pm$ 1.0
	ADC	78.9	91.9	2.6 $\pm$ 0.4

Table 6 The PK Parameters of 9106-IM-2 Following Single IV Injection in Nude Mice

Matrix	Group	T _{max} (hr)	C _{max} (ng/mL)	AUC _{0-168h} (hr $\cdot$ ng/mL)	t _{1/2} (hr)
Serum	1 mg/kg	0.083	0.055	1.11	NA
	5 mg/kg	4	0.236	12.0	39.7
Tumor	1 mg/kg	24	4.04	371	25.2
	5 mg/kg	48	21.3	2260	65.3

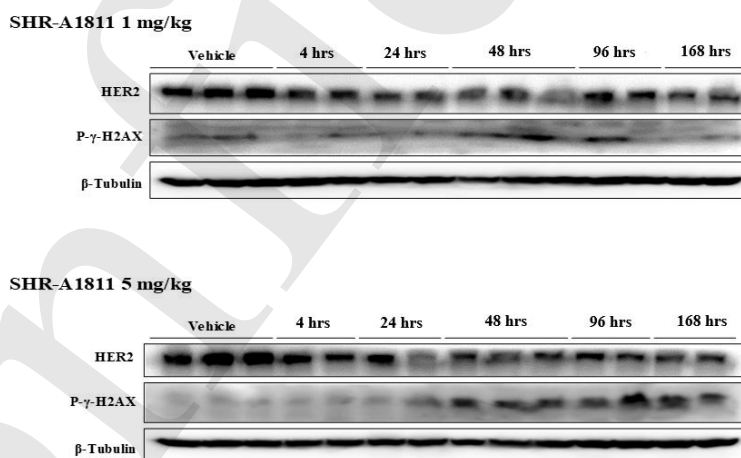


Figure 12 HER2 Levels and DNA Damage in Tumor Tissues Following Single IV Injection of SHR-A1811

5.2.1.4.2. *In Vivo* Anti-tumor Efficacy

Anti-tumor Efficacy Study of SHR-A1811 in NCI-N87 Human Gastric Cancer Cell Xenograft Model in Nude Mice

The purpose of this study was to evaluate and compare the anti-tumor efficacy of SHR-A1811 within NCI-N87 xenograft model in nude mice. This Non-GLP study was conducted by Shanghai Institute of Materia Medica, Chinese Academy of Science in 2019.

NCI-N87 cells were implanted subcutaneously into the right flank region of male BALB/c-nude mice (6-7 weeks old). Once tumors reached to the volume of 100-150 mm³, the mice were randomized into eight groups and then intravenously injected with vehicle, SHR-A1811 at 1, 2 or 5 mg/kg, or SHR-1805 at 10 mg/kg, or 0.1 mg/kg 9106-IM-2, or 5 mg/kg SHR-A1201. All the animals received single injection. Tumor volume and body weight were measured at time points indicated in Figure 13. The observation period lasted for up to 35 days.

SHR-A1811 reduced the tumor size significantly in a dose-dependent manner in NCI-N87 human gastric cancer xenograft model in nude mice. The tumor growth inhibition rate was 65%, 91%, and 133% for 1, 2, 5 mg/kg doses (IV, D0), respectively on day 24. In the 2 and 5 mg/kg groups, 2 and 7 animals displayed partial tumor regression respectively on day 24. In the 5 mg/kg SHR-A1201 group, the tumor growth inhibition rate was 92%, and no animal displayed tumor regression. In comparison, the tumor growth inhibition rate of SHR-1805 (5 mg/kg) and 9106-IM-2 (0.1 mg/kg) and combination was 40%, 9% and 51%, respectively, in NCI-N87 xenograft model. All the above treatments were well tolerated in xenograft model in nude mice. SHR-A1811 showed superior anti-tumor efficacy compared to SHR-A1201, SHR-1805 and 9106-IM-2 in NCI-N87 xenograft model. The results were shown in Figure 13 and Table 7. All animals were well tolerated during administration.

Table 7 Effects of SHR-A1811 on the Tumor Volumes of NCI-N87 Xenograft Model

Group	Dosing time	Route	Tumor volume (mean ± SEM, mm ³) D0	Tumor volume (mean ± SEM, mm ³) D24	%tumor inhibition rate D24	P value D24	Partial regression D24 (a)	No. animals at the end of study D24
vehicle	D0	IV	110.1 ± 1.5	1695.8 ± 124.9	-	-	0	10
1 mg/kg SHR-A1811	D0	IV	110.1 ± 2.6	660.0 ± 96.0	65	0.000	0	8
2 mg/kg SHR-A1811	D0	IV	112.0 ± 3.1	258.7 ± 66.9	91	0.000	2	8
5 mg/kg SHR-A1811	D0	IV	113.2 ± 3.4	75.8 ± 10.4	133	0.000	7	8
0.1 mg/kg 9106-IM-2	D0	IV	107.4 ± 1.5	1543.8 ± 83.8	9	0.363	0	8
5 mg/kg SHR-1805	D0	IV	111.5 ± 2.4	1067.7 ± 49.0	40**	0.001	0	8
5 mg/kg SHR-1805 + 0.1 mg/kg 9106-IM-2	D0	IV	115.3 ± 3.3	886.0 ± 133.9	51**	0.000	0	8
5 mg/kg SHR-A1201	D0	IV	116.5 ± 2.2	243.0 ± 43.7	92**	0.000	0	8

D0, the first dosing day. P values vs. vehicle control; ** $P < 0.01$ vs. SHR-A1811 at 5 mg/kg.

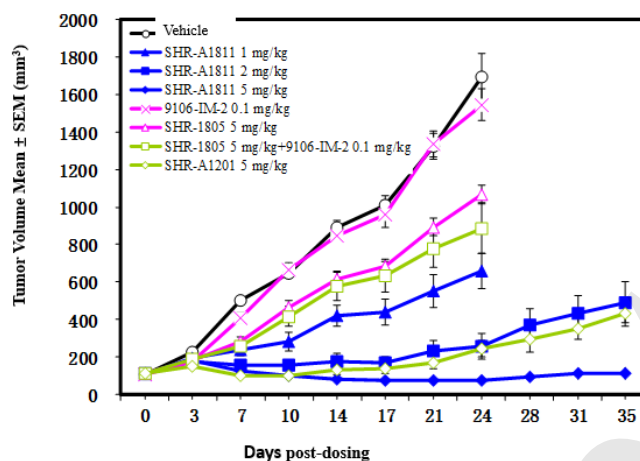


Figure 13 Effects of SHR-A1811 on the Tumor Volumes of NCI-N87 Xenograft Model

Anti-Tumor Efficacy Study of SHR-A1811 in NCI-N87/16-8 (T-DM1 Resistant) Human Gastric Cancer Cell Xenograft Model in Nude Mice

The purpose of this study was to evaluate and compare the anti-tumor efficacy of SHR-A1811 or SHR-A1201 in NCI-N87/16-8, which is a T-DM1 resistant xenograft model in nude mice. This Non-GLP study was conducted by Shanghai Institute of Materia Medica, Chinese Academy of Science in 2019.

NCI-N87/16-8 cells were implanted subcutaneously into the right flank region of female BALB/cJGpt-Foxn1^{nu}/Gpt-nude mice (4-8 weeks old). Once tumors reached to an average volume of 120 mm³, the mice were randomized into 4 groups and intravenously injected with vehicle, SHR-A1811 at 2 or 5 mg/kg or SHR-A1201 at 5 mg/kg. All the animals received single injection. Tumor volume and body weight were measured at time points indicated in Figure 14. The observation period lasted for up to 39 days.

SHR-A1811 decreased the tumor size significantly in a dose-dependent manner in NCI-N87/16-8 human gastric cancer, T-DM1 resistant xenograft model in nude mice. The tumor growth inhibition rate was 95%, 150%, and 14% for 2 and 5 mg/kg SHR-A1811, and 5 mg/kg SHR-A1201, respectively, on day 18. In 2 and 5 mg/kg SHR-A1811 group (8 mice per group), four and eight mice displayed partial tumor regression on day 39. All the above treatments were well tolerated in xenograft model in nude mice. SHR-A1811 showed superior anti-tumor efficacy compared to SHR-A1201 in NCI-N87 xenograft model. The results are shown in Table 8 and Figure 14.

Table 8 Effects of SHR-A1811 on the Tumor Volumes of NCI-N87/16-8 Xenograft Model

Group	Dosing time	Route	Tumor volume (mean ± SEM, mm ³) D0	Tumor volume (mean ± SEM, mm ³) D18	%tumor inhibition rate D18	P value D18	Partial regression	No. animals at the end of study
vehicle	D0	IV	120.9 ± 2.3	1738.7 ± 214.4	-	-	0	10
2 mg/kg SHR-A1811	D0	IV	120.2 ± 2.1	203.0 ± 63.4	95**	0.000	4	8
5 mg/kg SHR-A1811	D0	IV	120.5 ± 3.2	59.8 ± 2.1	150**	0.000	8	8

5 mg/kg SHR-A1201	D0	IV	120.8 ± 1.7	1505.3 ± 133.6	14	0.398	0	8
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D0, the first dose day; P values vs. vehicle; **P<0.01 vs. SHR-A1201 at 5 mg/kg.

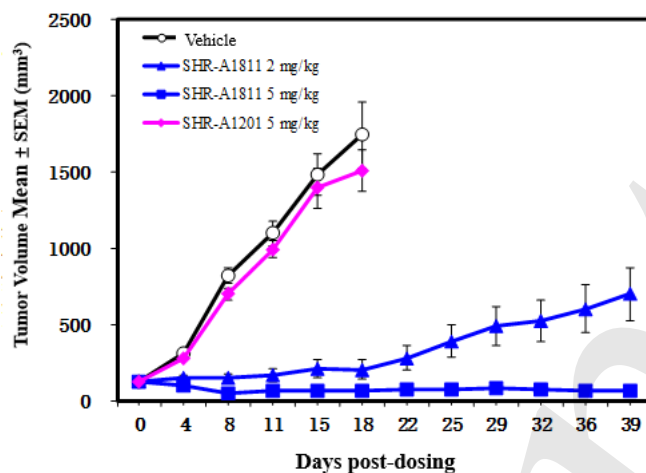


Figure 14 Effects of SHR-A1811 and SHR-A1201 on the Tumor Volumes of NCI-N87/16-8

Xenograft Model

Anti-Tumor Efficacy Study of SHR-A1811 in BC#197 Human Breast Cancer Patient-Derived Xenograft Model in Nude Mice

The purpose of this study was to evaluate and compare the anti-tumor efficacy of SHR-A1811 with SHR-A1201 or HRA00018-004 (produced in house with reference to the amino acid sequence of DS-8201a) in HER2 high-expression breast cancer BC#197 patient-derived xenograft (PDX) model in nude mice. This Non-GLP study was conducted by GenenDesign (Shanghai) Co., Ltd. in 2019.

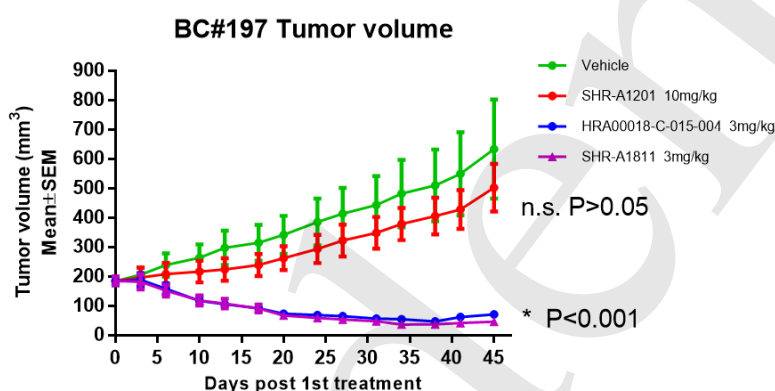
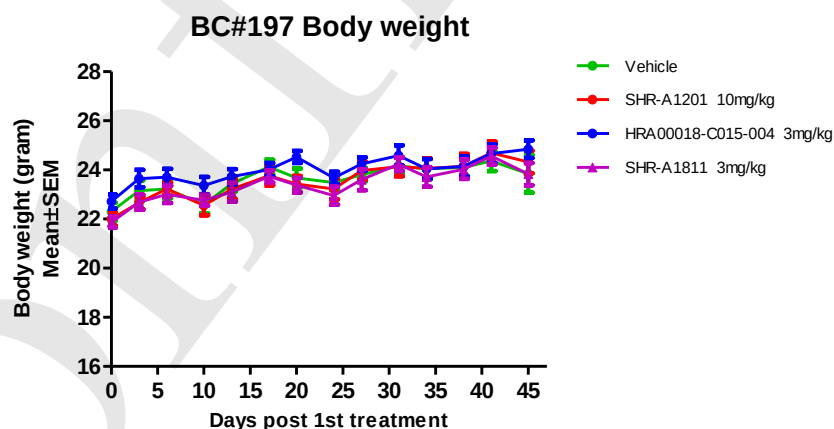
Seven to eight-week female BALB/c nude mice were implanted subcutaneously at the right flank with the BC#197 tumor. The treatments were started on day 36 after tumor implantation when the average tumor size reached approximately 185 mm³. The mice were intraperitoneal injected with vehicle, SHR-A1811, or HRA00018-004 at 3 mg/kg, or SHR-A1201 at 10 mg/kg. All the mice were received single dose injection. Tumor volume and body weight were measured at time points indicated in Figure 15. The observation period lasted for up to 45 days.

The results showed that 3 mg/kg SHR-A1811 and HRA00018-004 could significantly inhibit tumor growth, and tumor growth was delayed for more than 45 days as compared with the vehicle group. However, 10 mg/kg SHR-A1201 only exerted minor anti-tumor activity, which is not statistically different from that of the vehicle group ($P>0.05$). The results are shown in Table 9, Figure 15 and Figure 16.

Table 9 Effects of SHR-A1811 on the Tumor Volumes of BC#197 PDX Xenograft Model

Group	Dosing time	Route	Tumor volume (mean $\pm$ SEM, mm ³) D0	Tumor volume (mean $\pm$ SEM, mm ³) D45	%tumor inhibition rate D45	P value D45	No. animals at the end of study D45
vehicle	D0	i.p.	184.8 $\pm$ 14.20	510.7 $\pm$ 122.65	-	-	8
10 mg/kg SHR-A1201	D0	i.p.	185.3 $\pm$ 13.56	406.3 $\pm$ 61.83	20.45	>0.05	8
3 mg/kg HRA00018-004	D0	i.p.	185.2 $\pm$ 13.74	47.7 $\pm$ 8.86	90.67	<0.001	8
3 mg/kg SHR-A1811	D0	i.p.	184.5 $\pm$ 15.18	37.9 $\pm$ 7.41	92.58	<0.001	8

D0, the first dosing day. P values vs. vehicle.

**Figure 15 Effects of SHR-A1811, SHR-A1201 and HRA00018-004 on the Tumor Volumes of BC#197 Xenograft Model****Figure 16 Effects of SHR-A1811 on the Body Weights of BC#197 PDX Xenograft Model in Nude Mice**

Efficacy of SHR-A1811 on xenografts bearing human breast cancer BT-474/T721 in nude mice

Human breast cancer BT-474/T721 cells in cell cultured were resistant to trastuzumab, but subcutaneous xenografts of BT-474/T721 in nude mice were not resistant to SHR-1805. SHR-1805 (10 mg/kg, IV, D0) achieved a tumor inhibition rate of 83% against BT-474/T721, with partial tumor regression in 2/8 mice. SHR-A1811 (1, 3, and 10 mg/kg, IV, D0) dose-dependently and significantly inhibited the growth of subcutaneous xenografts of BT-474/T721 in nude mice, with tumor inhibition rates of 48%, 90%, and 119%, respectively. At doses of 3 mg/kg and 10 mg/kg, partial tumor regression was achieved in 3/8 and 6/8 mice, respectively. SHR-A1201 (10 mg/kg, IV, D0) achieved a tumor inhibition rate of 94% against BT-474/T721, with partial tumor regression in 4/8 mice. The above drugs were generally well tolerated in tumor-bearing mice with no body weight loss and other symptoms observed. The efficacy of SHR-A1811 10 mg/kg on BT-474/T721 was significantly stronger than that of SHR-1805 ($P < 0.01$), but there was no statistically significant difference compared with SHR-A1201 ($P > 0.05$, compared with 10 mg/kg dose group).

Table 10 Efficacy of SHR-A1811, SHR-1805, and SHR-A1201 on subcutaneous xenografts of human breast cancer BT-474/T721 in nude mice

Group	Administration	Route	Mean Tumor Volume (mm ³)		Mean Tumor Volume (mm ³)		Tumor Inhibition %		<i>P</i> Value	Partial Regression	Number of Animals per Group at the Start of the Experiment	Number of Animals per Group at the End of the Experiment
			D0	SEM	D23	SEM	T/C D23	Rate% D23				
Vehicle	D0	IV	120.6	± 3.3	428.3	± 23.1	-	-	-	0	10	10
SHR-A1811 1 mg/kg	D0	IV	121.6	± 3.5	282.9	± 45.8	52	48	0.007	0	8	8
SHR-A1811 3 mg/kg	D0	IV	119.8	± 3.5	149.8	± 20.8	10	90	0.000	3	8	8
SHR-A1811 10 mg/kg	D0	IV	124.0	± 4.2	99.9	± 8.2	-19	119	** 0.000	6	8	8
SHR-1805 10 mg/kg	D0	IV	117.4	± 2.0	170.4	± 19.9	17	83	0.000	2	8	8
SHR-A 1201 10 mg/kg	D0	IV	123.0	± 3.5	140.4	± 20.3	6	94	0.000	4	8	8

D0: time of the first dose; *P* value is for comparison with the solvent group; IV: intravenous injection;

** $P < 0.01$, compared with the SHR-1805 10 mg/kg group.

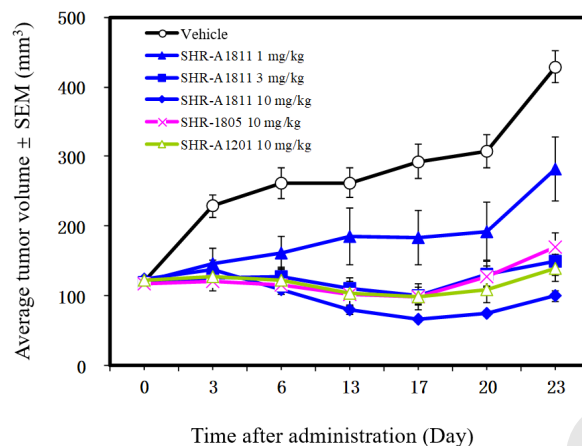


Figure 17 Efficacy of SHR-A1811, SHR-1805, and SHR-A1201 on subcutaneous xenografts of human breast cancer BT-474/T721 in nude mice

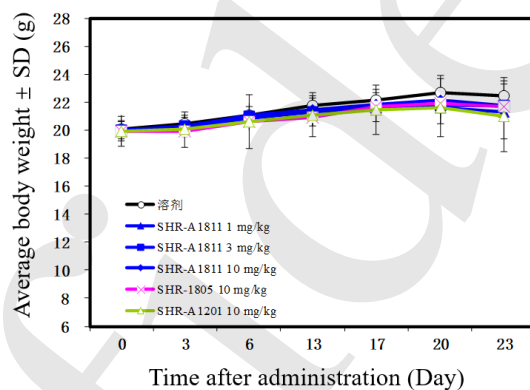


Figure 18 Effects of SHR-A1811, SHR-1805, and SHR-A1201 on body weight of tumor-bearing nude mice

5.2.2. Secondary Pharmacodynamics

No studies on secondary pharmacodynamics have been conducted to date.

5.2.3. Safety Pharmacology

5.2.3.1. Effects of 9106-IM-2 on hERG Currents

The purpose of this study was to evaluate the potential effects of 9106-IM-2 on hERG potassium currents in human embryonic kidney (HEK293) cells stably transfected with hERG channels. This GLP study was conducted by West China-Frontier PharmaTech Co., Ltd. in 2019.

Cells were incubated with 0.74, 2.22, 6.67 and 20 μ M of 9106-IM-2 or the positive

control Cisapride at 0.1 μ M, and hERG channel tail currents were recorded. The peak of the tail currents in the presence of test article or positive control were normalized with currents recorded in the presence of vehicle alone. The results showed that at the concentrations of 0.74, 2.22, 6.67 and 20 μ M, 9106-IM-2 inhibited the hERG current by a mean of 9.11%, 5.72%, 10.78% and 15.61%, with a mean normalized inhibition of 6.76%, 3.37%, 8.48% and 13.43%, respectively.

The maximum inhibition induced by 9106-IM-2 was less than 50% at concentration of 20 μ M, with IC_{50} was over 20 μ M.

In conclusion, the hERG potassium currents in HEK293 cells was not significantly inhibited by 9106-IM-2 at the concentrations of ≤ 20 μ M.

5.2.3.2. Effects of SHR-A1811 on CNS

The objective of this study was to assess the potential effects of SHR-A1811 on neurobehavioral functions in SD rats by using functional observational battery (FOB) after a single IV injection. This GLP study was conducted by West China-Frontier Pharma Tech Co., Ltd. in 2019.

Animals were assigned to 4 groups and intravenously injected with control (0.9% sodium chloride injection) or SHR-A1811 at 3, 10 and 30 mg/kg. Each group was composed of 5 rats/sex. The dose volume was 10 mL/kg. Neurobehavioral performances of animals were assessed with FOB at predose and approximately 0.25, 7, 24, 96, 168, 264 hrs of postdose.

The results showed that, during the experiment, there were no abnormalities in the general state, skin, hair or any other abnormal signs of the rats. No abnormalities were noted in home-cage observation, hand-held observation, open-field observation, stimulus response observation, grip strength or body temperature.

Therefore, the neurobehavioral performance of rats was not affected by a single IV injection of SHR-A1811 at 3, 10 and 30 mg/kg.

5.2.3.3. Effects of SHR-A1811 on Respiration and Cardiovascular Systems

The purpose of this GLP-compliant study was to assess the potential effects of single IV injection of SHR-A1811 on respiratory and cardiovascular systems in conscious monkeys using physiological signal telemetry system. This GLP study was conducted by West China-Frontier Pharma Tech Co., Ltd. in 2019.

A total of 60 monkeys were assigned to 6 groups, and intravenously injected with SHR-A1811 at 3, 10 or 40 mg/kg, or 9106-IM-2 at 0.8 mg/kg. Ten monkeys for each group (5 females and 5 males). The dose volume for negative control (0.9% sodium chloride injection) and SHR-A1811 was 10 mL/kg, and for vehicle control (a 10% SBE- β -CD solution containing 1.5% DMSO) and 9106-IM-2 was 8 mL/kg. Dosing once every 3 weeks, continuous administration for 6 weeks (3 times in total), 4 weeks for recovery. The ECG, blood pressure and breathing rate before the first dose and at 2, 24, 72, 144, 312, 480 hours after the first dose, 2 hours after the third dose and the end of the recovery period (day 28 of the recovery period) were tested.

There were no test article-related changes in any parameter at any dose level.

In conclusion, administration of SHR-A1811 and 9106-IM-2 did not induce any significant effects on ECG, blood pressure or respiratory frequency.

5.3. Nonclinical Pharmacokinetics

The *in vitro* stability of 9106-IM-2 in hepatocytes of different species, and inhibition and induction on major metabolic enzymes, and its potential effect on transporters was conducted. SD rats or cynomolgus monkeys were selected to investigate the *in vivo* pharmacokinetics of SHR-A1811 and 9106-IM-2, and the tissue distribution and excretion of SHR-A1811 in xenograft model in mice were studied.

5.3.1. Analytical Methods and Validation

5.3.1.1. Validation of a Bioanalysis Method for the Quantification of SHR-A1811 Total Antibody in Cynomolgus Monkey Serum

The purpose of this validation was to develop and validate an analytical method for quantification of SHR-A1811 total antibody in Cynomolgus monkey serum in pharmacokinetic and toxicokinetic analysis. This GLP study was conducted by West China Frontier PharmaTech Co., Ltd. in 2019.

Human HER2/ErbB2 protein at 1 µg/mL was as a capture antibody and Goat anti-Human IgG h+l (heavy and light chains) HRP Conjugated antibody (1:10,000) was used as a detection antibody.

The quantification range was 78.1-10,000 ng/mL, and the assay was within acceptable criteria with respect to accuracy, precision, reproducibility and stability.

5.3.1.2. Validation of a Bioanalysis Method for Quantification of SHR-A1811 ADC in Cynomolgus Monkey Serum

The purpose of this validation was to develop and validate an analytical method for quantification of SHR-A1811 ADC in Cynomolgus monkey serum in pharmacokinetic and toxicokinetic analysis. This GLP study was conducted by WestChina Frontier PharmaTech Co., Ltd. in 2019.

550-mIgG2 (mouse anti-toxin 9106-IM-2 monoclonal antibody) at 1 µg/mL was as a capture antibody and Goat anti-Human IgG h+l HRP Conjugated antibody (1:10,000) was used as a detection antibody.

The quantification range was 78.1-10,000 ng/mL, and the assay was within acceptable criteria with respect to accuracy, precision, reproducibility and stability.

5.3.1.3. Method validation for determination of SHR-A1811 total antibody concentration in the serum of SD rats by ELISA

The purpose of this validation study was to establish and validate an analytical method for quantification the concentration of SHR-A1811 total antibody in the serum of SD rats. This GLP study was conducted by Hubei Topgene Xinsheng Biotechnology Co., Ltd. in 2024.

HER2/ErbB2 protein was used as the capture antibody, and goat anti-human IgG light and heavy chain HRP antibody was used as the detection antibody. The linear range of the method was 50-3200 ng/mL, and the accuracy and precision, selectivity, hook effect/dilution linearity, specificity, reproducibility and stability all met the requirements of method validation.

5.3.1.4. Method validation for determination of SHR-A1811 concentration in the serum of SD rats by ELISA

The purpose of this validation study was to establish and validate an analytical method for quantification the concentration of SHR-A1811 in the serum of SD rats. This GLP study was conducted by Hubei Topgene Xinsheng Biotechnology Co., Ltd. in 2024.

HRP02918 (antibody against the small molecule moiety of SHR-A1811) was used as the capture antibody, and goat anti-human IgG light and heavy chain HRP antibody was used as the detection antibody. The linear range of the method was 50-3200 ng/mL, and the accuracy and precision, selectivity, hook effect/dilution linearity, specificity, reproducibility and stability all met the requirements of method validation.

5.3.1.5. Validation of a Bioanalysis Method for Quantification of 9106-IM-2 in Cynomolgus Monkey Plasma

The purpose of this validation was to develop and validate an LC-MS/MS analytical method for quantification of 9106-IM-2 in Cynomolgus monkey plasma for toxicokinetic analysis. This GLP study was conducted by WestChina Frontier PharmaTech Co., Ltd. in 2019. The non-GLP validation study of the LC-MS/MS analytical method for quantification of 9106-IM-2 in Cynomolgus monkey plasma for pharmacokinetic analysis was conducted by Center for Drug Metabolism and Pharmacokinetics Research/Shanghai Institute of *Materia Medica*, Chinese Academy of Sciences in 2019.

Plasma samples were processed by using a protein precipitation method. 9106-IM-2 and SHR167971 (Dxd, internal standard) were separated using Waters UPLC with ACQUITY UPLC-CSH C18 (1.7 μ m, 2.1*50 mm) analytical column and detected by MS/MS (QTRAP 6500) with a water-methanol gradient containing 0.2% formic acid and 3 mM ammonium acetate. The total run time was 4.0 min.

The range of quantification was 0.0500-50.0 ng/mL for toxicokinetics, and 0.0200-20.0 ng/mL for pharmacokinetics. Both assays were within acceptable criteria with respect to accuracy, precision, reproducibility and stability.

5.3.1.6. Validation of a Bioanalysis Method for Quantification of 9106-IM-2 in SD Rat Plasma

The purpose of this validation was to develop and validate an LC-MS/MS analytical method for quantification of 9106-IM-2 in SD rat plasma for toxicokinetic analysis. This GLP study was conducted by WestChina Frontier PharmaTech Co., Ltd. in 2019. The non-GLP validation study of the LC-MS/MS analytical method for quantification of 9106-IM-2 in SD rat plasma for pharmacokinetic analysis was conducted by Center for Drug Metabolism and Pharmacokinetics Research/Shanghai Institute of *Materia Medica*, Chinese Academy of Sciences in 2019.

Plasma samples were processed by using a protein precipitation method. 9106-IM-2 and SHR167971 (Dxd, internal standard) were separated using Waters UPLC with ACQUITY UPLC-CSH C18 (1.7 μ m, 2.1*50 mm) and ionized with ESI+ and detected by MS/MS (QTRAP 6500) with a water-methanol gradient containing 0.2% formic acid and 3 mM ammonium acetate. The total run time was 4.0 min

The range of quantification was 0.100-100 ng/mL for toxicokinetics, and 0.0200-20.0 ng/mL for pharmacokinetics. Both assays were within acceptable criteria with respect to accuracy, precision, reproducibility and stability.

5.3.1.7. Method validation for quantitative determination of 9106-IM-2 concentration in the serum of SD rats by LC-MS/MS

The objective of this validation study was to establish and validate an analytical method for quantification of 9106-IM-2 in the serum of SD rats. This GLP study was conducted by Hubei Topgene Xinsheng Biotechnology Co., Ltd. in 2024.

Serum samples were processed by protein precipitation, separated using an ACQUITY UPLC® HSS T3 1.8 μ m 2.1 $\times$ 100 mm column, and analyzed using an ACQUITY I Class/XevoTQ-XS LC-MS system. The linear range of the method was 0.10-50.00 ng/mL. The accuracy, precision, reproducibility, and stability of the method were within the acceptable ranges, and the method could be used to determine the concentration of 9106-IM-2 in SD rat serum.

5.3.1.8. Validation of an Anti-drug Antibody Assay for Immunogenicity Testing of SHR-A1811 in Cynomolgus Monkey Serum

The purpose of this validation was to develop and validate an anti-drug antibody assay for immunogenicity testing of SHR-A1811 in cynomolgus monkey serum. This GLP study was conducted by WestChina Frontier PharmaTech Co., Ltd. in 2019.

The serum samples were diluted with 300 mM acetic acid, and added with Master Mix, which contains biotin-labeled SHR-A1811 and SULFO-TAG SHR-A1811 at RT for 2 hrs. Samples were added into MSD GOLD 96-well Streptavidin Plate, and blocked with 5%BSA-1 $\times$ PBS, then detected using MSD for ECL value.

This validation was within acceptable criteria with respect to sensitivity, hook effect, system suitability, drug tolerance, specificity and stability. Floating screening cut point should be used for the sample analysis, and the additive corrective factor is 7.02. Confirmatory cut point is 26.00%.

5.3.2. Absorption and Pharmacokinetics

5.3.2.1. Caco-2 cell permeability study of 9106-IM-2

In this study, the Caco-2 cell model was used to evaluate the permeability and efflux ratio of 9106-IM-2. The integrity of the cell monolayer was determined using Lucifer yellow. Acyclovir and minoxidil were used as the low- and high-permeability positive compounds, respectively, and digoxin and zosuquidar as the positive substrate and inhibitor of P-gp, respectively. The results of positive compounds were within the acceptable range of the laboratory, indicating that the test system was normal. The apical (A) to basolateral (B) Papp values of 9106-IM-2 at concentrations of 0.75 μ M,

1.5 μ M, and 3 μ M were 0.236×10^{-6} cm/s, 0.242×10^{-6} cm/s, and 0.246×10^{-6} cm/s, respectively, suggesting that 9106-IM-2 had low permeability, and the efflux transporter P-gp might be involved in its transport.

5.3.2.2. Pharmacokinetic Study of SHR-A1811 or 9106-IM-2 after IV Infusion in Cynomolgus Monkeys

A total of 24 Cynomolgus monkeys were randomly assigned to 4 groups (3/sex/group). Monkeys in Groups 1-3 were intravenously infused with SHR-A1811 at 0.2, 2 and 6 mg/kg, respectively. Monkeys in Group 4 were infused with 9106-IM-2 at 0.5 mg/kg. The infusion time for SHR-A1811 is 30 min, and 5 min for 9106-IM-2.

The whole blood was collected through vein at different time points before and after administration and the serum or plasma was separated. The concentration of total antibody and ADC in the serum of cynomolgus monkey was determined by ELISA, the linear range was 78.1-10,000 ng/mL. The small molecule drug 9106-IM-2 in plasma was determined by LC-MS/MS, and the linear range is 0.02-20.0 ng/mL. The pharmacokinetic parameters were calculated by non-compartment model. See table 8-11 for the summary results of pharmacokinetic parameters of each determined substance.

After a single IV injection of SHR-A1811 0.6, 2, 6 mg/kg, the drugs in serum mainly existed in the form of ADC. The concentration of 9106-IM-2 in the monkey plasma at 0.6 mg/kg SHR-A1811 group was below the lower limit of quantitation (LLOQ) of 0.02 ng/mL. The total antibody, ADC and 9106-IM-2 showed non-linear pharmacokinetic characteristics in the dose range of 0.6-6 mg/kg. The increasing proportion of AUC was higher than that of the dose, and the serum clearance rate decreased with the increase of the dose. The stable distribution volume of total antibody and ADC in cynomolgus monkeys suggests that they are basically distributed in blood vessels. The half-life of the elimination of ADC in the serum of cynomolgus monkeys was 1.08-10.0 days on average, and it was prolonged with the increase of the dose, which was slightly faster than that of the total antibody (3.40-12.3 days). There was no significant gender difference in serum exposure of total antibody, ADC and 9106-IM-2 in cynomolgus monkeys. The pharmacokinetic parameters of SHR-A1811 and 9106-IM-2 are shown in Table 11 to Table 14.

After a single IV injection of 0.5 mg/kg 9106-IM-2 to the monkeys, it was a medium clearance drug with a plasma clearance rate of 16.7 mL/h/kg; its steady-state distribution volume - V_{ss} - was 0.687 L/kg, close to the total volume of body fluids; its end-point plasma elimination half-life was 5.72 h on average; there was no significant gender difference in plasma exposure.

Table 11 Pharmacokinetics Parameters of Total Antibody in Cyno Monkeys after Single IV

Injection of SHR-A1811 (Mean $\pm$ SD, n=3/sex)						
Dosage (mg/kg)	Sex	AUC _{0-t} (μ g·day/mL)	AUC _{0-∞} (μ g·day/mL)	t _{1/2} (day)	CL (mL/day/kg)	V _{ss} (L/kg)
0.6	Male	28.9 $\pm$ 8.4	29.4 $\pm$ 8.6	3.27 $\pm$	21.8 $\pm$ 7.2	0.0472 $\pm$
				1.48		0.0049

	Female	25.5 ± 6	26.2 ± 6.1	3.53 ± 0.89	23.9 ± 6.3	0.0485 ± 0.0078
	Total	27.2 ± 6.8	27.8 ± 6.9	3.40 ± 1.10	22.9 ± 6.2	0.0479 ± 0.0059
2	Male	171 ± 32	174 ± 34	9.47 ± 3.42	11.8 ± 2.4	0.0619 ± 0.0082
	Female	93.6 ± 12.5	94.2 ± 12.9	3.54 ± 2.28	21.5 ± 2.9	0.0542 ± 0.0087
	Total	132 ± 48	134 ± 50	6.50 ± 4.16	16.6 ± 5.8	0.058 ± 0.0086
6	Male	693 ± 145	715 ± 147	11.2 ± 3.48	8.61 ± 1.6	0.0752 ± 0.0124
	Female	420 ± 124	439 ± 135	13.3 ± 2.55	14.7 ± 5.1	0.122 ± 0.0184
	Total	557 ± 192	577 ± 197	12.3 ± 2.94	11.7 ± 4.8	0.0987 ± 0.0293

Table 12 Pharmacokinetics Parameters of ADC in Cyno Monkeys After Single IV Injection of SHR-A1811 (Mean±SD, n=3/sex)

Dosage (mg/kg)	Sex	AUC _{0-t} (µg·day/mL)	AUC _{0-∞} (µg·day/mL)	t _{1/2} (day)	CL (mL/day/kg)	V _{ss} (L/kg)
0.6	Male	23.5 ± 6.4	23.8 ± 6.5	1.30 ± 0.33	26.8 ± 8.5	0.0385 ± 0.0081
	Female	19.5 ± 7.1	20 ± 6.8	0.87 ± 0.15	32.3 ± 11	0.0352 ± 0.0044
	Total	21.5 ± 6.4	21.9 ± 6.3	1.08 ± 0.33	29.6 ± 9.1	0.0368 ± 0.0061
2	Male	149 ± 20.7	151 ± 21	4.89 ± 1.93	13.4 ± 2	0.0568 ± 0.0079
	Female	89 ± 14	89.5 ± 14	2.88 ± 2.42	22.7 ± 3.3	0.0526 ± 0.008
	Total	119 ± 36.6	120 ± 37.1	3.88 ± 2.25	18.1 ± 5.6	0.0547 ± 0.0075
6	Male	656 ± 142	674 ± 147	9.95 ± 3.8	9.18 ± 1.9	0.0775 ± 0.0147
	Female	436 ± 124	446 ± 128	10.1 ± 1.92	14.2 ± 4	0.1023 ± 0.0217
	Total	546 ± 169	560 ± 175	10.0 ± 2.7	11.7 ± 4	0.0899 ± 0.0214

Table 13 Pharmacokinetics Parameters of 9106-IM-2 in Cyno Monkeys After Single IV Injection of SHR-A1811 (Mean±SD, n=3/sex)

Dosage (mg/kg)	Sex	C _{max} (ng/mL)	AUC _{0-t} (ng·h/mL)	AUC _{0-∞} (ng·h/mL)	MRT (hr)	t _{1/2} (hr)
2	Male	0.693 ± 0.267	8.89 ± 1.5	10.9 ± 2.0	67.5 ± 22.5	54.1 ± 17.3
	Female	0.745 ± 0.152	8.03 ± 2.1	10.0 ± 1.3	39.1 ± 20.0	36.4 ± 9.5
	Total	0.719 ± 0.197	8.46 ± 1.7	10.5 ± 1.6	53.3 ± 24.6	45.2 ± 15.8
6	Male	0.811 ± 0.228	45.4 ± 5.2	51.5 ± 8.0	87.1 ± 34.7	75.4 ± 18.4
	Female	0.505 ±	31.6 ± 1.1	36.3 ± 3.4	77.3 ± 13.4	69.1 ± 16.4

Dosage (mg/kg)	Sex	C _{max} (ng/mL)	AUC _{0-t} (ng·h/mL)	AUC _{0-∞} (ng·h/mL)	MRT (hr)	t _{1/2} (hr)
		0.057				
	Total	0.658 ± 0.224	38.5 ± 8.3	43.9 ± 10	82.3 ± 24.3	72.3 ± 16

Table 14 Pharmacokinetics Parameters of 9106-IM-2 in Cyno Monkeys After Single IV**Injection of 0.5 mg/kg 9106-IM-2 (Mean±SD, n=3/sex)**

Sex	AUC _{0-t} (ng·h/mL)	AUC _{0-∞} (ng·h/mL)	MRT (h)	t _{1/2} (h)	CL (mL/h/kg)	V _{ss} (L/kg)
Male	498 ± 111	499 ± 112	0.82 ± 0.25	5.03 ± 0.71	17.3 ± 4.3	0.813 ± 0.072
Female	527 ± 0.0	528 ± 0.0	0.53 ± 0.02	6.76 ± 2.23	15.8 ± 0	0.498 ± 0.018
Total	510 ± 80	511 ± 81	0.70 ± 0.24	5.72 ± 1.55	16.7 ± 3.1	0.687 ± 0.18

5.3.2.3. Pharmacokinetic Study of 9106-IM-2 After a Single IV Injection in Sprague-Dawley (SD) Rat

The purpose of this study was to determine the pharmacokinetics of 9106-IM-2 in SD rat following a single IV injection at 0.06, 0.12 and 0.24 mg/kg. This non-GLP study was conducted by Center for Drug Metabolism and Pharmacokinetics Research/Shanghai Institute of *Materia Medica*, Chinese Academy of Sciences in 2019.

Eighteen SD rats were randomly assigned to 3 groups (6/group, 3/sex). Rats were administrated with 9106-IM-2 at 0.06, 0.12 and 0.24 mg/kg by single IV injection, respectively. A series of blood samples were collected from all the rats and plasma samples were prepared. The plasma concentrations of 9106-IM-2 were measured using a validated LC-MS/MS method. The pharmacokinetic parameters were calculated using non-compartment model.

After a single IV injection, the plasma clearance rate CL of 9106-IM-2 in rats was 45 mL/min/kg, which was a high clearance drug; the steady-state distribution volume V_{ss} was 1.29 L/kg, which was higher than the total volume of body fluids; 9106-IM-2 showed biphasic elimination characteristics in rats, and the elimination became slow after 4 hours, and the mean elimination half-life T_{1/2} was 0.73 h. There was no significant gender difference in plasma exposure. In the range of 0.06-0.24 mg/kg, the increase of AUC_{0-t} of 9106-IM-2 was in direct proportion to the increase of dose. The pharmacokinetic parameters for 9106-IM-2 were shown in [Table 15](#).

Table 15 Pharmacokinetic Parameters of 9106-IM-2 in SD Rat After Single IV Injection

(n=3/sex)							
Dosage (mg/kg)	Sex	AUC _{0-t} (ng·h/mL)	AUC _{0-∞} (ng·h/mL)	MRT (h)	t _{1/2} (h)	CL (mL/min/kg)	V _{ss} (L/kg)
0.06	Male	20.0 ± 1.5	20.0 ± 1.6	0.47 ± 0.09	0.65 ± 0.18	50.1 ± 3.7	1.4 ± 0.18
	Female	28.3 ± 4.9	28.4 ± 5.0	0.51 ± 0.09	0.68 ± 0.21	36.0 ± 6.7	1.07 ± 0.01
	Total	24.2 ± 5.6	24.2 ± 5.7	0.49 ± 0.08	0.67 ± 0.17	43.0 ± 9.1	1.23 ± 0.21
0.12	Male	39.0 ± 1.5	39.1 ± 1.6	0.47 ± 0.04	0.72 ± 0.07	51.2 ± 2.0	1.43 ± 0.07
	Female	44.7 ± 2.2	44.8 ± 2.3	0.51 ± 0.09	0.81 ± 0.08	44.7 ± 2.4	1.35 ± 0.18
	Total	41.9 ± 3.5	42.0 ± 3.6	0.49 ± 0.07	0.77 ± 0.08	47.9 ± 4.1	1.39 ± 0.13
0.24	Male	88.4 ± 16	88.4 ± 16	0.44 ± 0.01	0.69 ± 0.06	46.2 ± 8.0	1.22 ± 0.21
	Female	96.0 ± 3.8	96.3 ± 3.6	0.52 ± 0.06	0.83 ± 0.05	41.5 ± 1.7	1.30 ± 0.14
	Total	92.2 ± 11.2	92.5 ± 11.3	0.48 ± 0.06	0.76 ± 0.09	43.8 ± 5.7	1.26 ± 0.16

5.3.2.4. Pharmacokinetic study of a single intravenous injection of [³H]-9106-IM-2 in SD rats

After a single intravenous administration of 1 mg/150 µCi/kg [³H]-9106-IM-2 via the tail vein to 6 SD rats (3 male and 3 female), whole blood was collected before administration (pre-dose, 0 h) and at 5 min, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, and 8 h after administration, and plasma was obtained by centrifugation for the radioactivity pharmacokinetic study.

After a single intravenous injection of [³H]-9106-IM-2 at 1 mg/150 µCi/kg via the tail vein in SD rats, there were no significant sex differences in primary pharmacokinetic parameters between male and female animals. The primary pharmacokinetic parameters were as follows: AUC_{INF_obs} was 509.16 ± 46.61 h·ng Eq/g; AUC_{last} was 501.74 ± 46.36 h·ng Eq/g; C₀ was 1119.33 ± 193.31 ngEq/g; Cl_{obs} was 3956.66 ± 375.30 g/h/kg; C_{max} was 839.43 ± 125.42 ng Eq./g; T_{1/2_z} was 0.50 ± 0.02 h; and V_{ss_obs} was 5031.03 ± 884.88 g/kg.

5.3.3. Distribution

5.3.3.1. Plasma Protein Binding Study of 9106-IM-2

The purpose of this study was to determine the plasma protein binding (PPB) of 9106-IM-2 in human, mouse, rat and monkey plasma by using Rapid Equilibrium Dialysis

(RED) method. This non-GLP study was conducted by Center for Drug Metabolism and Pharmacokinetics Research/Shanghai Institute of *Materia Medica*, Chinese Academy of Sciences in 2019.

The PPB ratio was similar in plasma cross the species. The mean PPB ratios were 88.6%, 85.1%, 94.8 and 85.0% for human, monkey, rat and mouse, respectively. No concentration dependent was observed.

5.3.3.2. Tissue Distribution of ^{125}I -SHR-A1811 in Xenograft Model in Nude Mice

The purpose of this study was to evaluate tissue distribution of SHR-A1811 in xenograft model in nude mice. This non-GLP study was conducted by MITRO Biotech Co., Ltd. in 2019.

For examination of tissue distribution, 24 xenograft mice (3/sex/group) were assigned to 4 groups following IV injection of 5 mg/kg ^{125}I -SHR-A1811. The nude mice were euthanized at 4, 48, 168 and 336 hrs postdose. Radioactivity in the collected tissues was determined before and after trichloroacetic acid (TCA) protein precipitation.

The results showed that the total radioactivity content of thyroid gland accounted for 0.15%, 0.12% and 0.11% of the total radiation dose at 48 h, 168 h and 336 h post-dose respectively, which did not affect the reliability of tissue distribution test results.

Total radioactivity distribution (AUC values) of SHR-A1811 in different tissues or body fluid are ranked as follows: blood, tumor, lung, ovary, kidney, uterus, bladder, liver, spleen, heart, intestine, stomach, pancreas, eyes, fat, muscle and brain. The results were shown in Figure 19 and Figure 20. The results indicated that SHR-A1811 could hardly distributed to brain and not induce CNS toxicity in normal animal with whole blood-brain barrier due to its large molecular weight. While, 9106-IM-2, the cleaved metabolite of SHR-A1811, maybe distribute to brain and its potential interaction on the various transporters such as P-gp and BCRP.

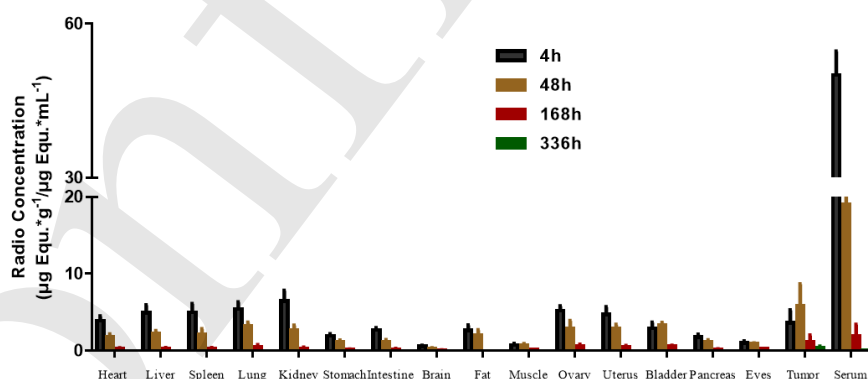


Figure 19 Radio Concentration of ^{125}I -SHR-A1811 at Different Time Points

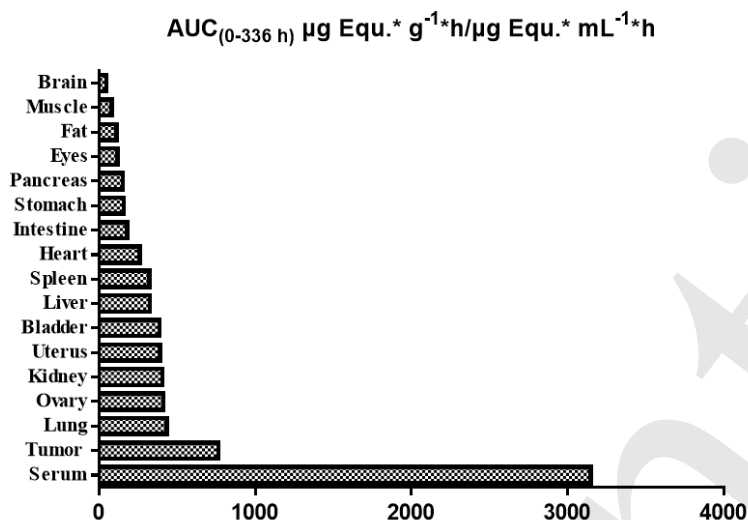


Figure 20 Accumulative Ratio of ^{125}I -SHR-A1811 in Xenograft Nude Mice via Single IV

Injection

5.3.3.3. Tissue distribution study after a single intravenous injection of [^3H]-SHR-A1811 in a NCI-N87 xenograft model of B-NDG mice

The distribution of [^3H]-SHR-A1811 (^3H label on the small molecule) in the B-NDG mouse NCI-N87 xenograft model was investigated. Twenty-four B-NDG mice were subcutaneously inoculated with NCI-N87 tumor cells on the right side. When the tumor volume reached 194.1-240.71 mm³, the mice were randomized into 4 groups (n = 6). After a single intravenous injection of 2 mg/150 μCi/kg [^3H]-SHR-A1811, tissue and blood samples (3 females and 3 males at each time point) were collected at 4 h, 24 h, 72 h, and 168 h after administration to determine the total radioactivity concentrations in different tissues, whole blood, and plasma of the animals.

The study results (Figure 21 and Figure 22) showed that: In female mice, the exposure ($\text{AUC}_{0-168 \text{ h}}$) in whole blood was 214,909.78 h·ng Eq./g, the exposure ($\text{AUC}_{0-168 \text{ h}}$) in plasma was 392,733.80 h·ng Eq./g, and the whole blood/plasma exposure ratio was 0.55, suggesting that the radioactive drug was mainly distributed in plasma; the exposure in spleen was higher than that in plasma, with a ratio to plasma exposure of 1.52; the exposure in tumor, duodenum, liver, ovaries, lungs, adrenal glands, bone, kidneys, heart, stomach wall, fat, pancreas, and muscle was lower than that in plasma, and the ratio to plasma exposure was 0.49, 0.48, 0.45, 0.39, 0.30, 0.29, 0.29, 0.21, 0.19, 0.13, 0.08, 0.07, and 0.04, respectively; the exposure in brain was lower than that in plasma, and the ratio to plasma was 0.01. In male mice, the exposure ($\text{AUC}_{0-168 \text{ h}}$) in whole blood was 231,633.09 h·ng Eq./g, the exposure ($\text{AUC}_{0-168 \text{ h}}$) in plasma was 425,869.82 h·ng Eq./g, and the whole blood/plasma exposure ratio was 0.54, suggesting that the radioactive drug was mainly distributed in plasma; the exposure in spleen was higher than that in plasma, with a ratio to plasma exposure of 1.43; the exposure in tumor, adrenal glands, duodenum, liver, lungs, bone, kidneys, heart, testis, stomach wall, pancreas, fat, and muscle was lower than that in plasma, and the ratio to plasma exposure was 0.60, 0.53, 0.52, 0.42, 0.32, 0.26, 0.24, 0.19, 0.16, 0.14, 0.06, 0.05, and

0.04, respectively; the exposure in brain was lower than that in plasma, and the ratio to plasma was 0.02.

The study results suggested that after intravenous injection, [^3H]-SHR-A1811 was widely distributed in the tissues of female and male mice, mainly in the spleen and plasma, followed by tumor, whole blood, duodenum, liver, adrenal gland, ovaries, lungs, bone, kidneys, heart, and testis, relatively less distributed in the gastric wall, pancreas, fat, and muscle, and rarely distributed in brain tissue.

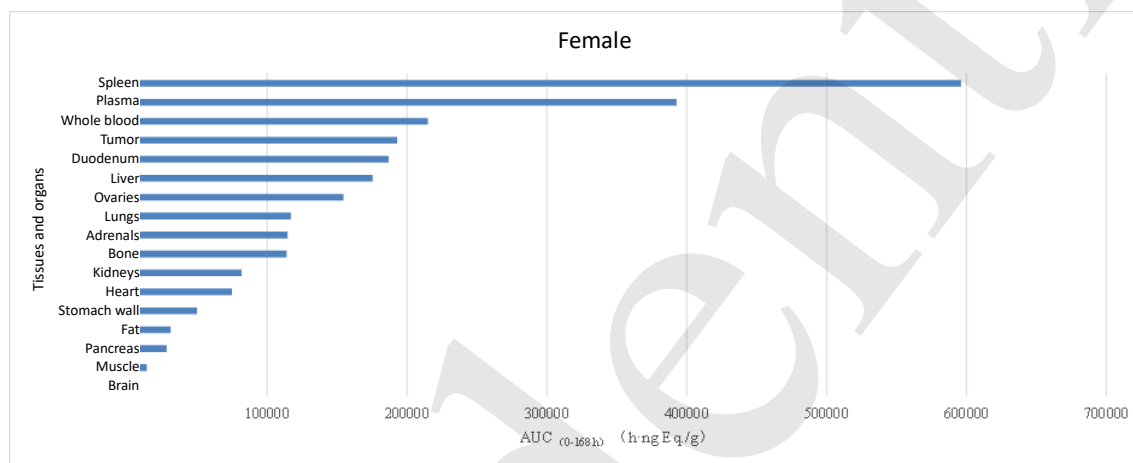


Figure 21 Radioactivity exposure AUC_{0-168 h} (h·ng Eq./g) in various tissues/body fluids at 0-168 h after a single intravenous injection of [^3H]-SHR-A1811 in the subcutaneous NCI-N87 xenograft model of B-NDG mice - females

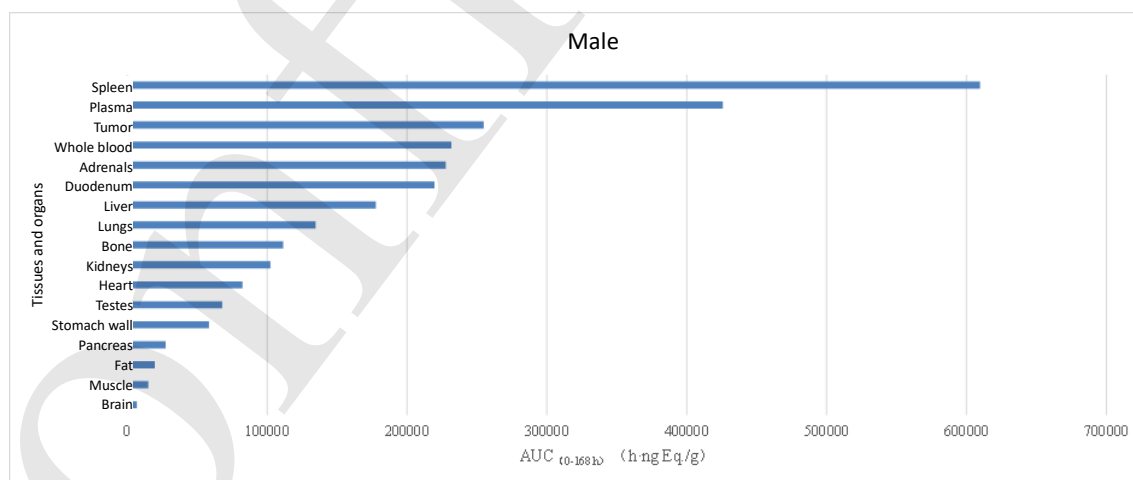


Figure 22 Radioactivity exposure AUC_{0-168 h} (h·ng Eq./g) in various tissues/body fluids at 0-168 h after a single intravenous injection of [^3H]-SHR-A1811 in the subcutaneous NCI-N87 xenograft model of B-NDG mice - males

5.3.4. Metabolism

5.3.4.1. Metabolic Stability Study of 9106-IM-2 in Hepatocytes of Different Species

The purpose of this study was to determine the *in vitro* metabolism profile of 9106-IM-2 by monitoring the clearance rate of the parent compound following incubation with hepatocytes isolated from mouse, rat, dog, monkey and human for 3 hrs. This non-GLP study was conducted by Center for Drug Metabolism and Pharmacokinetics Research/Shanghai Institute of *Materia Medica*, Chinese Academy of Sciences in 2019.

A stock solution of 9106-IM-2 was prepared in DMSO. The final concentration of DMSO in the incubation was 0.1% (v/v). All of the incubations were conducted at 37°C in William's Medium E (WME) containing 1.0×10^6 cells/mL hepatocyte and 3.0 μ M 9106-IM-2 in a total volume of 100 μ L. The reaction was terminated after 180 minutes incubation by adding equal volume of ice-cold acetonitrile. Each incubation was performed in duplicate. The samples were stored at -70°C until analysis. Equal volumes (150 μ L) of the two incubation samples from the same animal species were mixed with 300 μ L acetonitrile. The mixture was vortex-mixed for 1 minute and centrifuged at 14,000 rpm for 5 minutes. The supernatant (550 μ L) was evaporated to dryness under a stream of nitrogen at 40°C and then reconstituted in 150 μ L of acetonitrile: water (10: 90, v/v). A 7.0 μ L-aliquot of the mixture was injected for the UPLC-UV/Q-TOF MS analysis.

The result indicated that 9106-IM-2 was stable in hepatocytes of various animal species, but it was chemically unstable and undergone lactone ring-opening hydrolysis and further decarboxylative reaction after 3 h incubation at 37°C.

5.3.4.2. Metabolic Enzyme Phenotype of 9106-IM-2

The purpose of this study was to characterize cytochrome P450 (CYP450) enzymes responsible for the *in vitro* metabolism of 9106-IM-2 in human liver microsomes. This non-GLP study was conducted by Center for Drug Metabolism and Pharmacokinetics Research/Shanghai Institute of *Materia Medica*, Chinese Academy of Sciences in 2019.

The 9106-IM-2 metabolites in human liver microsomes and recombinant human CYP450 isoenzymes were identified by UPLC/Q-TOF MS method.

9106-IM-2 was relatively stable in the human liver microsomes incubation mixture without any inhibitors after 60-min incubation. A small amount of the lactone ring-opening hydrolytic metabolite M3, the lactone ring-opening hydrolytic and decarboxylated metabolite M1, the mono-oxidative metabolite M2, and dehydrogenated metabolite of M1 (M4) were detected. The addition of CYPs inhibitor ABT and CYP3A inhibitor ketoconazole significantly reduced the formation of M2 and M4, and did not affect the formation of other metabolites. Besides, the addition of CYP2D6 inhibitor quinidine also significantly inhibit the formation of M2. The metabolite profile of 9106-IM-2 detected in CYP3A4 incubation mixture was similar to that in human liver microsomes. A small amount of M2 was detected in the CYP2D6 incubation mixture. M1 and M3 could be detected in inactivated and various CYP

incubation mixtures.

In summary, 9106-IM-2 undergone lactone ring-opening hydrolysis (M3) and lactone ring ring-opening hydrolysis followed by decarboxylation (M1) in human liver microsomes incubation mixture, which were independent of P450 enzymes. 9106-IM-2 also undergone mono-oxidation (M2) and dehydrogenation of M1 (M4), which were P450-dependent. The production of M2 was mainly catalyzed by CYP3A4 and 2D6, and the formation of M4 was primarily mediated by CYP3A4.

5.3.4.3. Metabolites Identification of 9106-IM-2 in SD Rats and Cynomolgus Monkeys

UPLC-UV/Q-TOF MS was used to identify the possible metabolites in rats and cynomolgus monkeys after IV administration of SHR-A1811 or 9106-IM-2.

Judging from the peak area detected by UPLC-UV/Q-TOF MS method, after a single IV administration of 0.24 mg/kg 9106-IM-2 in rats, the plasma was dominated by the parent drug M0, followed by the lactone ring opening hydrolytic metabolite M3. After a single IV administration of 200 mg/kg SHR-A1811, the primary drug in urine was M0, followed by the M3; the primary drug in fecal samples was M0, and a small amount of mono-oxygenated metabolite M2 and M3 could be detected; the primary drug M0 was in bile, followed by M3 and M2. After 0.5 mg/kg 9106-IM-2 was administered intravenously to cynomolgus monkeys, M0 was the main drug in plasma, followed by M3.

In conclusion, in the plasma of rats and monkeys, the parent drugs are mainly, and seven metabolites were detected at low level, the main metabolic pathway is lactone ring opening hydrolysis and mono-oxidation.

5.3.5. Excretion

5.3.5.1. Excretion Study of 9106-IM-2 after a Single IV Injection in SD Rat

The purpose of this study was to determine the biliary, fecal, urinary excretion and mass balance of 9106-IM-2 after a single IV injection of SHR-A1811 to SD rats. This non-GLP study was conducted by Center for Drug Metabolism and Pharmacokinetics Research/Shanghai Institute of *Materia Medica*, Chinese Academy of Sciences in 2019.

Twelve SD rats were randomly assigned to 2 groups, 6 animals for Group1 (3/gender) and 6 animals for Group 2 (3/gender). Animals in Group 1 were cannulated in the bile ducts and administrated with SHR-A1811 at 200 mg/kg (equivalent to 50 mg/kg 9106-IM-2 according to the same molecular ratio) after full recovery. Bile samples were collected up to 48 h post-dose. Animals in Group 2 were administrated with SHR-A1811 at 200 mg/kg, and feces and urine samples were collected up to 14 days post-dose. The concentrations of 9106-IM-2 in bile, urine and feces were measured by a validated LC-MS/MS method and the accumulative excretion rate was calculated.

The results showed the biliary accumulative excretion rate of 9106-IM-2 was 15.8% in SD rats within 48 hours after IV administration of SHR-A1811 at 200 mg/kg, while urinary and fecal accumulative excretion rates were 5.23% and 38.0%, respectively.

The results demonstrated that the main excretion path of 9106-IM-2 was bile excretion in SD rats. The results were shown in Figure 23 and Figure 24.

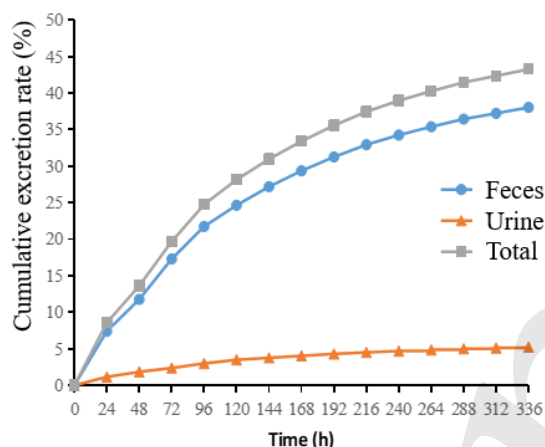


Figure 23 Urinary and Fecal Accumulative Excretion of 9106-IM-2 Following a Single IV Injection of 200 mg/kg SHR-A1811

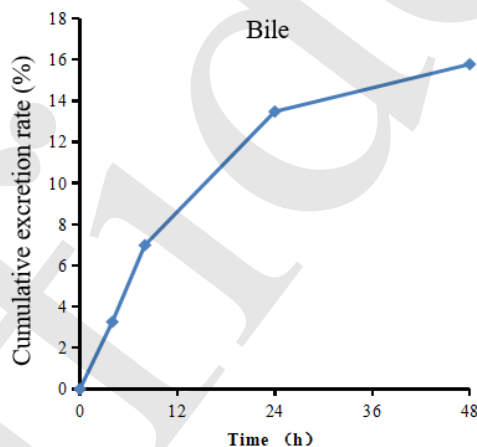


Figure 24 Bile Accumulative Excretion of 9106-IM-2 Following a Single IV Injection of 200 mg/kg SHR-A1811

5.3.5.2. Mass balance study after a single intravenous injection of [³H]-9106-IM-2 in SD rats

After a single intravenous injection of [³H]-9106-IM-2 at 1 mg/150 μ Ci/kg in SD rats, the cumulative excretion of total radioactivity in urine and feces within 0-168 h after administration (normal rats) and in urine, bile, and feces within 0-72 h after administration (bile duct cannulated rats) was investigated.

The study results showed that within 0-168 h after administration in normal SD rats,

there was no significant difference in the excretion pathways between male and female SD rats, with cumulative excretions of $90.68\% \pm 3.03\%$ and $90.25\% \pm 3.76\%$, respectively. The radioactivity was mainly excreted in feces (female $78.81\% \pm 30.53\%$; male $74.95\% \pm 10.87\%$) and to a lesser extent in urine (female $10.74\% \pm 5.11\%$; male $14.66\% \pm 0.44\%$). Within 0-72 h after administration in bile duct cannulated rats, the radioactivity in female animals was mainly excreted in urine and feces (urine: $35.86\% \pm 19.08\%$, feces: $9.25\% \pm 4.14\%$), followed by bile ($25.29\% \pm 39.32\%$). In male animals, the radioactive components were mainly excreted in bile ($53.23\% \pm 45.96\%$), followed by urine and feces ($25.91\% \pm 28.78\%$ and $7.59\% \pm 5.10\%$, respectively). The individual differences in the excretion pathways in bile duct cannulated rats may be affected by the operation of bile duct cannulation. Based on the above results, [3H]-9106-IM-2 was mainly excreted in feces through bile, and a small amount was excreted through urine in rats.

5.3.5.3. Mass balance study after a single intravenous injection of [3H]-SHR-A1811 in SD rats

After a single intravenous injection of [3H]-SHR-A1811 (^3H label on the small molecule moiety) at 1 mg/150 $\mu\text{Ci/kg}$ in SD rats, the cumulative excretion of total radioactivity in urine and feces within 0-672 h after administration (normal rats) and in urine, bile, and feces within 0-72 h after administration (bile duct cannulated rats) was investigated.

The study results showed that within 0-672 h after administration in normal SD rats, there was no significant difference in the excretion pathways between male and female rats, with cumulative excretions of $92.04\% \pm 2.37\%$ and $94.62\% \pm 2.69\%$, respectively. The radioactivity was mainly excreted in feces (female $79.52\% \pm 2.24\%$; male $76.32\% \pm 1.44\%$) and to a lesser extent in urine (female $7.05\% \pm 1.12\%$; male $10.25\% \pm 1.13\%$). Within 0-72 h after administration in bile duct cannulated rats, the radioactivity in female and male SD rat carcasses were 55.5% and 58.06%, respectively. Only < 50% of radioactivity was excreted through bile, urine, and feces. In female rats, the radioactivity was excreted through bile ($15.15\% \pm 6.70\%$), urine ($21.35\% \pm 4.62\%$), and feces ($3.16\% \pm 0.70\%$), respectively; in male rats, the radioactivity was excreted through bile ($19.63\% \pm 4.57\%$), urine ($15.89\% \pm 1.40\%$), and feces ($4.62\% \pm 2.63\%$), respectively. Based on the above results, [3H]-SHR-A1811 was mainly excreted in feces through bile, and a small amount was excreted through urine in rats.

5.3.6. Pharmacokinetic Drug-Drug Interactions

5.3.6.1. Inhibitory Activity of 9106-IM-2 on Main Cytochrome P450

The purpose of this study was to determine whether 9106-IM-2 was a potential inhibitor of P450 isoforms (CYP 1A2, 2C9, 2C19, 2D6, 3A4/5, 2C8, 2B6) by co-incubating the test article and probe substrate with human liver microsomes at 37°C for 5-20 min. This non-GLP study was conducted by Center for Drug Metabolism and Pharmacokinetics Research/Shanghai Institute of *Materia Medica*, Chinese Academy of Sciences in 2019.

Recombinant cytochrome P450 isozymes CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, CYP 3A4/5, CYP 2C8 and CYP 2B6 were incubated with selective substrates and 9106-IM-2 up to 100 μM . The rates of metabolism for the selective substrate were determined,

based on which IC₅₀ was calculated.

IC₅₀ of 9106-IM-2 was > 100 µM for all CYP isoforms, the result revealed that no inhibitory effect of 9106-IM-2 on cytochrome P450 isozymes was observed.

5.3.6.2. Direct and time-dependent inhibitory effects of 9106-IM-2 on major CYP enzymes

The direct and time-dependent inhibitory effects of 9106-IM-2 on specific cytochrome P450 enzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A in human liver microsomes were evaluated using the human liver microsome model. At the test concentration of 5 µM, the inhibition percentages of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A (midazolam and testosterone as substrates) by the direct inhibitory effect of 9106-IM-2 were 9.20%, 3.49%, -0.182%, 8.36%, 4.33%, 2.94%, -4.15%, and 3.69%, respectively. 9106-IM-2 had no time-dependent inhibition potential against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A (midazolam and testosterone as substrates). There was no significant difference between pre-incubation with and without NADPH, and the percentage of TDI was less than 20%. The results suggested that at the test concentration of 5 µM, 9106-IM-2 had no direct or time-dependent inhibition potential on the above cytochrome P450 enzymes.

5.3.6.3. *In Vitro* Inductive Activity of 9106-IM-2 on Cytochrome CYP 1A2, 2B6 and 3A4

The purpose of this study was to determine whether 9106-IM-2 had potential induction on cytochromes P450 1A2, 2B6 and 3A4 in primary human hepatocyte cultures. This non-GLP study was conducted by Center for Drug Metabolism and Pharmacokinetics Research/Shanghai Institute of *Materia Medica*, Chinese Academy of Sciences in 2019.

Three batches of primary human hepatocytes were incubated with 0, 0.005, 0.05 and 0.5 µM 9106-IM-2 for 72 hrs. The mRNA levels of CYP 1A2, 2B6 and 3A4 were determined by RT-PCR and the induction fold compared to the negative control was calculated.

Incubation with 9106-IM-2 resulted in decrease in mRNA levels of enzyme with extents less than 20% of that induced by the positive control, indicating that 9106-IM-2 did not induce cytochrome P450s in this study.

5.3.6.4. Study on the substrate potential and inhibitory effect of 9106-IM-2 on P-gp and BCRP

In this study, the Caco-2 cell model was used to evaluate whether 9106-IM-2 was a substrate and inhibitor of the efflux transporters multidrug resistance protein 1 (P-gp) and breast cancer resistance protein (BCRP). The results showed that 9106-IM-2 was a substrate of P-gp but not a substrate of BCRP. 9106-IM-2 had no inhibitory effect on P-gp or BCRP.

5.3.6.5. Study on the substrate potential and inhibitory effect of 9106-IM-2

The potential of 9106-IM-2 as a substrate of BSEP and its inhibitory effect on BSEP were investigated in the Sf9 vesicle system expressing the human BSEP gene. The

results showed that with 9106-IM-2 at the concentrations of 0.05, 0.5, and 1.5 μM , the uptake ratios of ATP (-/+ inhibitor) were -0.786, 1.16, and -1.71, respectively, and the uptake ratios of ATP (-inhibitor)/AMP (-inhibitor) were 1.27, 1.50, and 1.12, respectively, all of which were < 2 , suggesting that 9106-IM-2 was not a substrate of BSEP. In addition, 9106-IM-2 at a concentration of 1 μM had no inhibitory effect on BSEP-mediated transport of taurocholate.

5.3.6.6. Study on the substrate potential and inhibitory effect of 9106-IM-2 on SLC transporters

The substrate potential of 9106-IM-2 for some SLC transporters (OATP1B1 and OATP1B3) was investigated in HEK293 cell lines overexpressing SLC transporters, and its inhibitory effect on most SLC transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K) was evaluated.

In the substrate potential assay, the uptake ratio of 9106-IM-2 in HEK293 cell lines overexpressing OATP1B1 and OATP1B3 was > 2 , and the inhibition rate was $> 50\%$ after adding the corresponding inhibitors, suggesting that 9106-IM-2 was a substrate of transporters OATP1B1 and OATP1B3.

In the inhibition assay, 1 μM 9106-IM-2 inhibited the transport of 4-aminohippuric acid mediated by transporter OAT1 by 71.3%, the transport of estrone-3-sulfate mediated by transporter OAT3 by 6.53%, the transport of metformin mediated by transporter OCT1 by -4.50%, the transport of metformin mediated by transporter OCT2 by 10.8%, the transport of β -estradiol 17-(β -D-glucuronide) mediated by transporter OATP1B1 by 27.9%, the transport of β -estradiol 17-(β -D-glucuronide) mediated by transporter OATP1B3 by 3.64%, the transport of tetraethylamine mediated by transporter MATE1 by 17.1%, and the transport of tetraethylamine mediated by transporter MATE2-K by 8.94%. Further studies showed that within the test concentration range of 0.005-1.5 μM , the IC_{50} value of 9106-IM-2 for inhibiting the transport of 4-aminohippuric acid mediated by transporter OAT1 was 0.627 μM , and the maximum inhibition percentage was 60.7%.

5.3.7. Other Pharmacokinetic Studies

5.3.7.1. *In vitro* Plasma Stability of SHR-A1811

The purpose of this study was to investigate the *in vitro* stability of SHR-A1811 in SD rat, Cynomolgus monkey and human plasma by incubation. This non-GLP study was conducted by Center for Drug Metabolism and Pharmacokinetics Research/ Shanghai Institute of Materia Medica, Chinese Academy of Sciences (SIMM) in 2019.

The final incubation concentration of SHR-A1811 was 500-50000 ng/mL and the concentration of 9106-IM-2 was measured by LC-MS/MS after 7 days incubation at 37°C. The results showed that 9106-IM-2 in SD rat, Cynomolgus monkey and human plasma was 0.21%, 1.43% and 1.09%, which indicated that SHR-A1811 was very stable in plasma *in vitro*.

5.4. Toxicology**Table 16 Overview of Toxicology Studies for SHR-A1811**

Study Items		Dosage (mg/kg)	Dosing regimen	Main results
Single-dose toxicity in Cyno monkeys		50, 75	Single	MTD = 75 mg/kg
Repeat-dose toxicity in Cyno monkeys		3, 10, 40	Q3W * 3	HNSTD = 40 mg/kg
Repeat-dose toxicity in Cyno monkeys		3, 10, 40	Q3W * 5	HNSTD = 40 mg/kg
Immunogenicity in Cyno monkeys during repeat-dose toxicity study		3, 10, 40	Q3W * 3	10% (1/10) and 20% (2/10) in middle and high dose groups.
Embryo-fetal developmental toxicity study in SD rats		20, 60, 200	GD6, GD13	The NOAEL of SHR-A1811 for embryo-fetal developmental toxicity was less than 20 mg/kg
Tissue-Cross Reaction in Human		2.5, 20 µg/mL	/	Similar pattern with naked antibody.
Formulation toxicity	Hemolysis in vitro	5 mg/mL	/	Negative
	Local tolerance	3, 10, 40	Q3W * 3	Negative
	Vascular irritation test in Japanese rabbits	20	Single dose	Negative

Table 17 Overview of Toxicology Studies for 9106-IM-2

Study Items		Dosage (mg/kg)	Dosing regimen	Main results
Single-dose toxicity	SD rats	2, 4	Single dose	MTD = 4 mg/kg
	Cyno monkeys	1.5	Single dose	MTD = 1.5 mg/kg
Repeat-dose toxicity	4-week in SD rats	0.1, 0.3, 0.6/1.0	QW * 5	STD ₁₀ = 0.6 mg/kg
	13-week in SD rats	0.3, 0.6	Q3W * 13	HNSTD = 0.6 mg/kg
	6-week in cyno monkeys	0.8	Q3W * 3	HNSTD = 0.8 mg/kg
Genotoxicity	CHL	0.5, 1.5, 5, 15 µg/mL	/	Positive
	Ames	50, 150, 500, 1500, 5000 µg/plate	/	Negative
	Rat Bone Marrow Micronucleus	0.1, 0.3, 0.6/1.0	QW * 5	Positive
<i>In vitro</i> phototoxicity	3T3 cells	0.006-20.000 µg/mL	/	9106-IM-2 was predicted to be "phototoxic" within the test concentration range
<i>In vivo</i> phototoxicity	BN rats	0.3, 0.6	/	After a single intravenous injection of 9106-IM-2 in BN rats, no phototoxic reaction was observed after exposure to ultraviolet light.

5.4.1. Single-Dose Toxicity Studies

5.4.1.1. Single-Dose Toxicity Study in Cynomolgus Monkeys

The objective of this study was to evaluate the potential toxicity of SHR-A1811 and to compare its toxicity with 9106-IM-2 in Cynomolgus monkeys after a single IV injection, followed by a 3-week observation period. This GLP study was conducted by West China-Frontier Pharma Tech Co., Ltd in 2019.

Monkeys were randomly assigned to 4 groups and intravenously infused with negative control (0.9% NaCl injection), vehicle control (10%SBE-β-CD containing

1.5%DMSO), 9106-IM-2 at 1.5 mg/kg (with content of 9106-IM-2 equivalent to that in 75 mg/kg SHR-A1811), and SHR-A1811 at 50 and 75 mg/kg. Each group was composed of 3 monkeys (including female and male). The dose volume was 15 mL/kg. All animals were infused with a single dose.

No drug-related mortality or moribundity was observed during the whole study. One male monkey in the 75 mg/kg group of SHR-A1811 was observed successively yellow watery stool, emaciation, bow back and activity reduction; body weight continued to reduce, and the food intake decreased temporarily; WBC (NEU) increased, RET, RET% decreased; ALT, Urea, Crea, K⁺ increased and ALB, TP, Na⁺, Cl⁻, A/G decreased. The thymus volume of 9106-IM-2 group (1 monkey, 1/3) and SHR-A1811 75 mg/kg group (2 monkeys, 2/3) was decreased. Histopathological examination showed moderate lymphopenia in 9106-IM-2 group and severe lymphopenia in SHR-A1811 75 mg/kg group.

In addition, during the 3-week observation, monkeys in 9106-IM-2 group and SHR-A1811 group were no abnormalities in the general state, skin, hair, and with normal automatic activity. No abnormalities were observed in lead II ECG, blood pressure, hematological and biochemical examinations.

Based on these findings, the maximum tolerance dose (MTD) for 9106-IM-2 was 1.5 mg/kg, and for SHR-A1811 was 75 mg/kg, respectively.

5.4.1.2. Single-Dose Toxicity Study in Sprague Dawley Rats

The purpose of this study was to evaluate the potential toxicity of SHR-A1811 and to compare its toxicity with that of 9106-IM-2, in SD rats after a single IV injection, followed by a 14-day observation phase. This GLP study was conducted by West China-Frontier Pharma Tech Co., Ltd in 2019.

Rats were randomly assigned to 4 groups and intravenously injected with negative control (0.9% NaCl injection), vehicle control (10%SBE-β-CD containing 1.5%DMSO), 9106-IM-2 at 2 and 4 mg/kg. Each group was composed of 10 rats (5/sex). The dose volume was 40 mL/kg. All animals were administered with a single dose, followed by a 14-day observation phase.

Except for the increase of RET and RET% in each group of male rats, no obvious abnormal changes were observed. The maximum tolerance dose (MTD) for 9106-IM-2 was 4 mg/kg.

5.4.2. Repeat-Dose Toxicity

5.4.2.1. 6-Week Repeat-Dose Toxicity Study in Cynomolgus Monkeys

The objective of this study was to evaluate the potential toxicity, immunogenicity and immunotoxicity, to identify the target organs/tissues, and to provide toxicokinetics (TK) profiles after once every three weeks of IV infusion of SHR-A1811 in Cynomolgus monkeys for consecutively 3 doses, followed by a 4-week recovery phase. 9106-IM-2 was also included to compare their toxicity with that of SHR-A1811. This GLP study was conducted by West China-Frontier Pharma Tech Co., Ltd in 2019.

Monkeys were randomly assigned to 6 groups with 5 monkeys/sex per group, including

negative control, vehicle control, 9106-IM-2 0.8 mg/kg group (equivalent to the drug-loading capacity in SHR-A1811 40 mg/kg) and SHR-A1811 3, 10, 40 mg/kg groups. Animals in negative control and SHR-A1811 groups were intravenously injected with 0.9%NaCl injection or SHR-A1811 dose formulations at corresponding concentrations at a volume of 10 mL/kg, while animals in vehicle control and 9106-IM-2 groups were intravenously injected with vehicle control article (10%SBE- β -CD containing 1.5%DMSO) or 9106-IM-2 dose formulation at a volume of 8 mL/kg. They were administered once every three weeks for 6 consecutive weeks (3 doses in total) followed by a 4-week recovery phase. The first dosing day was defined as Day 1.

Clinical signs were observed daily in the dosing and recovery phases. Body weight and food consumption were recorded once a week in the dosing and recovery phases. Body temperature was measured at 2 and 24 hr after the 1st, 2nd, 3rd dosing and then at the end of recovery phase. Lead II ECG, blood pressure and respiratory rate were examined at predose and 2, 24, 72, 144, 312, 480 hr postdose of the 1st dosing, 2 hr postdose of the 3rd dosing and at the end of recovery phase. Ocular exam and urinalysis were conducted at the end of dosing and recovery phases. Blood samples were collected at the 6th and 20th day after the 2nd dosing, the 6th day after the 3rd dosing and at the end of recovery phase for the determination of hematology, clinical chemistry, immunoglobulin, complement, circulating immune complex and T lymphocyte subsets. Cytokines examination was performed at 1 and 24 hr postdose of the 1st dosing, 1 hr postdose of the 3rd dosing and at the end of recovery phase. Anti-drug antibody was determined on Day 14, 21 and 42 (14 days after the 1st dosing, at predose of the 2nd and 3rd dosing, respectively), at the day of dosing and recovery phase necropsies. Scheduled necropsy was conducted on 3 monkeys/sex/group at the end of dosing phase and on 2 monkeys/sex/group at the end of recovery phase. Animals were anesthetized, sampled for bone marrow smears, euthanatized for gross necropsy, organ weight measurement and histopathology examination.

Blood samples from animals in 9106-IM-2 and SHR-A1811 groups were collected at predose, 5 min after the administration beginning, immediately at the administration end (0-1 min postdose), then 4, 8, 24, 48, 96, 144, 312, 480 hr postdose of the first and last dosing. LC-MS/MS method was used for the determination of 9106-IM-2 concentration at each time point. ELISA method was used to determine the concentrations of SHR-A1811 and total antibody. TK parameters (including AUC_{0-t}, C_{max} and T_{max}) were also calculated.

Results

Clinical Observation: No mortality or moribundity was observed in each group during the dosing and recovery phases. There were no abnormalities in general status, spontaneous movement, skin, hair, feces, urine, or toxic signs observed.

Body Weight and Food Consumption: During the dosing phase, a slightly decreasing trend in body weight was observed in male monkeys of SHR-A1811 40 mg/kg group, which could recovery after the drug-withdrawal.

During the dosing and recovery phases, no abnormality in body weight was observed in the rest groups or in female monkeys of SHR-A1811 40 mg/kg group, and no abnormality in food consumption was observed in each group.

Body Temperature (Rectal Temperature), Lead II ECG and Blood Pressure: No abnormality in the body temperature was observed in each group at 2 and 24 hr postdose of the 1st, 2nd, 3rd dosing and at the end of recovery phase.

No arrhythmia in lead II ECG was observed in each group at 2, 24, 72, 144, 312, 480 hr after the 1st dosing, 2 hr after the last dosing, and at the end of recovery phase. And no abnormality was observed in heart rate, RR interval, P duration, PR interval, QRS duration, QT interval, QTcB, systolic pressure, diastolic pressure, mean arterial pressure or respiratory rate.

Hematology: At the 6th day after the 2nd dosing, monkeys administered with 9106-IM-2 were observed with decreased RET and RET%, and the female monkeys were additionally noted with decreased LYM; monkeys in SHR-A1811 40 mg/kg group were noted with decreased LYM, BASO, RET and RET%, while the female monkeys were additionally observed with decreased BASO%; monkeys at 10 mg/kg were found with decreased LYM, and BASO; the female monkeys at 3 mg/kg were noted with decreased LYM.

At the 20th day after the 2nd dosing, female monkeys administered with 9106-IM-2 were noted with decreased LYM and increased WBC, NEU, NEU%; monkeys in SHR-A1811 40 mg/kg group were observed with decreased LYM, LYM%, RBC, HGB and increased WBC, NEU, NEU%, RET, RET%; changes in LYM, WBC and NEU with slighter degree were found in SHR-A1811 10 mg/kg group and in the females at 3 mg/kg.

At the 6th day after the 3rd dosing, monkeys in 9106-IM-2 group were observed with decreased RET and RET%, while the females were additionally noted with decreased WBC, NEU, NEU%, LYM, RBC, HGB; monkeys in SHR-A1811 40 mg/kg group were observed with decreased WBC, LYM, BASO, RBC, HGB, and the females were additionally observed with decreased EOS, NEU%, RET, RET%; monkeys in SHR-A1811 10 mg/kg group were noted with decreased WBC, LYM, BASO, and the females were additionally observed with decreased EOS, NEU%, RBC, HGB. Slightly decreased WBC, NEU, LYM, RBC and HGB were observed in female monkeys at 3 mg/kg.

No abnormality in the rest hematology parameters was observed in each group at the 6th and 20th day after the 2nd dosing, and at the 6th day after the 3rd dosing. At the end of recovery phase, no abnormality in the hematology parameters was noted in each group, except for LYM in females administered with SHR-A1811 was still slightly lower than the negative control.

Clinical Chemistry: At each postdose time point and the end of recovery phase, there was no abnormality in AST, ALT, LDH, CK, CK-MB, ALP, GGT, Urea, Crea, UA, TP, ALB, A/G, TBIL, TG, CHOL, GLU, AMY-P, LIPC, Na⁺, K⁺, Cl⁻, Ca or P of monkeys in vehicle control group, 9106-IM-2 group and SHR-A1811 groups.

Immunological Parameters: There was no abnormality in immunoglobulin (IgG, IgA, IgM), complement (C3, C4) and circulating immune complex (CIC) of monkeys in each group at the 6th and 20th day after the 2nd dosing, the 6th day after the 3rd dosing and the end of recovery phase.

At the 20th day after the 2nd dosing, a slightly decreasing trend in the percentages of CD45⁺CD3⁺, CD45⁺CD3⁺CD4⁺ and CD45⁺CD3⁺CD8⁺ T lymphocyte subsets for female monkeys administered with SHR-A1811, which had recovered at the end of recovery phase.

There was no abnormality in T lymphocyte subsets of monkeys in vehicle control group, 9106-IM-2 group and that of male monkeys administered with SHR-A1811 at the 6th and 20th day after the 2nd dosing, the 6th day after the 3rd dosing and the end of recovery phase.

Cytokines: No abnormality in IL-2, IL-6, IL-10, TNF- α or IFN- γ was observed in vehicle control group, 9106-IM-2 group and SHR-A1811 groups at 1 and 24 hr after the first dosing, 1 hr after the last dosing and the end of recovery phase.

Urinalysis: There was no abnormality in urinary color, clarity, GLU, BIL, SG, KET, BLO, pH, URO, PRO, WBC or NIT of monkeys in vehicle control group, 9106-IM-2 group and SHR-A1811 groups at the end of dosing and recovery phases.

Ocular Exam: At the end of dosing and recovery phases, monkeys in each group were noted with no abnormality in retina, optic disk, cornea, iris, lens, posterior chamber and anterior chamber. The dioptric media, optic papilla and macula lutea were clear. The macular arch structure was normal. The diameter of retinal artery was even and veins were with no dilation and tortuosity.

Bone Marrow Smears: At the end of dosing and recovery phases, there was no abnormality in granulocytic series and its differentials (%), erythrocytic series and its differentials (%), lymphocyte (%), monocyte (%), other cells (%), megakaryocyte count and nucleated cell proliferation of monkeys in vehicle control group, 9106-IM-2 group and SHR-A1811 groups. The cell morphology was generally normal.

Organ Weight and Ratios: At the end of dosing phase, decreased organ weight and ratios of thymus were observed in SHR-A1811 40 mg/kg group, which was unobserved at the end of recovery phase.

There was no abnormality in the organ weight and ratios of brain, heart, thymus, liver, adrenal gland, spleen, testes, epididymides, uterus, thyroid gland and parathyroid gland of monkeys in the rest groups at the end of dosing and recovery phases.

Gross Necropsy: At the end of dosing phase, decreased size of thymus was observed in most monkeys (5/6, 2 males and 3 females) of SHR-A1811 40 mg/kg group, which was unobserved at the end of recovery phase.

No drug-related abnormalities in the size, morphology, color or texture were observed in brain, heart, liver, thymus, spleen, lung, kidney, adrenal gland, thyroid gland and parathyroid gland, gastrointestinal tract and reproductive system of monkeys in the rest groups at the end of dosing and recovery phases.

Histopathology: At the end of dosing phase, mild to marked decreased number of cortical lymphocytes of the thymus was noted in SHR-A1811 40 mg/kg group, which was unobserved at the end of recovery phase.

No drug-related pathological alterations were observed in the brain, heart, thymus, liver,

spleen, lung, kidney, adrenal gland, thyroid gland and parathyroid gland, gastrointestinal tract and reproductive system of monkeys in the rest groups at the end of dosing and recovery phases.

ADA: Anti-SHR-A1811 antibody was detected in 1 (1/10) and 2 (2/10) monkeys in SHR-A1811 10 and 40 mg/kg groups, respectively, with the first occurrence on Day 42 (at predose of the 3rd dosing) and Day 21 (at predose of the 2nd dosing). At the end of recovery phase, anti-SHR-A1811 antibody was detected in 1 (1/10) monkey at 40 mg/kg. No ADA was observed in 3 mg/kg group during the dosing and recovery phases.

Toxicokinetics: Cynomolgus monkeys were intravenously injected with SHR-A1811 at 3, 10 and 40 mg/kg (dosage ratio: 1:3.3:13.3). Critical TK parameters including T_{max} , C_{max} and AUC were calculated and shown in the [Table 18](#) to [Table 20](#).

After the first dosing, the mean AUC_{0-144h} of SHR-A1811 in the serum was 3820, 15800 and 50400 h·µg/mL for male monkeys, and the mean AUC_{0-480h} was 5340, 28800 and 92700 h·µg/mL, with the between-group ratio of 1: 5.4: 17.4; the mean AUC_{0-144h} of total antibody in the serum was 3470, 15300 and 48400 h·µg/mL, and the mean AUC_{0-480h} was 4680, 26800 and 86700 h·µg/mL, with the between-group ratio of 1: 5.7: 18.5; the mean AUC_{0-144h} of 9106-IM-2 in the plasma was 5.60, 25.3, 114 h·ng/mL, and the mean AUC_{0-480h} was 5.60, 33.8 and 151 h·ng/mL, with the between-group ratio of 1: 6.0: 27.0. The mean AUC_{0-144h} of SHR-A1811 in the serum was 3850, 12800 and 55300 h·µg/mL for female monkeys, and the mean AUC_{0-480h} was 5480, 22300 and 99500 h·µg/mL, with the between-group ratio of 1: 4.1: 18.2; the mean AUC_{0-144h} of total antibody in the serum was 3820, 15900 and 54900 h·µg/mL, and the mean AUC_{0-480h} was 5440, 27500 and 101000 h·µg/mL, with the between-group ratio of 1: 5.1: 18.6; the mean AUC_{0-144h} of 9106-IM-2 in the plasma was 3.16, 30.7 and 106 h·ng/mL, and the mean AUC_{0-480h} was 3.16, 39.7 and 140 h·ng/mL, with the between-group ratio of 1: 12.6: 44.3. Comparing the female monkeys with the male monkeys, the mean AUC_{0-480h} ratio (female/male) of SHR-A1811 was 1.0, 0.8 and 1.1, and the mean AUC_{0-480h} ratio of total antibody was 1.2, 1.0 and 1.2, and the mean AUC_{0-480h} ratio of 9106-IM-2 was 0.6, 1.2 and 0.9, respectively.

After the last dosing, the mean AUC_{0-144h} of SHR-A1811 in the serum was 4630, 23000 and 81000 h·µg/mL for male monkeys, with the between-group ratio of 1: 5.0: 17.5; the mean AUC_{0-144h} of total antibody in the serum was 4140, 20900 and 75700 h·µg/mL, with the between-group ratio of 1: 5.0: 18.3; the mean AUC_{0-144h} of 9106-IM-2 in the plasma was 6.56, 29.0 and 124 h·ng/mL, with the between-group ratio of 1: 4.4: 18.9. The mean AUC_{0-144h} of SHR-A1811 in the serum was 4470, 19900 and 75300 h·µg/mL for female monkeys, with the between-group ratio of 1: 4.5: 16.8; the mean AUC_{0-144h} of total antibody in the serum was 4250, 18400 and 73500 h·µg/mL, with the between-group ratio of 1: 4.3: 17.3; the mean AUC_{0-144h} of 9106-IM-2 in the plasma was 4.52, 33.8 and 104 h·ng/mL, with the between-group ratio of 1: 7.5: 23.0. Comparing the female monkeys with the male monkeys, the mean AUC_{0-144h} ratio (female/male) of SHR-A1811 was 1.0, 0.9 and 0.9, the mean AUC_{0-144h} ratio of total antibody was 1.0, 0.9 and 1.0, and the mean AUC_{0-144h} ratio of 9106-IM-2 was 0.7, 1.2 and 0.8, respectively.

When compared the last dosing with the first dosing, the mean of individual AUC_{0-144h} ratio for SHR-A1811 was 1.2, 1.5, 1.7 (male) and 1.2, 1.5, 1.4 (female), respectively; the mean of individual AUC_{0-144h} ratio for total antibody was 1.2, 1.4, 1.6 (male) and

1.1, 1.2, 1.4 (female), respectively; the mean of individual AUC_{0-144h} ratio for 9106-IM-2 was 1.2, 1.1, 1.1 (male) and 1.4, 1.1, 1.0 (female), respectively.

Cynomolgus monkeys were intravenously injected with 9106-IM-2 at 0.8 mg/kg. After the first dosing, the mean AUC_{0-144h} of 9106-IM-2 in the plasma was 1510 h·ng/mL for males and 1540 h·ng/mL for females, with the ratio (female/male) of 1.0. After the last dosing, the mean AUC_{0-144h} of 9106-IM-2 in the plasma was 1410 h·ng/mL for males and 1770 h·ng/mL for females, with the ratio (female/male) of 1.3. The mean individual AUC_{0-144h} ratio of the last dosing to the first dosing for 9106-IM-2 in monkey plasma was 1.0 for males and 1.2 for females.

The above results suggested the exposure of SHR-A1811 and total antibody in serum, as well as the plasma 9106-IM-2 exposure had no gender difference for monkeys over the dose range from 3 to 40 mg/kg. The exposure of SHR-A1811 and total antibody in serum, as well as the plasma 9106-IM-2 exposure for males increased basically dose-proportionally over the dose range from 3 to 40 mg/kg. For female monkeys, the plasma 9106-IM-2 exposure increased more than the dose-proportionality over the dose range from 3 to 10 mg/kg, while basically dose-proportionally over the dose range from 10 to 40 mg/kg. No apparent accumulation of SHR-A1811, total antibody or 9106-IM-2 was noted when monkeys were administered once every three weeks in 6 consecutive weeks (3 doses in total). When Cynomolgus monkeys were intravenously injected with 9106-IM-2 at 0.8 mg/kg, the plasma 9106-IM-2 exposure had no gender difference for monkeys. No apparent accumulation of 9106-IM-2 was noted when monkeys were administered once every three weeks in 6 consecutive weeks (3 doses in total).

Conclusion

Cynomolgus monkeys were intravenously injected with 9106-IM-2 at 0.8 mg/kg and SHR-A1811 at 3, 10, 40 mg/kg once every 3 weeks for 6 consecutive weeks followed by a 4-week recovery phase. The major toxicity of monkeys in SHR-A1811 40 mg/kg group was characterized as decreased number of cortical lymphocytes of the thymus and decreased LYM, NEU, RBC, RET. The hematology changes with slighter degree were observed in 9106-IM-2 0.8 mg/kg group, but the pathological alteration in thymus was not noted. The hematology changes with slighter degree were also observed in SHR-A1811 3 and 10 mg/kg groups. The above lesions had apparently recovered or were unobserved after the 4-week drug-withdrawal.

Some monkeys in SHR-A1811 10 and 40 mg/kg groups were detected with ADA from Day 21, suggesting certain immunogenicity was induced in monkeys.

Over the dose range from 3 to 40 mg/kg, the exposure of SHR-A1811 and total antibody in serum, as well as the plasma 9106-IM-2 exposure had no gender difference for monkeys; the exposure of SHR-A1811 and total antibody in serum, as well as the plasma 9106-IM-2 exposure for males increased basically dose-proportionally, while the plasma 9106-IM-2 exposure for females increased more than the dose-proportionality. No apparent accumulation of SHR-A1811 was observed after the 6-week repeated dosing (3 doses in total). When Cynomolgus monkeys were intravenously injected with 9106-IM-2 at 0.8 mg/kg, the plasma 9106-IM-2 exposure had no gender difference for monkeys. No apparent accumulation of 9106-IM-2 was noted after the 6-week repeated dosing (3 doses in total).

When Cynomolgus monkeys were intravenously injected with SHR-A1811 for 6 consecutive weeks (3 doses in total), the highest non-severely toxic dose (HNSTD) was 40 mg/kg (the AUC_{0-480h} of SHR-A1811 in serum was 114000, 176000 h·µg/mL, the total antibody was 121000, 158000 h·µg/mL, and the plasma 9106-IM-2 was 151, 188 h·ng/mL for females and males, respectively).

Table 18 Toxicokinetics parameters of ADC in Cynomolgus Monkeys After IV Infusion of SHR-A1811

Dosage (mg/kg)	Dosing period	AUC _{0-144h} (h·µg/mL)				AUC _{0-480h} (h·µg/mL)				C _{max} (µg/mL)				T _{max} (h)	
		Female		male		Female		male		Female		male		Female	male
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Median	median
3	1	3850	780	3820	332	5480	1570	5340	606	70.2	2.74	72.8	4.72	0.017	0.017
	43	4470	783	4630	704	9230	-	7980	-	84.1	9.10	88.0	16.2	0.017	0.017
10	1	12800	1100	15800	1870	22300	3420	28800	4390	219	15.0	237	27.9	0.017	0.017
	43	19900	4480	23000	4620	31000	-	35800	-	292	41.2	323	58.0	0.017	0.017
40	1	55300	2880	50400	9600	99500	7770	92700	24200	896	78.6	911	97.9	0.017	0.017
	43	75300	14600	81000	6830	114000	-	176000	-	1050	98.2	1270	239	0.017	0.017

Note: - means not available; 0.017 h means the time point of dosing finished; * means the animal number for AUC_{0-480h} calculation of last dosing is 2, no standard deviation.

Table 19 Toxicokinetics Parameters of TA in Cynomolgus Monkeys After IV Infusion of SHR-A1811

Dosage (mg/kg)	Dosing period	AUC _{0-144h} (h·µg/mL)				AUC _{0-480h} (h·µg/mL)				C _{max} (µg/mL)				T _{max} (h)	
		Female		male		Female		male		Female		male		Female	male
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Median	median
3	1	3820	417	3470	307	5440	825	4680	461	72.8	13.1	68.7	10.5	0.017	0.017
	43	4250	748	4140	625	8200	-	6940	-	77.7	4.70	80.8	14.8	0.017	0.017
10	1	15900	3040	15300	1590	27500	7360	26800	3390	243	7.92	249	27.0	0.017	0.017
	43	18400	3380	20900	2080	29900	-	36300	-	283	32.9	300	28.6	0.017	0.017
40	1	54900	2240	48400	11000	101000	8010	86700	24300	896	150	938	127	0.017	0.017
	43	73500	12400	75700	7730	121000	-	158000	-	1060	117	1190	202	0.017	0.017

Note: - means not available; 0.017 h means the time point of dosing finished; * means the animal number for AUC_{0-480h} calculation of last dosing is 2, no standard deviation.

Table 20 Toxicokinetics Parameters of 9106-IM-2 in Cynomolgus Monkeys After IV Infusion of SHR-A1811 or 9106-IM-2

Dosage (mg/kg)	Dosing period	AUC _{0-144h} (h·µg/mL)				AUC _{0-480h} (h·µg/mL)				C _{max} (µg/mL)				T _{max} (h)	
		Female		male		Female		male		Female		male		Female	male
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Median	median
0.8 (9106-IM-2)	1	1540	281	1510	326	1540	281	1510	326	679	123	667	146	0.017	0.017
	43	1770	292	1410	479	2010	-	1440	-	792	134	642	184	0.017	0.017
3	1	3.16	0.263	5.60	1.99	3.16	0.263	5.60	1.99	0.190	0.0276	0.230	0.0275	0.017	0.017
	43	4.52	1.54	6.56	3.34	5.14	-	7.35	-	0.280	0.0616	0.285	0.0215	0.017	0.017
10	1	30.7	7.65	25.3	2.95	39.7	8.84	33.8	2.02	1.02	0.145	0.932	0.238	0.017	0.017
	43	33.8	9.59	29.0	4.13	40.8	-	40.6	-	1.17	0.237	0.957	0.165	0.017	0.017
40	1	106	12.2	114	17.1	140	16.9	151	27.6	3.23	0.356	3.99	0.142	0.017	0.017
	43	104	11.5	124	14.1	151	-	188	-	3.29	0.261	3.99	0.539	0.017	0.017

Note: - means not available; 0.017 h means the time point of dosing finished; * means the animal number for AUC_{0-480h} calculation of last dosing is 2, no standard deviation.

5.4.2.2. 13-Week Repeat-Dose Toxicity Study in Cynomolgus Monkeys

The purpose of this study was to evaluate the potential toxicity and toxicokinetics profile of SHR-A1811 after 13-weeks of intravenous injection of SHR-A1811 to cynomolgus monkeys, and to identify target organs/tissues and the reversibility of the toxicity after the 4-week recovery phase. A total of 40 cynomolgus monkeys, half/sex, were randomly assigned into 4 groups and given with SHR-A1811 at 0 (0.9% NaCl injection), 3, 10 and 40 mg/kg (10 mL/kg) by intravenous injection once every 3 weeks for consecutively 5 doses, followed by a 4-week recovery phase.

After initiation of dosing, all animals were observed for mortality or moribundity once daily. All animals were observed for clinical signs starting nine days prior to dosing, and twice daily during the dosing and recovery periods. The animals were weighed twice during the acclimation period and once a week during the dosing and recovery periods. All animals were observed for food intake once daily from 9 days prior to dosing to the end of the recovery period (urine collection day and grouping day with withdrawal only). Electrocardiograms, and ophthalmologic examinations were performed before dosing (acclimation period), at the end of the dosing period, and at the end of the recovery period. Blood was collected for toxicokinetic studies at D1-D22, D64-D85, D105, and D119. Blood was collected for immunogenicity testing at D1, D14, D22, D43, D78, D91, D105, and D119. Blood was collected from all animals for hematological, coagulation, serum biochemistry and immune function (D42 and D84 only) during the acclimation period (2 times, of which only 1 time was performed during the immune function acclimation period), the mid-dosing period (D28, D42, D70 and D84), the end-dosing period (D91) and the recovery period (D119). Urine was collected for urinalysis and bone marrow smears were collected at the end of the acclimation, dosing and recovery periods (except for the acclimation period). The smears were not read under light microscopy because the clinical pathology and histopathology did not reveal any effect of the product on the hematopoietic system of the animals. At the end of the dosing period and the end of the recovery period, planned dissection was performed, organs were collected, major organs were weighed and organ coefficients were calculated, and organs and tissues of all animals (including injection sites) were examined histopathologically. Some kidney tissues were taken for microscopic observation of circulating immune complexes.

During the experimental period, no mortality or moribundity was observed, no abnormality of body weight, food intake, clinical observation, body temperature, ophthalmology, electrocardiogram (lead II), coagulation function, serum biochemistry, immune function, urine and fecal examination, gross anatomy, or renal immune complexes was observed.

A decrease in RET and RET% was observed in both male and female animals in the high dose group at mid-dose and at the end of the dosing period. The abnormality was found recovered during the recovery period.

Toxicokinetics: The gender difference (higher in males than females) for 9106-IM-2 plasma exposure ($AUC_{(0-t)}$) was observed in low and mid dose group after the first dose administration, as well as in the low dose group after the last dose administration. Except for the above, there was no significant gender difference for exposure levels ($AUC_{(0-t)}$ and C_{max}) was observed across different dose levels. After the first administration, the increase of $AUC_{(0-t)}$ of 9106-IM-2 in plasma of both male and

female animals in all dose groups was higher than the proportional increase of dose level. The increase of $C_{\max}$ of 9106-IM-2 in plasma of female animals was proportional to the increase of dose level, and the increase of $C_{\max}$ of 9106-IM-2 in plasma of male animals was lower than the proportional increase of dose. For ADC, the increase of $AUC_{(0-t)}$ and $C_{\max}$ of ADC in serum of both male and female animals in each dose group was proportional to the dose increase. For total antibody, the increase of $AUC_{(0-t)}$ in serum of female animals and $C_{\max}$ of both male and female animals in each dose group was proportional to the dose increase, but the increase of $AUC_{(0-t)}$ of total antibody in serum of male animals was higher than the dose increase ratio. After the last dose administration, the increase in $AUC_{(0-t)}$ of plasma 9106-IM-2 and serum ADC and total antibody in all dose groups of animals was higher than the dose increase ratio, and the increase in $C_{\max}$ of plasma 9106-IM-2 and serum ADC and total antibody in all dose groups of animals was proportional to the dose increase. After 13 weeks of repeated administration, no significant accumulation of 9106-IM-2 in plasma and ADC and total antibody in serum exposure ($AUC_{(0-t)}$ and $C_{\max}$) was observed in male and female animals of all dose groups. Anti-drug antibodies (ADA) had no significant impact on the exposure.

Immunogenicity: The ADA positive ratio was 2/10, 1/10, 2/10 and 0/10 in vehicle group, low dose group, mid dose group and high dose group, respectively.

Histopathology examination: Compared with the vehicle group, the absolute and relative weight (organ/brain ratio) of the thymus decreased in male animals in high-dose group at the end of dosing period. The gross necropsy showed the decreased size of thymus was observed in one male animal in the high-dose group. Histopathological examination at the end of the dosing period showed mild to moderate lymphocytopenia in the thymus of both male and female animals in the high-dose group. Based on the incidence and the degree of lesions, as well as the changes in the weight of thymus organs and the results of gross necropsy, it was concluded that the thymus lesions were related to the donor. At the end of the recovery period, all the above lesions were fully recovered.

In conclusion, the cynomolgus monkeys were given SHR-A1811 at doses of 0, 3, 10 and 40 mg/kg intravenously for 13 consecutive weeks. No mortality or moribundity was observed during the study period. A decrease in RET and RET% was observed in both male and female animals in the high-dose group at the middle and the end of the dosing period. The main target organ was defined as thymus, as mild to moderate decrease of thymic lymphocytes in both male and female animals in the high-dose group at the end of the dosing period was observed, as well as a decrease in both absolute and relative thymus weights (organ-to-body ratio and organ-to-brain ratio) in males in the high-dose group. All the above toxicities could be recovered during the recovery period. Under this study condition, the highest non-severe toxic dose (HNSTD) of SHR-A1811 was established at 40 mg/kg. The corresponding AUC_{0-t} of ADC, total antibody and 9106-IM-2 at D64 in female was 71300 h·μg/mL, 101000 h·μg/mL and 112 h·ng/mL, respectively. In male, the AUC_{0-t} of ADC, total antibody and 9106-IM-2 at D64 was 78500 h·μg/mL, 103000 h·μg/mL 166 h·ng/mL, respectively.

5.4.2.3. 4-Week Repeat-Dose Toxicity Study in SD Rats

The objective of this study was to evaluate the potential toxicity of 9106-IM-2, identify the target organs/tissues and provide toxicokinetic profiles after once-weekly intravenous injection of 9106-IM-2 for 4 consecutive weeks in SD rats. This GLP study was conducted by West China-Frontier Pharma Tech Co., Ltd in 2019.

Rats were randomly assigned to 5 groups and intravenously injected with negative control (0.9% NaCl injection), vehicle control (10%SBE- β -CD containing 1.5%DMSO), 9106-IM-2 at 0.1, 0.3, 0.6/1.0 mg/kg. Each main study group was composed of 15 rats/sex. The satellite groups were set for TK sampling, with 4 rats/sex for the control and vehicle group and 8 rats/sex for 9106-IM-2 groups. The dose volume was 10 mL/kg. All animals were intravenously injected once a week for 5 consecutive weeks (for 0.6/1.0 mg/kg group, the first 3 doses was 0.6 mg/kg, and 1.0 mg/kg for the last 2 doses), followed by a 4-week recovery phase.

No drug-related mortality or moribundity was observed during the whole study. The main toxic target organs of 9106-IM-2 were immune and hematopoietic system (cortex lymphocyte decreased, necrosis in thymus, lymphocyte decreased in lymph node, hematopoietic cell decreased, red cell percentage, medium and young red cell percentage, late red cell percentage and nucleated cell proliferation frequency distribution decreased in bone marrow, thymus weight and coefficient decreased, peripheral blood RBC, HGB, WBC, NEU, LYM decreased). All the above changes were observed in the 0.6/1.0 mg/kg group. In the 0.3 mg/kg group, the above-mentioned bone marrow, thymus and cervical lymph node lesions with light degree and low incidence were observed. In the 0.1 mg/kg group, only the weight and coefficient of thymus decreased. After 4 weeks of recovery phase, none of the above lesions were found.

In the dose range of 0.1-0.6/1.0 mg/kg, there was no significant gender difference in the exposure of 9106-IM-2 in the plasma of rats after the first and last administration; the proportion of increase in the exposure was basically the same as the proportion of increase in the dose; there was no significant accumulation of 9106-IM-2 in rats after 4 weeks of continuous administration (5 times in total). Critical TK parameters including T_{max} , C_{max} and AUC were calculated and shown in the [Table 21](#).

SD rats was injected intravenously with 9106-IM-2 for 4 weeks (5 times in total). The highest non-severe toxic dose (HNSTD) was 0.6/1.0 mg/kg. The AUC_{last} of 9106-IM-2 in the plasma of female and male rats was 333 and 399 hr·ng/mL, respectively.

Table 21 Toxicokinetics Parameters of 9106-IM-2 in SD Rats After Intravenous Injection of 9106-IM-2 (n=10, 5 animals/sex)

Sex	Dosage (mg/kg)	Dosing period	AUC _{last} (hr·μg/mL)		C ₀ (ng/mL)	
			Mean	SD	Mean	SD
Female	0.1	1	27.6	7.86	110	48.6
		29	40.3	5.17	187	78.1
	0.3	1	86.2	8.20	375	115
		29	97.2	32.3	557	241
	0.6	1	185	39.6	584	126

Sex	Dosage (mg/kg)	Dosing period	AUC _{last} (hr·µg/mL)		C ₀ (ng/mL)	
			Mean	SD	Mean	SD
Male	1.0	22	300	101	1100	487
		29	333	76.5	1280	543
	0.1	1	29.7	5.73	131	54.3
		29	43.4	12.7	193	18.4
	0.3	1	86.9	11.3	313	59.2
		29	95.2	13.5	513	162
	0.6	1	220	37.8	988	188
		22	348	41.9	1130	164
	1.0	22	348	41.9	1130	164
		29	399	50.6	1420	197

5.4.2.4. 13-Week Repeat-Dose Toxicity Study in SD Rats

This study included a vehicle control group and 9106-IM-2 0.3 and 0.6 mg/kg groups, with 38 rats in each group (8 for the concomitant TK test), 15 male and 15 female. Rats in each group were intravenously injected with vehicle (1.5% DMSO + 98.5% [10% SBE-β-CD]) or 9106-IM-2 dose formulations at corresponding concentrations with a volume of 10 mL/kg. The vehicle control group and each 9106-IM-2 group were administered once a week for 13 consecutive doses, followed by a 4-week recovery period.

During the study, no death/moribundity or abnormal clinical manifestations related to the test article were observed in animals in each group. At the end of dosing, the organ weight, organ-to-brain weight ratio, and organ-to-body weight ratio of thymus decreased in the male rats in the 9106-IM-2 0.6 mg/kg group. Both gross necropsy and histopathological examination showed no abnormal changes related to the test article. After a 4-week recovery period, the above lesions were clearly recovered. Additionally, no abnormal changes were observed in the general condition, body weight, food consumption, ophthalmological examination, urinalysis, hematology, blood biochemistry, bone marrow smear, other organ weights and ratios, and histological examination in rats in the vehicle control group and each 9106-IM-2 dose group.

Within the dose range of 0.3-0.6 mg/kg, there was no significant gender difference in plasma exposure of 9106-IM-2, and the drug exposure increased dose-proportionally. After 13 consecutive doses, there was no significant accumulation of 9106-IM-2 in each group.

Under the conditions of this study, SD rats were intravenously injected with 9106-IM-2 at 0.3 and 0.6 mg/kg once weekly for 13 consecutive weeks (13 doses in total), followed by a 4-week recovery period. The HNSTD of 9106-IM-2 was 0.6 mg/kg (AUC_{last} was 422 h*ng/mL in male rats and 240 h*ng/mL in female rats at the end of the 13th dose at this dose level).

5.4.3. Genotoxicity

5.4.3.1. Ames Test

The objective of this study was to evaluate the mutagenic potential of 9106-IM-2 in

Salmonella Typhimurium in the presence or absence of rat liver S9 metabolic activation system. This GLP study was conducted by West China-Frontier Pharma Tech Co., Ltd. in 2019.

The test was conducted in systems with or without metabolic activation. The five histidine auxotroph strains of *S. typhimurium* TA97a, TA98, TA100, TA102 and TA1535, were used in this test. 9106-IM-2 at 5000 µg/plate was chosen as the top concentration for this study. Additional four concentrations of 1500, 500, 150 and 50 µg/plate were also tested. The vehicle control (DMSO) and positive control (different positive substances) groups were also included. Three parallel plates were designed for each concentration. The test was repeated once, and the results of the two tests were consistent.

Under the experimental condition, no gene mutations were observed at 50, 150, 500, 1500 and 5000 µg /plate of 9106-IM-2 in all tester strains with or without S9, and thus the result of this Ames test was concluded to be negative.

5.4.3.2. *In Vitro* Mammalian Chromosome Aberration Test in Chinese Hamster Lung (CHL) Cells

The objective of this study was to evaluate the genotoxicity of 9106-IM-2, as measured by its ability to induce chromosomal aberrations in cultured Chinese Hamster Lung (CHL) cells. This GLP study was conducted by West China-Frontier Pharma Tech Co., Ltd. in 2019.

The test was conducted in systems with or without metabolic activation. The cells were exposed to test article for 4 hrs with S9 activation, and for 4 and 24 hrs without S9 activation. The conventional dosing volume ratio of 2% was used. Based on the cytotoxicity of test article, the cells were exposed to 9106-IM-2 at concentrations of 0.25, 0.5, 1.5, 5 and 15 µg/mL for 4 or 24 hrs, respectively. Vehicle control (DMSO) and various positive control groups were included in the test. Slides were prepared for cell suspensions after harvest, and then stained with Giemsa solution. Two hundred (200) metaphase cells were evaluated, and chromosome aberration rate for each group was calculated.

When exposed for 4 hrs with or without S9, above 0.5 µg/mL of 9106-IM-2 could cause a significant increase in chromosome structural aberration rate. And exposed for 24 hrs without S9, above 0.25 µg/mL of 9106-IM-2 could cause a significant increase in chromosome structural aberration rate.

Therefore, the result of chromosome aberration test was concluded as positive and 9106-IM-2 is a clastogen.

5.4.3.3. *In vivo* Rat Bone Marrow Micronucleus Assay

9106-IM-2 cause a significant decrease in the PCE/(PCE+NCE) ratio, and there was a significant dose response. The positive control was positive, but no chromosome integrity damage or abnormal chromosome separation was caused in bone marrow cells, therefore, the result was positive.

5.4.4. Carcinogenicity

No carcinogenicity studies have been conducted.

5.4.5. Reproductive and Developmental Toxicity

5.4.5.1. Embryo-fetal developmental toxicity study of 9106-IM-2 and SHR-A1811 via intravenous injection in SD rats

Pregnant rats were intravenously injected with 0.25 mg/kg, 0.5 mg/kg, and 1 mg/kg 9106-IM-2 on GD6, GD10, GD13, and GD17; and intravenously injected with 20 mg/kg, 60 mg/kg, and 200 mg/kg SHR-A1811 on GD6 and GD13. No test article-related miscarriage, premature labor, moribundity, or animal death was observed. No abnormal changes in clinical symptoms related to the test article were found.

In the 9106-IM-2 low-dose group, the daily weight gain, food consumption, and live fetus rate decreased, while the rates of total fetal resorption and post-implantation loss increased. In the 9106-IM-2 medium- and high-dose groups, the body weight, food consumption, ovarian weight, gravid uterus weight (weight of uterus plus fetuses), number of live fetuses, live fetus rate, total litter weight, and mean litter weight decreased, while the number of early fetal resorptions, total number of fetal resorptions, the rate of total fetal resorption rate and post-implantation loss increased; 1 dam each in the medium- and high-dose groups had intrauterine effusion. The incidence of intraventricular hemorrhage in fetuses increased in each dose group of 9106-IM-2.

The body weight, food consumption, ovarian weight, and gravid uterus weight (weight of uterus plus fetuses) decreased in all SHR-A1811 dose groups; most fetuses (only 27 surviving fetuses) in the SHR-A1811 low-dose group and all fetuses in the SHR-A1811 medium- and high-dose groups were lost before and after implantation; developmental delay, external malformations (exencephaly, syndactyly, and oligodactyly), visceral abnormalities (ventricular hemorrhage), and skeletal malformations (missing metatarsal/phalangeal bones), as well as decreased ossification of metacarpals, sternebrae ossification, and ossification in grade 0 of occipital bone were observed in surviving fetuses in the SHR-A1811 low-dose group; pus was observed in the uterus of a few dams in the SHR-A1811 low- and high-dose groups.

In summary, under the conditions of this study, the NOAEL of 9106-IM-2 for embryo-fetal developmental toxicity was less than 0.25 mg/kg, at which the AUC_{0-t} and C_{max} after administration on GD17 in pregnant rats were 132.59 h·ng/mL and 500.77 ng/mL, respectively; the NOAEL of SHR-A1811 for embryo-fetal developmental toxicity was less than 20 mg/kg, at which the $AUC_{0-168\text{ h}}$ and C_{max} of total antibody after administration on GD13 in pregnant rats were 36,020.2 h·μg/mL and 547.7 μg/mL, respectively; the $AUC_{0-168\text{ h}}$ of ADC was 43875.3 h·μg/mL, and C_{max} was 569.5 μg/mL. The $AUC_{0-168\text{ h}}$ of 9106-IM-2 was 185.29 h·ng/mL, and C_{max} was 3.58 ng/mL.

5.4.6. Tissue Cross Reactivity in Human Tissues

The objective of this study was to determine the cross-reactivity of SHR-A1811 in normal fresh frozen human tissues. This GLP study was conducted by West China-Frontier Pharma Tech Co., Ltd in 2019.

In this study, an immunohistochemistry staining method was applied to determine the

binding activity of the biotinylated SHR-A1811 (Test Article), biotinylated SHR-1805 (Reference Control) and biotinylated human IgG1 (Control Article) at concentrations of 2.5 and 20 µg/mL with 33 kinds of normal fresh frozen human tissues (3 donors per tissue).

The staining results showed that SHR-A1811 could bind to skin, sweat glands, gastric mucosa, lung alveoli, bronchi, pancreatic ducts, thyroid, uterine glands, duodenal mucosa, tonsils, bladder, fallopian tubes, kidney tubules, breast and salivary duct epithelial cells, pancreas, duodenum, stomach, salivary glands, breast and prostate acinar cells, cerebellum and cerebral glial cells.

In summary, the positive staining was in the cytoplasm or nucleus, and no positive signal was seen on the cell membrane surface; the binding pattern was consistent with the antibody SHR-1805.

5.4.7. Formulation Toxicity Studies

5.4.7.1. *In Vitro* Hemolysis Test

The objective of this *in vitro* GLP study was to evaluate whether SHR-A1811 could induce hemolysis using rabbit red blood cell suspension and to provide reference for clinical usage. This GLP study was conducted by West China-Frontier Pharma Tech Co., Ltd in 2019.

Under the experimental condition, 5 mg/mL SHR-A1811 did not induce hemolysis or agglutination in rabbit red blood cell suspension, and thus the test result was concluded as negative.

5.4.7.2. Local Tolerance

At 3, 10 and 40 mg/kg SHR-A1811 did not induce local irritation at the injection site in the repeat-dose toxicity studies performed in Cynomolgus monkeys.

The local irritation test conducted after the change of packaging materials showed that after a single intravenous injection of 10 mg/mL SHR-A1811 for injection with a volume of 2 mL/kg to Japanese white rabbits at a dose of 20 mg/kg, no irritation to the blood vessels and surrounding tissues at the injection site was observed.

5.4.7.3. Phototoxicity Studies of 9106-IM-2

The *in vitro* 3T3 cell neutral red uptake assay showed that 9106-IM-2 was predicted to be "phototoxic" within the test concentration range of 0.006-20.000 µg/mL. In an *in vivo* experiment, BN rats were given a single intravenous injection of 9106-IM-2 at 0.3 and 0.6 mg/kg, and no phototoxic reaction was observed under ultraviolet light after administration. Therefore, the phototoxicity results of 9106-IM-2 were negative.

5.5. Nonclinical Assessment of Safety

SHR-A1811 retained similar binding affinity to both human and Cynomolgus monkey HER2 as the naked antibody SHR-1805 mAb without cross-reactivity with rat HER2. Binding of SHR-A1811 to HER2 overexpressing cells resulted in internalization into the lysosomes, leading to decreased level of extracellular HER2 and inhibition of HER2 downstream signaling, and induce DNA damage signaling pathway. SHR-A1811 could

also release the DNA topoisomerase I inhibitor to induce cell apoptosis in HER2 overexpressing cells. SHR-A1811 showed the bystander effect that T-DM1 did not have. It could kill the HER2 high-expression tumor cells and inhibit the growth of HER2 low-expression tumor cells nearby. SHR-A1811 exerted significant anti-tumor efficacy in multiple xenografts models as well as breast cancer patient-derived xenograft (PDX) models with high expression of HER2.

Pharmacokinetics studies indicated that SHR-A1811 had a non-linear pharmacokinetic property with half-life of 2-6 days in Cynomolgus monkeys. SHR-A1811 was mainly distributed to HER2 high-expression tumors except the serum, and metabolized by excretion in feces.

The Caco-2 cell permeability study indicated that the toxin 9106-IM-2 was a low-permeability drug. It was a moderate-to-high-clearance drug in cynomolgus monkeys and rats. There was no obvious species difference in plasma protein binding, which was about 85.0%-94.8%. 9106-IM-2 was stable in hepatocytes of various species, but was chemically unstable after incubation at 37 °C for 3 h, and could undergo lactone ring-opening hydrolysis and decarboxylation, resulting in metabolites M3 and M1. In human liver microsomes, the metabolite M2 was mainly formed through mono-oxidation by CYP3A4 and 2D6, and M4 was formed by CYP3A4-catalyzed lactone ring-opening hydrolysis, decarboxylation, and dehydrogenation. 9106-IM-2 had no direct inhibition or time-dependent inhibition or induction on major CYP450 liver drug enzymes. 9106-IM-2 was a substrate of P-gp but not a substrate of BCRP. 9106-IM-2 had no inhibitory effect on P-gp or BCRP. 9106-IM-2 was a substrate of transporters OATP1B1 and OATP1B3. The IC₅₀ value for OAT1 inhibition was 0.627 μM, and the maximum inhibition percentage was 60.7%. It had no inhibitory effect on most SLC transporters (OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K) other than OAT1. 9106-IM-2 was neither a substrate nor an inhibitor of BSEP.

Single- and repeat-dose toxicology studies in Cynomolgus monkeys showed similar toxicity profiles with the 9106-IM-2, suggesting toxicities were mediated primarily by 9106-IM-2. In 6-week and 13-week repeat-dose toxicity studies, the Highest Non-Severely Toxic Dose (HNSTD) was 40 mg/kg in Cynomolgus monkeys. In addition, during the repeat-dose toxicity study, no adverse effects on cardiovascular systems or irritation at the injection site were noted.

6. EFFECTS IN HUMANS

As of 13 May 2025, twenty-five clinical studies of SHR-A1811 were conducted by the sponsor, one of them was a clinical study associated with SHR-A1811 in the HRS-8080 research and development project (HRS-8080-202). Except for one international multi-center study (SHR-A1811-I-101), the remaining 24 studies were conducted in China, with trial indications including breast cancer, gastric cancer or gastroesophageal junction adenocarcinoma, colorectal cancer, non-small cell lung cancer, biliary cancer and ovarian cancer, etc. All the studies were ongoing. The information of 25 clinical studies is summarized in [Table 22](#).

Table 22 Overview of Ongoing Clinical Studies of SHR-A1811

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
SHR-A1811-I-101/ NCT04446260	Phase I/ Australia, USA, Korea, China (including Taiwan)	A Phase 1 Multi-Country Multi-Center, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of SHR-A1811 in HER2 Expressing or Mutated Advanced Malignant Solid Tumor Subjects	Multi-country multi-center, open-label, dose escalation, PK expansion and indication expansion	<u>Part 1 - Dose Escalation</u> SHR-A1811 at doses of 1.0, 2.0, 3.2, 4.8, 6.4 and 8.0 mg/kg, IV infusion, Q3W. <u>Part 2 - PK Expansion</u> Four dose groups (4.8, 5.6, 6.4 and 8.0 mg/kg) of SHR-A1811 were selected for PK expansion. <u>Part 3 - Indication Expansion</u> Select 3 doses (4.8, 5.6 and 6.4 mg/kg) of SHR-A1811 for indication expansion.	Subjects with HER2 expressing or mutated advanced solid tumors who have failed current standard-of-care, males or females ≥ 18 years of age (for subjects from Taiwan, China and Korea, their ages should be ≥ 20 years and ≥ 19 years, respectively).	At most, 36 subjects will be enrolled in one region in Part 1, 30 - 60 subjects will be enrolled in Part 2, and 121 - 190 subjects will be enrolled in Part 3/ 396 subjects/ 396 subjects
SHR-A1811-I-102/ NCT04513223	Phase I/ China	Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of SHR-	Single-arm, open-label, dose escalation, PK	<u>Part 1 - Dose Escalation</u> SHR-A1811 at doses of 3.2, 4.8, 6.4 and	Subjects with HER2 expressing advanced gastric or gastroesophageal	80 - 114 subjects/ 101 subjects/ 101 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
		A1811, in Patients with HER2-expressing Advanced Gastric or Gastroesophageal Junction Adenocarcinoma and Colorectal Cancer: a Phase 1 Study	expansion and efficacy expansion	8.0 mg/kg, IV infusion, Q3W. <u>Part 2 - PK Expansion</u> Select 2 doses (4.8 and 6.4 mg/kg) of SHR-A1811 for PK expansion. <u>Part 3 - Efficacy Expansion</u> SHR-A1811 6.4 mg/kg Q3W.	junction adenocarcinoma and colorectal cancer that is refractory to or intolerable with standard treatment, or for which no standard treatment is available, males or females, 18 - 75 years (inclusive) of age.	
SHR-A1811-I-103/ NCT04818333	Phase I/II/ China	Phase I/II Clinical Study of the Safety, Tolerability, Pharmacokinetics, and Efficacy of SHR-A1811 for Injection in Subjects with Advanced Non-small Cell Lung Cancer Who Have HER2 Expression,	Open-label, dose escalation, PK expansion and efficacy expansion	<u>Phase I</u> <u>Part 1 - Dose Escalation</u> SHR-A1811 at doses of 3.2, 4.8, 5.6, 6.4 and 8.0 mg/kg IV infusion Q3W. <u>Part 2 - PK Expansion</u> Select 4.8 and 5.6 mg/kg dose of SHR-A1811 for PK expansion.	Subjects who has previously received platinum-based chemotherapy for advanced or metastatic NSCLC, has developed disease progression during or after treatment, or is unable to tolerate platinum-based chemotherapy,	The sample size of Phase I: Part 1: 15 - 30 subjects; Part 2: 8 - 30 subjects; Part 3: approximately 30 subjects for each indication; the sample size of Phase II: 90 subjects/

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
		Amplification, or Mutation		<u>Part 3 - Efficacy Expansion</u> Select RP2D of SHR- A1811 based on the dose escalation and the PK expansion for efficacy expansion. <u>Phase II</u> 4.8 mg/kg IV infusion, Q3W.	males or females, 18 - 75 years (inclusive) of age.	157 subjects/ 157 subjects
SHR-A1811- 105/ NCT06710990	Phase I/China	A Multicenter, Open- Label, Fixed - Sequence Study to Evaluate Drug-Drug Interaction of Ritonavir and Itraconazole on the Pharmacokinetics of SHR-A1811 In Subjects with HER2- Expressing Advanced Breast Cancer	Multicenter, Open- Label, Fixed - Sequence	<u>Stage I (Main Study)</u> SHR-A1811 4.8 mg/kg, IV, Q3W. Ritonavir 200 mg, PO, BID from C2D17 to C3D16. Itraconazole 200 mg, PO, BID on D1 and QD thereafter from C2D17 to C3D16. <u>Stage II (Extension Study)</u>	Subjects with HER2- expressing advanced breast cancer who have failed or have no effective standard treatment, females $\geq$ 18 years of age.	16-32 subjects/ 13 subjects/ 7 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				SHR-A1811 4.8 mg/kg, IV, Q3W.		
SHR-A1811- II-201/ NCT05349409	Phase Ib/II/ China	A Phase Ib/II Clinical Study on the Dosage Exploration and Efficacy Expansion of SHR-A1811 for Injection in Combination with Fuzuloparib Capsule in HER2-Expressing Advanced Solid Tumors of Patients	Multi-center, single- arm, open-label, dose exploration and efficacy expansion	<u>Dose Exploration Stage</u> SHR-A1811 3.2, 4.8 and 6.4 mg/kg, IV, Q3W; fuzuloparib 50 or 100 mg, twice daily (BID). Based on the safety analysis and tolerance observation, SMC decided to add the group of SHR-A1811 4.8 mg/kg Q3W combined with fuzuloparib 30 or 50 mg QD for tolerance observation. <u>Efficacy Expansion Stage</u> Using the RP2D determined in the dose exploration stage, fuzuloparib once daily	HER2-expressing advanced malignant tumors of patients, males or females ≥ 18 years of age.	Dose Exploration Stage: about 23-54 subjects; Efficacy Expansion Stage: 70-140 subjects/ 31 subjects/ 31 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				(QD) or BID, and SHR-A1811 Q3W.		
SHR-A1811-II-202/ NCT05353361	Phase Ib/II/ China	A Phase Ib/II Multicenter, Open-Label Clinical Trial of SHR-A1811 Injection in Combination with Pyrotinib or Pertuzumab or Adebrelimab or Paclitaxel for Injection (Albumin Bound) in Breast Cancer	Multi-center, open-label, dose exploration and efficacy expansion	<u>Phase 1 (Dose Exploration Stage)</u> <i>SHR-A1811 in combination with Pyrotinib</i> The initial dose of SHR-A1811 is 3.2 mg/kg, IV, Q3W, with a cycle of every 3 weeks (21 days). The initial dose of Pyrotinib is 320 mg, orally once daily (QD), with a cycle of every 3 weeks. <i>SHR-A1811 in combination with Pertuzumab</i> The initial dose of SHR-A1811 is 3.2 mg/kg, IV,	Phase 1: Patients with HER2-positive unresectable or metastatic breast cancer who have received trastuzumab and chemotherapy, and have received at least one-line standard treatment during the recurrent and metastatic stages; or patients with triple negative unresectable or metastatic breast cancer who have received at least one-line standard treatment during the recurrent and metastatic stages;	Around 168-686 subjects/ 159 subjects/ 159 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				Q3W, with a cycle of every 3 weeks (21 days). The dose of Pertuzumab is the recommended dose stated in the product label, with an initial dose of 840 mg followed by a dose of 420 mg administered every 3 weeks. <i>SHR-A1811 in combination with Adebrelimab</i> HER-2 Positive Breast Cancer The initial dose of SHR-A1811 is 3.2 mg/kg, IV, Q3W, with a cycle of every 3 weeks (21 days). Triple Negative Breast Cancer	Phase 2: Patients with HER2-positive unresectable or metastatic breast cancer who have not received systemic anti-tumor therapy during the recurrent and metastatic stages (≤ 1st line endocrine therapy is acceptable); or patients with triple negative unresectable or metastatic breast cancer who have not received systemic anti-tumor therapy during the recurrent and metastatic stages; or patients with HER2-positive early or locally advanced breast cancer.	

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				The initial dose of SHR-A1811 is 4.8 mg/kg, IV, Q3W, with a cycle of every 3 weeks (21 days). The dose of Adebrelimab is fixed at 1200 mg, Q3W. <i>A1811 + Nab-Paclitaxel</i> The initial dose of SHR-A1811 is 3.2 mg/kg, IV, Q3W, with a cycle of every 3 weeks (21 days). The dose of <i>Nab-Paclitaxel</i> is fixed at 260 mg/m², Q3W. <u>Phase 2 (Efficacy Expansion Stage)</u> After completing the dose exploration, one or two dose(s) will be selected for efficacy expansion.		

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
SHR-A1811- II-203/ NCT05482568	Phase Ib/II/ China	Phase IB/II Clinical Study of the Safety, Tolerability, Pharmacokinetics, and Efficacy of Injectable SHR-A1811 in Combination with Pyrotinib or Adebrelimab in Subjects with Advanced Non-small Cell Lung Cancer with HER2	Open-label, multi-center, dose escalation and efficacy exploration	Part A: SHR-A1811 in Combination with Pyrotinib <u>Dose Escalation Stage</u> (Phase Ib): Using the "i3+3" design, four dose groups are pre-set: starting from SHR-A1811 3.2 mg/kg Q3W/pyrotinib 320 mg QD, if no DLT is observed, the dose will be increased to SHR-A1811 4.8 mg/kg Q3W/pyrotinib 320 mg QD and SHR-A1811 4.8 mg/kg Q3W/pyrotinib 400 mg QD. <u>Efficacy Exploration Stage (Phase II):</u> The RP2D of SHR-A1811 in combination	Patients with HER2 mutation, amplification or overexpression and advanced non-small cell lung cancer who have failed standard treatment. Aged 18-75 years (inclusive), males or females.	Dose Escalation Stage: 3-6 subjects for each dose in Part A and Part B; Efficacy Exploration Stage: up to 50 subjects for each arm in Part A and Part B/ 126 subjects/ 125 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				with pyrotinib determined in the dose escalation stage will be used for efficacy exploration. Part B: SHR-A1811 in Combination with Adebrelimab <u>Dose Escalation Stage (Phase Ib):</u> Using the "i3+3" design, the fixed dose of Adebrelimab is 20 mg/kg Q3W, and two doses of SHR-A1811 are pre-set at 3.2 mg/kg Q3W and 4.8 mg/kg Q3W, with the dose escalating from low to high. <u>Efficacy exploration stage (Phase II):</u> The RP2D of SHR-A1811 in combination		

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				with fixed dose for adebreliamab will be used for efficacy exploration.		
SHR-A1811- Ib/II-205/ NCT05671822	Phase Ib/II/ China	A Phase Ib/II Study of SHR-A1811 Combinations in Patients with Advanced/Metastatic HER2-expressing Gastric /Gastroesophageal Junction Adenocarcinoma	Open-label, multi- center	<u>Phase Ib</u> - Ib-1: SHR-A1811 combined with SHR-1701, with a starting dose of 4.8 mg/kg and a ramp-up dose of 6.4 mg/kg for SHR-A1811, and a fixed dose of 1800 mg for SHR-1701; - Ib-2: SHR-A1811 combined with capecitabine, with a starting dose of 4.8 mg/kg and a ramp-up dose of 6.4 mg/kg for SHR-A1811, and a fixed dose of 1000 mg/m² for capecitabine, with a	Phase Ib (excluding Ib-4, Ib-5 and Ib-6): Patients with HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma who have failed or cannot tolerate standard treatment and have previously received anti-HER2 therapy. Phase Ib (4, 5 and 6) & II: HER2-expressing advanced gastric or gastroesophageal junction adenocarcinoma	Phase Ib: Up to 78 subjects; Phase II: 180 subjects/ 76 subjects/ 76 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				preset reduced dose of 750 mg/m²; • Ib-3: SHR-A1811 combined with SHR-1701 and capecitabine, with lower doses determined by Ib-1 and Ib-2 for SHR-A1811, 4.8 mg/kg for SHR-A1811, a fixed dose of 1800 mg for SHR-1701, and 1000 mg/m² for capecitabine; • Ib-4: SHR-A1811 combined with capecitabine and adabrelimab, with doses determined by Ib-2 for SHR-A1811 and capecitabine, 4.8 mg/kg for SHR-A1811, 1000 mg/m² for	patients who have not received any systemic anti-tumor treatment. Aged 18-75 years (inclusive), males or females.	

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				capecitabine, and a fixed dose of 1200 mg for adabrelinab; • Ib-5: SHR-A1811 combined with capecitabine, adabrelinab and oxaliplatin, with doses determined by Ib-2 for SHR-A1811 and capecitabine, 4.8 mg/kg for SHR-A1811, 1000 mg/m ² for capecitabine, a fixed dose of 1200 mg for adabrelinab, and a starting dose of oxaliplatin 80 mg/m ² , increased to 100 mg/m ² (if tolerated), or reduced to 60 mg/m ² (if not tolerated).		

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				Ib-6: SHR-A1811 combined with adabrelimab and 5-FU, with the dose of 4.8 mg/kg for SHR-A1811, a fixed dose of 1200 mg for adabrelimab, and a starting dose of 5-FU 800 mg/(m²*d), or reduced to 600 mg/(m²*d) (if not tolerated). <u>Phase II</u> The planned dosing regimen for HER2-positive patients: Cohort II-A1: SHR-A1811 + adabrelimab + capecitabine; Cohort II-A2: SHR-A1811 + adabrelimab; Cohort II-A3: SHR-A1811 + capecitabine;		

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				Cohort II-A4: SHR-A1811 + adabrelinab + 5-FU; Cohort II-A5: SHR-A1811 + 5-FU; The planned dosing regimen for HER2-low patients: Cohort B: SHR-A1811 + adabrelinab + capecitabine ± oxaliplatin		
SHR-A1811-206/ NCT05792410	Phase Ib/II/ China	An Open, Multicenter Phase Ib/II Clinical Study of SHR-A1811 Combined with Dalpiciclib, Fulvestrant, Bevacizumab or Letrozole/Anastrozole in Patients with HER2-Low Advanced	Open-label, multi-center, dose exploration and efficacy expansion	<u>Phase I (Dose Escalation Stage)</u> <i>SHR-A1811 in combination with Dalpiciclib</i> The initial dose of SHR-A1811 is 2.0 mg/kg, administered intravenously every 3 weeks (21 days) for one cycle.	Patients with unresectable or metastatic breast cancer with histologically or cytologically confirmed low expression of HER2 (IHC2+/ISH-, IHC1+/ISH-, or untested). Prior anti-	Around 88-300 subjects/ 97 subjects/ 97 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
		or Metastatic Breast Cancer.		The initial dose of daltapiclib is 100 mg, taken orally once a day for 2 weeks followed by 1 week off as a treatment course. <i>SHR-A1811 in combination with Fulvestrant</i> The initial dose of SHR-A1811 is 6.4 mg/kg, administered intravenously every 3 weeks (21 days) for one cycle. Fulvestrant dosage is per the recommended dose in the instructions, with an initial dose of 500 mg given every 2 weeks for first cycle and every 4 weeks for subsequent	tumor treatment requirements: Patients who are hormone receptor (HR) positive, in the dose escalation stage, they must have received at least one line of endocrine therapy and are allowed to have $\leq$ second line chemotherapy; in the efficacy expansion stage, they are allowed to have not received more than first-line endocrine therapy without chemotherapy. Patients who are HR-negative, in the dose escalation stage, they must have received at	

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				cycle for a treatment course. <i>SHR-A1811 in combination with Bevacizumab</i> The initial dose of SHR-A1811 is 6.4 mg/kg, administered intravenously every 3 weeks (21 days) for one cycle. The dose of bevacizumab is fixed at 15 mg/kg, administered intravenously every 3 weeks. <u>Phase II (Expansion Stage)</u> After completing the dose-escalation stage, at least one dose will be	least one line of chemotherapy; in the efficacy expansion stage, they must have not received any systemic anti-tumor treatment in the recurrent /metastatic stage. Aged 18-75 years (inclusive), males or females.	

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				chosen for efficacy expansion.		
SHR-A1811-207/ NCT05845138	Phase Ib/II/ China	An Open-Label, Multi-Center Phase Ib/II study of SHR-A1811 Combined with Capecitabine in Treatment of Unresectable of Metastatic Breast Cancer with Low HER2 Expression	Multi-center, open-label, dose exploration and efficacy expansion	<u>Phase I (Dose Escalation Stage)</u> SHR-A1811 in combination with Capecitabine The initial dose of SHR-A1811 is 4.8 or 5.6 mg/kg, administered intravenously every 3 weeks (21 days) for one cycle. Capecitabine dosage is per the recommended dose in the instructions, with an initial dose of 1000 mg/m ² given twice a day for 2 weeks followed by 1 week off as a treatment course for one cycle.	Patients with histologically or cytologically confirmed HER2 low-expression (IHC2+/ISH-, IHC1+/ISH-, or untested) unresectable or metastatic breast cancer. Aged 18 to 75 years (inclusive), females.	Around 18-116 subjects/ 24 subjects/ 24 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				<u>Phase II (Expansion Stage)</u> After completing the dose-escalation stage, at least one dose will be chosen for efficacy expansion.		
SHR-A1811-208/ NCT06015048	Phase Ib/II/ China	A Phase Ib/II Study to Evaluate the Safety, Tolerability and Efficacy of SHR-A1811 Combined with Other Antitumor Therapies in Advanced Solid Tumors.	Single arm, open-label, dose escalation/efficacy expansion	Part A SHR-A1811 in combination with Pyrotinib Dose escalation phase (phase Ib) Using the "i3+3" design, five dose groups are pre-set: SHR-A1811 +pyrotinib. Efficacy expansion phase (phase II) The RP2D of SHR-A1811 in combination with pyrotinib determined in the dose escalation	Patients with histologically or cytologically confirmed HER2-expressing or HER-2 functional mutation unresectable locally advanced or metastatic solid tumors. Aged 18 to 75 years (inclusive), males or females.	Up to 460 subjects/ 74 subjects/ 74 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				stage will be used for efficacy exploration. Part B SHR-A1811 in combination with chemotherapy Part B1 SHR-A1811 in combination with mFOLFOX6 and BP102 Dose escalation phase (phase Ib) Using the "i3+3" design, four combinations are included, several dose groups are pre-set: • IB1: SHR-A1811 + Calcium Levofolinate + 5-Fluorouracil; • IB2: SHR-A1811 + 5-Fluorouracil + Calcium		

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				Levofolinate + Oxaliplatin; • IB3: SHR-A1811 + 5-Fluorouracil + Calcium Levofolinate + Oxaliplatin + BP102; • IB4: SHR-A1811 + 5-Fluorouracil + Calcium Levofolinate + BP102. Efficacy expansion phase (phase II) The combinations and RP2D determined in the dose escalation stage will be used for efficacy exploration. Part B2 SHR-A1811 in combination with BP102		

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				Dose escalation phase (phase Ib) Using the "i3+3" design, three dose groups are pre-set: SHR-A1811+BP102 Efficacy expansion phase (phase II) The RP2D of SHR-A1811 in combination with BP102 determined in the dose escalation stage will be used for efficacy exploration. Part C SHR-A1811 in combination with SHR-9839 ± 5-Fluorouracil Part C1 SHR-A1811 in combination with SHR-9839 Dose escalation phase (phase Ib)		

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				Using the "BOIN" design, 2 dose groups are pre-set: SHR-A1811 + SHR-9839. Efficacy expansion phase (phase II) The RP2D of SHR-A1811 in combination with SHR-9839 determined in the dose escalation stage will be used for efficacy exploration. Part C2 SHR-A1811 in combination with SHR-9839 and 5- Fluorouracil Dose escalation phase (phase Ib) Using the "BOIN" design, 2 dose groups are pre-set: SHR-A1811 + SHR-9839 + 5-		

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				Fluorouracil + Calcium Levofolinate. Efficacy expansion phase (phase II) The RP2D of SHR-A1811 in combination with SHR- 9839 and 5-Fluorouracil determined in the dose escalation stage will be used for efficacy exploration.		
SHR-A1811- 209/ NCT05896020	Phase II/ China	An Open-label, Multicenter Phase II Clinical Study of SHR-A1811 for Injection in the Treatment of Gynaecological Malignancies	Open-label, multi- center	SHR-A1811: 4.8 mg/kg, administered intravenously every 3 weeks (21 days) for one cycle.	Patients with advanced cervical cancer, recurrent ovarian cancer and endometrial cancer. Aged 18 to 75 years (inclusive).	Around 30-225 subjects/ 116 subjects/ 116 subjects
SHR-A1811- 212/ NCT06413745	Phase II/China	A Phase II Clinical Study of SHR-A1811 in Patients with	Multicenter, Single- arm	SHR-A1811: 6.4 mg/kg, IV, every 3 weeks (21 days) for one cycle.	Patients with HER2- expressing/amplified, locally advanced,	60-65 subjects/ 36 subjects/ 35 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
		HER2-expressing/Amplified, Locally Advanced, Unresectable or Metastatic Biliary Tract Cancer (BTC) Who Have Previously Failed First or Second-line Systemic Therapy			unresectable or metastatic biliary tract cancer (BTC) who have previously failed first or second-line systemic therapy. Aged 18 to 75 years (inclusive), males or females.	
SHR-A1811-213/ NCT06592625	Phase II/ China	A Multicenter, Single-arm, Phase 2 Study of Neoadjuvant SHR-A1811 Plus Adebrelimab Injection for Early-stage or Locally Advanced HR Negative or Low Expression/HER2 Low Expression Breast Cancer	Multicenter, Single-arm	SHR-A1811: 4.8 mg/kg, IV, Q3W, up to 6 cycles. Adebrelimab: 1200 mg/cycle, IV, Q3W, up to 6 cycles.	Females aged 18 to 75 (inclusive). Stage I: Patients with HER2 low expression, HR expression of $0 \leq \text{HR} < 10\%$. Stage II: Patients with HER2 low expression, HR expression of $10\% \leq \text{HR} < 50\%$.	Around 60 subjects/ 11 subjects/ 11 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
SHR-A1811- 215/ NCT06778031	Phase II/ China	An Open-label, Multicenter Phase II Clinical Study of SHR-A1811 in the Treatment of HER2- positive Locally Advanced or Metastatic Biliary Tract Cancer	Open-label, Multicenter, Dose Exploration/Efficacy Exploration	SHR-A1811: initial dose of 4.8 mg/kg, IV, Q3W. Adebrelimab: 1200 mg/cycle, IV, Q3W, up to 35 cycles of administration. SHR-8068: 280 mg at C1D1, 70 mg at C5 and subsequent cycles, IV, Q6W, up to 17 cycles of administration.	Females aged 18 to 75 years (inclusive). Patients with HER2- positive locally advanced or metastatic biliary tract cancer.	Around 33-54 subjects/ 6 subjects/ 5 subjects
SHR-A1811- 216-OC/ NCT06840002	Phase Ib / II/China	An Open, Multicenter Phase Ib / II Clinical Study of SHR-A1811 Combined with Chemotherapy for Platinum Sensitive Recurrent Ovarian Cancer	Multicenter, Single- Arm, Open, Dose Exploration/Efficacy Expansion	SHR-A1811: 3.2, 4, 4.8 mg/kg, IV, Q3W. Carboplatin: AUC 5 mg/mL/min, IV, Q3W, up to 6 cycles. Oxaliplatin: 85 mg/m ² , IV, Q3W, up to 6 cycles. Bevacizumab: 15 mg/kg, IV, Q3W.	Patients with platinum- sensitive recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have previously received 1-3 lines of platinum-based treatment. Females	Around 126-144 subjects/ 18 subjects/ 10 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
					aged 18 to 75 years (inclusive).	
HRS-8080- 202/ NCT06222879	Phase Ib/II/China	A Multi-center, Open-label Phase Ib/II Clinical Study on the Safety, Tolerability, Pharmacokinetics and Efficacy of HRS-8080 or SHR-A2009 Combined with Anti-tumor Therapy in Patients with Unresectable or Metastatic Breast Cancer	Multi-center, Open-label	<u>Stage I (Dose Exploration)</u> HRS-8080: initial dose of 600 mg, QD, administered orally with warm water on an empty stomach. Continue to receive treatment with each 21 days for one cycle. SHR-A1811: initial dose of 4.8 mg/kg, IV, Q3W, each 21 days for one cycle. SHR-A2009: Part B initial dose of 6.0 mg/kg, IV, Q3W, each 21 days for one cycle. Part C initial dose of 8.0 mg/kg, IV, Q3W, each 21 days for one cycle.	Females aged 18 to 75 years (inclusive). Part A: Patients with ER positive, HER2 positive or low-expression metastatic or locally advanced breast cancer. Part B: Patients with ER positive, HER2 positive or negative metastatic or locally advanced breast cancer. Part C: Patients with triple negative metastatic or locally advanced breast cancer.	Dose Exploration: around 9-60 subjects; Efficacy Expansion: around 300 subjects/ 12 subjects/ 5 subjects

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				Adebrelimab: 1200 mg, IV, Q3W. <u>Stage II (Efficacy Expansion)</u> The efficacy expansion will be conducted using the combination therapy and RP2D determined during the dose exploration stage.		
SHR-A1811- III-301/ NCT05424835	Phase III/ China	A Phase III, Multicenter, Randomized, Open- Label, Parallel Controlled Study of SHR-A1811 Versus Pyrotinib in Combination with Capecitabine for HER2-Positive, Unresectable and/or Metastatic Breast	Randomized, Open- label, parallel controlled, multicenter	Eligible subjects with advanced/metastatic HER2-positive breast cancer are randomized in a ratio of 1:1 to experimental arm and control arm. <u>Experimental arm (SHR- A1811):</u> The dose of SHR-A1811 is 4.8 or 6.4 mg/kg, administered	Patients with unresectable or metastatic HER2 positive breast cancer previously treated with anti-HER-2 monoclonal antibody and Taxane in recurrent and metastatic stage. Aged 18-75 years (inclusive), females.	269 subjects/ 381 subjects/ about 191 subjects*

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
		Cancer Subjects Previously Treated with Trastuzumab and Taxane		intravenously every 3 weeks (21 days) for one cycle. <u>Control arm (Pyrotinib in combination with Capecitabine):</u> Pyrotinib: 400 mg, taken orally once a day for 21 consecutive days as one cycle. Capecitabine: 1000 mg/m ² , administered twice a day, for 21 days as one cycle.		
SHR-A1811- 305/ NCT06126640	Phase III/ China	A Phase III, Multicenter, Randomized, Open- Label, Active- Controlled Study of SHR-A1811 Versus Trastuzumab Emtansine (T-DM1)	Randomized, open- label, active- controlled, multicenter	Eligible subjects are randomized in a ratio of 1:1 to experimental arm and control arm. <u>Experimental arm (SHR- A1811):</u> The dose of SHR-A1811 is 4.8 mg/kg,	Patients with early- stage HER2-positive breast cancer after neoadjuvant therapy and radical surgery for breast cancer. Residual invasive cancer confirmed by	1600 subjects/ 1062 subjects/ 514 subjects*

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
		in HER2-Positive Primary Breast Cancer Participants with Residual Invasive Disease Following Neoadjuvant Therapy		administered intravenously every 3 weeks (21 days) for one cycle. <u>Control arm (T-DM1):</u> 3.6 mg/kg, IV, Q3W, with a cycle of every 3 weeks (21 days).	pathological examination after radical surgery. Aged 18-75 years (inclusive), females.	
SHR-A1811-III-306/ NCT05814354	Phase III/ China	A Randomized, Open, Parallel-controlled, Multicenter Phase III Trial of SHR-A1811 Versus Investigator Chemotherapy in HER2-low Expressing Recurrent/Metastatic Breast Cancer	Randomized, open-label, active-controlled, multicenter	Eligible subjects are randomized in a ratio of 1:1 to experimental arm and control arm. <u>Experimental arm (SHR-A1811):</u> The dose of SHR-A1811 is 6.4 mg/kg, administered intravenously once every 3 weeks (21 days) for one cycle. <u>Control arm (Investigator chemotherapy):</u>	Patients with recurrent or metastatic HER2 low-expressing breast cancer previously treated with ≤ 1 line of chemotherapy in recurrent and metastatic stage. Aged 18-75 years (inclusive), females.	530 subjects/ 496 subjects/ 237 subjects*

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				Capecitabine: 1000-1250 mg/m ² , taken orally twice a day for 14 consecutive days from D1-14 with 21 days as one cycle. Eribulin: 1.4 mg/m ² , IV, administered on D1 and D8 of each cycle, with 21 days as one cycle. Gemcitabine: 1000-1250 mg/m ² , IV, administered on D1, D8 and D15 of each cycle, with 28 days as one cycle, or administered on D1 and D8 of each cycle, with 21 days as one cycle. Paclitaxel: 175 mg/m ² , IV, administered on D1 of each cycle, with 21 days as one cycle, or 80		

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				mg/m ² , IV, administered weekly. Albumin-bound paclitaxel: 260 mg/m ² , IV, administered on D1 of each cycle, with 21 days as one cycle. 100 mg/m ² , or 125 mg/m ² , IV, administered on D1, D8 and D15 of each cycle, with 28 days as one cycle, or administered on D1 and D8 of each cycle, with 21 days as one cycle.		
SHR-A1811-307/ NCT06057610	Phase III/ China	A Phase III Multicenter, Randomized, Open-label, Active-Controlled Study of SHR-A1811 With or Without Pertuzumab	Randomized, open-label, active-controlled, multicenter	Eligible subjects are randomized in a ratio of 1:1:1 to experimental arm A, experimental arm B and control arm. <u>Experimental arm A (SHR-A1811):</u>	Patients with histologically or cytologically confirmed HER2-Positive recurrent or metastatic breast cancer not previously	864 subjects/ 756 subjects/ 494 subjects*

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
		Versus Trastuzumab, Pertuzumab and Docetaxel in HER2-Positive Recurrent or Metastatic Breast Cancer		The dose is 4.8 mg/kg, IV, once every 3 weeks (21 days) for one cycle. <u>Experimental arm B (SHR-A1811+ Pertuzumab):</u> SHR-A1811: The dose is 4.8 mg/kg, IV, once every 3 weeks (21 days) for one cycle. Pertuzumab: IV, starting dose of 840 mg followed by dose of 420 mg every 3 weeks (21 days) for one cycle. <u>Control arm (Trastuzumab, Pertuzumab and Docetaxel):</u> Trastuzumab: IV, starting dose of 8 mg/kg followed by dose of 6 mg/kg every	treated with systemic anti-tumor therapy in recurrent and metastatic stage (1 line of endocrine therapy is acceptable). Aged 18-75 years (inclusive), females.	

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				3 weeks (21 days) for one cycle. Pertuzumab: IV, starting dose of 840 mg followed by dose of 420 mg every 3 weeks (21 days) for one cycle. Docetaxel: IV, starting dose of 75 mg/m ² every 3 weeks (21 days) for one cycle.		
SHR-A1811-308/ NCT06123494	Phase III/ China	A Phase 3, Multicenter, Randomized, Open-label Study of SHR-A1811 (HER2-ADC) Compared with the Chemotherapy Treatment Chosen by the Investigators for Subjects with HER2-positive Metastatic	Randomized, open-label, active-controlled, multicenter	Eligible subjects are randomized in a ratio of 1:1 to experimental arm and control arm. <u>Experimental arm (SHR-A1811):</u> The dose of SHR-A1811 is 6.4 mg/kg, IV, once every 3 weeks (21 days) for one cycle.	Patients with histologically or cytologically confirmed HER2-positive metastatic and/or unresectable gastric or gastroesophageal junction adenocarcinoma progressed on or after	360 subjects/ 39 subjects/ 20 subjects*

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
		and/or Unresectable Gastric Cancer or Gastroesophageal Junction Adenocarcinoma Who Have Progressed on or After First-line Anti-HER2 Therapy- containing Regimen		<u>Control arm (Investigator Chemotherapy):</u> Ramucirumab+Paclitaxel: IV, Ramucirumab at dose of 8 mg/kg on D1 and D15 every 4 weeks for one cycle combined with Paclitaxel at dose of 80 mg/m ² on D1, D8 and D15 every 4 weeks for one cycle. Paclitaxel: IV, 80 mg/m ² on D1, D8 and D15 every 4 weeks for one cycle. Docetaxel: IV, 75 mg/m ² on D1 every 3 weeks for one cycle. Irinotecan: IV, 150 mg/m ² on D1 every 2 weeks for one cycle.	first-line anti-HER2 therapy-containing regimen. Aged 18-75 years (inclusive), females.	

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
SHR-A1811-309/ NCT06199973	Phase III/ China	A Phase 3, Multicenter, Randomized, Open-label Study of Injection of SHR-A1811 Versus Physician Choice Treatment in Patients with Advanced Colorectal Cancer Who Had Failed to Respond to Oxaliplatin, 5-FU, and Irinotecan	Randomized, open-label, active-controlled, multicenter	Eligible subjects are randomized in a ratio of 2:1 to experimental arm and control arm. <u>Experimental arm (SHR-A1811):</u> The dose of SHR-A1811 is 4.8 mg/kg, IV, once every 3 weeks (21 days) for one cycle. <u>Control arm (physician choice treatment):</u> TAS-102: taken orally with 35 mg/m² twice a day on D1-D5 and D8-D12 every 4 weeks for one cycle. Regorafenib: taken orally with 160 mg once a day on D1-D21 every 4 weeks for one cycle.	Patients with HER2-positive unresectable locally advanced or distant metastatic RAS/RAF wild-type colorectal cancer diagnosed histologically or cytologically after treatment with oxaliplatin, 5-FU and irinotecan. Aged 18-75 years (inclusive), males or females.	120 subjects/ 112 subjects/ 70 subjects*

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				Fruquintinib: taken orally with 5 mg once a day on D1-D21 every 4 weeks for one cycle.		
SHR-A1811-310/ NCT06430437	Phase III/China	A Randomized, Open-Label, Multicenter Phase III Study of SHR-A1811 for First-Line Treatment in Subjects with HER2-Mutated Advanced or Metastatic Non-Small Cell Lung Cancer	Randomized, open-label, multicenter	Eligible subjects are randomized in a ratio of 1:1 to experimental arm and control arm. <u>Experimental arm (SHR-A1811):</u> The dose of SHR-A1811 is 4.8 mg/kg, IV on D1 per cycle, every 3 weeks (21 days) for one cycle. <u>Control arm</u> <u>(Camrelizumab combined with physician choice of platinum-based doublet chemotherapy):</u> The administration sequence is as follows: camrelizumab is to be	Patients with HER2-mutated advanced or metastatic non-small cell lung cancer not previously treated with systemic antitumor therapy. Aged 18-75 years (inclusive), males or females.	Around 300 subjects/ 27 subjects/ 12 subjects*

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				administered first, followed by a minimum 30-minute interval before administering either pemetrexed or paclitaxel, with subsequent administration of carboplatin or cisplatin. Camrelizumab: 200 mg/once, IV on D1 per cycle, every 3 weeks (21 days) for one cycle. Pemetrexed: 500 mg/m ² , IV on D1 per cycle, every 3 weeks (21 days) for one cycle (only applicable to non-squamous carcinoma). Paclitaxel: 175 mg/m ² , IV on D1 per cycle, every 3 weeks (21 days) for one cycle.		

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				Cisplatin: 75 mg/m ² , IV on D1 per cycle, every 3 weeks (21 days) for one cycle.		
SHR-A1811-315/ NCT06828354	Phase III/China	An Open-label, Randomized, Multicenter Phase III Clinical Trial of SHR-A1811 Versus Investigator-selected Chemotherapy for Platinum-resistant Relapsed Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Randomized, open-label, positive-control, multicenter	Eligible subjects are randomized in a ratio of 1:1 to experimental arm and control arm. <u>Experimental arm (SHR-A1811):</u> The dose of SHR-A1811 is 4.8 mg/kg, IV on D1 per cycle, every 3 weeks (21 days) for one cycle. <u>Control arm (Physician choice of chemotherapy, including Doxorubicin Hydrochloride Liposome Injection, Paclitaxel, Topotecan, or Gemcitabine):</u>	Patients with HER2-expression platinum-resistant relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer (platinum-resistant relapsed defines as disease progression occurring either during platinum-based therapy or within <183 days after the last dose of platinum-based treatment). Aged 18-75 years (inclusive), males or females.	Around 300 subjects/ 15 subjects/ 4 subjects*

Study ID/ NCT#	Phase/ Country	Study Title	Study Design	Dosing Regimen	Study Population	Planned Enrollment/ Actual Enrollment/ SHR-A1811 Exposure
				The investigator selects one of the following treatment regimens, which is determined prior to randomization. Doxorubicin Hydrochloride Liposome Injection: 40 mg/m², IV on D1 per cycle, every 4 weeks for one cycle. Paclitaxel: 80 mg/m², IV on D1, D8, D15, D22 per cycle, every 4 weeks for one cycle. Topotecan: 4 mg/m², IV on D1, D8, D15 per cycle, every 4 weeks for one cycle. Gemcitabine: 1000 mg/m², IV on D1, D8 per cycle, every 3 weeks for one cycle.		

Safety data Cut-off Date: 13 May 2025.

*For Study SHR-A1811-III-301, SHR-A1811-305, SHR-A1811-III-306, SHR-A1811-307, SHR-A1811-308, SHR-A1811-309, SHR-A1811-310 and SHR-A1811-315, SHR-A1811 exposure was estimated based on the randomization scheme and the actual number of subjects treated as of 13 May 2025.

6.1. Pharmacokinetic and Metabolism Studies in Humans**6.1.1. Pharmacokinetic Studies****6.1.1.1. Study SHR-A1811-I-101**

As of 29 Feb 2024, intensive PK data of 1.0, 2.0, 3.2, 4.8, 5.6, 6.4 and 8.0 mg/kg in dose escalation and PK expansion was available. PK parameters were calculated using actual sampling time, actual administration time and actual administration dose. Since the PK characteristics of the Asian group and the non-Asian group are similar, and there are fewer subjects with intensive PK samples collected from the non-Asian group, the following PK parameter results are the summarized PK parameters of the Asian and non-Asian groups. Preliminary PK data shows that, in the dose range of 1.0-8.0 mg/kg, the exposure of ADC and total antibody were similar at each dose level, and increased with the increasing dose. The average elimination half-life of ADC after single administration was about 2.8-7.8 days, and increased with the increasing dose, while the clearance of SHR-A1811 showed decreased trend with the increasing dose, and the geometric mean volume of distribution is about 3.4-4.0 L. After multiple intravenous infusions of SHR-A1811, mild accumulation of total antibody and ADC was observed. In the dose range of 1.0-8.0 mg/kg, the exposure of released 9106-IM-2 after single and multiple administrations of SHR-A1811 was relatively low, and the exposure increased with the increase of the dose. The geometric mean C_{max} of released 9106-IM-2 in the highest dose group of 8.0 mg/kg was 3.89 ng/mL. Within the dose range of 1.0 to 8.0 mg/kg, the half-life of released 9106-IM-2 averaged about 3.3 to 5.8 days. No accumulation of released 9106-IM-2 was observed after multiple intravenous infusions of SHR-A1811.

Table 23 Summary of Pharmacokinetic Parameters of ADC After a Single Intravenous Infusion of SHR-A1811 in Study SHR-A1811-I-101

PK Parameters	Units	1.0 mg/kg		2.0 mg/kg		3.2 mg/kg		4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8.0 mg/kg	
		Geomean (GeoCV%)		Geomean (GeoCV%)		Geomean (GeoCV%)		Geomean (GeoCV%)		Geomean (GeoCV%)		Geomean (GeoCV%)		Geomean (GeoCV%)	
		N		N		N		N		N		N		N	
T_{max}	day	6	0.0660 (0.0611, 0.146)	6	0.0649 (0.0618, 0.0708)	5	0.0632 (0.0625, 0.146)	34	0.0660 (0.0604, 0.399)	21	0.0708 (0.0583, 0.405)	34	0.0639 (0.0590, 0.158)	19	0.0938 (0.0583, 0.395)
C_{max}	µg/mL	6	20.6 (30.5)	6	40.8 (20.6)	5	71.0 (12.8)	34	109 (19.4)	21	131 (13.7)	34	144 (17.6)	19	182 (16.9)
AUC_{0-21d}	day*µg/mL	5	72.7 (30.2)	6	178 (32.9)	5	373 (7.82)	33	598 (23.6)	21	762 (20.7)	34	813 (36.2)	18	1130 (18.7)
AUC_{INF}	day*µg/mL	5	73.3 (30.3)	6	183 (35.3)	5	393 (8.70)	33	657 (26.1)	20	839 (23.3)	34	915 (41.5)	18	1320 (21.6)

PK Parameters	Units	1.0 mg/kg		2.0 mg/kg		3.2 mg/kg		4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
t _{1/2}	day	5	2.84 (0.184)	6	3.90 (0.987)	5	4.94 (0.317)	33	6.13 (1.24)	20	6.48 (1.15)	34	6.73 (2.14)	18	7.79 (1.48)
Cl	L/day	5	0.840 (32.4)	6	0.629 (34.4)	5	0.566 (28.6)	33	0.435 (22.6)	20	0.440 (25.3)	34	0.433 (43.0)	18	0.348 (18.2)
V _{ss}	L	5	3.44 (34.2)	6	3.42 (32.0)	5	3.96 (23.1)	33	3.58 (16.7)	20	3.92 (19.8)	34	3.76 (16.7)	18	3.59 (19.3)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).

Table 24 Summary of Pharmacokinetic Parameters of Total Antibody After a Single Intravenous Infusion of SHR-A1811 in Study SHR-A1811-I-101

PK Parameters	Units	1.0 mg/kg		2.0 mg/kg		3.2 mg/kg		4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	5	0.0632 (0.0611, 0.144)	4	0.0642 (0.0618, 0.0708)	5	0.0632 (0.0625, 0.146)	2 6	0.0663 (0.0604, 0.399)	2 0	0.0708 (0.0583, 0.405)	24	0.0653 (0.0590, 0.397)	1 3	0.142 (0.0583, 0.151)
C _{max}	μg/mL	5	21.2 (28.7)	4	37.5 (14.1)	5	74.9 (13.0)	2 6	108 (20.4)	2 0	133 (14.4)	24	146 (19.7)	1 3	184 (17.4)
AUC _{0-21d}	day*μg/mL	5	68.9 (31.0)	4	170 (35.8)	5	369 (10.2)	2 5	590 (24.1)	1 9	789 (21.0)	24	760 (40.8)	1 2	1160 (18.9)
AUC _{INF}	day*μg/mL	5	69.3 (31.2)	4	175 (38.9)	5	390 (11.6)	2 5	652 (26.3)	1 8	880 (25.4)	24	842 (45.6)	1 2	1390 (21.7)
t _{1/2}	day	5	2.74 (0.202)	4	4.04 (1.15)	5	5.12 (0.508)	2 5	6.28 (1.29)	1 8	6.63 (1.40)	24	6.20 (1.89)	1 2	8.53 (1.81)
Cl	L/day	5	0.888 (34.1)	4	0.618 (42.0)	5	0.570 (29.7)	2 5	0.432 (24.7)	1 8	0.419 (25.9)	24	0.486 (44.7)	1 2	0.347 (19.0)
V _{ss}	L	5	3.50 (30.8)	4	3.43 (33.0)	5	4.06 (24.2)	2 5	3.66 (21.1)	1 8	3.81 (17.9)	24	3.93 (18.8)	1 2	3.88 (18.0)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).

Table 25 Summary of Pharmacokinetic Parameters of Released 9106-IM-2 After a Single Intravenous Infusion of SHR-A1811 in Study SHR-A1811-I-101

I-101															
PK Paramet ers	Units	1.0 mg/kg		2.0 mg/kg		3.2 mg/kg		4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	6	1.07 (0.143, 1.10)	6	0.713 (0.394, 1.05)	5	1.04 (0.391, 1.07)	34	0.399 (0.143, 2.96)	21	0.407 (0.392, 7.12)	34	0.406 (0.144, 3.01)	19	0.401 (0.147, 1.05)
	ng/m L	6	0.605 (49.2)	6	1.01 (47.9)	5	1.37 (11.8)	34	2.76 (32.0)	21	3.15 (37.1)	34	3.48 (43.3)	19	3.89 (33.2)
AUC _{0-21d}	day*n g/mL	3	3.82 (31.3)	6	5.82 (48.7)	5	7.58 (22.8)	33	15.4 (28.8)	20	19.7 (37.5)	32	20.9 (30.3)	18	25.7 (25.6)
	day*n g/mL	3	3.87 (31.7)	6	6.07 (47.3)	5	8.02 (23.3)	33	16.3 (28.7)	18	19.9 (24.5)	32	22.5 (29.5)	18	27.8 (25.9)
AUC _{INF}	day	3	3.26 (0.389)	6	4.45 (1.31)	5	5.27 (1.28)	33	4.99(0.942)	18	5.36 (0.622)	32	5.59 (1.30)	18	5.78 (0.930)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).**Table 26 Summary of Pharmacokinetic Parameters of ADC After Multiple (the 3rd) Intravenous Infusions of SHR-A1811 in Study SHR-A1811-I-101**

101									
PK Parameters	Units	4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	25	0.0410 (0.0229, 1.02)	17	0.0361 (0.0215, 0.380)	21	0.104 (0.0243, 0.125)	9	0.117 (0.0347, 0.356)
C _{max}	μg/mL	25	111 (21.6)	17	129 (15.2)	21	161 (17.4)	9	226 (14.4)
AUC _{ss}	day*μg/mL	24	750 (25.3)	16	916 (23.7)	21	1140 (29.9)	9	1630 (18.1)
AUC _{INF}	day*μg/mL	24	885 (29.4)	16	1110 (28.1)	21	1380 (37.4)	9	2070 (22.7)
t _{1/2}	day	24	7.99 (1.53)	16	8.50 (1.53)	21	8.32 (1.90)	9	9.07 (1.49)
CL _{ss}	L/day	24	0.362 (23.8)	16	0.396 (17.8)	21	0.339 (26.4)	9	0.271 (17.0)
V _{ss}	L	24	3.87 (22.1)	16	4.54 (14.6)	21	3.82 (12.9)	9	3.51 (20.7)

PK Parameters	Units	4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
Rac_AUC		24	1.31 (12.0)	16	1.25 (16.5)	21	1.31 (13.2)	8	1.39 (10.3)
TEI		24	1.20 (13.2)	16	1.12 (16.7)	21	1.15 (13.2)	8	1.16 (11.0)

$T_{\max}$ is expressed as median (min, max), $t_{1/2}$ is expressed as mean (SD).

Table 27 Summary of Pharmacokinetic Parameters of Total Antibody After Multiple (the 3rd) Intravenous Infusions of SHR-A1811 in Study SHR-A1811-I-101

PK Parameters	Units	4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
$T_{\max}$	day	25	0.0361 (0.0222, 0.374)	17	0.0417 (0.0215, 0.380)	21	0.104 (0.0243, 0.125)	9	0.108 (0.0347, 0.368)
$C_{\max}$	µg/mL	25	114 (20.8)	17	141 (23.5)	21	160 (20.1)	9	208 (4.68)
AUC_{ss}	day*µg/mL	24	782 (29.6)	16	971 (24.2)	21	1150 (31.2)	9	1620 (12.4)
AUC_{INF}	day*µg/mL	24	932 (35.4)	16	1180 (30.3)	19	1350 (37.3)	9	2080 (18.4)
$t_{1/2}$	day	24	8.13 (1.85)	16	8.62 (1.64)	19	8.43 (1.90)	9	9.70 (1.33)
CL_{ss}	L/day	24	0.347 (26.8)	16	0.374 (20.4)	21	0.336 (28.0)	9	0.274 (13.5)
V_{ss}	L	24	3.79 (22.1)	16	4.39 (18.6)	19	3.93 (19.1)	9	3.70 (21.9)
Rac_AUC		20	1.31 (14.0)	14	1.25 (14.1)	13	1.35 (14.7)	6	1.39 (4.29)
TEI		20	1.19 (15.0)	14	1.11 (14.2)	13	1.20 (14.3)	6	1.13 (10.9)

$T_{\max}$ is expressed as median (min, max), $t_{1/2}$ is expressed as mean (SD).

Table 28 Summary of Pharmacokinetic Parameters of Released 9106-IM-2 After Multiple (the 3rd) Intravenous Infusions of SHR-A1811 in Study

SHR-A1811-I-101									
PK Parameters	Units	4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	25	0.368 (0.117, 2.99)	17	0.368 (0.116, 1.06)	21	0.370 (0.112, 2.95)	9	0.372 (0.106, 2.96)
C _{max}	ng/mL	25	2.39 (40.4)	17	2.50 (26.9)	21	3.41 (34.4)	9	3.70 (30.1)
AUC _{ss}	day*ng/mL	23	14.9 (31.2)	17	17.2 (28.7)	21	23.0 (32.2)	8	24.9 (15.6)
AUC _{INF}	day*ng/mL	23	16.2 (30.2)	17	19.1 (29.0)	21	25.3 (32.5)	8	28.2 (14.6)
t _{1/2}	day	23	5.97 (0.993)	17	6.36 (0.917)	21	6.23 (0.949)	8	7.12 (1.03)
Rac_AUC		23	1.01 (24.3)	16	0.971 (18.8)	21	1.05 (19.0)	8	1.05 (8.42)
TEI		23	0.965 (24.0)	15	0.921 (17.9)	21	0.970 (18.3)	8	0.965 (9.3)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).

6.1.1.2. Study SHR-A1811-I-102

As of 03 April 2024, intensive PK data of 3.2, 4.8, 6.4 and 8.0 mg/kg was available. PK parameters were calculated using actual sampling time, actual administration time and actual administration dose. Preliminary PK data shows that, in the dose range of 3.2-8.0 mg/kg, the exposure of ADC and total antibody were similar at each dose level, and increased with the increasing dose. The average elimination half-life of ADC after single administration was about 4.9-7.2 days, and showed increased trend with the increasing dose, while the clearance of SHR-A1811 showed decreased trend with the increasing dose, and the geometric mean volume of distribution is about 4.2-5.2 L. After multiple intravenous infusions of SHR-A1811, mild accumulation of total antibody and ADC was observed. Within the dose range of 3.2-8.0 mg/kg, the half-life of released 9106-IM-2 averaged about 4.8 to 6.4 days after a single administration. No accumulation of released 9106-IM-2 was observed after multiple intravenous infusions of SHR-A1811.

Table 29 Summary of Pharmacokinetic Parameters of ADC After a Single Intravenous Infusion of SHR-A1811 in Study SHR-A1811-I-102

PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	0.0653 (0.0604, 0.144)	12	0.0667 (0.0590, 0.0715)	12	0.0639 (0.0569, 0.145)	6	0.0667 (0.0625, 0.156)
C _{max}	µg/mL	3	64.6 (8.64)	12	89.1 (18.4)	12	120 (19.6)	6	152 (22.5)
AUC _{0-21d}	day*µg/mL	3	321 (3.40)	11	481 (23.0)	11	615 (28.6)	6	890 (20.4)
AUC _{INF}	day*µg/mL	3	337 (2.05)	11	543 (26.7)	11	687 (33.0)	6	1020 (22.3)
t _{1/2}	day	3	4.91 (0.444)	11	6.96 (1.40)	11	6.54 (1.88)	6	7.19 (2.20)
V _{ss}	L	3	4.21 (28.4)	11	5.15 (28.0)	11	4.59 (28.5)	6	4.57 (18.9)
Cl	L/day	3	0.624 (22.6)	11	0.560 (28.8)	11	0.546 (32.5)	6	0.487 (21.2)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).**Table 30 Summary of Pharmacokinetic Parameters of Total antibody After a Single Intravenous Infusion of SHR-A1811 in Study SHR-A1811-I-102**

PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	0.0653 (0.0604, 0.144)	10	0.0684 (0.0590, 0.153)	9	0.0646 (0.0569, 0.144)	6	0.0667 (0.0625, 0.156)
C _{max}	µg/mL	3	68.0 (4.91)	10	94.6 (18.0)	9	122 (21.1)	6	159 (23.2)
AUC _{0-21d}	day*µg/mL	3	336 (4.61)	9	523 (26.8)	9	623 (30.9)	6	925 (19.2)
AUC _{INF}	day*µg/mL	3	355 (3.09)	9	596 (31.1)	9	701 (35.8)	6	1080 (21.0)
t _{1/2}	day	3	5.08 (0.534)	9	7.22 (1.44)	9	6.71 (2.15)	6	7.68 (2.41)
V _{ss}	L	3	4.13 (28.1)	9	4.96 (23.7)	9	4.57 (28.6)	6	4.58 (21.5)
Cl	L/day	3	0.593 (23.4)	9	0.521 (25.5)	9	0.535 (30.2)	6	0.460 (20.6)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).

Table 31 Summary of Pharmacokinetic Parameters of Released 9106-IM-2 After a Single Intravenous Infusion of SHR-A1811 (Mean ± SD) in Study

SHR-A1811-I-102									
PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	1.04 (0.394, 3.06)	11	0.399 (0.153, 1.07)	12	0.399 (0.141, 1.04)	6	0.399 (0.395, 1.03)
C _{max}	ng/mL	3	2.77 (23.7)	11	2.98 (62.8)	12	3.76 (50.3)	6	5.83 (97.1)
AUC _{0-21d}	day·ng/mL	3	16.6 (37.6)	9	17.0 (69.4)	11	19.8 (51.4)	5	24.6 (17.4)
AUC _{INF}	day·ng/mL	3	17.3 (38.3)	9	18.7 (73.9)	11	21.1 (52.8)	5	26.3 (18.2)
t _{1/2}	day	3	4.78 (0.321)	9	6.43 (1.65)	11	5.22 (1.33)	5	5.46 (1.02)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).**Table 32 Summary of Pharmacokinetic Parameters of ADC After Multiples Intravenous Infusions of SHR-A1811 in Study SHR-A1811-I-102**

PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	0.122 (0.0243, 0.360)	9	0.108 (0.0160, 0.353)	5	0.0361 (0.0236, 0.113)	1	0.0333 (0.0333, 0.0333)
C _{max}	μg/mL	3	60.8 (6.80)	9	100 (18.9)	5	108 (12.6)	1	121 (NaN)
AUC _{ss}	day*μg/mL	3	344 (12.5)	9	688 (29.2)	4	665 (15.8)	1	849 (NaN)
AUC _{INF}	day*μg/mL	3	380 (16.4)	9	813 (35.1)	4	767 (22.9)	1	1040 (NaN)
t _{1/2}	day	3	6.24 (1.62)	9	7.95 (1.58)	4	7.30 (2.01)	1	8.77 (NaN)
CL _{ss}	L/day	3	0.588 (13.3)	9	0.442 (37.3)	4	0.557 (18.3)	1	0.498 (NaN)
V _{ss}	L	3	4.83 (35.4)	9	4.77 (30.0)	4	5.52 (10.3)	1	6.01 (NaN)
Rac_AUC		3	1.07 (15.3)	9	1.41 (18.6)	3	1.37 (11.1)	1	1.22 (NaN)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).

Table 33 Summary of Pharmacokinetic Parameters of Total Antibody After Multiples Intravenous Infusions of SHR-A1811 in Study SHR-A1811-I-**102**

PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	0.122 (0.0243, 0.360)	9	0.0431 (0.0160, 0.353)	5	0.0361 (0.0236, 0.113)	1	0.117 (0.117, 0.117)
C _{max}	µg/mL	3	63.8 (7.96)	9	106 (19.8)	5	117 (11.4)	1	117 (NaN)
AUC _{ss}	day*µg/mL	3	361 (14.3)	9	725 (31.8)	4	721 (16.5)	1	827 (NaN)
AUC _{INF}	day*µg/mL	3	396 (17.6)	9	881 (39.8)	4	839 (23.6)	1	1010 (NaN)
t _{1/2}	day	3	6.03 (1.37)	9	8.65 (1.93)	4	7.76 (2.13)	1	8.84 (NaN)
CL _{ss}	L/day	3	0.561 (11.5)	9	0.419 (40.2)	4	0.514 (20.2)	1	0.511 (NaN)
V _{ss}	L	3	4.61 (32.3)	9	4.84 (29.4)	4	5.21 (9.68)	1	6.27 (NaN)
Rac_AUC		3	1.07 (17.9)	7	1.25 (12.8)	3	1.38 (17.7)	1	1.15 (NaN)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).**Table 34 Summary of Pharmacokinetic Parameters of Released 9106-IM-2 After Multiples Intravenous Infusions of SHR-A1811 in Study SHR-A1811-I-102**

PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		6.4 mg/kg		8.0 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	0.994 (0.360, 1.04)	9	0.367 (0.358, 14.0)	5	0.366 (0.360, 0.992)	1	0.369 (0.369, 0.369)
C _{max}	ng/mL	3	2.88 (20.9)	9	2.84 (49.2)	5	2.74 (13.4)	1	2.97 (NaN)
AUC _{ss}	day*ng/mL	3	15.8 (30.9)	9	18.4 (83.1)	3	15.9 (19.2)	1	18.2 (NaN)
AUC _{INF}	day*ng/mL	3	17.6 (37.0)	8	18.1 (81.1)	3	17.6 (24.1)	1	20.5 (NaN)
t _{1/2}	day	3	6.18 (1.53)	8	5.85 (1.45)	3	6.11 (1.19)	1	6.56 (NaN)
Rac_AUC		3	0.953 (9.09)	7	1.04 (26.3)	3	0.899 (30.4)	1	0.770 (NaN)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).

6.1.1.3. Study SHR-A1811-I-103

As of 13 May 2024, the PK evaluations after single and multiple doses in the SHR-A1811-I-103 study, including the 3.2, 4.8, 5.6, 6.4, and 8.0 mg/kg dose groups, have been completed. PK data shows that, in the dose range of 3.2-8.0 mg/kg, the exposure of ADC and total antibody were similar at each dose level, and increased with the increasing dose. The average elimination half-life of ADC after single administration was about 5.07-7.42 days, and the geometric mean volume of distribution was about 3.62-4.15 L. After multiple intravenous infusions of SHR-A1811, mild accumulation of total antibody and ADC was observed after multiple administration. After a single administration of SHR-A1811, exposure of released 9106-IM-2 was low. Within the dose range of 3.2 to 8.0 mg/kg, the half-life of released 9106-IM-2 averaged about 4.74 to 5.68 days after a single administration. No accumulation of released 9106-IM-2 was observed after multiple intravenous infusions of SHR-A1811.

Table 35 Summary of Pharmacokinetic Parameters of ADC After a Single Intravenous Infusion of SHR-A1811 in Study SHR-A1811-I-103

PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	0.0688 (0.0639, 0.0701)	43	0.0632 (0.0590, 0.381)	11	0.0660 (0.0611, 0.165)	3	0.0625 (0.0576, 0.0625)	3	0.0625 (0.0625, 0.0625)
C _{max}	μg/mL	3	76.3 (11.4)	43	104 (20.1)	11	132 (12.9)	3	162 (17.7)	3	174 (12.9)
AUC _{0-21d}	day*μg/mL	3	390 (9.90)	41	578 (22.2)	10	740 (11.1)	3	736 (10.5)	3	954 (25.0)
	day*μg/mL	3	411 (9.59)	41	640 (24.6)	10	837 (12.7)	3	817 (21.0)	3	1110 (40.5)
AUC _{INF}	day	3	5.07 (0.376)	41	6.35 (1.00)	10	6.91 (0.979)	3	6.47 (3.36)	3	7.42 (3.46)
Cl	L/day	3	0.502 (11.8)	41	0.452 (24.8)	10	0.401 (20.3)	3	0.534 (41.9)	3	0.406 (44.3)
V _{ss}	L	3	3.61 (11.2)	41	3.89 (22.5)	10	3.75 (20.5)	3	4.13 (45.8)	3	3.78 (11.5)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).

Table 36 Summary of Pharmacokinetic Parameters of Total antibody After a Single Intravenous Infusion of SHR-A1811 in Study SHR-A1811-I-103

PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	0.0688 (0.0639, 0.0701)	43	0.0632 (0.0583, 0.147)	11	0.0653 (0.0604, 0.147)	3	0.0625 (0.0625, 0.140)	3	0.0625 (0.0625, 0.146)
C _{max}	μg/mL	3	72.2 (8.80)	43	106 (20.1)	11	130 (13.0)	3	156 (18.9)	3	171 (8.95)
AUC _{0-21d}	day*μg/mL	3	366 (11.2)	42	576 (22.6)	10	744 (11.2)	3	729 (8.94)	3	933 (23.0)
AUC _{INF}	day*μg/mL	3	387 (10.9)	42	644 (25.6)	10	847 (13.0)	3	817 (21.0)	3	1090 (39.0)
t _{1/2}	day	3	5.14 (0.258)	42	6.65 (1.22)	10	7.14 (0.947)	3	6.62 (3.67)	3	7.57 (3.59)
Cl	L/day	3	0.534 (10.6)	42	0.451 (25.7)	10	0.396 (18.1)	3	0.534 (41.3)	3	0.412 (42.5)
V _{ss}	L	3	3.91(11.3)	42	4.03 (22.5)	10	3.82 (16.9)	3	4.34 (45.4)	3	3.94 (12.8)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).**Table 37 Summary of Pharmacokinetic Parameters of Released 9106-IM-2 After a Single Intravenous Infusion of SHR-A1811 in Study SHR-A1811-I-103**

PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	0.398 (0.396, 0.401)	43	0.396 (0.146, 1.06)	11	0.396 (0.147, 1.02)	3	0.396 (0.389, 0.396)	3	1.06 (0.396, 1.06)
C _{max}	ng/mL	3	1.53 (11.6)	43	2.45 (43.3)	11	2.49 (26.0)	3	4.36 (53.8)	3	3.78 (25.9)
AUC _{0-21d}	day*ng/mL	3	8.54 (8.65)	41	13.4 (36.1)	10	14.6(20.9)	4	22.4 (28.9)	3	22.5 (432.4)
AUC _{INF}	day*ng/mL	3	8.93 (8.63)	40	14.3 (35.9)	10	15.7 (20.2)	3	23.8 (29.0)	3	24.2 (32.3)
t _{1/2}	day	3	4.74 (0.0395)	40	5.19 (0.628)	10	5.68 (1.15)	3	5.33 (1.46)	3	5.49 (1.11)

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).

Table 38 Summary of Pharmacokinetic Parameters of ADC After Multiples Intravenous Infusions of SHR-A1811 in Study SHR-A1811-I-103

PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	0.124 (0.115, 0.132)	38	0.0333 (0.0208, 0.125)	8	0.0354 (0.0215, 0.115)	1	0.0208 (0.0208, 0.0208)	-	-
C _{max}	µg/mL	3	70.2 (8.71)	38	118 (18.1)	8	137 (13.9)	1	160 (NaN)	-	-
AUC _{ss}	day*µg/m	3	470 (11.9)	35	843 (21.5)	7	1010 (9.11)	1	897 (NaN)	-	-
	L									-	-
AUC _{INF}	day*µg/m	3	522 (9.70)	35	987 (26.7)	7	1180 (10.4)	1	945 (NaN)	-	-
	L									-	-
t _{1/2}	day	3	6.72 (0.816)	35	7.95 (1.75)	7	7.97 (0.824)	1	4.84 (NaN)	-	-
CL _{ss}	L/day	3	0.439 (9.55)	35	0.348 (22.0)	7	0.325 (16.5)	1	0.357 (NaN)	-	-
V _{ss}	L	3	3.80(5.50)	35	3.57 (22.4)	7	3.43 (19.7)	1	2.48 (NaN)	-	-
Rac AUC		3	1.21 (1.97)	36	1.46 (20.7)	6	1.40 (12.1)	1	1.18 (NaN)	-	-

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).**Table 39 Summary of Pharmacokinetic Parameters of Total Antibody After Multiples Intravenous Infusions of SHR-A1811 in Study SHR-A1811-I-**

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PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	0.115 (0.0389, 0.132)	38	0.104 (0.0208, 0.125)	8	0.104 (0.0333, 0.115)	1	0.0208 (0.0208, 0.0208)	-	-
C _{max}	µg/mL	3	69.7 (11.2)	38	120 (15.6)	8	138 (12.6)	1	157 (NaN)	-	-
AUC _{ss}	day*µg/m	3	472 (10.3)	36	861 (21.1)	7	1050 (9.3)	1	909 (NaN)	-	-
	L									-	-
AUC _{INF_obs}	day*µg/m	3	527 (7.83)	36	1010 (26.4)	6	1240 (11.3)	1	962 (NaN)	-	-
	L									-	-
t _{1/2}	day	3	6.84 (1.10)	36	8.10 (1.74)	6	8.32 (1.02)	1	4.94 (NaN)	-	-
CL _{ss}	L/day	3	0.437 (11.3)	36	0.339 (21.3)	6	0.313 (16.7)	1	0.352 (NaN)	-	-

PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
V _{ss}	L	3	3.89 (11.7)	36	3.50 (20.3)	6	3.49 (22.4)	1	2.50 (NaN)	-	-
Rac_AUC		3	1.29 (1.01)	36	1.50 (18.8)	6	1.43 (6.57)	1	1.21 (NaN)	-	-

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).

Table 40 Summary of Pharmacokinetic Parameters of Released 9106-IM-2 After Multiples Intravenous Infusions of SHR-A1811 in Study SHR-A1811-I-103

PK Parameters	Units	3.2 mg/kg		4.8 mg/kg		5.6 mg/kg		6.4 mg/kg		8 mg/kg	
		N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)	N	Geomean (GeoCV%)
T _{max}	day	3	0.124 (0.115, 0.132)	38	0.104 (0.102, 7.02)	8	0.110 (0.103, 0.119)	1	0.105 (0.105, 0.105)	-	-
C _{max}	ng/mL	3	1.05 (11.9)	38	1.54 (44.6)	8	1.91 (26.7)	1	2.54 (NaN)	-	-
AUC _{ss}	day*ng/mL	3	6.73(22.7)	30	12.3(29.5)	6	14.0(15.8)	1	13.0 (NaN)	-	-
AUC _{INF}	day*ng/mL	3	7.26 (21.7)	29	13.8 (27.4)	5	15.3 (18.2)	1	13.8 (NaN)	-	-
t _{1/2}	day	3	5.67 (0.497)	29	6.23 (1.00)	5	6.65 (1.40)	1	5.61 (NaN)	-	-
Rac_AUC		3	0.788 (15.1)	30	0.892 (19.5)	5	0.976 (7.89)	1	0.766 (NaN)	-	-

T_{max} is expressed as median (min, max), t_{1/2} is expressed as mean (SD).

6.2. Safety and Efficacy

6.2.1. Safety

The clinical safety data presented in this section are from the clinical studies summarized in [Table 22](#), which included 25 studies that were still ongoing as of 13 May 2025. The study indications include breast cancer, gastric cancer or gastroesophageal junction adenocarcinoma, colorectal cancer, non-small cell lung cancer, biliary cancer and ovarian cancer, etc.

Apart from the 8 pivotal, ongoing randomized, open-label with treatment-masked studies, a pooled safety analysis was carried out for the remaining 17 SHR-A1811 clinical studies. The safety analysis has been summarized in the following population categories: SHR-A1811 monotherapy, SHR-A1811 in combination with adabrelimab, SHR-A1811 in combination with pertuzumab, and SHR-A1811 in combination with other drugs. The studies pooled in each category are listed as follows. Safety data from these studies are presented as pooled data.

SHR-A1811 monotherapy:

- SHR-A1811-I-101
- SHR-A1811-I-102
- SHR-A1811-I-103
- SHR-A1811-I-105
- SHR-A1811-II-203 (Phase II: SHR-A1811 monotherapy group)
- SHR-A1811-206 (SHR-A1811 monotherapy group)
- SHR-A1811-209
- SHR-A1811-212

SHR-A1811 in combination with adabrelimab:

- SHR-A1811-II-202 (SHR-A1811 combined with adabrelimab group)
- SHR-A1811-II-203 (Phase I Part B & Phase II: SHR-A1811 combined with adabrelimab group)
- SHR-A1811-213
- SHR-A1811-215 (SHR-A1811 combined with adabrelimab group);

SHR-A1811 in combination with pertuzumab:

- SHR-A1811-II-202 (SHR-A1811 combined with pertuzumab group);

SHR-A1811 in combination with other drugs:

- SHR-A1811-II-201 (SHR-A1811 combined with fuzuloparib group)
- SHR-A1811-II-202 (SHR-A1811 combined with pyrotinib group)
- SHR-A1811-II-202 (SHR-A1811 combined with paclitaxel-albumin group)
- SHR-A1811-II-203 (Phase I Part A: SHR-A1811 combined with pyrotinib group)
- SHR-A1811-Ib/II-205 (SHR-A1811 combined with SHR-1701 and capecitabine group)
- SHR-A1811-Ib/II-205 (SHR-A1811 combined with SHR-1701 group)
- SHR-A1811-Ib/II-205 (Phase I Part B & Phase II: SHR-A1811 combined with capecitabine group)
- SHR-A1811-Ib/II-205 (Phase I Part B & Phase II: SHR-A1811 combined with adabrelimab and capecitabine group)
- SHR-A1811-Ib/II-205 (Phase I Part B & Phase II: SHR-A1811 combined with adabrelimab, oxaliplatin and capecitabine group)

- SHR-A1811-Ib/II-205 (Phase I Part B & Phase II: SHR-A1811 combined with adabrelinab and 5-FU group)
- SHR-A1811-206 (SHR-A1811 combined with fulvestrant group)
- SHR-A1811-206 (SHR-A1811 combined with letrozole/anastrozole group)
- SHR-A1811-207 (SHR-A1811 combined with capecitabine group)
- SHR-A1811-208 (SHR-A1811 combined with pyrotinib group)
- SHR-A1811-208 (SHR-A1811 + calcium levofolinate + 5-FU)
- SHR-A1811-208 (SHR-A1811 + calcium levofolinate + 5-FU + oxaliplatin)
- SHR-A1811-208 (SHR-A1811 + calcium levofolinate + 5-FU + bevacizumab)
- SHR-A1811-208 (SHR-A1811 + calcium levofolinate + 5-FU + oxaliplatin + bevacizumab)
- SHR-A1811-208 (SHR-A1811+bevacizumab)
- SHR-A1811-216-OC (SHR-A1811 combined with carboplatin and bevacizumab group)
- SHR-A1811-216-OC (SHR-A1811 combined with bevacizumab group)
- HRS-8080-202 (SHR-A1811 combined with HRS-8080);

For the ongoing 8 pivotal, random, open-label with treatment-masked studies, only all-causality AEs/SAEs/deaths/AESIs were available and safety data are presented in a treatment masked format for each study separately to preserve the blinded integrity of these ongoing pivotal studies. These studies are listed as follows: SHR-A1811-III-301, SHR-A1811-305, SHR-A1811-III-306, SHR-A1811-307, SHR-A1811-308, SHR-A1811-309, SHR-A1811-310 and SHR-A1811-315.

AEs in this IB are all treatment-emergent adverse events (TEAEs). Treatment-related adverse events (TRAEs) refer to any TEAEs assessed by the investigators as “definitely related”, “possibly related”, or “unassessable” to any study drug (including SHR-A1811, pyrotinib, fuzuloparib, pertuzumab, adabrelinab, fulvestrant, SHR-1701, letrozole, anastrozole, dalpiciclib, calcium levofolinate, 5-FU, oxaliplatin, bevacizumab, capecitabine, paclitaxel-albumin, HRS-8080, adabrelinab, SHR-8068, carboplatin). SHR-A1811 related AEs refer to any TEAEs related to SHR-A1811. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 28.0, and displayed by System Organ Class (SOC) and Preferred Term (PT).

Unless otherwise noted, all safety data available in the clinical database through 13 May 2025 have been used to generate this report.

6.2.1.1. SHR-A1811 Monotherapy

The studies included in the pooled safety analysis of subjects receiving SHR-A1811 monotherapy were SHR-A1811-I-101, SHR-A1811-I-102, SHR-A1811-I-103, SHR-A1811-I-105, SHR-A1811-II-203, SHR-A1811-206 and SHR-A1811-209, and SHR-A1811-212. A total of 853 subjects were exposed to SHR-A1811 monotherapy.

6.2.1.1.1. AEs

The incidence of TEAEs and Grade ≥ 3 TEAEs were 99.4% (848/853) and 74.7% (637/853), respectively ([Table 41](#)).

The most commonly reported TEAEs with an incidence of $\geq 10\%$ included neutrophil count decreased (82.2%), anaemia (81.4%), white blood cell count decreased (76.6%),

nausea (61.1%), platelet count decreased (50.8%), vomiting (45.0%), decreased appetite (43.1%), alopecia (39.4%), aspartate aminotransferase increased (39.2%), alanine aminotransferase increased (35.9%), hypoalbuminaemia (34.7%), weight decreased (31.8%), gamma-glutamyltransferase increased (26.5%), hypertriglyceridaemia (26.4%), proteinuria (25.4%), lymphocyte count decreased (22.9%), blood alkaline phosphatase increased (22.2%), urinary tract infection (21.7%), hyperglycaemia (21.6%), hypokalaemia (21.1%), blood lactate dehydrogenase increased (20.5%), diarrhea (20.3%), fatigue (19.9%), hyponatraemia (19.2%), constipation (18.4%), hyperuricaemia (17.8%), COVID-19 (17.2%), asthenia (15.4%), pyrexia (15.2%), stomatitis (14.2%), upper respiratory tract infection (13.5%), hypercholesterolaemia (12.9%), hypocalcaemia (12.8%), cough (12.7%), blood creatinine increased, blood bilirubin increased (11.5% each), dizziness (11.1%), pneumonia (10.4%).

The Grade ≥ 3 TEAEs with an incidence of $\geq 2\%$ included neutrophil count decreased (49.8%), white blood cell count decreased (34.7%), anaemia (28.1%), platelet count decreased (19.9%), lymphocyte count decreased (10.0%), hypokalaemia (4.8%), pneumonia (3.4%), gamma-glutamyltransferase increased (3.0%), febrile neutropenia (2.7%), neoplasm progression (2.2%).

Table 41 TEAEs with an Incidence $\geq 5\%$ or Grade ≥ 3 TEAEs with an Incidence $\geq 1\%$ of

Subjects in the SHR-A1811 Monotherapy Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853) n (%)	
	All Grades	Grade ≥ 3
Subjects with any TEAE	848 (99.4)	637 (74.7)
Investigations	795 (93.2)	519 (60.8)
Neutrophil count decreased	701 (82.2)	425 (49.8)
White blood cell count decreased	653 (76.6)	296 (34.7)
Platelet count decreased	433 (50.8)	170 (19.9)
Aspartate aminotransferase increased	334 (39.2)	10 (1.2)
Alanine aminotransferase increased	306 (35.9)	12 (1.4)
Weight decreased	271 (31.8)	3 (0.4)
Gamma-glutamyltransferase increased	226 (26.5)	26 (3.0)
Lymphocyte count decreased	195 (22.9)	85 (10.0)
Blood alkaline phosphatase increased	189 (22.2)	4 (0.5)
Blood lactate dehydrogenase increased	175 (20.5)	0
Blood bilirubin increased	98 (11.5)	13 (1.5)
Blood creatinine increased	98 (11.5)	1 (0.1)
Weight increased	84 (9.8)	2 (0.2)
Blood cholesterol increased	79 (9.3)	0
Fibrin D dimer increased	62 (7.3)	0
Electrocardiogram QT prolonged	57 (6.7)	9 (1.1)
Bilirubin conjugated increased	52 (6.1)	8 (0.9)
White blood cells urine positive	51 (6.0)	0

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853) n (%)	
	All Grades	Grade ≥ 3
Blood thyroid stimulating hormone increased	46 (5.4)	0
Blood creatine phosphokinase increased	44 (5.2)	3 (0.4)
Gastrointestinal disorders	718 (84.2)	75 (8.8)
Nausea	521 (61.1)	7 (0.8)
Vomiting	384 (45.0)	10 (1.2)
Diarrhoea	173 (20.3)	13 (1.5)
Constipation	157 (18.4)	0
Stomatitis	121 (14.2)	7 (0.8)
Abdominal pain	70 (8.2)	2 (0.2)
Mouth ulceration	54 (6.3)	0
Abdominal distension	44 (5.2)	0
Blood and lymphatic system disorders	703 (82.4)	251 (29.4)
Anaemia	694 (81.4)	240 (28.1)
Febrile neutropenia	23 (2.7)	23 (2.7)
Metabolism and nutrition disorders	684 (80.2)	91 (10.7)
Decreased appetite	368 (43.1)	15 (1.8)
Hypoalbuminaemia	296 (34.7)	2 (0.2)
Hypertriglyceridaemia	225 (26.4)	16 (1.9)
Hyperglycaemia	184 (21.6)	5 (0.6)
Hypokalaemia	180 (21.1)	41 (4.8)
Hyponatraemia	164 (19.2)	10 (1.2)
Hyperuricaemia	152 (17.8)	0
Hypercholesterolaemia	110 (12.9)	1 (0.1)
Hypocalcaemia	109 (12.8)	3 (0.4)
Hypomagnesaemia	51 (6.0)	4 (0.5)
Hypophosphataemia	46 (5.4)	1 (0.1)
General disorders and administration site conditions	495 (58.0)	42 (4.9)
Fatigue	170 (19.9)	7 (0.8)
Asthenia	131 (15.4)	8 (0.9)
Pyrexia	130 (15.2)	4 (0.5)
Malaise	78 (9.1)	4 (0.5)
Influenza like illness	62 (7.3)	0
Chest discomfort	45 (5.3)	2 (0.2)
Death	13 (1.5)	13 (1.5)
Infections and infestations	466 (54.6)	105 (12.3)
Urinary tract infection	185 (21.7)	10 (1.2)
COVID-19	147 (17.2)	5 (0.6)
Upper respiratory tract infection	115 (13.5)	7 (0.8)
Pneumonia	89 (10.4)	29 (3.4)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853) n (%)	
	All Grades	Grade ≥ 3
Skin and subcutaneous tissue disorders	408 (47.8)	5 (0.6)
Alopecia	336 (39.4)	1 (0.1)
Rash	60 (7.0)	1 (0.1)
Skin hyperpigmentation	59 (6.9)	0
Respiratory, thoracic and mediastinal disorders	278 (32.6)	27 (3.2)
Cough	108 (12.7)	0
Epistaxis	52 (6.1)	3 (0.4)
Renal and urinary disorders	273 (32.0)	18 (2.1)
Proteinuria	217 (25.4)	3 (0.4)
Haematuria	60 (7.0)	2 (0.2)
Nervous system disorders	228 (26.7)	11 (1.3)
Dizziness	95 (11.1)	2 (0.2)
Headache	54 (6.3)	3 (0.4)
Cardiac disorders	224 (26.3)	8 (0.9)
Sinus tachycardia	53 (6.2)	0
Sinus bradycardia	45 (5.3)	0
Musculoskeletal and connective tissue disorders	148 (17.4)	9 (1.1)
Back pain	43 (5.0)	1 (0.1)
Vascular disorders	88 (10.3)	16 (1.9)
Hypertension	34 (4.0)	9 (1.1)
Endocrine disorders	67 (7.9)	0
Hypothyroidism	57 (6.7)	0
Psychiatric disorders	63 (7.4)	2 (0.2)
Insomnia	53 (6.2)	2 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	43 (5.0)	30 (3.5)
Neoplasm progression	19 (2.2)	19 (2.2)
Malignant neoplasm progression	9 (1.1)	9 (1.1)

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

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

Coded using MedDRA Version 28.0.

6.2.1.1.2. Treatment-Related AEs

The incidence of TRAEs (SHR-A1811 related AEs) and Grade ≥ 3 TRAEs were 98.7% (842/853) and 67.8% (578/853), respectively ([Table 42](#)).

The TRAEs with an incidence of $\geq 10\%$ included neutrophil count decreased (81.8%), anaemia (79.0%), white blood cell count decreased (76.3%), nausea (60.4%), platelet count decreased (50.3%), vomiting (43.3%), decreased appetite (41.5%), alopecia (39.4%), aspartate aminotransferase increased (37.4%), alanine aminotransferase increased (34.0%), hypoalbuminaemia (29.5%), weight decreased (26.3%), gamma-

glutamyltransferase increased (24.2%), lymphocyte count decreased (22.2%), hypertriglyceridaemia (20.4%), proteinuria (20.3%), blood alkaline phosphatase increased (19.6%), fatigue (18.9%), blood lactate dehydrogenase increased (17.7%), hyperglycaemia (17.6%), hypokalaemia (16.1%), hyponatraemia (15.2%), diarrhoea (15.1%), asthenia (14.3%), hyperuricaemia (14.2%), stomatitis (13.6%), constipation (13.4%), urinary tract infection (12.8%), hypocalcaemia (10.3%), blood bilirubin increased (10.0%).

The Grade ≥ 3 TRAEs with an incidence of $\geq 2\%$ included neutrophil count decreased (49.4%), white blood cell count decreased (34.6%), anaemia (27.0%), platelet count decreased (19.2%), lymphocyte count decreased (9.4%), hypokalaemia (4.1%), febrile neutropenia (2.7%), gamma-glutamyltransferase increased (2.5%).

Table 42 TRAEs with an Incidence $\geq 5\%$ or Grade ≥ 3 TRAEs with an Incidence $\geq 1\%$ of

Subjects in the SHR-A1811 Monotherapy Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853) n (%)	
	All Grades	Grade ≥ 3
Subjects with any TRAE	842 (98.7)	578 (67.8)
Investigations	779 (91.3)	509 (59.7)
Neutrophil count decreased	698 (81.8)	421 (49.4)
White blood cell count decreased	651 (76.3)	295 (34.6)
Platelet count decreased	429 (50.3)	164 (19.2)
Aspartate aminotransferase increased	319 (37.4)	6 (0.7)
Alanine aminotransferase increased	290 (34.0)	10 (1.2)
Weight decreased	224 (26.3)	2 (0.2)
Gamma-glutamyltransferase increased	206 (24.2)	21 (2.5)
Lymphocyte count decreased	189 (22.2)	80 (9.4)
Blood alkaline phosphatase increased	167 (19.6)	3 (0.4)
Blood lactate dehydrogenase increased	151 (17.7)	0
Blood bilirubin increased	85 (10.0)	4 (0.5)
Blood creatinine increased	80 (9.4)	0
Blood cholesterol increased	68 (8.0)	0
Electrocardiogram QT prolonged	47 (5.5)	9 (1.1)
Bilirubin conjugated increased	43 (5.0)	4 (0.5)
Gastrointestinal disorders	690 (80.9)	43 (5.0)
Nausea	515 (60.4)	7 (0.8)
Vomiting	369 (43.3)	9 (1.1)
Diarrhoea	129 (15.1)	9 (1.1)
Stomatitis	116 (13.6)	7 (0.8)
Constipation	114 (13.4)	0
Mouth ulceration	48 (5.6)	0
Blood and lymphatic system disorders	680 (79.7)	241 (28.3)
Anaemia	674 (79.0)	230 (27.0)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853)	
	n (%)	
	All Grades	Grade ≥ 3
Febrile neutropenia	23 (2.7)	23 (2.7)
Metabolism and nutrition disorders	631 (74.0)	70 (8.2)
Decreased appetite	354 (41.5)	13 (1.5)
Hypoalbuminaemia	252 (29.5)	0
Hypertriglyceridaemia	174 (20.4)	11 (1.3)
Hyperglycaemia	150 (17.6)	4 (0.5)
Hypokalaemia	137 (16.1)	35 (4.1)
Hyponatraemia	130 (15.2)	8 (0.9)
Hyperuricaemia	121 (14.2)	0
Hypocalcaemia	88 (10.3)	2 (0.2)
Hypercholesterolaemia	79 (9.3)	0
Hypomagnesaemia	47 (5.5)	3 (0.4)
General disorders and administration site conditions	402 (47.1)	24 (2.8)
Fatigue	161 (18.9)	7 (0.8)
Asthenia	122 (14.3)	7 (0.8)
Malaise	74 (8.7)	3 (0.4)
Pyrexia	68 (8.0)	2 (0.2)
Skin and subcutaneous tissue disorders	398 (46.7)	4 (0.5)
Alopecia	336 (39.4)	1 (0.1)
Skin hyperpigmentation	59 (6.9)	0
Rash	51 (6.0)	1 (0.1)
Infections and infestations	209 (24.5)	38 (4.5)
Urinary tract infection	109 (12.8)	4 (0.5)
Pneumonia	37 (4.3)	12 (1.4)
Renal and urinary disorders	203 (23.8)	5 (0.6)
Proteinuria	173 (20.3)	1 (0.1)
Nervous system disorders	172 (20.2)	2 (0.2)
Dizziness	78 (9.1)	0
Endocrine disorders	55 (6.4)	0
Hypothyroidism	47 (5.5)	0

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SOC=system organ class, TRAE=treatment-related adverse event.

Coded using MedDRA Version 28.0.

6.2.1.1.3. AEs Associated with Permanent Discontinuation of SHR-A1811

Sixty-seven (67/853, 7.9%) subjects had TEAEs leading to permanent discontinuation of SHR-A1811, and these TEAEs that occurred in ≥2 subjects included interstitial lung disease (19 subjects, 2.2%), platelet count decreased (12 subjects, 1.4%), neutrophil count decreased, white blood cell count decreased (4 subjects each, 0.5%), vomiting, septic shock (3 subjects each, 0.4%), pneumonitis, gamma-glutamyltransferase increased, bilirubin conjugated increased, blood bilirubin increased, pneumonia, and

anaemia (2 subjects each, 0.2%) (Table 43).

Fifty-five (55/853, 6.4%) subjects had TRAEs leading to permanent discontinuation of SHR-A1811, and these TRAEs that occurred in ≥ 2 subjects included interstitial lung disease (19 subjects, 2.2%), platelet count decreased (12 subjects, 1.4%), neutrophil count decreased, white blood cell count decreased (4 subjects each, 0.5%), vomiting (3 subjects, 0.4%), pneumonitis, gamma-glutamyltransferase increased, and anaemia (2 subjects each, 0.2%) (Table 43).

Table 43 TEAEs and TRAEs Associated with Permanent Discontinuation of SHR-A1811 in the SHR-A1811 Monotherapy Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853) n (%)	
	TEAE	TRAE
Subjects with any TEAE Associated with Permanent Discontinuation of SHR-A1811	67 (7.9)	55 (6.4)
Respiratory, thoracic and mediastinal disorders	23 (2.7)	22 (2.6)
Uncoded	1 (0.1)	1 (0.1)
Interstitial lung disease	19 (2.2)	19 (2.2)
Pneumonitis	2 (0.2)	2 (0.2)
Dyspnoea	1 (0.1)	1 (0.1)
Organising pneumonia	1 (0.1)	0
Respiratory failure	1 (0.1)	1 (0.1)
Investigations	20 (2.3)	19 (2.2)
Platelet count decreased	12 (1.4)	12 (1.4)
Neutrophil count decreased	4 (0.5)	4 (0.5)
White blood cell count decreased	4 (0.5)	4 (0.5)
Bilirubin conjugated increased	2 (0.2)	1 (0.1)
Blood bilirubin increased	2 (0.2)	1 (0.1)
Gamma-glutamyltransferase increased	2 (0.2)	2 (0.2)
Amylase increased	1 (0.1)	1 (0.1)
Blood bilirubin unconjugated increased	1 (0.1)	0
Ejection fraction decreased	1 (0.1)	1 (0.1)
International normalised ratio increased	1 (0.1)	1 (0.1)
Lymphocyte count decreased	1 (0.1)	1 (0.1)
Gastrointestinal disorders	8 (0.9)	6 (0.7)
Vomiting	3 (0.4)	3 (0.4)
Colitis	1 (0.1)	1 (0.1)
Gastrooesophageal reflux disease	1 (0.1)	1 (0.1)
Haematemesis	1 (0.1)	0
Haematochezia	1 (0.1)	1 (0.1)
Intestinal fistula	1 (0.1)	0
Nausea	1 (0.1)	1 (0.1)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853) n (%)	
	TEAE	TRAE
Infections and infestations	8 (0.9)	4 (0.5)
Septic shock	3 (0.4)	1 (0.1)
Pneumonia	2 (0.2)	1 (0.1)
Pneumonia bacterial	1 (0.1)	1 (0.1)
Skin infection	1 (0.1)	0
Urinary tract infection	1 (0.1)	1 (0.1)
Blood and lymphatic system disorders	5 (0.6)	5 (0.6)
Anaemia	2 (0.2)	2 (0.2)
Febrile neutropenia	1 (0.1)	1 (0.1)
Myelosuppression	1 (0.1)	1 (0.1)
Pancytopenia	1 (0.1)	1 (0.1)
Cardiac disorders	3 (0.4)	2 (0.2)
Cardiac failure acute	1 (0.1)	1 (0.1)
Cardiac failure congestive	1 (0.1)	1 (0.1)
Pericardial effusion	1 (0.1)	0
General disorders and administration site conditions	3 (0.4)	3 (0.4)
Asthenia	1 (0.1)	1 (0.1)
Multiple organ dysfunction syndrome	1 (0.1)	1 (0.1)
Pain	1 (0.1)	1 (0.1)
Hepatobiliary disorders	3 (0.4)	3 (0.4)
Hepatic failure	1 (0.1)	1 (0.1)
Hepatic function abnormal	1 (0.1)	1 (0.1)
Liver injury	1 (0.1)	1 (0.1)
Nervous system disorders	3 (0.4)	2 (0.2)
Central nervous system necrosis	1 (0.1)	0
Hypoaesthesia	1 (0.1)	1 (0.1)
Seizure	1 (0.1)	1 (0.1)
Metabolism and nutrition disorders	2 (0.2)	2 (0.2)
Decreased appetite	1 (0.1)	1 (0.1)
Electrolyte imbalance	1 (0.1)	1 (0.1)
Renal and urinary disorders	2 (0.2)	1 (0.1)
Haematuria	1 (0.1)	0
Renal failure	1 (0.1)	1 (0.1)
Vascular disorders	2 (0.2)	1 (0.1)
Hypotension	1 (0.1)	1 (0.1)
Shock	1 (0.1)	0
Musculoskeletal and connective tissue disorders	1 (0.1)	0
Myalgia	1 (0.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1)	0

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853) n (%)	
	TEAE	TRAE
Leukaemia	1 (0.1)	0

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event,

TRAE=treatment-related adverse event.

Coded using MedDRA Version 28.0.

6.2.1.1.4. SAEs

A total of 325 (38.1%) subjects had SAEs, and SAEs with an incidence of $\geq 2\%$ included platelet count decreased (84 subjects, 9.8%), neutrophil count decreased (59 subjects, 6.9%), anaemia (57 subjects, 6.7%), white blood cell count decreased (51 subjects, 6.0%), pneumonia (32 subjects, 3.8%), febrile neutropenia (20 subjects, 2.3%), neoplasm progression (19 subjects, 2.2%) (Table 44).

A total of 216 (25.3%) subjects had SARs, and SARs with an incidence of $\geq 2\%$ included platelet count decreased (84 subjects, 9.8%), neutrophil count decreased (59 subjects, 6.9%), anaemia (52 subjects, 6.1%), white blood cell count decreased (51 subjects, 6.0%), febrile neutropenia (20 subjects, 2.3%) (Table 44).

Table 44 SAEs and SARs Reported in at Least 1% of Subjects in the SHR-A1811

Monotherapy Pool by Preferred Term		
System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853) n (%)	
	SAE	SAR
Subjects with any TE-SAE	325 (38.1)	216 (25.3)
Investigations	111 (13.0)	110 (12.9)
Platelet count decreased	84 (9.8)	84 (9.8)
Neutrophil count decreased	59 (6.9)	59 (6.9)
White blood cell count decreased	51 (6.0)	51 (6.0)
Infections and infestations	96 (11.3)	37 (4.3)
Pneumonia	32 (3.8)	14 (1.6)
Urinary tract infection	9 (1.1)	4 (0.5)
Blood and lymphatic system disorders	72 (8.4)	67 (7.9)
Anaemia	57 (6.7)	52 (6.1)
Febrile neutropenia	20 (2.3)	20 (2.3)
Gastrointestinal disorders	60 (7.0)	37 (4.3)
Vomiting	13 (1.5)	13 (1.5)
Respiratory, thoracic and mediastinal disorders	36 (4.2)	23 (2.7)
Interstitial lung disease	16 (1.9)	16 (1.9)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853) n (%)	
	SAE	SAR
General disorders and administration site conditions	32 (3.8)	16 (1.9)
Death	13 (1.5)	3 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	29 (3.4)	0
Neoplasm progression	19 (2.2)	0
Malignant neoplasm progression	9 (1.1)	0

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SAE=serious adverse event, SAR=serious adverse reaction, SOC=system organ class.

Coded using MedDRA Version 28.0.

6.2.1.1.5. AEs Associated with Outcome of Death

Sixty-five (65/853, 7.6%) subjects had TEAEs with an outcome of death, and these Fatal TEAEs that occurred in ≥ 2 subjects which included neoplasm progression (19 subjects, 2.2%), death (13 subjects, 1.5%), malignant neoplasm progression (9 subjects, 1.1%), pneumonia, septic shock (3 subjects each, 0.4%), multiple organ dysfunction syndrome, interstitial lung disease, and haemoptysis (2 subjects each, 0.2%) (Table 45).

Nine (9/853, 1.1%) subjects had TRAEs with an outcome of death, which were death (3 subjects, 0.4%), pneumonia, pancytopenia concurrent with colitis, pneumonia bacterial concurrent with interstitial lung disease, myelosuppression concurrent with multiple organ dysfunction syndrome and septic shock, interstitial lung disease, seizure (1 subject each, 0.1%) (Table 45).

Table 45 TEAEs Associated with Outcome of Death of SHR-A1811 in the SHR-A1811

Monotherapy Pool by Preferred Term		
System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853) n (%)	
	TEAE	TRAE
Subjects with any Fatal TEAE	65 (7.6)	9 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	28 (3.3)	0
Neoplasm progression	19 (2.2)	0
Malignant neoplasm progression	9 (1.1)	0
General disorders and administration site conditions	15 (1.8)	4 (0.5)
Death	13 (1.5)	3 (0.4)
Multiple organ dysfunction syndrome	2 (0.2)	1 (0.1)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 Monotherapy (N=853) n (%)	
	TEAE	TRAE
Infections and infestations	13 (1.5)	3 (0.4)
Pneumonia	3 (0.4)	1 (0.1)
Septic shock	3 (0.4)	1 (0.1)
Biliary tract infection	1 (0.1)	0
COVID-19	1 (0.1)	0
COVID-19 pneumonia	1 (0.1)	0
Device related infection	1 (0.1)	0
Pneumonia bacterial	1 (0.1)	1 (0.1)
Sepsis	1 (0.1)	0
Septic encephalopathy	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	6 (0.7)	2 (0.2)
Haemoptysis	2 (0.2)	0
Interstitial lung disease	2 (0.2)	2 (0.2)
Dyspnoea	1 (0.1)	0
Respiratory failure	1 (0.1)	0
Nervous system disorders	3 (0.4)	1 (0.1)
Cerebrovascular accident	1 (0.1)	0
Epilepsy	1 (0.1)	0
Seizure	1 (0.1)	1 (0.1)
Blood and lymphatic system disorders	2 (0.2)	2 (0.2)
Myelosuppression	1 (0.1)	1 (0.1)
Pancytopenia	1 (0.1)	1 (0.1)
Gastrointestinal disorders	2 (0.2)	1 (0.1)
Colitis	1 (0.1)	1 (0.1)
Haematemesis	1 (0.1)	0

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event,

TRAE=treatment-related adverse event.

Coded using MedDRA Version 28.0.

Table 46 below summarizes all treatment-related deaths reported in the clinical trials of single-agent SHR-A1811 as of 13 May 2025.

Table 46 Individual Listing of Treatment-Related Deaths Through 13 May 2025 - SHR-**A1811 Monotherapy**

Study ID	Age/Gender/ Nationality	Dose	Cause of Death MedDRA Preferred Term [verbatim term]
SHR-A1811-I-101	60-year-old Australian Male	4.8 mg/kg	Pneumonia [lung infection]
SHR-A1811-I-101	61-year-old Australian Female	6.4 mg/kg	Pancytopenia concurrent with colitis [pancytopenia concurrent with colitis]
SHR-A1811-I-101	72-year-old Korean Male	8.0 mg/kg	Pneumonia bacterial concurrent with interstitial lung disease [the suspicion of bacterial pneumonia concurrent with interstitial pneumonia]
SHR-A1811-I-101	54-year-old Chinese Female	6.4 mg/kg	Death [unexplained death]
SHR-A1811-I-101	34-year-old Chinese Female	6.4 mg/kg	Myelosuppression concurrent with multiple organ dysfunction syndrome and Septic shock [grade iv myelosuppression concurrent with multiple organ failure and septic shock]
SHR-A1811-I-102	59-year-old Chinese Male	6.4 mg/kg	Death [death unexplained]
SHR-A1811-I-102	70-year-old Chinese Male	6.4 mg/kg	Death [death unexplained]
SHR-A1811-I-103	55-year-old Chinese Female	6.4 mg/kg	Interstitial lung disease [acute interstitial pneumonia]
SHR-A1811-II-203	51-year-old Chinese Male	4.8 mg/kg	Seizure [seizure]

Data cutoff date: 13 May 2025.

6.2.1.2. SHR-A1811 in Combination with Adebrelimab

The studies included in the pooled safety analysis of subjects receiving SHR-A1811 in combination with adebrelimab were SHR-A1811-II-202, SHR-A1811-II-203, SHR-A1811-213 and SHR-A1811-215. A total of 141 subjects were exposed to SHR-A1811 and adebrelimab in this treatment group.

6.2.1.2.1. AEs

The incidence of TEAEs and Grade ≥ 3 TEAEs were 96.5% (136/141) and 68.1% (96/141), respectively (Table 47).

The TEAEs with an incidence of $\geq 10\%$ included white blood cell count decreased (79.4%), neutrophil count decreased (77.3%), anaemia (68.8%), nausea (56.0%), aspartate aminotransferase increased (51.8%), alanine aminotransferase increased (45.4%), vomiting (44.0%), platelet count decreased, alopecia (35.5% each), decreased appetite (31.9%), gamma-glutamyltransferase increased (31.2%), urinary tract infection (30.5%), lymphocyte count decreased, blood alkaline phosphatase increased (28.4% each), weight decreased (27.7%), hypoalbuminaemia (24.1%), hyponatraemia (19.1%), hypokalaemia (17.7%), blood lactate dehydrogenase increased, upper respiratory tract infection (17.0% each), hypertriglyceridaemia, hyperglycaemia (16.3% each), blood creatinine increased (15.6%), hyperuricaemia (14.9%), diarrhea, cough (14.2% each), fibrin D dimer increased (13.5%), stomatitis, asthenia (12.1% each), constipation, haematuria (11.3% each), dizziness (10.6%).

The Grade ≥ 3 TEAEs with an incidence of $\geq 2\%$ included neutrophil count decreased (37.6%), white blood cell count decreased (19.1%), lymphocyte count decreased (11.3%), anaemia (10.6%), platelet count decreased (7.1%), gamma-glutamyltransferase increased, febrile neutropenia, and hypokalaemia (4.3% each), aspartate aminotransferase increased, diarrhea, asthenia, and death (2.8% each), alanine aminotransferase increased, nausea, vomiting, leukopenia, and upper respiratory tract infection (2.1% each).

Table 47 TEAEs with an incidence $\geq 5\%$ or Grade ≥ 3 TEAEs with an incidence $\geq 1\%$ of

Subjects in the SHR-A1811 in Combination with Adebrelimab Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Adebrelimab (N=141) n (%)	
	All Grades	Grade ≥ 3
Subjects with any TEAE	136 (96.5)	96 (68.1)
Investigations	131 (92.9)	72 (51.1)
White blood cell count decreased	112 (79.4)	27 (19.1)
Neutrophil count decreased	109 (77.3)	53 (37.6)
Aspartate aminotransferase increased	73 (51.8)	4 (2.8)
Alanine aminotransferase increased	64 (45.4)	3 (2.1)
Platelet count decreased	50 (35.5)	10 (7.1)
Gamma-glutamyltransferase increased	44 (31.2)	6 (4.3)
Blood alkaline phosphatase increased	40 (28.4)	0
Lymphocyte count decreased	40 (28.4)	16 (11.3)
Weight decreased	39 (27.7)	1 (0.7)
Blood lactate dehydrogenase increased	24 (17.0)	0
Blood creatinine increased	22 (15.6)	0
Fibrin D dimer increased	19 (13.5)	1 (0.7)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Adebrelimab (N=141) n (%)	
	All Grades	Grade ≥ 3
Electrocardiogram QT prolonged	12 (8.5)	1 (0.7)
C-reactive protein increased	11 (7.8)	0
Blood bilirubin increased	10 (7.1)	1 (0.7)
Electrocardiogram T wave abnormal	10 (7.1)	0
Blood creatine phosphokinase increased	9 (6.4)	0
Blood thyroid stimulating hormone increased	9 (6.4)	0
Weight increased	9 (6.4)	1 (0.7)
Blood urea increased	7 (5.0)	0
Thyroxine increased	7 (5.0)	0
Gastrointestinal disorders	106 (75.2)	13 (9.2)
Nausea	79 (56.0)	3 (2.1)
Vomiting	62 (44.0)	3 (2.1)
Diarrhoea	20 (14.2)	4 (2.8)
Stomatitis	17 (12.1)	1 (0.7)
Constipation	16 (11.3)	0
Abdominal pain	9 (6.4)	0
Chronic gastritis	7 (5.0)	1 (0.7)
Blood and lymphatic system disorders	99 (70.2)	21 (14.9)
Anaemia	97 (68.8)	15 (10.6)
Leukopenia	7 (5.0)	3 (2.1)
Febrile neutropenia	6 (4.3)	6 (4.3)
Metabolism and nutrition disorders	95 (67.4)	8 (5.7)
Decreased appetite	45 (31.9)	0
Hypoalbuminaemia	34 (24.1)	0
Hyponatraemia	27 (19.1)	1 (0.7)
Hypokalaemia	25 (17.7)	6 (4.3)
Hyperglycaemia	23 (16.3)	0
Hypertriglyceridaemia	23 (16.3)	0
Hyperuricaemia	21 (14.9)	0
Hypercholesterolaemia	12 (8.5)	0
Hypoproteinaemia	12 (8.5)	0
Hypocalcaemia	10 (7.1)	2 (1.4)
Hypomagnesaemia	9 (6.4)	0
Hypophosphataemia	7 (5.0)	0
Infections and infestations	71 (50.4)	8 (5.7)
Urinary tract infection	43 (30.5)	2 (1.4)
Upper respiratory tract infection	24 (17.0)	3 (2.1)
Pneumonia	7 (5.0)	2 (1.4)
General disorders and administration site conditions	57 (40.4)	9 (6.4)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Adebrelimab (N=141) n (%)	
	All Grades	Grade ≥ 3
Asthenia	17 (12.1)	4 (2.8)
Pyrexia	13 (9.2)	1 (0.7)
Fatigue	12 (8.5)	0
Malaise	8 (5.7)	0
Death	4 (2.8)	4 (2.8)
Skin and subcutaneous tissue disorders	57 (40.4)	0
Alopecia	50 (35.5)	0
Rash	11 (7.8)	0
Cardiac disorders	47 (33.3)	2 (1.4)
Sinus tachycardia	11 (7.8)	0
Supraventricular extrasystoles	9 (6.4)	0
Ventricular extrasystoles	8 (5.7)	0
Mitral valve incompetence	7 (5.0)	0
Sinus bradycardia	7 (5.0)	0
Tricuspid valve incompetence	7 (5.0)	0
Pericardial effusion	4 (2.8)	2 (1.4)
Respiratory, thoracic and mediastinal disorders	47 (33.3)	4 (2.8)
Cough	20 (14.2)	0
Obstructive airways disorder	11 (7.8)	0
Lung diffusion disorder	8 (5.7)	0
Renal and urinary disorders	31 (22.0)	2 (1.4)
Haematuria	16 (11.3)	0
Proteinuria	13 (9.2)	0
Nervous system disorders	27 (19.1)	4 (2.8)
Dizziness	15 (10.6)	2 (1.4)
Headache	8 (5.7)	1 (0.7)
Endocrine disorders	18 (12.8)	0
Hypothyroidism	11 (7.8)	0
Injury, poisoning and procedural complications	12 (8.5)	1 (0.7)
Infusion related reaction	9 (6.4)	0
Psychiatric disorders	8 (5.7)	1 (0.7)
Insomnia	7 (5.0)	0

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

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

Coded using MedDRA Version 28.0.

6.2.1.2.2. Treatment-Related AEs

The incidence of TRAEs and Grade ≥ 3 TRAEs were 96.5% (136/141) and 63.1% (89/141), respectively ([Table 48](#)).

The TRAEs with an incidence of $\geq 10\%$ included white blood cell count decreased (79.4%), neutrophil count decreased (77.3%), anaemia (68.1%), nausea (54.6%), aspartate aminotransferase increased (51.8%), alanine aminotransferase increased (45.4%), vomiting (43.3%), alopecia (35.5%), platelet count decreased (34.8%), decreased appetite (31.9%), gamma-glutamyltransferase increased (29.8%), lymphocyte count decreased, blood alkaline phosphatase increased (27.7% each), weight decreased (25.5%), hypoalbuminaemia (21.3%), urinary tract infection (19.1%), hypertriglyceridaemia, hyponatraemia (16.3% each), blood lactate dehydrogenase increased, hyperglycaemia (15.6% each), blood creatinine increased, hypokalaemia (14.9% each), hyperuricaemia (14.2%), diarrhea, stomatitis (12.1% each), fibrin D dimer increased, asthenia (11.3% each).

The Grade ≥ 3 TRAEs with an incidence of $\geq 2\%$ included neutrophil count decreased (37.6%), white blood cell count decreased (19.1%), lymphocyte count decreased (11.3%), anaemia (10.6%), platelet count decreased (7.1%), gamma-glutamyltransferase increased, febrile neutropenia (4.3% each), hypokalaemia (3.5%), aspartate aminotransferase increased, diarrhea (2.8% each), alanine aminotransferase increased, nausea, vomiting, leukopenia, and asthenia (2.1% each).

The incidence of SHR-A1811 related AEs and Grade ≥ 3 SHR-A1811 related AEs were 96.5% (136/141) and 63.1% (89/141), respectively. The types and incidence of All grades and Grade ≥ 3 SHR-A1811 related AEs were similar to those of All grades and Grade ≥ 3 TRAEs, with no major difference identified between TRAEs and SHR-A1811 related AEs (Table 48).

Table 48 TRAEs with an Incidence $\geq 5\%$ or Grade ≥ 3 TRAEs with an Incidence $\geq 1\%$ of Subjects in the SHR-A1811 in Combination with Adebrelimab Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Adebrelimab (N=141) n (%)			
	TRAE	SHR-A1811- Related AE	Grade 3 TRAE	Grade 3 SHR-A1811- related AE
Subjects with any TRAE	136 (96.5)	136 (96.5)	89 (63.1)	89 (63.1)
Investigations	130 (92.2)	130 (92.2)	72 (51.1)	72 (51.1)
Neutrophil count decreased	109 (77.3)	109 (77.3)	53 (37.6)	53 (37.6)
White blood cell count decreased	112 (79.4)	112 (79.4)	27 (19.1)	27 (19.1)
Platelet count decreased	49 (34.8)	49 (34.8)	10 (7.1)	10 (7.1)
Aspartate aminotransferase increased	73 (51.8)	73 (51.8)	4 (2.8)	4 (2.8)
Alanine aminotransferase increased	64 (45.4)	64 (45.4)	3 (2.1)	3 (2.1)
Weight decreased	36 (25.5)	36 (25.5)	1 (0.7)	1 (0.7)

SHR-A1811 in Combination with Adebrelimab				
(N=141)				
System Organ Class (SOC)	n (%)			
Preferred Term (PT)	TRAE	SHR-A1811-Related AE	Grade 3 TRAE	Grade 3 SHR-A1811-related AE
Lymphocyte count decreased	39 (27.7)	39 (27.7)	16 (11.3)	16 (11.3)
Gamma-glutamyltransferase increased	42 (29.8)	42 (29.8)	6 (4.3)	6 (4.3)
Blood alkaline phosphatase increased	39 (27.7)	39 (27.7)	0	0
Blood lactate dehydrogenase increased	22 (15.6)	22 (15.6)	0	0
Blood bilirubin increased	10 (7.1)	10 (7.1)	1 (0.7)	1 (0.7)
Blood creatinine increased	21 (14.9)	21 (14.9)	0	0
Fibrin D dimer increased	16 (11.3)	16 (11.3)	1 (0.7)	1 (0.7)
Blood thyroid stimulating hormone increased	8 (5.7)	8 (5.7)	0	0
Blood creatine phosphokinase increased	8 (5.7)	8 (5.7)	0	0
Electrocardiogram QT prolonged	10 (7.1)	10 (7.1)	1 (0.7)	1 (0.7)
Electrocardiogram T wave abnormal	9 (6.4)	8 (5.7)	0	0
Blood urea increased	7 (5.0)	7 (5.0)	0	0
C-reactive protein increased	7 (5.0)	7 (5.0)	0	0
Thyroxine increased	7 (5.0)	7 (5.0)	0	0
Gastrointestinal disorders	106 (75.2)	106 (75.2)	12 (8.5)	12 (8.5)
Nausea	77 (54.6)	77 (54.6)	3 (2.1)	3 (2.1)
Vomiting	61 (43.3)	61 (43.3)	3 (2.1)	3 (2.1)
Diarrhoea	17 (12.1)	17 (12.1)	4 (2.8)	4 (2.8)
Stomatitis	17 (12.1)	17 (12.1)	1 (0.7)	1 (0.7)
Constipation	11 (7.8)	11 (7.8)	0	0
Abdominal pain	8 (5.7)	8 (5.7)	0	0
Chronic gastritis	7 (5.0)	7 (5.0)	1 (0.7)	1 (0.7)
Blood and lymphatic system disorders	98 (69.5)	98 (69.5)	21 (14.9)	21 (14.9)
Anaemia	96 (68.1)	96 (68.1)	15 (10.6)	15 (10.6)
Leukopenia	7 (5.0)	7 (5.0)	3 (2.1)	3 (2.1)
Febrile neutropenia	6 (4.3)	6 (4.3)	6 (4.3)	6 (4.3)

SHR-A1811 in Combination with Adebrelimab				
(N=141)				
System Organ Class (SOC)	n (%)			
Preferred Term (PT)	TRAE	SHR-A1811-Related AE	Grade 3 TRAE	Grade 3 SHR-A1811-related AE
Metabolism and nutrition disorders	91 (64.5)	91 (64.5)	6 (4.3)	6 (4.3)
Decreased appetite	45 (31.9)	45 (31.9)	0	0
Hypoalbuminaemia	30 (21.3)	30 (21.3)	0	0
Hypertriglyceridaemia	23 (16.3)	23 (16.3)	0	0
Hypokalaemia	21 (14.9)	21 (14.9)	5 (3.5)	5 (3.5)
Hyponatraemia	23 (16.3)	23 (16.3)	0	0
Hyperglycaemia	22 (15.6)	21 (14.9)	0	0
Hyperuricaemia	20 (14.2)	20 (14.2)	0	0
Hypocalcaemia	8 (5.7)	8 (5.7)	1 (0.7)	1 (0.7)
Hypercholesterolaemia	9 (6.4)	9 (6.4)	0	0
Hypomagnesaemia	8 (5.7)	8 (5.7)	0	0
Hypoproteinaemia	10 (7.1)	10 (7.1)	0	0
Skin and subcutaneous tissue disorders	56 (39.7)	56 (39.7)	0	0
Alopecia	50 (35.5)	50 (35.5)	0	0
Rash	10 (7.1)	7 (5.0)	0	0
General disorders and administration site conditions	42 (29.8)	41 (29.1)	4 (2.8)	4 (2.8)
Fatigue	12 (8.5)	12 (8.5)	0	0
Asthenia	16 (11.3)	14 (9.9)	3 (2.1)	3 (2.1)
Malaise	8 (5.7)	8 (5.7)	0	0
Pyrexia	8 (5.7)	8 (5.7)	1 (0.7)	1 (0.7)
Infections and infestations	37 (26.2)	36 (25.5)	4 (2.8)	4 (2.8)
Urinary tract infection	27 (19.1)	27 (19.1)	1 (0.7)	1 (0.7)
Upper respiratory tract infection	5 (3.5)	5 (3.5)	2 (1.4)	2 (1.4)
Renal and urinary disorders	23 (16.3)	23 (16.3)	2 (1.4)	2 (1.4)
Proteinuria	11 (7.8)	11 (7.8)	0	0
Haematuria	8 (5.7)	8 (5.7)	0	0
Cardiac disorders	39 (27.7)	39 (27.7)	0	0
Sinus tachycardia	10 (7.1)	10 (7.1)	0	0
Supraventricular extrasystoles	7 (5.0)	7 (5.0)	0	0
Ventricular extrasystoles	8 (5.7)	8 (5.7)	0	0
Mitral valve incompetence	7 (5.0)	7 (5.0)	0	0

SHR-A1811 in Combination with Adebrelimab (N=141)				
System Organ Class (SOC) Preferred Term (PT)	n (%)			
	TRAE	SHR-A1811- Related AE	Grade 3 TRAE	Grade 3 SHR-A1811- related AE
Respiratory, thoracic and mediastinal disorders	33 (23.4)	32 (22.7)	1 (0.7)	1 (0.7)
Cough	13 (9.2)	13 (9.2)	0	0
Nervous system disorders	20 (14.2)	20 (14.2)	3 (2.1)	3 (2.1)
Dizziness	11 (7.8)	11 (7.8)	2 (1.4)	2 (1.4)
Endocrine disorders	17 (12.1)	10 (7.1)	0	0
Hypothyroidism	11 (7.8)	6 (4.3)	0	0
Injury, poisoning and procedural complications	11 (7.8)	11 (7.8)	1 (0.7)	1 (0.7)
Infusion related reaction	9 (6.4)	9 (6.4)	0	0

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SOC=system organ class, TRAE=treatment-related adverse event.

Coded using MedDRA Version 28.0.

6.2.1.2.3. AEs Associated with Permanent Discontinuation of SHR-A1811

Nine (9/141, 6.4%) subjects had TEAEs leading to permanent discontinuation of SHR-A1811, among which interstitial lung disease were reported in 3 subjects (2.1%) with all other events occurred in a single subject, which included platelet count decreased, vomiting, nausea, febrile neutropenia, pericardial effusion, pleural effusion, death, and thyroiditis subacute (1 subject each, 0.7%). Seven (7, 5.0%) subjects experienced events assessed by investigator as treatment-related: interstitial lung disease (3 subjects, 2.1%), and the following events each reported in 1 subject (0.7%): platelet count decreased, vomiting, nausea, febrile neutropenia, and thyroiditis subacute ([Table 49](#)).

Table 49 TEAEs and TRAEs Associated with Permanent Discontinuation of SHR-A1811 in the SHR-A1811 in Combination with Adebrelimab Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Adebrelimab (N=141) n (%)	
	TEAE	TRAE
Subjects with any TEAE Associated with Permanent Discontinuation of SHR-A1811	9 (6.4)	7 (5.0)
Respiratory, thoracic and mediastinal disorders	4 (2.8)	3 (2.1)
Interstitial lung disease	3 (2.1)	3 (2.1)
Pleural effusion	1 (0.7)	0
Investigations	1 (0.7)	1 (0.7)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Adebrelimab (N=141) n (%)	
	TEAE	TRAE
Platelet count decreased	1 (0.7)	1 (0.7)
Gastrointestinal disorders	1 (0.7)	1 (0.7)
Vomiting	1 (0.7)	1 (0.7)
Nausea	1 (0.7)	1 (0.7)
Blood and lymphatic system disorders	1 (0.7)	1 (0.7)
Febrile neutropenia	1 (0.7)	1 (0.7)
Cardiac disorders	1 (0.7)	0
Pericardial effusion	1 (0.7)	0
General disorders and administration site conditions	1 (0.7)	0
Death	1 (0.7)	0
Endocrine disorders	1 (0.7)	1 (0.7)
Thyroiditis subacute	1 (0.7)	1 (0.7)

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event,

TRAE=treatment-related adverse event.

Coded using MedDRA Version 28.0.

6.2.1.2.4. SAEs

Forty-eight (48/141, 34.0%) subjects had SAEs, and SAEs with an incidence of $\geq 2\%$ included interstitial lung disease, pneumonia (5 subjects each, 3.5%), neutrophil count decreased, vomiting, nausea, death, and asthenia (4 subjects each, 2.8%), anaemia, febrile neutropenia, and pneumonitis (3 subjects each, 2.1%).

Thirty-five (35/141, 24.8%) subjects had SARs, and SARs with an incidence of $\geq 2\%$ included interstitial lung disease (5 subjects, 3.5%), neutrophil count decreased, vomiting, and nausea (4 subjects each, 2.8%), asthenia, and febrile neutropenia (3 subjects each, 2.1%). In all the SARs, one case of immune-mediated lung disease was considered unrelated to SHR-A1811 by the investigator, the remaining of the SARs were all deemed related to SHR-A1811.

The SAEs with an incidence of at least 1% are listed in table below ([Table 50](#)).

Table 50 SAEs Reported in at Least 1% of Subject in the SHR-A1811 in Combination with Adebrelimab Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Adebrelimab (N=141) n (%)		
	SAE	SAR	SHR-A1811 Related
Subjects with any TE-SAE	48 (34.0)	35 (24.8)	34 (24.1)
Gastrointestinal disorders	11 (7.8)	10 (7.1)	10 (7.1)
Nausea	4 (2.8)	4 (2.8)	4 (2.8)
Vomiting	4 (2.8)	4 (2.8)	4 (2.8)
Respiratory, thoracic and mediastinal disorders	11 (7.8)	8 (5.7)	7 (5.0)
Interstitial lung disease	5 (3.5)	5 (3.5)	5 (3.5)
Pneumonitis	3 (2.1)	2 (1.4)	2 (1.4)
General disorders and administration site conditions	8 (5.7)	3 (2.1)	3 (2.1)
Asthenia	4 (2.8)	3 (2.1)	3 (2.1)
Death	4 (2.8)	0	0
Infections and infestations	7 (5.0)	2 (1.4)	2 (1.4)
Pneumonia	5 (3.5)	1 (0.7)	1 (0.7)
Investigations	7 (5.0)	7 (5.0)	7 (5.0)
Neutrophil count decreased	4 (2.8)	4 (2.8)	4 (2.8)
Platelet count decreased	2 (1.4)	2 (1.4)	2 (1.4)
White blood cell count decreased	2 (1.4)	2 (1.4)	2 (1.4)
Blood and lymphatic system disorders	6 (4.3)	5 (3.5)	5 (3.5)
Anaemia	3 (2.1)	2 (1.4)	2 (1.4)
Febrile neutropenia	3 (2.1)	3 (2.1)	3 (2.1)
Cardiac disorders	3 (2.1)	1 (0.7)	1 (0.7)
Pericardial effusion	2 (1.4)	0	0

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities, PT=preferred term, SAE=serious adverse event, SAR=serious adverse reaction, SOC=system organ class.

Coded using MedDRA Version 28.0.

6.2.1.2.5. AEs Associated with Outcome of Death

Eight (8/141, 5.7%) subjects had TEAEs with an outcome of death, including death (4 subjects, 2.8%), interstitial lung disease, metastases to meninges, completed suicide, and pericardial effusion (1 subject each, 0.7%). One (1, 0.7%) subject had TRAE with an outcome of death, which was interstitial lung disease ([Table 51](#)).

Table 51 TEAEs Associated with Outcome of Death of SHR-A1811 in the SHR-A1811 in**Combination with Adebrelimab Pool by Preferred Term**

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Adebrelimab (N=141) n (%)	
	TEAE	TRAE
Subjects with any Fatal TEAE	8 (5.7)	1 (0.7)
General disorders and administration site conditions	4 (2.8)	0
Death	4 (2.8)	0
Cardiac disorders	1 (0.7)	0
Pericardial effusion	1 (0.7)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7)	0
Metastases to meninges	1 (0.7)	0
Psychiatric disorders	1 (0.7)	0
Completed suicide	1 (0.7)	0
Respiratory, thoracic and mediastinal disorders	1 (0.7)	0
Interstitial lung disease	1 (0.7)	1 (0.7)*

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event,

TRAE=treatment-related adverse event.

* This fatal AE was recorded in the EDC system as "unrelated" to the study drugs. This entry was updated to "related" after DLP.

Coded using MedDRA Version 28.0.

Table 52 below summarizes all treatment-related deaths reported in the clinical trials of SHR-A1811 combined with Adebrelimab as of 13 May 2025.

Table 52 Individual Listing of Treatment-Related Deaths Through 13 May 2025 - SHR-A1811 in Combination with Adebrelimab

Study ID	Age/Gender/ Nationality	Dose	Cause of Death MedDRA Preferred Term [verbatim term]
SHR-A1811-II-203	70-year-old Chinese Male	SHR-A1811 4.8 mg/kg + Adebrelimab 1200 mg	Interstitial lung disease [interstitial pneumonia]

Data cutoff date: 13 May 2025.

6.2.1.3. SHR-A1811 in Combination with Pertuzumab

The study included in the pooled safety analysis of subjects receiving SHR-A1811 in combination with pertuzumab was SHR-A1811-II-202. A total of 75 subjects were exposed to SHR-A1811 in combination with pertuzumab.

6.2.1.3.1. AEs

The incidence of TEAEs and Grade ≥ 3 TEAEs were 100% (75/75) and 78.7% (59/75), respectively (Table 53).

The TEAEs with an incidence of $\geq 10\%$ included neutrophil count decreased (86.7%), nausea (84.0%), white blood cell count decreased (80.0%), anaemia (78.7%), vomiting, weight decreased (65.3% each), diarrhoea (60.0%), aspartate aminotransferase increased, alopecia (58.7% each), alanine aminotransferase increased (53.3%), decreased appetite (49.3%), urinary tract infection (46.7%), hypokalaemia (41.3%), platelet count decreased, hypoalbuminaemia, and lymphocyte count decreased (40.0% each), blood alkaline phosphatase increased (33.3%), gamma-glutamyltransferase increased (32.0%), hypertriglyceridaemia, hyperglycaemia (29.3% each), hyponatraemia, COVID-19 (28.0% each), malaise (24.0%), stomatitis, pyrexia (22.7% each), hypocalcaemia (21.3%), blood lactate dehydrogenase increased (20.0%), hyperuricaemia, upper respiratory tract infection, asthenia, and fatigue (18.7% each), cough, fibrin D dimer increased (17.3% each), proteinuria, blood bilirubin increased, and urinary occult blood positive (16.0% each), constipation, hypercholesterolaemia, dizziness, haematuria, influenza like illness, and infusion related reaction (14.7% each), blood creatinine increased, blood thyroid stimulating hormone increased, sinus tachycardia, and tricuspid valve incompetence (13.3% each), blood cholesterol increased, arrhythmia (12.0% each), mouth ulceration, mitral valve incompetence, and rash (10.7% each).

The Grade ≥ 3 TEAEs with an incidence of $\geq 2\%$ included neutrophil count decreased (54.7%), white blood cell count decreased (34.7%), anaemia (21.3%), platelet count decreased, lymphocyte count decreased, and hypokalaemia (12.0% each), weight decreased (10.7%), alanine aminotransferase increased (6.7%), pneumonia, gamma-glutamyltransferase increased, and aspartate aminotransferase increased (4.0% each), and diarrhoea, vomiting, nausea, stomatitis, febrile neutropenia, fatigue, and malaise (2.7% each).

Table 53 TEAEs with an incidence $\geq 5\%$ or Grade ≥ 3 TEAEs with an incidence $\geq 1\%$ of Subjects in the SHR-A1811 in Combination with Pertuzumab Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Pertuzumab (N=75) n (%)	
	All Grades	Grade ≥ 3
Subjects with any TEAE	75 (100.0)	59 (78.7)
Gastrointestinal disorders	75 (100.0)	10 (13.3)
Nausea	63 (84.0)	2 (2.7)
Vomiting	49 (65.3)	2 (2.7)
Diarrhoea	45 (60.0)	2 (2.7)
Stomatitis	17 (22.7)	2 (2.7)
Constipation	11 (14.7)	1 (1.3)
Mouth ulceration	8 (10.7)	0

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Pertuzumab (N=75) n (%)	
	All Grades	Grade ≥ 3
Flatulence	4 (5.3)	0
Toothache	4 (5.3)	0
Oesophageal stenosis	1 (1.3)	1 (1.3)
Pancreatitis acute	1 (1.3)	1 (1.3)
Upper gastrointestinal haemorrhage	1 (1.3)	1 (1.3)
Investigations	74 (98.7)	48 (64.0)
Neutrophil count decreased	65 (86.7)	41 (54.7)
White blood cell count decreased	60 (80.0)	26 (34.7)
Weight decreased	49 (65.3)	8 (10.7)
Aspartate aminotransferase increased	44 (58.7)	3 (4.0)
Alanine aminotransferase increased	40 (53.3)	5 (6.7)
Lymphocyte count decreased	30 (40.0)	9 (12.0)
Platelet count decreased	30 (40.0)	9 (12.0)
Blood alkaline phosphatase increased	25 (33.3)	1 (1.3)
Gamma-glutamyltransferase increased	24 (32.0)	3 (4.0)
Blood lactate dehydrogenase increased	15 (20.0)	0
Fibrin D dimer increased	13 (17.3)	0
Blood bilirubin increased	12 (16.0)	1 (1.3)
Urinary occult blood positive	12 (16.0)	0
Blood creatinine increased	10 (13.3)	0
Blood thyroid stimulating hormone increased	10 (13.3)	0
Blood cholesterol increased	9 (12.0)	0
High density lipoprotein decreased	7 (9.3)	0
Prohormone brain natriuretic peptide increased	7 (9.3)	0
Urobilinogen urine increased	7 (9.3)	0
Weight increased	7 (9.3)	0
Blood urea increased	6 (8.0)	0
Bilirubin conjugated increased	5 (6.7)	1 (1.3)
Blood creatine phosphokinase increased	5 (6.7)	0
Urine ketone body present	5 (6.7)	0
Bilirubin urine present	4 (5.3)	0
Electrocardiogram QT prolonged	4 (5.3)	1 (1.3)
Lipoprotein increased	4 (5.3)	0
Metabolism and nutrition disorders	65 (86.7)	12 (16.0)
Decreased appetite	37 (49.3)	1 (1.3)
Hypokalaemia	31 (41.3)	9 (12.0)
Hypoalbuminaemia	30 (40.0)	1 (1.3)
Hyperglycaemia	22 (29.3)	1 (1.3)
Hypertriglyceridaemia	22 (29.3)	0

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Pertuzumab (N=75) n (%)	
	All Grades	Grade ≥ 3
Hyponatraemia	21 (28.0)	0
Hypocalcaemia	16 (21.3)	0
Hyperuricaemia	14 (18.7)	0
Hypercholesterolaemia	11 (14.7)	0
Hypercalcaemia	6 (8.0)	0
Hyperlipidaemia	6 (8.0)	0
Hypophosphataemia	5 (6.7)	0
Hypochloraemia	4 (5.3)	0
Malnutrition	1 (1.3)	1 (1.3)
Blood and lymphatic system disorders	59 (78.7)	18 (24.0)
Anaemia	59 (78.7)	16 (21.3)
Febrile neutropenia	2 (2.7)	2 (2.7)
Myelosuppression	1 (1.3)	1 (1.3)
Infections and infestations	55 (73.3)	4 (5.3)
Urinary tract infection	35 (46.7)	0
COVID-19	21 (28.0)	1 (1.3)
Upper respiratory tract infection	14 (18.7)	0
Pneumonia	7 (9.3)	3 (4.0)
Influenza	5 (6.7)	0
Bronchitis	2 (2.7)	1 (1.3)
General disorders and administration site conditions	51 (68.0)	5 (6.7)
Malaise	18 (24.0)	2 (2.7)
Pyrexia	17 (22.7)	0
Asthenia	14 (18.7)	1 (1.3)
Fatigue	14 (18.7)	2 (2.7)
Influenza like illness	11 (14.7)	0
Oedema peripheral	4 (5.3)	0
Skin and subcutaneous tissue disorders	49 (65.3)	1 (1.3)
Alopecia	44 (58.7)	0
Rash	8 (10.7)	0
Skin hyperpigmentation	7 (9.3)	0
Drug eruption	1 (1.3)	1 (1.3)
Cardiac disorders	30 (40.0)	0
Sinus tachycardia	10 (13.3)	0
Tricuspid valve incompetence	10 (13.3)	0
Arrhythmia	9 (12.0)	0
Mitral valve incompetence	8 (10.7)	0
Aortic valve incompetence	4 (5.3)	0
Left ventricular dysfunction	4 (5.3)	0

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Pertuzumab (N=75) n (%)	
	All Grades	Grade ≥ 3
Sinus bradycardia	4 (5.3)	0
Supraventricular extrasystoles	4 (5.3)	0
Supraventricular tachycardia	4 (5.3)	0
Ventricular extrasystoles	4 (5.3)	0
Respiratory, thoracic and mediastinal disorders	23 (30.7)	0
Cough	13 (17.3)	0
Epistaxis	5 (6.7)	0
Renal and urinary disorders	20 (26.7)	0
Proteinuria	12 (16.0)	0
Haematuria	11 (14.7)	0
Injury, poisoning and procedural complications	17 (22.7)	1 (1.3)
Infusion related reaction	11 (14.7)	0
Radius fracture	1 (1.3)	1 (1.3)
Nervous system disorders	16 (21.3)	1 (1.3)
Dizziness	11 (14.7)	1 (1.3)
Headache	5 (6.7)	0
Seizure	1 (1.3)	1 (1.3)
Musculoskeletal and connective tissue disorders	13 (17.3)	1 (1.3)
Back pain	2 (2.7)	1 (1.3)
Endocrine disorders	10 (13.3)	0
Hypothyroidism	6 (8.0)	0
Psychiatric disorders	9 (12.0)	1 (1.3)
Insomnia	6 (8.0)	0
Delirium	1 (1.3)	1 (1.3)

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

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

Coded using MedDRA Version 28.0.

6.2.1.3.2. Treatment-Related AEs

The incidence of TRAEs and Grade ≥ 3 TRAEs were 100% (75/75) and 74.7% (56/75), respectively ([Table 54](#)).

The TRAEs with an incidence of $\geq 10\%$ included neutrophil count decreased (86.7%), nausea (82.7%), white blood cell count decreased (80.0%), anaemia (78.7%), vomiting (65.3%), diarrhoea (60.0%), alopecia, weight decreased (58.7% each), aspartate aminotransferase increased (57.3%), alanine aminotransferase increased (53.3%), decreased appetite (49.3%), urinary tract infection (41.3%), lymphocyte count decreased (40.0%), platelet count decreased, hypoalbuminaemia (38.7% each), hypokalaemia (37.3%), blood alkaline phosphatase increased (32.0%), gamma-glutamyltransferase increased, hyperglycaemia (29.3% each), hyponatraemia (28.0%),

hypertriglyceridaemia (25.3%), stomatitis, malaise (22.7% each), hypocalcaemia (20.0%), blood lactate dehydrogenase increased, fatigue (18.7% each), proteinuria, asthenia, hyperuricaemia, and blood bilirubin increased (16.0% each), pyrexia, fibrin D dimer increased, haematuria, urinary occult blood positive, and infusion related reaction (14.7% each), constipation, blood thyroid stimulating hormone increased, and tricuspid valve incompetence (13.3% each), hypercholesterolaemia, blood creatinine increased, and dizziness (12.0% each), upper respiratory tract infection, blood cholesterol increased, mitral valve incompetence, sinus tachycardia, rash, and arrhythmia (10.7% each).

The Grade ≥ 3 TRAEs with an incidence of $\geq 2\%$ included neutrophil count decreased (54.7%), white blood cell count decreased (34.7%), anaemia (18.7%), lymphocyte count decreased (12.0%), platelet count decreased, hypokalaemia, and weight decreased (10.7% each), alanine aminotransferase increased (6.7%), gamma-glutamyltransferase increased, aspartate aminotransferase increased (4.0% each), diarrhoea, vomiting, pneumonia, febrile neutropenia, stomatitis, and fatigue (2.7% each).

The incidence of SHR-A1811 related AEs and Grade ≥ 3 SHR-A1811 related AEs were 100% (75/75) and 74.7% (56/75), respectively. The types and incidence of All grades and Grade ≥ 3 SHR-A1811 related AEs were similar to those of All grades and Grade ≥ 3 TRAEs, with no major difference identified between TRAEs and SHR-A1811 related AEs. Among the common TRAEs, one each case of nausea, alopecia, diarrhoea, oedema peripheral, sinus tachycardia and infusion related reaction were determined to be unrelated to SHR-A1811 (Table 54).

Table 54 TRAEs with an Incidence $\geq 5\%$ or Grade ≥ 3 TRAEs with an Incidence $\geq 1\%$ of Subjects in the SHR-A1811 in Combination with Pertuzumab Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Pertuzumab (N=75) n (%)			
	TRAE	SHR-A1811- Related AE	Grade 3 TRAE	Grade 3 SHR-A1811- related AE
Subjects with any TRAE	75 (100.0)	75 (100.0)	56 (74.7)	56 (74.7)
Gastrointestinal disorders	75 (100.0)	75 (100.0)	8 (10.7)	8 (10.7)
Nausea	62 (82.7)	62 (82.7)	1 (1.3)	1 (1.3)
Vomiting	49 (65.3)	49 (65.3)	2 (2.7)	2 (2.7)
Diarrhoea	45 (60.0)	44 (58.7)	2 (2.7)	2 (2.7)
Stomatitis	17 (22.7)	17 (22.7)	2 (2.7)	2 (2.7)
Constipation	10 (13.3)	10 (13.3)	1 (1.3)	1 (1.3)
Mouth ulceration	7 (9.3)	7 (9.3)	0	0
Pancreatitis acute	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)
Investigations	74 (98.7)	74 (98.7)	48 (64.0)	48 (64.0)
Neutrophil count decreased	65 (86.7)	65 (86.7)	41 (54.7)	41 (54.7)

SHR-A1811 in Combination with Pertuzumab				
(N=75)				
System Organ Class (SOC)	n (%)			
Preferred Term (PT)	TRAE	SHR-A1811-Related AE	Grade 3 TRAE	Grade 3 SHR-A1811-related AE
White blood cell count decreased	60 (80.0)	60 (80.0)	26 (34.7)	26 (34.7)
Weight decreased	44 (58.7)	44 (58.7)	8 (10.7)	8 (10.7)
Aspartate aminotransferase increased	43 (57.3)	43 (57.3)	3 (4.0)	3 (4.0)
Alanine aminotransferase increased	40 (53.3)	40 (53.3)	5 (6.7)	5 (6.7)
Lymphocyte count decreased	30 (40.0)	30 (40.0)	9 (12.0)	9 (12.0)
Platelet count decreased	29 (38.7)	29 (38.7)	8 (10.7)	8 (10.7)
Blood alkaline phosphatase increased	24 (32.0)	24 (32.0)	1 (1.3)	1 (1.3)
Gamma-glutamyltransferase increased	22 (29.3)	22 (29.3)	3 (4.0)	3 (4.0)
Blood lactate dehydrogenase increased	14 (18.7)	14 (18.7)	0	0
Blood bilirubin increased	12 (16.0)	12 (16.0)	1 (1.3)	1 (1.3)
Fibrin D dimer increased	11 (14.7)	11 (14.7)	0	0
Urinary occult blood positive	11 (14.7)	11 (14.7)	0	0
Blood thyroid stimulating hormone increased	10 (13.3)	10 (13.3)	0	0
Blood creatinine increased	9 (12.0)	9 (12.0)	0	0
Blood cholesterol increased	8 (10.7)	8 (10.7)	0	0
High density lipoprotein decreased	7 (9.3)	7 (9.3)	0	0
Prohormone brain natriuretic peptide increased	7 (9.3)	7 (9.3)	0	0

SHR-A1811 in Combination with Pertuzumab				
(N=75)				
System Organ Class (SOC)	n (%)			
Preferred Term (PT)	TRAE	SHR-A1811-Related AE	Grade 3 TRAE	Grade 3 SHR-A1811-related AE
Urobilinogen urine increased	6 (8.0)	6 (8.0)	0	0
Bilirubin conjugated increased	5 (6.7)	5 (6.7)	1 (1.3)	1 (1.3)
Blood creatine phosphokinase increased	5 (6.7)	5 (6.7)	0	0
Blood urea increased	5 (6.7)	5 (6.7)	0	0
Electrocardiogram QT prolonged	4 (5.3)	4 (5.3)	1 (1.3)	1 (1.3)
Lipoprotein increased	4 (5.3)	4 (5.3)	0	0
Urine ketone body present	4 (5.3)	4 (5.3)	0	0
Metabolism and nutrition disorders	63 (84.0)	63 (84.0)	11 (14.7)	11 (14.7)
Decreased appetite	37 (49.3)	37 (49.3)	1 (1.3)	1 (1.3)
Hypoalbuminaemia	29 (38.7)	29 (38.7)	0	0
Hypokalaemia	28 (37.3)	28 (37.3)	8 (10.7)	8 (10.7)
Hyperglycaemia	22 (29.3)	22 (29.3)	1 (1.3)	1 (1.3)
Hyponatraemia	21 (28.0)	21 (28.0)	0	0
Hypertriglyceridaemia	19 (25.3)	19 (25.3)	0	0
Hypocalcaemia	15 (20.0)	15 (20.0)	0	0
Hyperuricaemia	12 (16.0)	12 (16.0)	0	0
Hypercholesterolaemia	9 (12.0)	9 (12.0)	0	0
Hypercalcaemia	6 (8.0)	6 (8.0)	0	0
Hyperlipidaemia	6 (8.0)	6 (8.0)	0	0
Hypophosphataemia	5 (6.7)	5 (6.7)	0	0
Hypochloraemia	4 (5.3)	4 (5.3)	0	0
Malnutrition	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)
Blood and lymphatic system disorders	59 (78.7)	59 (78.7)	16 (21.3)	16 (21.3)
Anaemia	59 (78.7)	59 (78.7)	14 (18.7)	14 (18.7)
Febrile neutropenia	2 (2.7)	2 (2.7)	2 (2.7)	2 (2.7)
Myelosuppression	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)
Skin and subcutaneous tissue disorders	49 (65.3)	48 (64.0)	1 (1.3)	1 (1.3)
Alopecia	44 (58.7)	43 (57.3)	0	0
Rash	8 (10.7)	8 (10.7)	0	0

SHR-A1811 in Combination with Pertuzumab				
(N=75)				
System Organ Class (SOC)	n (%)			
Preferred Term (PT)	TRAE	SHR-A1811-Related AE	Grade 3 TRAE	Grade 3 SHR-A1811-related AE
Skin hyperpigmentation	7 (9.3)	7 (9.3)	0	0
Drug eruption	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)
General disorders and administration site conditions	45 (60.0)	43 (57.3)	4 (5.3)	4 (5.3)
Malaise	17 (22.7)	17 (22.7)	1 (1.3)	1 (1.3)
Fatigue	14 (18.7)	14 (18.7)	2 (2.7)	2 (2.7)
Asthenia	12 (16.0)	12 (16.0)	1 (1.3)	1 (1.3)
Pyrexia	11 (14.7)	11 (14.7)	0	0
Oedema peripheral	4 (5.3)	3 (4.0)	0	0
Infections and infestations	40 (53.3)	40 (53.3)	3 (4.0)	3 (4.0)
Urinary tract infection	31 (41.3)	31 (41.3)	0	0
Upper respiratory tract infection	8 (10.7)	8 (10.7)	0	0
Pneumonia	5 (6.7)	5 (6.7)	2 (2.7)	2 (2.7)
Bronchitis	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)
Cardiac disorders	27 (36.0)	27 (36.0)	0	0
Tricuspid valve incompetence	10 (13.3)	10 (13.3)	0	0
Arrhythmia	8 (10.7)	8 (10.7)	0	0
Mitral valve incompetence	8 (10.7)	8 (10.7)	0	0
Sinus tachycardia	8 (10.7)	7 (9.3)	0	0
Aortic valve incompetence	4 (5.3)	4 (5.3)	0	0
Left ventricular dysfunction	4 (5.3)	4 (5.3)	0	0
Sinus bradycardia	4 (5.3)	4 (5.3)	0	0
Supraventricular extrasystoles	4 (5.3)	4 (5.3)	0	0
Supraventricular tachycardia	4 (5.3)	4 (5.3)	0	0
Ventricular extrasystoles	4 (5.3)	4 (5.3)	0	0
Renal and urinary disorders	20 (26.7)	20 (26.7)	0	0
Proteinuria	12 (16.0)	12 (16.0)	0	0
Haematuria	11 (14.7)	11 (14.7)	0	0

SHR-A1811 in Combination with Pertuzumab				
(N=75)				
System Organ Class (SOC)	n (%)			
Preferred Term (PT)	TRAE	SHR-A1811-Related AE	Grade 3 TRAE	Grade 3 SHR-A1811-related AE
Nervous system disorders	13 (17.3)	13 (17.3)	0	0
Dizziness	9 (12.0)	9 (12.0)	0	0
Headache	4 (5.3)	4 (5.3)	0	0
Respiratory, thoracic and mediastinal disorders	13 (17.3)	13 (17.3)	0	0
Cough	6 (8.0)	6 (8.0)	0	0
Injury, poisoning and procedural complications	12 (16.0)	11 (14.7)	0	0
Infusion related reaction	11 (14.7)	10 (13.3)	0	0
Endocrine disorders	10 (13.3)	10 (13.3)	0	0
Hypothyroidism	6 (8.0)	6 (8.0)	0	0

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SOC=system organ class, TRAE=treatment-related adverse event.

Coded using MedDRA Version 28.0.

6.2.1.3.3. AEs Associated with Permanent Discontinuation of SHR-A1811

Four (4/75, 5.3%) subject had TEAEs leading to permanent discontinuation of SHR-A1811, which included platelet count decreased, pneumonia, anaemia, and pneumonitis (1 subject each, 1.3%). Except for pneumonia, other events were assessed as treatment related by the investigator ([Table 55](#)).

Table 55 TEAEs and TRAEs Associated with Permanent Discontinuation of SHR-A1811 in the SHR-A1811 in Combination with Pertuzumab Pool by Preferred Term

SHR-A1811 in Combination with Pertuzumab		
(N=75)		
System Organ Class (SOC)	n (%)	
Preferred Term (PT)	TEAE	TRAE
Subjects with any TEAE Associated with Permanent Discontinuation of SHR-A1811	4 (5.3)	3 (4.0)
Blood and lymphatic system disorders	1 (1.3)	1 (1.3)
Anaemia	1 (1.3)	1 (1.3)
Infections and infestations	1 (1.3)	0
Pneumonia	1 (1.3)	0
Investigations	1 (1.3)	1 (1.3)
Platelet count decreased	1 (1.3)	1 (1.3)
Respiratory, thoracic and mediastinal disorders	1 (1.3)	1 (1.3)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Pertuzumab (N=75) n (%)	
	TEAE	TRAE
Pneumonitis	1 (1.3)	1 (1.3)

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event,

TRAE=treatment-related adverse event.

Coded using MedDRA Version 28.0.

6.2.1.3.4. SAEs

Seventeen (17/75, 22.7%) subjects had SAEs, which were anaemia (5 subjects, 6.7%), platelet count decreased, neutrophil count decreased, pneumonia, and vomiting (2 subjects each, 2.7%) and all the remaining events occurred in a single subject. Among these, except for pneumonia, COVID-19, oesophageal stenosis and radius fracture (1 subject each, 1.3%), all the other events were assessed as treatment related by the investigator. All SARs were considered to be related to SHR-A1811.

Due to the number of subjects exposed to SHR-A1811 in this treatment group being less than 100, the incidence rate of a single SAE is greater than 1%. The SAEs with rate of at least 1% listed in table below are the summary data of all occurred SAEs (Table 56).

Table 56 SAEs Reported in at Least 1% of Subject in the SHR-A1811 in Combination with Pertuzumab Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Pertuzumab (N=75) n (%)		
	SAE	SAR	SHR-A1811 Related
Subjects with any TE-SAE	17 (22.7)	14 (18.7)	14 (18.7)
Blood and lymphatic system disorders	6 (8.0)	6 (8.0)	6 (8.0)
Anaemia	5 (6.7)	5 (6.7)	5 (6.7)
Febrile neutropenia	1 (1.3)	1 (1.3)	1 (1.3)
Myelosuppression	1 (1.3)	1 (1.3)	1 (1.3)
Gastrointestinal disorders	4 (5.3)	3 (4.0)	3 (4.0)
Vomiting	2 (2.7)	2 (2.7)	2 (2.7)
Oesophageal stenosis	1 (1.3)	0	0
Pancreatitis acute	1 (1.3)	1 (1.3)	1 (1.3)
Investigations	4 (5.3)	4 (5.3)	4 (5.3)
Neutrophil count decreased	2 (2.7)	2 (2.7)	2 (2.7)
Platelet count decreased	2 (2.7)	2 (2.7)	2 (2.7)
White blood cell count decreased	1 (1.3)	1 (1.3)	1 (1.3)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Pertuzumab (N=75) n (%)		
	SAE	SAR	SHR-A1811 Related
Infections and infestations	3 (4.0)	2 (2.7)	2 (2.7)
Pneumonia	2 (2.7)	1 (1.3)	1 (1.3)
Bronchitis	1 (1.3)	1 (1.3)	1 (1.3)
COVID-19	1 (1.3)	0	0
General disorders and administration site conditions	1 (1.3)	1 (1.3)	1 (1.3)
Asthenia	1 (1.3)	1 (1.3)	1 (1.3)
Injury, poisoning and procedural complications	1 (1.3)	0	0
Radius fracture	1 (1.3)	0	0
Metabolism and nutrition disorders	1 (1.3)	1 (1.3)	1 (1.3)
Malnutrition	1 (1.3)	1 (1.3)	1 (1.3)

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,
PT=preferred term, SAE=serious adverse event, SAR=serious adverse reaction, SOC=system organ
class.

Coded using MedDRA Version 28.0.

6.2.1.3.5. AEs Associated with Outcome of Death

One (1/75, 1.3%) subject had TEAEs with an outcome of death, which was pneumonia and assessed as unrelated to study treatment by the investigator.

6.2.1.4. SHR-A1811 in Combination with Other Drugs

The studies included in the pooled safety analysis of subjects receiving SHR-A1811 in combination with other drugs (including fuzuloparib, pyrotinib, fulvestrant, SHR-1701, letrozole, anastrozole, dalpiciclib, calcium levofolinate, 5-FU, oxaliplatin, bevacizumab, capecitabine, paclitaxel-albumin, HRS-8080, addebrelimab, SHR-8068, carboplatin) were SHR-A1811-II-201, SHR-A1811-202, SHR-A1811-II-203, SHR-A1811-Ib/II-205, SHR-A1811-206, SHR-A1811-207, SHR-A1811-208, SHR-A1811-216-OC and HRS-8080-202. A total of 360 subjects were exposed to SHR-A1811 in combination with other drugs.

6.2.1.4.1. AEs

The incidence of TEAEs and Grade ≥ 3 TEAEs were 97.5% (351/360) and 70.8% (255/360), respectively (Table 57).

The TEAEs with an incidence of $\geq 10\%$ included anaemia (80.6%), neutrophil count decreased (79.4%), white blood cell count decreased (76.9%), nausea (57.8%), aspartate aminotransferase increased (43.9%), decreased appetite (41.9%), alanine aminotransferase increased (41.4%), platelet count decreased (40.8%), vomiting (38.6%), hypoalbuminaemia, diarrhoea (34.7% each), weight decreased (30.6%),

alopecia (30.0%), proteinuria (28.6%), lymphocyte count decreased (27.8%), hypertriglyceridaemia (27.2%), blood alkaline phosphatase increased (25.0%), constipation (24.4%), gamma-glutamyltransferase increased (23.6%), hypokalaemia (23.3%), blood lactate dehydrogenase increased (22.8%), hyponatraemia (22.2%), urinary tract infection (19.2%), hyperglycaemia (16.7%), hypercholesterolaemia (16.4%), upper respiratory tract infection (16.1%), hyperuricaemia, stomatitis, and hypocalcaemia (15.8% each), asthenia (15.6%), blood bilirubin increased, malaise (14.2% each), fatigue (13.6%), pyrexia (12.5%), blood creatinine increased (11.7%), cough (11.4%), alpha hydroxybutyrate dehydrogenase increased (11.1%).

The Grade ≥ 3 TEAEs with an incidence of $\geq 2\%$ included neutrophil count decreased (47.5%), white blood cell count decreased (28.6%), anaemia (14.7%), platelet count decreased (12.5%), lymphocyte count decreased (6.9%), diarrhoea (5.6%), pneumonia (5.0%), hypokalaemia (4.7%), vomiting (3.3%), decreased appetite (2.8%), febrile neutropenia (2.5%), nausea, stomatitis (2.2% each).

Table 57 TEAEs with an incidence $\geq 5\%$ or Grade ≥ 3 TEAEs with an incidence $\geq 1\%$ of

Subjects in the SHR-A1811 in Combination with Other Drugs Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Other Drugs (N=360) n (%)	
	All Grades	Grade ≥ 3
Subjects with any TEAE	351 (97.5)	255 (70.8)
Investigations	335 (93.1)	198 (55.0)
Neutrophil count decreased	286 (79.4)	171 (47.5)
White blood cell count decreased	277 (76.9)	103 (28.6)
Aspartate aminotransferase increased	158 (43.9)	5 (1.4)
Alanine aminotransferase increased	149 (41.4)	3 (0.8)
Platelet count decreased	147 (40.8)	45 (12.5)
Weight decreased	110 (30.6)	4 (1.1)
Lymphocyte count decreased	100 (27.8)	25 (6.9)
Blood alkaline phosphatase increased	90 (25.0)	1 (0.3)
Gamma-glutamyltransferase increased	85 (23.6)	6 (1.7)
Blood lactate dehydrogenase increased	82 (22.8)	0
Blood bilirubin increased	51 (14.2)	4 (1.1)
Blood creatinine increased	42 (11.7)	0
Alpha hydroxybutyrate dehydrogenase increased	40 (11.1)	0
Faecal occult blood positive	35 (9.7)	0
Blood thyroid stimulating hormone increased	33 (9.2)	0
Blood cholesterol increased	30 (8.3)	0
Fibrin D dimer increased	27 (7.5)	0
Blood creatine phosphokinase increased	22 (6.1)	0
Lipase increased	22 (6.1)	1 (0.3)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Other Drugs (N=360) n (%)	
	All Grades	Grade ≥ 3
Weight increased	22 (6.1)	1 (0.3)
Blood urea increased	19 (5.3)	0
Urinary occult blood positive	19 (5.3)	0
Gastrointestinal disorders	297 (82.5)	63 (17.5)
Nausea	208 (57.8)	8 (2.2)
Vomiting	139 (38.6)	12 (3.3)
Diarrhoea	125 (34.7)	20 (5.6)
Constipation	88 (24.4)	0
Stomatitis	57 (15.8)	8 (2.2)
Abdominal distension	19 (5.3)	0
Mouth ulceration	19 (5.3)	3 (0.8)
Intestinal obstruction	5 (1.4)	4 (1.1)
Blood and lymphatic system disorders	291 (80.8)	66 (18.3)
Anaemia	290 (80.6)	53 (14.7)
Leukopenia	27 (7.5)	6 (1.7)
Febrile neutropenia	9 (2.5)	9 (2.5)
Metabolism and nutrition disorders	290 (80.6)	35 (9.7)
Decreased appetite	151 (41.9)	10 (2.8)
Hypoalbuminaemia	125 (34.7)	0
Hypertriglyceridaemia	98 (27.2)	7 (1.9)
Hypokalaemia	84 (23.3)	17 (4.7)
Hyponatraemia	80 (22.2)	2 (0.6)
Hyperglycaemia	60 (16.7)	0
Hypercholesterolaemia	59 (16.4)	0
Hyperuricaemia	57 (15.8)	0
Hypocalcaemia	57 (15.8)	4 (1.1)
Hypermagnesaemia	26 (7.2)	0
Hyperphosphataemia	25 (6.9)	0
Hypercalcaemia	24 (6.7)	0
Hypophosphataemia	24 (6.7)	0
General disorders and administration site conditions	178 (49.4)	10 (2.8)
Asthenia	56 (15.6)	2 (0.6)
Malaise	51 (14.2)	2 (0.6)
Fatigue	49 (13.6)	1 (0.3)
Pyrexia	45 (12.5)	0
Infections and infestations	162 (45.0)	38 (10.6)
Urinary tract infection	69 (19.2)	2 (0.6)
Upper respiratory tract infection	58 (16.1)	6 (1.7)
Pneumonia	29 (8.1)	18 (5.0)

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Other Drugs (N=360) n (%)	
	All Grades	Grade ≥ 3
COVID-19	26 (7.2)	3 (0.8)
Skin and subcutaneous tissue disorders	152 (42.2)	4 (1.1)
Alopecia	108 (30.0)	0
Palmar-plantar erythrodysesthesia syndrome	18 (5.0)	3 (0.8)
Renal and urinary disorders	117 (32.5)	3 (0.8)
Proteinuria	103 (28.6)	0
Haematuria	22 (6.1)	0
Cardiac disorders	106 (29.4)	4 (1.1)
Sinus bradycardia	27 (7.5)	0
Sinus tachycardia	18 (5.0)	0
Respiratory, thoracic and mediastinal disorders	96 (26.7)	6 (1.7)
Cough	41 (11.4)	2 (0.6)
Epistaxis	31 (8.6)	0
Nervous system disorders	76 (21.1)	6 (1.7)
Dizziness	30 (8.3)	0
Vascular disorders	39 (10.8)	7 (1.9)
Hypertension	23 (6.4)	5 (1.4)
Endocrine disorders	36 (10.0)	1 (0.3)
Hypothyroidism	26 (7.2)	0
Psychiatric disorders	29 (8.1)	0
Insomnia	24 (6.7)	0

Abbreviations: AE=adverse event, MedDRA=Medical Dictionary for Regulatory Activities,

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

Coded using MedDRA Version 28.0

6.2.1.4.2. Treatment-Related AEs

The incidence of TRAEs and Grade ≥ 3 TRAEs were 96.7% (348/360) and 66.1% (238/360), respectively ([Table 58](#)).

The TRAEs with an incidence of $\geq 10\%$ included neutrophil count decreased (79.2%), anaemia (78.9%), white blood cell count decreased (76.7%), nausea (56.4%), aspartate aminotransferase increased (41.9%), decreased appetite (41.7%), platelet count decreased (40.6%), alanine aminotransferase increased (40.0%), vomiting (38.1%), diarrhoea (31.9%), hypoalbuminaemia (30.6%), alopecia (29.4%), lymphocyte count decreased (27.2%), proteinuria (25.3%), weight decreased, hypertriglyceridaemia (24.4% each), blood alkaline phosphatase increased (22.5%), gamma-glutamyltransferase increased, blood lactate dehydrogenase increased (21.9% each), hyponatraemia (20.3%), hypokalaemia (19.4%), constipation (18.1%), urinary tract infection, stomatitis (15.6% each), asthenia (15.3%), hypocalcaemia (14.4%), hyperglycaemia, hypercholesterolaemia (13.9% each), hyperuricaemia (13.6%), blood bilirubin increased, malaise (13.3% each), fatigue (12.8%), blood creatinine increased (11.1%),

alpha hydroxybutyrate dehydrogenase increased (10.8%).

The Grade ≥ 3 TRAEs with an incidence of $\geq 2\%$ included neutrophil count decreased (47.5%), white blood cell count decreased (28.6%), anaemia (14.2%), platelet count decreased (12.2%), lymphocyte count decreased (6.9%), diarrhoea (5.6%), hypokalaemia (4.2%), vomiting (3.3%), decreased appetite (2.8%), febrile neutropenia (2.5%), nausea, pneumonia (2.2% each).

The incidence of SHR-A1811 related AEs and Grade ≥ 3 SHR-A1811 related AEs were 96.4% (347/360) and 65.6% (236/360), respectively. The types and incidence of All grades and Grade ≥ 3 SHR-A1811 related AEs were similar to those of All grades and Grade ≥ 3 TRAEs, with no major difference identified between TRAEs and SHR-A1811 related AEs. Among the common Grade ≥ 3 TRAEs, only one case out of all 20 diarrhoea TRAE cases was determined to be unrelated to SHR-A1811 ([Table 58](#)).

Table 58 TRAEs with an incidence $\geq 5\%$ or Grade ≥ 3 TRAEs with an incidence $\geq 1\%$ of Subjects in the SHR-A1811 in Combination with Other Drugs Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Other Drugs (N=360) n (%)			
	TRAE	SHR-A1811-Related AE	Grade 3 TRAE	Grade 3 SHR-A1811-related AE
Subjects with any TRAE	348 (96.7)	347 (96.4)	238 (66.1)	236 (65.6)
Investigations	330 (91.7)	329 (91.4)	197 (54.7)	197 (54.7)
Neutrophil count decreased	285 (79.2)	285 (79.2)	171 (47.5)	171 (47.5)
White blood cell count decreased	276 (76.7)	276 (76.7)	103 (28.6)	103 (28.6)
Aspartate aminotransferase increased	151 (41.9)	151 (41.9)	5 (1.4)	5 (1.4)
Platelet count decreased	146 (40.6)	146 (40.6)	44 (12.2)	44 (12.2)
Alanine aminotransferase increased	144 (40.0)	144 (40.0)	3 (0.8)	3 (0.8)
Lymphocyte count decreased	98 (27.2)	98 (27.2)	25 (6.9)	25 (6.9)
Weight decreased	88 (24.4)	85 (23.6)	4 (1.1)	4 (1.1)
Blood alkaline phosphatase increased	81 (22.5)	81 (22.5)	1 (0.3)	1 (0.3)
Blood lactate dehydrogenase increased	79 (21.9)	79 (21.9)	0	0
Gamma-glutamyltransferase increased	79 (21.9)	79 (21.9)	5 (1.4)	5 (1.4)
Blood bilirubin increased	48 (13.3)	48 (13.3)	3 (0.8)	3 (0.8)
Blood creatinine increased	40 (11.1)	40 (11.1)	0	0

SHR-A1811 in Combination with Other Drugs				
(N=360)				
System Organ Class (SOC)	n (%)			
	TRAЕ	SHR-A1811-Related AE	Grade 3 TRAЕ	Grade 3 SHR-A1811-related AE
Alpha hydroxybutyrate dehydrogenase increased	39 (10.8)	38 (10.6)	0	0
Blood thyroid stimulating hormone increased	28 (7.8)	28 (7.8)	0	0
Blood cholesterol increased	25 (6.9)	25 (6.9)	0	0
Fibrin D dimer increased	25 (6.9)	25 (6.9)	0	0
Faecal occult blood positive	24 (6.7)	24 (6.7)	0	0
Blood creatine phosphokinase increased	21 (5.8)	21 (5.8)	0	0
Lipase increased	20 (5.6)	20 (5.6)	1 (0.3)	1 (0.3)
Blood urea increased	18 (5.0)	18 (5.0)	0	0
Blood and lymphatic system disorders	286 (79.4)	285 (79.2)	64 (17.8)	64 (17.8)
Anaemia	284 (78.9)	283 (78.6)	51 (14.2)	51 (14.2)
Leukopenia	27 (7.5)	27 (7.5)	6 (1.7)	6 (1.7)
Febrile neutropenia	9 (2.5)	9 (2.5)	9 (2.5)	9 (2.5)
Gastrointestinal disorders	283 (78.6)	282 (78.3)	54 (15.0)	53 (14.7)
Nausea	203 (56.4)	200 (55.6)	8 (2.2)	8 (2.2)
Vomiting	137 (38.1)	135 (37.5)	12 (3.3)	12 (3.3)
Diarrhoea	115 (31.9)	111 (30.8)	20 (5.6)	19 (5.3)
Constipation	65 (18.1)	64 (17.8)	0	0
Stomatitis	56 (15.6)	52 (14.4)	7 (1.9)	7 (1.9)
Abdominal distension	18 (5.0)	18 (5.0)	0	0
Mouth ulceration	18 (5.0)	18 (5.0)	3 (0.8)	3 (0.8)
Metabolism and nutrition disorders	276 (76.7)	276 (76.7)	31 (8.6)	31 (8.6)
Decreased appetite	150 (41.7)	150 (41.7)	10 (2.8)	10 (2.8)
Hypoalbuminaemia	110 (30.6)	110 (30.6)	0	0
Hypertriglyceridaemia	88 (24.4)	88 (24.4)	5 (1.4)	5 (1.4)
Hyponatraemia	73 (20.3)	73 (20.3)	2 (0.6)	2 (0.6)
Hypokalaemia	70 (19.4)	69 (19.2)	15 (4.2)	15 (4.2)
Hypocalcaemia	52 (14.4)	52 (14.4)	4 (1.1)	4 (1.1)
Hypercholesterolaemia	50 (13.9)	50 (13.9)	0	0
Hyperglycaemia	50 (13.9)	48 (13.3)	0	0
Hyperuricaemia	49 (13.6)	49 (13.6)	0	0
Hypermagnesaemia	24 (6.7)	24 (6.7)	0	0
Hypercalcaemia	23 (6.4)	23 (6.4)	0	0

SHR-A1811 in Combination with Other Drugs (N=360)				
System Organ Class (SOC) Preferred Term (PT)	n (%)			
	TRAE	SHR-A1811- Related AE	Grade 3 TRAE	Grade 3 SHR-A1811- related AE
Hyperphosphataemia	23 (6.4)	23 (6.4)	0	0
Hypophosphataemia	22 (6.1)	21 (5.8)	0	0
General disorders and administration site conditions	156 (43.3)	155 (43.1)	6 (1.7)	6 (1.7)
Asthenia	55 (15.3)	55 (15.3)	2 (0.6)	2 (0.6)
Malaise	48 (13.3)	47 (13.1)	2 (0.6)	2 (0.6)
Fatigue	46 (12.8)	45 (12.5)	1 (0.3)	1 (0.3)
Pyrexia	31 (8.6)	31 (8.6)	0	0
Skin and subcutaneous tissue disorders	149 (41.4)	135 (37.5)	4 (1.1)	2 (0.6)
Alopecia	106 (29.4)	106 (29.4)	0	0
Palmar-plantar erythrodysesthesia syndrome	18 (5.0)	8 (2.2)	3 (0.8)	2 (0.6)
Infections and infestations	102 (28.3)	102 (28.3)	16 (4.4)	16 (4.4)
Urinary tract infection	56 (15.6)	56 (15.6)	1 (0.3)	1 (0.3)
Upper respiratory tract infection	25 (6.9)	25 (6.9)	3 (0.8)	3 (0.8)
Pneumonia	18 (5.0)	18 (5.0)	8 (2.2)	8 (2.2)
Renal and urinary disorders	101 (28.1)	101 (28.1)	1 (0.3)	1 (0.3)
Proteinuria	91 (25.3)	91 (25.3)	0	0
Cardiac disorders	87 (24.2)	87 (24.2)	2 (0.6)	2 (0.6)
Sinus bradycardia	20 (5.6)	20 (5.6)	0	0
Nervous system disorders	62 (17.2)	61 (16.9)	3 (0.8)	3 (0.8)
Dizziness	24 (6.7)	23 (6.4)	0	0
Respiratory, thoracic and mediastinal disorders	58 (16.1)	56 (15.6)	1 (0.3)	1 (0.3)
Epistaxis	22 (6.1)	21 (5.8)	0	0
Cough	20 (5.6)	20 (5.6)	0	0
Endocrine disorders	31 (8.6)	26 (7.2)	1 (0.3)	1 (0.3)
Hypothyroidism	22 (6.1)	19 (5.3)	0	0
Vascular disorders	28 (7.8)	26 (7.2)	3 (0.8)	3 (0.8)
Hypertension	19 (5.3)	17 (4.7)	3 (0.8)	3 (0.8)

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SOC=system organ class, TRAE=treatment-related adverse event.

Coded using MedDRA Version 28.0.

6.2.1.4.3. AEs Associated with Permanent Discontinuation of SHR-A1811

Twelve (12/360, 3.3%) subjects had TEAEs leading to permanent discontinuation of SHR-A1811, and these TEAEs that occurred in ≥ 2 subjects were neutrophil count decreased (3 subjects, 0.8%), white blood cell count decreased, gamma-glutamyltransferase increased (2 subjects each, 0.6%), with all the remaining events reported in a single subject.

Nine (9/360, 2.5%) subjects had TRAEs leading to permanent discontinuation of SHR-A1811, and these TRAEs that occurred in ≥ 2 subjects were neutrophil count decreased (3 subjects, 0.8%), white blood cell count decreased, gamma-glutamyltransferase increased (2 subjects each, 0.6%) (Table 59).

Table 59 TEAEs and TRAEs Associated with Permanent Discontinuation of SHR-A1811 in the SHR-A1811 in Combination with Other Drugs Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Other Drugs (N=360) n (%)	
	TEAE	TRAE
Subjects with any TEAE Associated with Permanent Discontinuation of SHR-A1811	12 (3.3)	9 (2.5)
Gastrointestinal disorders	4 (1.1)	3 (0.8)
Ascites	1 (0.3)	0
Intestinal obstruction	1 (0.3)	1 (0.3)
Lower gastrointestinal haemorrhage	1 (0.3)	1 (0.3)
Upper gastrointestinal haemorrhage	1 (0.3)	1 (0.3)
Investigations	4 (1.1)	4 (1.1)
Neutrophil count decreased	3 (0.8)	3 (0.8)
Gamma-glutamyltransferase increased	2 (0.6)	2 (0.6)
White blood cell count decreased	2 (0.6)	2 (0.6)
Platelet count decreased	1 (0.3)	1 (0.3)
Blood and lymphatic system disorders	1 (0.3)	1 (0.3)
Anaemia	1 (0.3)	1 (0.3)
Infections and infestations	1 (0.3)	1 (0.3)
Pneumonia	1 (0.3)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	0
Gastric cancer	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	1 (0.3)	1 (0.3)
Interstitial lung disease	1 (0.3)	1 (0.3)
Skin and subcutaneous tissue disorders	1 (0.3)	0
Eczema	1 (0.3)	0

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event,

TRAE=treatment-related adverse event.

Coded using MedDRA Version 28.0.

6.2.1.4.4. SAEs

A total of 105 (29.2%) subjects had SAEs, and SAEs with an incidence of $\geq 2\%$ included pneumonia (19 subjects, 5.3%), platelet count decreased (18 subjects, 5.0%), anaemia (12 subjects, 3.3%), neutrophil count decreased (11 subjects, 3.1%), white blood cell count decreased (10 subjects, 2.8%), vomiting (9 subjects, 2.5%).

A total of 73 (20.3%) subjects had SARs, and SARs with an incidence of $\geq 2\%$ included platelet count decreased (18 subjects, 5.0%), neutrophil count decreased (11 subjects, 3.1%), pneumonia, anaemia, and white blood cell count decreased (10 subjects each, 2.8%), vomiting (9 subjects, 2.5%). Except for one case of immune-mediated lung disease, all the other SARs were considered to be related to SHR-A1811 (Table 60).

Table 60 SAEs Reported in at Least 1% of Subject in the SHR-A1811 in Combination with Other Drugs Pool by Preferred Term

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Other Drugs (N=360) n (%)		
	SAE	SAR	SHR-A1811 Related
Subjects with any TE-SAE	105 (29.2)	73 (20.3)	72 (20.0)
Gastrointestinal disorders	32 (8.9)	23 (6.4)	23 (6.4)
Vomiting	9 (2.5)	9 (2.5)	9 (2.5)
Intestinal obstruction	4 (1.1)	3 (0.8)	3 (0.8)
Upper gastrointestinal haemorrhage	4 (1.1)	4 (1.1)	4 (1.1)
Infections and infestations	29 (8.1)	14 (3.9)	14 (3.9)
Pneumonia	19 (5.3)	10 (2.8)	10 (2.8)
Investigations	26 (7.2)	25 (6.9)	25 (6.9)
Platelet count decreased	18 (5.0)	18 (5.0)	18 (5.0)
Neutrophil count decreased	11 (3.1)	11 (3.1)	11 (3.1)
White blood cell count decreased	10 (2.8)	10 (2.8)	10 (2.8)
Blood and lymphatic system disorders	17 (4.7)	15 (4.2)	15 (4.2)
Anaemia	12 (3.3)	10 (2.8)	10 (2.8)
Febrile neutropenia	4 (1.1)	4 (1.1)	4 (1.1)

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities,

PT=preferred term, SAE=serious adverse event, SAR=serious adverse reaction, SOC=system organ class.

Coded using MedDRA Version 28.0.

6.2.1.4.5. AEs Associated with Outcome of Death

Eleven (11/360, 3.1%) subjects had TEAEs with an outcome of death and three cases were assessed as treatment related by the investigator, which included pneumonia (2 subjects, 0.6%), sepsis (1 subject, 0.3%). All three of these fatal TRAEs were considered to be related to SHR-A1811 (Table 61).

Table 61 TEAEs Associated with Outcome of Death of SHR-A1811 in the SHR-A1811 in**Combination with Other Drugs Pool by Preferred Term**

System Organ Class (SOC) Preferred Term (PT)	SHR-A1811 in Combination with Other Drugs (N=360) n (%)		
	TEAE	TRAE	SHR-A1811 Related
Subjects with any Fatal TEAE	11 (3.1)	3 (0.8)	3 (0.8)
Infections and infestations	4 (1.1)	3 (0.8)	3 (0.8)
Pneumonia	3 (0.8)	2 (0.6)	2 (0.6)
Sepsis	1 (0.3)	1 (0.3)	1 (0.3)
General disorders and administration site conditions	3 (0.8)	0	0
Death	3 (0.8)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.8)	0	0
Neoplasm progression	2 (0.6)	0	0
Metastases to meninges	1 (0.3)	0	0
Gastrointestinal disorders	1 (0.3)	0	0
Gastrointestinal perforation	1 (0.3)	0	0

Abbreviations: AE=adverse event, MedDRA =Medical Dictionary for Regulatory Activities, PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event.

Coded using MedDRA Version 28.0.

Table 62 below summarizes all treatment-related deaths reported on clinical trials of SHR-A1811 in combination with other drugs as of 13 May 2025.

Table 62 Individual Listing of Treatment-Related Deaths Through 13 May 2025 - SHR-A1811 in Combination with Other Drugs

Study ID	Age/Gender/ Nationality	Study Treatment	Cause of Death MedDRA Preferred Term [verbatim term]
SHR-A1811-II-201	71-year-old Chinese Male	SHR-A1811 3.2 mg/kg + Fuzuloparib 50 mg BID	Pneumonia [lung infection]
SHR-A1811-II-201	71-year-old Chinese Female	SHR-A1811 4.8 mg/kg + Fuzuloparib 30 mg QD	Pneumonia [lung infection]

Study ID	Age/Gender/ Nationality	Study Treatment	Cause of Death MedDRA Preferred Term [verbatim term]
SHR-A1811- 206	69-year-old Chinese Female	SHR-A1811 6.4 mg/kg + Fulvestrant	Sepsis [septicemia]

Data cutoff date: 13 May 2025.

6.2.1.5. Studies not included in the pooled analysis

6.2.1.5.1. Study SHR-A1811-III-301

As of 13 May 2025, the study enrollment was ongoing. A total of 381 breast cancer subjects were enrolled, and 380 of them received SHR-A1811 monotherapy or pyrotinib combined with capecitabine. To avoid bias in the final analysis, the safety information for this study is summarized in a treatment masked format.

6.2.1.5.1.1 AEs

A total of 380 (100.0%) subjects had TEAEs, and TEAEs with an incidence of $\geq 10\%$ included anaemia (68.7%), neutrophil count decreased (67.4%), white blood cell count decreased (62.6%), nausea (61.6%), diarrhoea (61.1%), vomiting (48.9%), aspartate aminotransferase increased (46.6%), weight decreased (44.7%), alanine aminotransferase increased (43.9%), hypertriglyceridaemia (36.8%), decreased appetite (35.5%), hyperuricaemia (30.8%), hypokalaemia (28.4%), blood creatinine increased, hypoalbuminaemia (26.1% each), palmar-plantar erythrodysesthesia syndrome, urinary tract infection (25.3% each), blood bilirubin increased, platelet count decreased (23.9% each), gamma-glutamyltransferase increased (20.3%), alopecia (19.2%), hyperglycaemia (18.7%), malaise (18.4%), blood lactate dehydrogenase increased (18.2%), leukopenia (17.4%), lymphocyte count decreased (17.1%), hypercholesterolaemia (16.8%), weight increased, hyponatraemia (15.8% each), fatigue (15.5%), blood alkaline phosphatase increased (14.7%), stomatitis (14.5%), dizziness (12.9%), proteinuria (12.1%), upper respiratory tract infection (11.8%), pyrexia (11.1%), constipation (10.5%), influenza like illness (10.3%), asthenia, cough (10.0% each).

A total of 263 (69.2%) subjects had Grade ≥ 3 TEAEs, and Grade ≥ 3 TEAEs with an incidence of $\geq 2\%$ included neutrophil count decreased (35.3%), white blood cell count decreased (15.3%), diarrhoea (12.6%), anaemia (9.7%), hypokalaemia (6.1%), platelet count decreased (5.8%), lymphocyte count decreased (4.7%), palmar-plantar erythrodysesthesia syndrome (4.5%), hypertriglyceridaemia (3.2%), decreased appetite (2.9%), vomiting (2.4%), alanine aminotransferase increased, nausea, and pneumonia (2.1% each).

6.2.1.5.1.2 SAEs

A total of 67 (17.6%) subjects had SAEs, and SAEs reported in at least 2 subjects included platelet count decreased, anaemia (9 subjects each, 2.4%), neutrophil count decreased (8 subjects, 2.1%), pneumonia (7 subjects, 1.8%), vomiting (6 subjects, 1.6%), white blood cell count decreased, febrile neutropenia (5 subjects each, 1.3%), diarrhoea, nausea (4 subjects each, 1.1%), alanine aminotransferase increased, aspartate aminotransferase increased, and decreased appetite (3 subjects each, 0.8%),

osteomyelitis, septic shock, upper respiratory tract infection, electrolyte imbalance, hypokalaemia, death, interstitial lung disease, pneumonitis, acute kidney injury, and neoplasm progression (2 subjects each, 0.5%).

6.2.1.5.1.3 AEs Associated with Outcome of Death

Eight (8/380, 2.1%) subjects had TEAEs with an outcome of death, which included septic shock, death, and neoplasm progression (2 subjects each, 0.5%), pneumonia, myelosuppression (1 subject each, 0.3%).

6.2.1.5.1.4 AEs of Special Interest

A total of 9 (2.4%) subjects had AEs of special interest, which included electrocardiogram QT prolonged (4 subjects, 1.1%), interstitial lung disease (2 subjects, 0.5%), cardiac failure, myocardial injury, and hypertension (1 subject each, 0.3%).

6.2.1.5.2. Study SHR-A1811-305

As of 13 May 2025, the study enrollment was ongoing. A total of 1062 breast cancer subjects were enrolled, and 1027 of them received SHR-A1811 monotherapy or trastuzumab emtansine (T-DM1) monotherapy. To avoid bias in the final analysis, the safety information for this study is summarized in a treatment masked format.

6.2.1.5.2.1 AEs

A total of 996 (97.0%) subjects had TEAEs, and TEAEs with an incidence of $\geq 10\%$ included platelet count decreased (68.5%), neutrophil count decreased, white blood cell count decreased (64.5% each), aspartate aminotransferase increased (59.0%), alanine aminotransferase increased (57.8%), anaemia (51.5%), nausea (42.2%), gamma-glutamyltransferase increased (30.3%), lymphocyte count decreased (29.1%), hypertriglyceridaemia (27.0%), decreased appetite (26.3%), vomiting (22.4%), hypokalaemia (17.9%), radiation pneumonitis (16.6%), blood alkaline phosphatase increased (15.5%), hypercholesterolaemia (15.1%), radiation skin injury (14.7%), upper respiratory tract infection, urinary tract infection (13.0% each), hyperuricaemia (12.4%), weight decreased (12.3%), constipation (11.9%), blood lactate dehydrogenase increased, dizziness (11.5% each), alopecia (11.4%), malaise (10.2%).

A total of 782 (76.1%) subjects had Grade ≥ 3 TEAEs, and Grade ≥ 3 TEAEs with an incidence of $\geq 2\%$ included platelet count decreased (36.8%), neutrophil count decreased (35.0%), white blood cell count decreased (24.1%), lymphocyte count decreased (15.6%), anaemia (8.7%), aspartate aminotransferase increased (5.7%), alanine aminotransferase increased (5.4%), gamma-glutamyltransferase increased (4.3%), leukopenia (4.1%).

6.2.1.5.2.2 SAEs

A total of 206 (20.1%) subjects had SAEs, and SAEs reported in at least 2 subjects included platelet count decreased (103 subjects, 10.0%), white blood cell count decreased (19 subjects, 1.9%), neutrophil count decreased, anaemia (18 subjects each, 1.8%), pneumonia (15 subjects, 1.5%), aspartate aminotransferase increased (14 subjects, 1.4%), alanine aminotransferase increased (13 subjects, 1.3%), radiation skin injury (9 subjects, 0.9%), nausea, vomiting, and radiation pneumonitis (7 subjects each,

0.7%), gamma-glutamyltransferase increased, febrile neutropenia (5 subjects each, 0.5%), interstitial lung disease, decreased appetite (4 subjects each, 0.4%), pneumonia bacterial, pulmonary embolism, hypokalaemia, and asthenia (3 subjects each, 0.3%), blood bilirubin increased, bronchitis, herpes zoster, upper respiratory tract infection, diarrhoea, haemorrhoids, and deep vein thrombosis (2 subjects each, 0.2%).

6.2.1.5.2.3 AEs Associated with Outcome of Death

One (1/1027, 0.1%) subject had TEAEs with an outcome of death, which was pneumonia.

6.2.1.5.2.4 AEs of Special Interest

A total of 21 (2.0%) subjects had AEs of special interest, which included radiation pneumonitis (16 subjects, 1.6%), interstitial lung disease (4 subjects, 0.4%), electrocardiogram qt prolonged (1 subject, 0.1%).

6.2.1.5.3. Study SHR-A1811-III-306

As of 13 May 2025, the study enrollment was ongoing. A total of 496 breast cancer subjects were enrolled, and 474 of them received SHR-A1811 monotherapy or investigator's choice of chemotherapy. To avoid bias in the final analysis, the safety information for this study is summarized in a treatment masked format.

6.2.1.5.3.1 AEs

A total of 461 (97.3%) subjects had TEAEs, and TEAEs with an incidence of $\geq 10\%$ included neutrophil count decreased (79.5%), white blood cell count decreased (75.5%), anaemia (67.5%), aspartate aminotransferase increased (57.0%), alanine aminotransferase increased (54.0%), platelet count decreased (47.5%), alopecia (42.0%), nausea (38.4%), decreased appetite (29.7%), hypertriglyceridaemia (27.0%), gamma-glutamyltransferase increased (23.8%), vomiting (23.4%), urinary tract infection (20.9%), weight decreased (20.0%), hypokalaemia (19.8%), hypoalbuminaemia (18.1%), lymphocyte count decreased (17.5%), blood lactate dehydrogenase increased (17.3%), hypercholesterolaemia, malaise (16.5% each), hyperuricaemia (15.0%), blood alkaline phosphatase increased (14.8%), hyperglycaemia, constipation (14.6% each), diarrhoea (13.9%), fatigue (13.1%), blood bilirubin increased (12.7%), hyponatraemia, hypoesthesia (12.4% each), pyrexia (12.0%), hypocalcaemia (11.2%), asthenia (10.5%), dizziness (10.1%).

A total of 329 (69.4%) subjects had Grade ≥ 3 TEAEs, and Grade ≥ 3 TEAEs with an incidence of $\geq 2\%$ included neutrophil count decreased (56.8%), white blood cell count decreased (39.7%), anaemia (19.6%), platelet count decreased (16.9%), lymphocyte count decreased (6.3%), leukopenia (4.6%), hypokalaemia (4.0%), febrile neutropenia (3.8%), hypertriglyceridaemia (3.6%), gamma-glutamyltransferase increased (3.0%), pneumonia (2.3%), aspartate aminotransferase increased, alanine aminotransferase increased (2.1% each).

6.2.1.5.3.2 SAEs

A total of 120 (25.3%) subjects had SAEs, and SAEs reported in at least 2 subjects included platelet count decreased (44 subjects, 9.3%), neutrophil count decreased,

white blood cell count decreased (37 subjects each, 7.8%), febrile neutropenia (16 subjects, 3.4%), anaemia (15 subjects, 3.2%), pneumonia (14 subjects, 3.0%), alanine aminotransferase increased (8 subjects, 1.7%), aspartate aminotransferase increased, vomiting (7 subjects each, 1.5%), nausea (6 subjects, 1.3%), pleural effusion, death (4 subjects each, 0.8%), dyspnea, interstitial lung disease, hypokalaemia, asthenia, dizziness, and cardiac failure (3 subjects each, 0.6%), blood bilirubin increased, gamma-glutamyltransferase increased, leukopenia, myelosuppression, gastroenteritis, herpes zoster, respiratory tract infection, lower gastrointestinal haemorrhage (2 subjects each, 0.4%).

6.2.1.5.3.3 AEs Associated with Outcome of Death

Eleven (11/474, 2.3%) subjects had TEAEs with an outcome of death, which included death (4 subjects, 0.8%), cardiac failure (2 subjects, 0.4%), interstitial lung disease, obstructive airways disorder, acute hepatic failure, cerebral infarction, and uncoded AE*(verbatim: pneumonia [pneumonia viral accompanied by pneumocystis carinii pneumonia]) (1 subject each, 0.2%).

6.2.1.5.3.4 AEs of Special Interest

Fourteen (14/474, 3.0%) subjects had AEs of special interest, and AESIs reported in at least 2 subjects included electrocardiogram QT prolonged, interstitial lung disease (4 subjects each, 0.8%), cardiac failure (2 subjects, 0.4%).

6.2.1.5.4. Study SHR-A1811-307

As of 13 May 2025, the study enrollment was ongoing. A total of 756 breast cancer subjects were enrolled, and 740 of them received SHR-A1811 monotherapy, or SHR-A1811 combined with pertuzumab, or trastuzumab combined with pertuzumab and docetaxel. To avoid bias in the final analysis, the safety information for this study is summarized in a treatment masked format.

6.2.1.5.4.1 AEs

A total of 727 (98.2%) subjects had TEAEs, and TEAEs with an incidence of $\geq 10\%$ included neutrophil count decreased (83.6%), white blood cell count decreased (82.0%), alopecia (75.1%), anaemia (61.1%), nausea (55.7%), alanine aminotransferase increased (51.5%), aspartate aminotransferase increased (46.6%), decreased appetite (44.9%), diarrhoea (41.8%), vomiting (35.4%), hypertriglyceridaemia (31.5%), gamma-glutamyltransferase increased (23.1%), weight decreased (21.9%), constipation (21.5%), hypokalaemia (19.3%), hypoalbuminaemia (18.8%), urinary tract infection (17.4%), platelet count decreased (17.3%), fatigue (16.6%), insomnia (16.1%), hypercholesterolaemia (15.9%), blood lactate dehydrogenase increased (15.4%), malaise (15.3%), hyperglycaemia (15.1%), stomatitis (14.6%), asthenia (14.3%), lymphocyte count decreased (13.9%), blood alkaline phosphatase increased, hyperuricaemia (13.8% each), upper respiratory tract infection (13.0%), dizziness (12.7%), hyponatraemia (12.3%), hypocalcaemia (11.8%), pyrexia (10.0%).

A total of 509 (68.8%) subjects had Grade ≥ 3 TEAEs, and Grade ≥ 3 TEAEs with an incidence of $\geq 2\%$ included neutrophil count decreased (57.8%), white blood cell count decreased (31.1%), febrile neutropenia (5.0%), hypokalaemia (3.8%), anaemia (3.5%), diarrhoea (3.0%), lymphocyte count decreased (2.8%), alanine aminotransferase

increased, platelet count decreased (2.2% each).

6.2.1.5.4.2 SAEs

A total of 120 (16.2%) subjects had SAEs, and SAEs reported in at least 2 subjects included febrile neutropenia (27 subjects, 3.6%), white blood cell count decreased (26 subjects, 3.5%), neutrophil count decreased (20 subjects, 2.7%), vomiting (13 subjects, 1.8%), platelet count decreased (8 subjects, 1.1%), alanine aminotransferase increased, pneumonia (7 subjects each, 0.9%), decreased appetite (6 subjects, 0.8%), aspartate aminotransferase increased (5 subjects, 0.7%), haemorrhoids, nausea, hyponatraemia, pyrexia, and cerebral infarction (4 subjects each, 0.5%), asthenia (3 subjects, 0.4%), anaemia, abdominal pain, diarrhoea, pneumonia mycoplasmal, respiratory tract infection, soft tissue infection, hypokalaemia, type 2 diabetes mellitus, and peripheral vein thrombosis (2 subjects each, 0.3%).

6.2.1.5.4.3 AEs Associated with Outcome of Death

Four (4/740, 0.5%) subjects had TEAEs with an outcome of death, which included Interstitial lung disease, respiratory failure, disease progression, and neoplasm progression (1 subject each, 0.1%).

6.2.1.5.4.4 AEs of Special Interest

Fourteen (14/740, 1.9%) subject had AEs of special interest, and AESIs reported in at least 2 subjects included mitral valve disease, blood pressure increased, and interstitial lung disease (2 subjects each, 0.3%).

6.2.1.5.5. Study SHR-A1811-308

As of 13 May 2025, the study enrollment was ongoing. A total of 39 gastric cancer or gastroesophageal junction adenocarcinoma subjects were enrolled and received SHR-A1811 monotherapy or investigator's choice of chemotherapy. To avoid bias in the final analysis, the safety information for this study is summarized in a treatment masked format.

6.2.1.5.5.1 AEs

A total of 37 (94.9%) subjects had TEAEs, and TEAEs reported with an incidence of $\geq 10.0\%$ included white blood cell count decreased (79.5%), neutrophil count decreased (74.4%), anaemia (69.2%), platelet count decreased, hypoalbuminaemia (43.6% each), decreased appetite (41.0%), vomiting (35.9%), weight decreased, alopecia (33.3% each), aspartate aminotransferase increased (30.8%), nausea (25.6%), alanine aminotransferase increased, hypocalcaemia (23.1% each), faecal occult blood positive, hypokalaemia (20.5% each), gamma-glutamyltransferase increased, lymphocyte count decreased, hyponatraemia, constipation, diarrhoea, and upper respiratory tract infection (15.4% each), hypoproteinaemia, fatigue (12.8% each), blood alkaline phosphatase increased, blood bilirubin increased, hypochloroemia, abdominal pain, pyrexia, hypoesthesia, and proteinuria (10.3% each).

A total of 29 (74.4%) subjects had Grade ≥ 3 TEAEs, and Grade ≥ 3 TEAEs reported in at least 2 subjects ($\geq 5.1\%$) included neutrophil count decreased (53.8%), white blood cell count decreased (41.0%), anaemia (23.1%), platelet count decreased (20.5%),

febrile neutropenia, fatigue (7.7% each), gamma-glutamyltransferase increased, lymphocyte count decreased, decreased appetite, and hypokalaemia (5.1% each).

6.2.1.5.5.2 SAEs

A total of 14 (35.9%) subjects had SAEs, and SAEs reported in at least 2 subjects included anaemia, febrile neutropenia, and white blood cell count decreased (3 subjects each, 7.7%), neutrophil count decreased, decreased appetite (2 subjects each, 5.1%).

6.2.1.5.5.3 AEs Associated with Outcome of Death

Two (2/39, 5.1%) subjects had TEAEs with an outcome of death, which included influenza, septic shock (1 subject each, 2.6%).

6.2.1.5.5.4 AEs of Special Interest

One (1/39, 2.6%) subject experienced AE of special interest (PT: interstitial lung disease).

6.2.1.5.6. Study SHR-A1811-309

As of 13 May 2025, the study enrollment was ongoing. A total of 112 colorectal cancer subjects were enrolled, and 105 of them received SHR-A1811 monotherapy or investigator's choice of therapy. To avoid bias in the final analysis, the safety information for this study is summarized in a treatment masked format.

6.2.1.5.6.1 AEs

A total of 96 (91.4%) subjects had TEAEs, and TEAEs reported with an incidence of $\geq 10.0\%$ included anaemia (56.2%), white blood cell count decreased (53.3%), neutrophil count decreased (51.4%), nausea (27.6%), platelet count decreased (25.7%), decreased appetite (23.8%), diarrhoea (21.9%), aspartate aminotransferase increased, hypoalbuminaemia (20.0% each), vomiting (19.0%), alanine aminotransferase increased (16.2%), constipation, fatigue (15.2% each), alopecia (13.3%), gamma-glutamyltransferase increased (12.4%), asthenia (11.4%), abdominal distension, hypertension (10.5% each).

A total of 50 (47.6%) subjects had Grade ≥ 3 TEAEs, and Grade ≥ 3 TEAEs reported in at least 2 subjects ($\geq 1.9\%$) included neutrophil count decreased (22.9%), anaemia (12.4%), white blood cell count decreased (11.4%), platelet count decreased (8.6%), blood bilirubin increased (4.8%), alanine aminotransferase increased, hypertension (2.9% each), aspartate aminotransferase increased, gamma-glutamyltransferase increased, bilirubin conjugated increased, nausea, vomiting, ascites, intestinal obstruction, myelosuppression, hyponatraemia, and septic shock (1.9% each).

6.2.1.5.6.2 SAEs

Twenty-eight (2/1058, 26.7%) subjects had SAE, and SAEs reported in at least 2 subjects ($\geq 1.9\%$) included neutrophil count decreased (4.8%), pneumonia (3.8%), alanine aminotransferase increased, anaemia (2.9% each), aspartate aminotransferase increased, blood bilirubin increased, platelet count decreased, white blood cell count decreased, myelosuppression, and intestinal obstruction (1.9% each).

6.2.1.5.6.3 AEs Associated with Outcome of Death

Six (6/105, 5.7%) subjects had TEAE with an outcome of death, which included pelvic infection in combination with septic shock and tumour necrosis, sepsis, neoplasm progression, myelosuppression, death, and acute kidney injury (1 subject each, 1.0%).

6.2.1.5.6.4 AEs of Special Interest

One (1/105, 1.0%) subject had AEs of special interest, which were alanine aminotransferase increased, aspartate aminotransferase increased, and blood bilirubin increased.

6.2.1.5.7. Study SHR-A1811-310

As of 13 May 2025, the study enrollment was ongoing. A total of 27 non-small cell lung cancer subjects were enrolled, and 24 of them received SHR-A1811 monotherapy or camrelizumab combined with platinum-based dual drug chemotherapy. To avoid bias in the final analysis, the safety information for this study is summarized in a treatment masked format.

6.2.1.5.7.1 AEs

A total of 17 (70.8%) subjects had TEAEs, and TEAEs reported with an incidence of $\geq 10.0\%$ included neutrophil count decreased (54.2%), white blood cell count decreased, decreased appetite (45.8% each), nausea (41.7%), asthenia (29.2%), anaemia (25.0%), alanine aminotransferase increased, platelet count decreased, and alopecia (20.8% each), vomiting (16.7%), aspartate aminotransferase increased, lymphocyte count decreased, and hypertriglyceridaemia (12.5% each).

A total of 8 (33.3%) subjects had Grade ≥ 3 TEAEs, and Grade ≥ 3 TEAEs reported in at least 2 subjects ($\geq 8.3\%$) included neutrophil count decreased (25.0%), white blood cell count decreased (8.3%).

6.2.1.5.7.2 SAEs

Five (5/24, 20.8%) subjects had SAEs, with each event occurring in one subject, which were immune-mediated lung disease, pneumothorax, enteritis, sudden cardiac death, hypersensitivity, femur fracture, neutrophil count decreased, and white blood cell count decreased (4.2% each).

6.2.1.5.7.3 AEs Associated with Outcome of Death

One (1/24, 4.2%) subject experienced AE associated with outcome of death, which was sudden cardiac death.

6.2.1.5.7.4 AEs of Special Interest

No subject had AEs of special interest.

6.2.1.5.8. Study SHR-A1811-315

As of 13 May 2025, the study enrollment was ongoing. A total of 15 epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer subjects were enrolled, and

eight of them received SHR-A1811 monotherapy or investigator's choice of chemotherapy. To avoid bias in the final analysis, the safety information for this study is summarized in a treatment masked format.

6.2.1.5.8.1 AEs

A total of 5 (62.5%) subjects had TEAEs, and TEAEs reported in at least 2 subjects ($\geq 25.0\%$) included nausea, vomiting (37.5% each), malaise, lymphocyte count decreased, platelet count decreased, white blood cell count decreased, and anaemia (25.0% each).

One (1/8, 12.5%) subject had Grade ≥ 3 TEAEs, which were platelet count decreased, white blood cell count decreased, and neutrophil count decreased.

6.2.1.5.8.2 SAEs

No subject had SAEs.

6.2.1.5.8.3 AEs Associated with Outcome of Death

No subject had AEs associated with outcome of death.

6.2.1.5.8.4 AEs of Special Interest

No subject had AEs of special interest.

6.2.2. Efficacy

6.2.2.1. SHR-A1811 in Advanced Solid Tumors

6.2.2.1.1. SHR-A1811-I-101

As of the data cutoff date on 30 Sep 2024, the antitumor activity of SHR-A1811 by prior treatment lines in metastatic breast cancer (BC) patients and updated efficacy data of SHR-A1811 in this study was presented at the 2025 St. Gallen International Breast Cancer Conference (SGBCC) (1). Between 7 Sep 2020 and 4 Jun 2024, a total of 396 patients were enrolled. In the HER2-positive BC cohort, 66.9% of patients had an ECOG PS of 1 and a median of 3 (range: 2-5) prior lines of therapy, with a median sum of diameters (SOD) of target lesion measuring 49.8 mm. For HER2-low BC cohort, 60.9% of patients had an ECOG PS of 1 and a median of 2 (range: 1-4) prior lines of therapy, with a median SOD of target lesion measuring 50.1 mm. The median follow-up for all patients, patients with HER2-positive BC, and patients with HER2-low BC was 11.1 months (95% CI: 9.8-12.0), 17.6 months (95% CI: 14.3-22.7), and 10.6 months (95% CI: 9.0-14.0), respectively.

The ORR was 79.4% (95% CI: 71.6-85.9) in HER2-positive BC, 60.9% (95% CI: 51.1-70.1) in HER2-low BC, and ranged from 18.2% to 50.0% in various non-breast tumor types. Responses were durable, with median DoR of 23.6 months (95% CI: 16.2-NE) in HER2-positive BC, 12.4 months (95% CI: 8.1-23.4) in HER2-low BC. SHR-A1811 showed a trend toward longer PFS in metastatic BC patients who had received fewer

prior lines of therapy (NE vs 44.0 vs 16.5 months with 1, 2, or ≥ 3 prior lines of therapy in HER2-positive BC, respectively; 16.4 vs. 11.3 vs. 9.8 months in HER2-low BC).

This updated analysis confirms the promising efficacy of SHR-A1811 in heavily pretreated advanced solid tumors with HER2 expression or mutations.

6.2.2.2. SHR-A1811 in GC/GEJ or CRC

6.2.2.2.1. SHR-A1811-102

A multicenter, open-label, phase I trial was conducted to evaluate SHR-A1811 in HER2-expressing advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJ) or colorectal cancer (CRC) who failed or had no available or applicable standard treatment. The study included dose escalation, PK expansion and clinical expansion phases. Preliminary results from this trial were presented in the abstract published at the 2025 International Gastric Cancer Congress (IGCC) (2).

As of the data cutoff date of 29 Feb 2024, 100 patients had been enrolled and received at least one dose of SHR-A1811. Among them, 57 patients had HER2-expressing GC/GEJ, and 43 patients had HER2-expressing CRC. At baseline, over 90% of the patients in both groups had an ECOG PS of 1. In the GC/GEJ cohort, 70.2% of patients were HER2-positive and 21.1% were HER2 low-expressing, whereas in the CRC cohort, 86.0% of patients were HER2-positive, with none classified as HER2 low-expressing. The median follow-up period was 11.4 months (range: 1.4-32.5) for GC/GEJ and 13.8 months (range: 2.7-26.1) for CRC.

In the HER2-positive GC/GEJ cohort (n=40), the ORR was 45.0% (95% CI: 29.3–61.5), with a median PFS of 9.0 months (95% CI: 7.0–11.3) and a median overall survival (OS) of 16.3 months (95% CI: 12.4–NR). In the HER2 low-expressing GC/GEJ cohort (n=12), the ORR was 25.0% (95% CI: 5.5–57.2), with a median PFS of 12.2 months (95% CI: 2.8–14.0) and a median OS of NR (95% CI: 4.11–NR). For the HER2-positive CRC cohort (n=37), the ORR was 40.5% (95% CI: 24.8–57.9), with a median PFS of 9.5 months (95% CI: 7.3–11.2) and a median OS of 22.7 months (95% CI: 17.5–NR). Based on the study findings, the 6.4 mg/kg dose of SHR-A1811 was selected for clinical expansion.

These results suggest that SHR-A1811, a novel ADC targeting HER2, could be a promising strategy for HER2-expressing GC/GEJ and CRC.

6.2.2.3. SHR-A1811 in NSCLC

6.2.2.3.1. SHR-A1811-I-103

The HORIZON-Lung study consisted of two stages: Phase 1 stage and Phase 2 stage. The results of each stage were published separately in journal literatures (3, 4).

As of the data cutoff date for phase 1 (11 Apr 2023), 63 patients were enrolled in this stage of the trial. The enrolled population had a median of two prior lines of systemic

treatment, with 27.0% presenting with brain metastases at study entry and 88.9% of patients had an ECOG PS of 1 at enrollment. The recommended phase 2 dose (RP2D) was determined to be 4.8 mg/kg based on Phase 1 findings. Among patients treated with the 4.8 mg/kg dose, the ORR was 41.9% (95% CI: 27.0-57.9), and the DCR was 95.3% (95% CI: 84.2-99.4). The median duration of response (DOR) was 13.7 months (95% CI: 5.5-NR), while the median PFS was 8.4 months (95% CI: 7.1-15.0).

In Phase 2, a total of 94 patients were enrolled and treated as of the data cutoff date on 14 Jun 2024. Patients had a median of two prior lines of therapy (range: 1–2), with 24 (26%) patients presenting brain metastases at study entry and 81% of patients had an ECOG PS of 1 at baseline. The median duration of follow-up was 8.7 months (range: 7.0-10.4). Sixty-nine (73%; 95% CI: 63.3-82.0) of 94 patients had an ORR and 98.9% (95% CI: 94.2-100.0) had reached a DCR. In patients with an objective response, the median DOR was not reached (95% CI: 8.3-NR). The median PFS was 11.5 months (95% CI: 9.9–NR), with a PFS rate at 6 months of 86.8% (95% CI: 77.4–92.5). OS data were not mature, with three (3%) deaths in 94 patients.

SHR-A1811 demonstrated clinically meaningful efficacy in pretreated advanced HER2-mutant NSCLC.

6.2.2.4. SHR-A1811 in TNBC

6.2.2.4.1. SHR-A1811-II-202

The preliminary findings from the SHR-A1811 plus adbrelimab cohort in unresectable or metastatic triple negative breast cancer (TNBC) were presented at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting (5). As of the data cutoff date (31 Mar 2025), 50 TNBC patients had been enrolled and treated with SHR A1811 plus adbrelimab, including 8 patients in the phase 1b trial and 42 patients in the phase 2 trial. In phase 2, all enrolled patients received SHR-A1811 plus adbrelimab as first-line systematic antitumor therapy for TNBC, 33.3% of patients had ≥ 3 metastases sites, 52.4% were HER2 low (IHC 2+/ISH or IHC 1+)/ultra-low (IHC 0 or 1), and 71.4% were PD L1 positive (CPS ≥ 1).

The median follow-up time for the efficacy expansion cohort in phase 2 was 7.6 months (range: 1-15). In the phase 2 trial, the ORR was 69.0% (95% CI: 52.9-82.4), and the DCR was 92.9% (95% CI: 80.5-98.5). Median PFS was not reached, with a 6-month PFS rate of 92.0% (95% CI: 77.0-97.4). In terms of PD L1 expression status, the ORR was 80.0% (24/30) and 41.7% (5/12), and 6-month PFS was 95.8% (95% CI: 73.9-99.4) and 80.0% (95% CI: 40.9-94.6) in CPS ≥ 1 subgroup (n=30) and CPS <1 subgroup (n=12), respectively.

So far, the data demonstrated that SHR-A1811 plus adbrelimab had a good safety and tolerability profile. The combination showed encouraging antitumor activity in unresectable or metastatic TNBC, irrespective of HER2 or PD-L1 expression status.

6.3. Marketing Experience

As of 13 May 2025, SHR-A1811 has not been approved for marketing in any country or region.

6.4. References

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3. Li Z, Song Z, Hong W, Yang N, Wang Y, Jian H, et al. SHR-A1811 (antibody-drug conjugate) in advanced HER2-mutant non-small cell lung cancer: a multicenter, open-label, phase 1/2 study. Signal Transduct Target Ther. 2024;9(1):182.
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5. Liang Y, Zhang Q, Liao L, Ouyang Q, Han X, Wang Y, et al. SHR A1811 plus adebrelimab in unresectable or metastatic triple negative breast cancer: results from a phase 1b/2 expansion cohort. ASCO 2025, Abstract #1103.

7. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

7.1. Mechanism of Action and Intended Indications

SHR-A1811, developed independently by Hengrui, is an ADC targeted at HER2. It is composed of a humanized recombinant anti-HER2 IgG1 monoclonal antibody (SHR-1805, monoclonal antibody developed based on the amino acid sequence of trastuzumab) partially covalently linked to the small molecule SHR169106. SHR169106 is composed of a cleavable linker containing maleimide tetrapeptide (GGFG) and a DNA topoisomerase I inhibitor-9106-IM-2 (Research number: SHR169265). SHR-A1811 can specifically bind to the HER2 on the tumor cell surface, and subsequently the conjugate is endocytosed into the cell, and transported to the lysosome. The free toxin SHR169265 is released via cathepsin hydrolysis, which can inhibit the activity of DNA topoisomerase I, and lead to the tumor cell apoptosis. Due to high permeability, SHR169265 has a bypass killing effect, which penetrates into the surrounding cells after release from tumor cells, and can kill HER2-negative cells as well.

SHR-A1811 is intended for the treatment of malignant tumors.

7.2. Dosage and Method of Administration

At present, SHR-A1811 is in the early stage of clinical development. The dosage and method of administration of SHR-A1811 is specified in the clinical study protocol.

7.3. Contraindications

SHR-A1811 is contraindicated in subjects who are known to be allergic to the active substance (SHR-A1811) or any of the excipients.

7.4. Special Warnings and Precautions for Use

Based on the cumulative data of SHR-A1811 in clinical database as of 13 May 2025, neutropenia, Interstitial Lung Disease (ILD)/pneumonitis, left ventricular dysfunction, gastrointestinal toxicity and embryo-fetal toxicity need to be closely monitored in clinical trials.

7.4.1. Neutropenia

Hematological toxicity had relatively high incidences in the patients receiving similar HER2 targeted ADCs, especially neutropenia. Severe hematologic adverse reactions can further increase the risk of infection. In the non-clinical repeated-dose toxicity study of SHR-A1811, hematologic toxicity such as decreased white blood cells, decreased neutrophils, and decreased lymphocytes were observed.

In clinical studies, among the 853 subjects exposed to SHR-A1811 monotherapy, neutrophil count decreased TRAE occurred in 81.8% of subjects (Grade ≥ 3 : 49.4%), febrile neutropenia TRAE occurred in 2.7% of subjects (Grade ≥ 3 : 2.7%), neutropenia

TRAE occurred in 0.6% of subjects (Grade ≥ 3 : 0.1%). One subject (0.1%) in SHR-A1811 6.4 mg/kg dose group had TRAE with an outcome of death, which was pancytopenia. This subject was diagnosed with colorectal cancer, and was hospitalized for Grade 4 pancytopenia and Grade 4 colitis 14 days after the first dose, and passed away after 3 days possibly due to febrile neutropenia/sepsis. Since the event occurred during the DLT observation period, granulocyte colony-stimulating factor (G-CSF) was not allowed to use as a prevention method. One subject (0.1%) diagnosed as cervix carcinoma in SHR-A1811 6.4 mg/kg dose group had TRAE with an outcome of death, which was myelosuppression in combination with septic shock and multiple organ failure. The subject had a history of anemia and hypoproteinaemia. After initial treatment, the subject began to develop fever, and then developed grade 4 myelosuppression which caused grade 4 septic shock, and then led to grade 4 multiple organ failure 8 days after the initial treatment, which also met the criteria of SAEs with seriousness of life threatening and were non-DLT, non-AESI, and died several days later due to multiple organ failure.

Among the 141 subjects in the treatment group of SHR-A1811 and adrelinimab, neutrophil count decreased TRAE occurred in 77.3% of subjects (Grade ≥ 3 : 37.6%), febrile neutropenia TRAE occurred in 4.3% of subjects (Grade ≥ 3 : 4.3%). No subjects had neutropenia TRAEs with an outcome of death.

Among the 75 subjects exposed to SHR-A1811 and pertuzumab, neutrophil count decreased TRAE occurred in 86.7% of subjects (Grade ≥ 3 : 54.7%), febrile neutropenia TRAE occurred in 2.7% of subjects (Grade ≥ 3 : 2.7%). No subjects had neutropenia TRAEs with an outcome of death.

Among the 360 subjects exposed to SHR-A1811 and therapies, neutrophil count decreased TRAE occurred in 79.2% of subjects (Grade ≥ 3 : 47.5%), febrile neutropenia TRAE occurred in 2.5% of subjects (Grade ≥ 3 : 2.5%), neutropenia TRAE occurred in 0.6% of subjects (Grade ≥ 3 : 0.3%). No subjects had neutropenia TRAEs with an outcome of death.

Exclude subjects with existing or high risk of neutrophil count decreased before enrollment, and enrolled subjects must have normal bone marrow and organ function. Provide guidelines in the protocols for dose interruption, delay, reduction or discontinuation to better manage neutrophil count decreased and febrile neutropenia. Preventive medications may be considered for subjects with high risk factors of febrile neutropenia. Hematological test should be regularly performed during the study, relevant safety information should be collected and reported in accordance with the protocols.

7.4.2. Interstitial Lung Disease (ILD)/Pneumonitis

Interstitial lung disease (ILD)/Pneumonitis, including fatal cases, have been reported with similar HER2 targeted ADC ENHERTU.

In clinical studies, among the 853 subjects exposed to SHR-A1811 monotherapy, TRAEs of ILD, pneumonitis were reported in 32 subjects (3.8%), 9 subjects (1.1%), respectively. Most of cases were Grade 1-2 in severity. Five subjects (0.6%) experienced Grade ≥ 3 ILDs, including 2 fatal cases that were reported in the previous period. One was a 72-year-old male subject with advanced gastric cancer in SHR-

A1811 8.0 mg/kg dose group and the other was a 55-year-old female subject with advanced non-small cell lung cancer in SHR-A1811 6.4 mg/kg dose group, and both subjects had concurrent pulmonary infection. Pneumonitis occurred in 13 subjects (1.5%), all of which were grade 1-2 in severity, 9 (1.1%) of which were considered as related to study treatment by investigator.

Among the 141 subjects in the treatment group of SHR-A1811 and adbreliamab, TRAEs of ILDs and pneumonitis were reported in 5 subjects (3.5%) and 3 subjects (2.1%), respectively. One subject (0.7%) experienced an ILD TRAE leading to death. The subject was a 71-year-old male patient with non-small cell lung cancer received SHR-A1811 at dose of 4.8mg/kg combined with adbreliamab. The subject's death may be associated with high pulmonary tumor burden and subsequent infection.

Among the 75 subjects in the treatment group of SHR-A1811 and pertuzumab, there were no ILD reported. Pneumonitis occurred in 1 subject (1.3%), the event was of grade 1 in severity and considered as related to study treatment by investigator.

Among the 360 subjects in the treatment group of SHR-A1811 and other therapies, TRAEs of ILDs and pneumonitis were reported in 3 subjects (0.8%) and 5 subjects (1.4%), respectively. One subject (0.3%) experienced a Grade 4 ILD.

Among these pivotal phase 3 trials not included in the pooled safety analysis, Grade 5 ILDs were reported in two subjects. One subject was a 69-year-old female breast cancer patient, with baseline pulmonary metastases, left lung inflammation, and a right lung bulla. She received SHR-A1811 4.8mg/kg combined with pertuzumab. The death was likely the result of multiple factors including the tumor, interstitial lung disease, and infection. Another subject was a 70-year-old female breast cancer patient with baseline bilateral lung metastases and chronic bilateral pulmonary inflammation, who received SHR A1811 at dose of 6.4 mg/kg. The death was likely multifactorial, involving tumor, ILD, and infection.

In clinical studies, exclude subjects with history of clinically significant lung diseases (e.g., interstitial pneumonia, pneumonitis, pulmonary fibrosis, and severe radiation pneumonitis) or suspected to have these diseases by imaging at screening period. Provide guidelines in the protocols for dose interruption, delay, reduction or discontinuation to better manage ILD/pneumonitis. If a subject experiences asymptomatic ILD/pneumonitis (Grade 1), administration of SHR-A1811 should be interrupted until resolved. If a subject experiences symptomatic ILD/pneumonitis (Grade 2 or greater), SHR-A1811 should be permanently discontinued, and corticosteroid treatments should be initiated promptly as soon as ILD/pneumonitis is suspected. Monitor regularly signs and symptoms of ILD/pneumonitis, additional tests may be performed if ILD/pneumonitis is suspected.

7.4.3. Left Ventricular Dysfunction

Cardiotoxicity is a common toxicity of anti-HER2 drugs, usually manifested by left ventricular ejection fraction (LVEF) decreased. In the labeling of ENHERTU, there have been reports of adverse reactions with LVEF decreased, most of which were grade 1-2 in severity.

In clinical studies, among the 853 subjects exposed to SHR-A1811 monotherapy, TRAEs of ejection fraction decreased, left ventricular dysfunction and cardiac failure were reported in 27 subjects (3.2%), 5 subjects (0.6%) and 2 subjects (0.2%), respectively. The other TRAEs related to left ventricular dysfunction were reported only in one subject for each term, which included cardiac failure congestive, cardiac failure acute, cardiomyopathy, and pulmonary oedema. Grade ≥ 3 TRAEs related to left ventricular dysfunction included ejection fraction decreased (4 subjects, 0.4%), cardiac failure acute and cardiomyopathy (1 subject each, 0.1%). Of these, One subject (0.1%) developed grade 3 cardiomyopathy SAR, which was characterized by ventricular premature beats, palpitations, and ejection fraction decreased, and was recovering after treatment.

Among the 141 subjects in the treatment group of SHR-A1811 and adabrelimab, TRAEs of ejection fraction decreased and left ventricular dysfunction were each reported in 2 subjects (1.4%). One subject (1.7%) experienced a Grade 3 ejection fraction decreased TRAE.

Among the 75 subjects in the treatment group of SHR-A1811 and pertuzumab, TRAEs of left ventricular dysfunction and pulmonary oedema were reported in 4 subjects (5.3%) and 1 subject (1.3%), respectively. No Grade ≥ 3 TRAEs related to left ventricular dysfunction occurred in this pool.

Among the 360 subjects in the treatment group of SHR-A1811 and other therapies, TRAEs of left ventricular dysfunction, cardiac failure and cardiac failure congestive were reported in 4 subjects (1.1%), 3 subjects (0.8%) and 1 subject (0.3%), respectively. One subject (0.3%) experienced Grade 3 cardiac failure TRAE.

In clinical studies, exclude subjects with potentially high risk, such as symptomatic congestive heart failure (NYHA $\geq$ II). Left ventricular ejection fraction should be regularly performed during the study. Provide guidelines in the protocols for dose interruption, delay, reduction or discontinuation. SHR-A1811 should be permanently discontinued if a subject experiences confirmed symptomatic congestive heart failure.

7.4.4. Gastrointestinal Toxicity

Gastrointestinal toxicity, including nausea, vomiting, diarrhoea had relatively high incidences in the patients receiving similar HER2 targeted ADCs.

In clinical studies, among the 853 subjects exposed to SHR-A1811 monotherapy, gastrointestinal toxicity TRAEs occurred in $\geq 10.0\%$ of subjects included nausea (all grades: 60.4%, Grade ≥ 3 : 0.8%), vomiting (all grades: 43.3%, Grade ≥ 3 : 1.1%), decreased appetite (all grades: 41.5%, Grade ≥ 3 : 1.5%), diarrhoea (all grades: 15.1%, Grade ≥ 3 : 1.1%), stomatitis (all grades: 13.6%, Grade ≥ 3 : 0.8%) and constipation (all grades: 13.4%, Grade ≥ 3 : 0). No subjects had gastrointestinal toxicity TRAEs with an outcome of death.

Among the 141 subjects in the treatment group of SHR-A1811 and adabrelimab, gastrointestinal toxicity TRAEs occurred in $\geq 10.0\%$ of subjects included nausea (all grades: 54.6%, Grade ≥ 3 : 2.1%), vomiting (all grades: 43.3%, Grade ≥ 3 : 2.1%), decreased appetite (all grades: 31.9%, Grade ≥ 3 : 0), diarrhoea (all grades: 12.1%, Grade ≥ 3 : 2.8%), stomatitis (all grades: 12.1%, Grade ≥ 3 : 0.7%). No subjects had

gastrointestinal toxicity TRAEs with an outcome of death.

Among the 75 subjects exposed to SHR-A1811 and pertuzumab, gastrointestinal toxicity TRAEs occurred in $\geq 10.0\%$ of subjects included nausea (all grades: 82.7%, Grade ≥ 3 : 1.3%), vomiting (all grades: 65.3%, Grade ≥ 3 : 2.7%), diarrhoea (all grades: 58.7%, Grade ≥ 3 : 2.7%), decreased appetite (all grades: 49.3%, Grade ≥ 3 : 1.3%), stomatitis (all grades: 22.7%, Grade ≥ 3 : 2.7%) and constipation (all grades: 13.3%, Grade ≥ 3 : 1.3%). No subjects had gastrointestinal toxicity TRAEs with an outcome of death.

Among the 360 subjects exposed to SHR-A1811 and other therapies, gastrointestinal toxicity TRAEs occurred in $\geq 10.0\%$ of subjects included nausea (all grades: 55.6%, Grade ≥ 3 : 2.2%), decreased appetite (all grades: 41.7%, Grade ≥ 3 : 2.8%), vomiting (all grades: 37.5%, Grade ≥ 3 : 3.3%), diarrhoea (all grades: 30.8%, Grade ≥ 3 : 5.3%), constipation (all grades: 17.8%, Grade ≥ 3 : 0), and stomatitis (all grades: 14.4%, Grade ≥ 3 : 1.9%). No subjects had gastrointestinal toxicity TRAEs with an outcome of death.

Provide guidelines in the protocols for dose interruption, delay, reduction or discontinuation to better manage gastrointestinal toxicity. Preventive medications for nausea and vomiting may be considered after DLT observation period. Attention should be paid to electrolyte balance in subjects with severe symptoms that interfere with eating.

7.4.5. Embryo-fetal Toxicity

Genotoxicity was observed in non-clinical studies of SHR-A1811, and the result of in vitro chromosomal aberration test on Chinese Hamster Lung (CHL) cells was positive. Non-clinical embryo-fetal developmental toxicity study of SHR-A1811 in SD rats observed abnormalities in surviving fetuses such as developmental delay, external malformations, visceral abnormalities, and skeletal malformations. In the post-marketing report of similar drug ENHERTU, it was observed that the use of HER2 targeted ADC during pregnancy resulted in oligohydramnios and fetal dysplasia.

Exclude pregnant women at screening. Pregnancy test is performed at screening, or before first dose. Only subjects with negative test results are permitted to receive study treatment. The highly effective contraception for both female subjects of child-bearing potential (CBP) and male subjects with partners of CBP were described in Section 7.6.

7.5. Interaction with Other Medicinal Products and Other Formulations

A drug-drug interaction (DDI) study (SHR-A1811-I-105) is currently ongoing to evaluate the potential pharmacokinetic interactions between SHR-A1811 and ritonavir (a strong CYP3A4 inhibitor) and itraconazole (a strong CYP3A4 and P-gp inhibitor).

7.6. Fertility, Pregnancy, and Lactation

No reproductive and developmental toxicity studies have been conducted to date. Thus, SHR-A1811 should not be used in pregnant women, and female subjects of CBP and male subjects with partners of CBP should comply with the contraceptive requirement specified in the clinical study protocol, and use highly contraceptive measures during the treatment period and 7 months after last dose of SHR-A1811.

There is no information available on the presence of SHR-A1811 in human milk. It is recommended to avoid breastfeeding during the treatment period and 7 months after last dose of SHR-A1811.

7.7. Effects on Ability to Drive and Use Machines

No specific clinical study was conducted to evaluate the effect of SHR-A1811 on the ability to drive or operate machines. However, there are some of the adverse reactions (such as fatigue, dizziness, cognitive disorder) that may affect some subjects' ability to drive or operate machine.

7.8. Undesirable Effects

7.8.1. Adverse Drug Reactions

As of 13 May 2025, pooled safety analysis consisted of 17 clinical studies of SHR-A1811, which were SHR-A1811-I-101, SHR-A1811-I-102, SHR-A1811-I-103, SHR-A1811-I-105, SHR-A1811-II-201, SHR-A1811-II-202, SHR-A1811-II-203, SHR-A1811-Ib/II-205, SHR-A1811-206, SHR-A1811-207, SHR-A1811-208, SHR-A1811-209, SHR-A1811-212, SHR-A1811-213, SHR-A1811-215, SHR-A1811-216-OC, and HRS-8080-202. A total of 1429 cancer patients were treated with SHR-A1811 monotherapy or in combination with other drugs.

The details of SHR-A1811 related AEs reported across the four pooled population groups – SHR-A1811 monotherapy, SHR-A1811 in combination with adabrelimab, SHR-A1811 in combination with pertuzumab, and SHR-A1811 in combination with other drugs – can be found in Sections [6.2.1.1.2](#), [6.2.1.2.2](#), [6.2.1.3.2](#), and [6.2.1.4.2](#), respectively.

A total of 1400 (98.0%) subjects had SHR-A1811 related AEs, and SHR-A1811 related AEs with an incidence of $\geq 5\%$ were neutrophil count decreased (81.0%), anaemia (77.8%), white blood cell count decreased (76.9%), nausea (59.8%), platelet count decreased (45.7%), vomiting (43.0%), aspartate aminotransferase increased, decreased appetite (41.0% each), alanine aminotransferase increased (37.6%), alopecia (37.4%), hypoalbuminaemia (29.5%), weight decreased (27.2%), lymphocyte count decreased (24.9%), gamma-glutamyltransferase increased (24.4%), blood alkaline phosphatase increased (21.8%), hypertriglyceridaemia (21.3%), diarrhea (21.1%), proteinuria (20.1%), blood lactate dehydrogenase increased (18.6%), hypokalaemia (17.8%), hyponatraemia (17.3%), hyperglycaemia (16.9%), fatigue (16.2%), urinary tract infection (15.6%), asthenia (14.2%), stomatitis, hyperuricaemia (14.1% each), constipation (13.9%), hypocalcaemia (11.4%), blood bilirubin increased (10.8%), blood creatinine increased (10.5%), hypercholesterolaemia (10.3%), malaise (10.2%), dizziness (8.5%), pyrexia (8.3%), blood cholesterol increased (7.3%), fibrin D dimer increased (6.2%), blood thyroid stimulating hormone increased (5.9%), cough (5.6%), hypothyroidism (5.5%), mouth ulceration, rash, and skin hyperpigmentation (5.4% each), blood creatine phosphokinase increased (5.1%), electrocardiogram qt prolonged, upper respiratory tract infection (5.0% each).

7.8.2. Reference Safety Information (RSI) for Expectedness Assessment of SAR

The Reference Safety Information (RSI) is used for the assessment of expectedness of serious adverse drug reactions that are reported in SHR-A1811 clinical trials. This RSI

does not represent a comprehensive overview of the safety profile of SHR-A1811 which is presented in Section 7.8.1 Adverse Drug Reactions.

The RSI presented in Table 63 includes only the AEs that have been previously reported more than once as serious and treatment related (i.e., Serious Adverse Reactions [SARs]) in SHR-A1811 clinical trials and where, after a thorough assessment by the sponsor, reasonable evidence of a causal relationship between the event and the SHR-A1811 exists.

All expected SARs in this section are listed based on the Hengrui safety database, and reported on accumulative frequency by MedDRA (v28.0) SOC and PT, the frequency categories are based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); or very rare ($< 1/10,000$).

Table 63 Incidence of Expected Serious Adverse Reactions for SHR-A1811

SOC PT	Estimated Number of Subjects Exposed to SHR-A1811 (N=2971)	
	Frequency	All SARs n (%)
Investigations		
Platelet count decreased	common	193 (6.5)
Neutrophil count decreased*	common	156 (5.3)
White blood cell count decreased	common	142 (4.8)
Lymphocyte count decreased	uncommon	4 (0.1)
Alanine aminotransferase increased	uncommon	18 (0.6)
Aspartate aminotransferase increased	uncommon	13 (0.4)
Gamma-glutamyltransferase increased	uncommon	5 (0.2)
Blood and lymphatic system disorders		
Anaemia	common	117 (3.9)
Febrile neutropenia	common	75 (2.5)
Myelosuppression	uncommon	8 (0.3)
Gastrointestinal disorders		
Vomiting	common	54 (1.8)
Nausea	common	30 (1.0)
Diarrhoea	uncommon	9(0.3)
Functional gastrointestinal disorder	uncommon	4 (0.1)
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease	common	33 (1.1)
Pneumonitis	uncommon	5 (0.2)
Epistaxis	uncommon	3 (0.1)
General disorders and administration site conditions		

SOC PT	Estimated Number of Subjects Exposed to SHR-A1811 (N=2971)	
	Frequency	All SARs n (%)
Asthenia	uncommon	20 (0.7)
Infections and infestations		
Pneumonia	common	46 (1.6)
Gastroenteritis	uncommon	5 (0.2)
Hepatobiliary disorders		
Hepatic function abnormal	uncommon	6 (0.2)
Metabolism and nutrition disorders		
Decreased appetite	uncommon	19 (0.6)
Hypokalaemia	uncommon	11 (0.4)
Hyponatraemia	uncommon	6 (0.2)
Injury, poisoning and procedural complications		
Infusion related reaction	uncommon	4 (0.1)
Immune system disorders		
Hypersensitivity	rare	2 (0.07)

Data cutoff date: 13 May 2024.

*including Neutrophil count decreased and Neutropenia

All fatal or life-threatening SARs will be reported as suspected unexpected SARs (SUSARs). Like any medicinal products, disease progression and lack of efficacy may occur in subjects receiving SHR-A1811. Careful assessment for causality should be performed if disease progression appears to be accelerated by SHR-A1811.

7.9. Overdose

At present, it is not clear what symptoms may be caused by overdose of SHR-A1811, and there is no specific treatment for overdose of SHR-A1811.

If overdose is suspected, SHR-A1811 should be discontinued immediately and the subject should be closely monitored, and corresponding supportive treatment can be given if necessary.

7.10. Drug Abuse and Dependence

No specific clinical study was conducted to evaluate drug abuse or dependence potential of SHR-A1811. No sign suggestive of drug abuse or dependence was observed in the nonclinical or clinical studies.