ClinicalTrials.gov Document Cover Page
Clinical Protocol
Study CS1001-201
Study Title: A Single-Arm, Multicenter, Phase II Clinical Trial of CS1001 in Subjects with Relapsed or Refractory Extranodal Natural Killer/ T Cell Lymphoma
Document Date: 25 Feb 2021
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Clinical Trial Protocol

Protocol Title:	**A Single-Arm, Multicenter, Phase II Clinical Trial of CS1001 in Subjects with Relapsed or Refractory Extranodal Natural Killer/ T Cell Lymphoma**
Protocol No.:	**CS1001-201**
Current Version Number:	**25 Feb 2021, Version 3.0**
Previous Version Number:	**01 Jul 2020, Version 2.0**
Study Phase:	**II**
Sponsor:	**CStone Pharmaceuticals (Suzhou) Co., Ltd.** **CStone Pharmaceuticals (Shanghai) Co., Ltd.** E168, 2nd Floor, 218 Xinghu Str., A1 Building, North Block, BioBay, Suzhou Industrial Park, Suzhou, China 211-20, 2nd Floor, 38 Debao Rd., Free Trade Zones, Shanghai, China

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Confidentiality Statement

Signature Page for Sponsor

Protocol Title:	A Single-Arm, Multicenter, Phase II Clinical Trial of CS1001 in Subjects with Relapsed or Refractory Extranodal Natural Killer/ T Cell Lymphoma
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CStone Pharmaceuticals will carefully fulfill the duties of sponsors according to current Good Clinical Practice of relevant countries and regions and be responsible for the initiating, submitting, organizing, sponsoring and monitoring this clinical study. Patients with serious adverse events during the clinical study will be provided with active intervention and the corresponding treatment expense will be covered by sponsor according to applicable national regulatory requirements. Adequate financial compensation will be offered to patients who experience damage confirmed to be consequence of investigational product-induced serious adverse effect.

I have participated in the development of and discussion on this study protocol and agree to its contents. I have fully understood sponsor's duties related with this trial protocol and agree to conduct clinical study per this protocol and applicable regulatory requirements.

Sponsor: **CStone Pharmaceuticals (Suzhou) Co., Ltd.**

CStone Pharmaceuticals (Shanghai) Co., Ltd.

Signature Page for Investigator

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This protocol is a confidential document of **CStone Pharmaceuticals (Suzhou) Co., Ltd. and CStone Pharmaceuticals (Shanghai) Co., Ltd.** for confidential circulation. I confirm I have read through and understand this protocol and will follow the protocol in the study. Furthermore, I will abide by the ethics principles in Declaration of Helsinki, Good Clinical Practice and applicable regulatory requirements during the study. By signing for this document, I agree that I will not make public or disclose any non-public information herein without prior written permission from **CStone Pharmaceuticals (Suzhou) Co., Ltd. and CStone Pharmaceuticals (Shanghai) Co., Ltd.**

Note to investigator: Please sign your name and date on this signature page. Fill in printed names of you and your site to conduct this trial. A copy of this signature page will be returned to **CStone Pharmaceuticals (Suzhou) Co., Ltd. and CStone Pharmaceuticals (Shanghai) Co., Ltd.**

I have read through the full text of the protocol and agree to follow it in the study.

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SYNOPSIS

Version 3.0 **Date: 25 February 2021**	**Protocol No.:** CS1001-201
Experimental Drug: CS1001	
Title of Study: A Single-Arm, Multicenter, Phase II Clinical Trial of CS1001 in Subjects with Relapsed or Refractory Extranodal Natural Killer/ T Cell Lymphoma (R/R ENKTL)	
Number of Sites: Multiple sites	
Study Phase: Phase II	

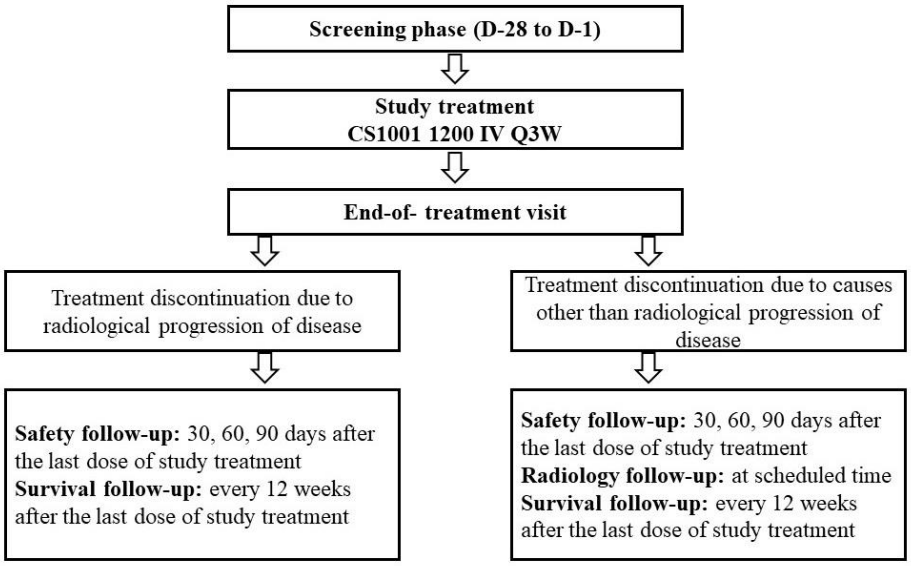
Objectives and Endpoints:

Objectives	Endpoints
Primary objectives	**Primary endpoints**
To evaluate the efficacy of CS1001 in subjects with R/R ENKTL	Objective response rate (ORR) assessed by the independent radiological review committee (IRRC) according to *Criteria for Response Assessment of Lymphoma: Lugano 2014 Classification*
Secondary objectives	**Secondary endpoints**
To evaluate the efficacy of CS1001 in subjects with R/R ENKTL	ORR assessed by investigators; Complete response rate (CRR), partial response rate (PRR), time to response (TTR), duration of response (DoR) assessed by IRRC and investigators
To evaluate the safety of CS1001 in subjects with R/R ENKTL	Frequency and severity of adverse events (AEs) and frequency of serious adverse events (SAEs)
To characterize the pharmacokinetics (PK) of CS1001	To determine the peak and trough serum concentration of CS1001
To evaluate the immunogenicity of CS1001	Number and percentage of subjects with anti-drug antibody (ADA)
Exploratory objectives	**Exploratory endpoints**
To evaluate the progression-free survival (PFS) and overall survival (OS) of R/R ENKTL subjects	6-months PFS rate, 6-month OS rate
To evaluate genetic aberrations in R/R ENKTL by whole-exome sequencing test of tumor tissues	The association between genetic aberrations and efficacy

Study design and methods:

This is a multicenter, single-arm phase II study to evaluate the efficacy and safety of CS1001 monotherapy in R/R ENKTL.

Eighty eligible patients with R/R ENKTL who failed prior asparaginase-based treatment regimen(s) are assigned to receive CS1001 1200 mg intravenous (IV) infusion every three weeks (Q3W) until disease progression, intolerable to study treatment, consent withdrawal, death, or other causes specified in the protocol. The duration of treatment will be up to 24 months.



For immune therapies such as CS1001, **pseudo-progression** may occur due to immune cell infiltration and other mechanisms as manifested by an apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, for progressive disease (PD) suspected by the investigator as pseudo-progression, treatment may continue until confirmation of PD with repeated imaging at least 4 weeks later (or preferred at the next scheduled regular imaging time point). All of the following criteria must be met to continue the treatment:

a. Absence of clinically significant symptoms and signs of PD (including worsening laboratory values)
b. Stable Eastern Cooperative Oncology Group Performance Status (ECOG PS)
c. Absence of rapid progression of disease or PD at critical anatomical sites that necessitates urgent medical intervention

The primary endpoint of this trial is ORR, defined as the percentage of subjects whose best overall response (BOR) is either CR or PR, as assessed by IRRC based on Criteria for Response Assessment of Lymphoma: Lugano 2014 Classification (hereinafter referred to as 'Lugano 2014 classification'). The final efficacy analysis of the primary endpoint will be performed when the last subject completes the efficacy assessment of up to 24 weeks.

Safety follow-up visits should be conducted 30, 60, 90 days after the last dose of study treatment. Safety follow-up period refers to the 90 days after the last dose of the investigational treatment or the start of new anti-cancer treatment, whichever occurs earlier. Survival follow-up should be conducted every 12 weeks after the last dose of study treatment. Apart from subjects who discontinue treatment due to disease progression assessed by tumor imaging, radiological assessment should be performed at scheduled time points until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first.

Key Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Subjects who are willing to participate in this trial; fully understand and are fully informed of this trial, and are able to provide written informed consent form (ICF); are willing and able to follow all study procedures.
2. Subjects are ≥ 18 years and ≤ 75 years of age on the day of signing informed consent.
3. Subjects must have a histologically confirmed ENKTL at the study site. Both nasal and non-nasal ENKTL are allowed.
4. Subjects must have relapsed or refractory ENKTL failing asparaginase-based chemotherapy or chemoradiotherapy. (Relapse: disease progression after response to the last treatment; refractory: no response to the last treatment.)
5. ECOG PS of 0 or 1.
6. Life expectancy ⩾ 12 weeks.
7. Subjects must have at least one evaluable or measurable lesion per Lugano 2014 classification [An evaluable lesion is a lymph node or extranodal lesion with radioactive uptake higher than liver on ^{18}F-Fluorodeoxyglucose/ Positron Emission Tomography (^{18}FDG/PET) and with typical lymphoma characteristics on PET and (or) computed tomography (CT); Measurable lesion: the longest diameter (LDi) is of > 15 mm for nodal lesion or >10 mm for extranodal lesion (if the only measurable lesion has received prior radiotherapy, the subject must have evidence of radiological progression after radiotherapy), and concurrent elevated uptake of ^{18}FDG]. Absence of measurable lesion with diffuse ^{18}FDG uptake increase in the liver should be ruled out first.
8. Subjects must provide stained tumor tissue sections and corresponding pathological reports or unstained tumor tissue sections (or tissue block) for central pathology review. Investigators may enroll subjects before the result of central pathology review.
9. Subjects must have adequate organ function and bone marrow function without severe hematopoietic disorder, or heart, lung, liver or kidney dysfunction or immune deficiency (no blood transfusion, granulocyte colony-stimulating factor or other relevant medical supporting care within 14 days before the first dose of study treatment):
    a) Absolute neutrophil count ≥ 1.0×10^9 /L;
    b) Platelets ≥ 50×10^9 /L;
    c) Hemoglobin ≥ 8 g/dL;
    d) Creatinine clearance ≥ 40 mL/min (according to Cockcroft-Gault equation);
    e) Serum total bilirubin ≤ 1.5 × ULN, unless considered to be due to Gilbert's disease, where it must be ≤3 × ULN
    f) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.5 × ULN;
    g) Coagulation: International normalized ratio (INR) ≤ 1.5 × ULN; prothrombin time (PT) and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN (unless the subject is on anti-coagulant therapy and PT and APTT at screening are within the expected range for patients on anti-coagulant).
10. Subjects with prior anti-cancer treatment can only be enrolled when the toxicity of prior anti-cancer treatment has recovered to baseline or ≤ Grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03. For patients with irreversible Grade 2 toxicities (e.g. thrombocytopenia, anemia, neurotoxicity, alopecia, and hearing impairment) that is anticipated to be unlikely to worsen during study treatment, the subject can be enrolled after approval by the medical monitor of the sponsor.
11. Women of childbearing potential (WOCBP, as defined in Section 4.1.4) must have a negative serum pregnancy test ≤7 days before the first dose of investigational product. WOCBP or fertile

men and their WOCBP partners must agree to use an effective contraceptive method from providing signed ICF through 6 months after the last dose of the investigational product. (Refer to Section 4.1.5 for details.)

Exclusion Criteria:

1. Aggressive natural killer-cell leukemia or ENKTL patients who have any degree of leukemic involvement will be excluded.
2. Concomitant with hemophagocytic lymphohistiocytosis.
3. Current or historical primary central nervous system lymphoma (PCNSL) or secondary CNS involvement.
4. Prior allogeneic organ transplantation.
5. Allogenic hematopoietic stem cell transplantation (HSCT) ≤ 5 years before the first dose of investigational product. (Patients are permitted to enroll if they received allogenic HSCT more than 5 years before the first dose of investigational product and without any current graft-versus-host reaction.)
6. Current participation in another clinical study or use of any investigational drug within 4 weeks before the first dose of investigational product in this trial.
7. Autologous HSCT within 90 days before the first dose of investigational product.
8. Subjects with an active autoimmune disease that requires systemic treatment in the past two years. (Hormone replacement therapy is not considered as systemic therapy such as the patient has type I diabetes mellitus, hypothyroidism that can be managed with thyroid hormone replacement only, or adrenal insufficiency or pituitary insufficiency that requires a physiological dose of corticosteroid replacement). Subjects are permitted to enroll if they have an autoimmune disease that didn't require any systemic treatment in the past two years.
9. Subjects received systemic corticosteroid or any other immunosuppressive therapy within 14 days before the first dose of the investigational product; subjects are permitted to use topical, ocular, intra-articular, intranasal and inhaled corticosteroids (with minimal systemic absorption); a short course (≤ 7 days) of corticosteroids for prophylaxis (e.g., hypersensitivity to contrast media) or for treatment of non-autoimmune conditions (e.g., delayed hypersensitivity caused by contacting allergens).]
10. A known additional malignancy within 5 years prior to the first dose of investigational product. Subjects with locally curable malignancies (including basal cell carcinoma of skin, squamous cell carcinoma of skin, breast cancer in situ or cervical cancer in situ, etc.) that have undergone curative therapy are permitted to enroll.
11. Subjects who have had prior chemotherapy, immunotherapy, biological therapy (including cancer vaccine, cytokine therapy or growth factors to treat cancer) used as a systemic treatment for cancer, within 28 days before the first dose of investigational product.
12. Subjects who underwent a major surgical procedure within 28 days before the first dose of investigational product or radiotherapy within 90 days before the first dose of investigational product.
13. Any use of traditional Chinese medicines or herbal preparations with anti-tumor indications within 7 days before the first dose of investigational product.
14. Has received a live vaccine within 28 days before the first dose of investigational product. (Attenuated influenza vaccine is allowed).
15. Known history of human immunodeficiency virus (HIV) infection and/or acquired immune deficiency syndrome (AIDS).
16. Subjects at the active phase of chronic hepatitis B or with active hepatitis C. Subjects who are hepatitis B surface antigen (HBsAg) positive or hepatitis C virus (HCV) antibody-positive at screening must not be enrolled until further definitive testing with hepatitis B virus (HBV) DNA titers (≤ 2500 copies/mL or 500 IU/mL) and HCV RNA tests (≤ the lower limit of detection) can

conclusively rule out the presence of active hepatitis B or C that requires treatment, respectively. Subjects that carry the hepatitis B virus, with stable hepatitis B (HBV DNA titer ≤ 2500 copies/mL or 500 IU/mL) after medical treatment or with cured hepatitis C are permitted to enroll.

17. History of interstitial lung disease (except for those induced by radiation therapies and are asymptomatic).
18. Active tuberculosis infection.
19. Any active infection requiring systemic anti-infection therapy within 14 days before the first dose of investigational product.
20. Subjects who have received prior therapy with an anti-programmed cell death protein-1 monoclonal antibody (anti-PD-1 monoclonal antibody), anti-programmed cell death-ligand 1 monoclonal antibody (anti PD-L1 monoclonal antibody) or anti cytotoxic T-lymphocyte-associated protein 4 monoclonal antibody (anti-CTLA-4 monoclonal antibody).
21. Subjects with a known severe allergy to monoclonal antibodies (≥ Grade 3 per CTCAE v 4.03) or uncontrolled allergic asthma.
22. Women in pregnancy or lactation.
23. Subjects with active alcohol or drug dependence.
24. Subjects with uncontrollable concomitant diseases including but not limited to symptomatic congestive heart failure, uncontrolled hypertension, unstable angina, active gastrointestinal ulcer or hemorrhagic disorders.
25. Subjects with a history of psychiatric disease; or subjects with incapacity or limited capacity.
26. Underlying condition that in the investigator's opinion would increase the risk of investigational product administration or confound the assessment for its toxicity.
27. Subjects in the investigator’s opinion are not suitable for participating in this trial.

Number of Subjects:

Approximately 80 subjects with R/R ENKTL will be enrolled

Study Treatment:

CS1001 1200 mg, intravenous infusion for no less than 60 minutes, every 3 weeks (Q3W; 21 days).

Duration of Study:

This trial will be divided into three periods: screening period (28 days before the first dose of investigational product), treatment period (up to 2 years), and the follow-up period.

Study Evaluation:

Safety:

Safety assessments will include vital signs, physical examinations, electrocardiograms (ECG), ECOG PS, radiology, and incidence and severity of adverse events (AEs) and serious adverse events (SAEs).

AEs will be coded using the preferred term (PT) and system organ class (SOC) in Medical Dictionary for Regulatory Activities (MedDRA), International Conference for Harmonization (ICH).

The safety of the investigational product will be assessed according to CTCAE v4.03.

Efficacy:

Efficacy evaluation will be performed by investigators and IRRC based on Lugano 2014 classification. Contrast-enhanced CT will be performed at screening and every 12 weeks after the first dose of investigational product. Examined sites include head and neck region (that must include nasal cavity, palatum durum, anterior cranial fossa, and nasopharynx), chest, abdomen, and pelvis. For patients allergic to CT contrast media, enhanced magnetic resonance imaging (MRI) will be used as an alternative. Positron emission tomography / computed tomography (PET/CT) will be performed at screening, Week 12, and

Week 24. Only enhanced CT will be used for follow-up tumor imaging after first radiological CR or Week 24, whichever comes first. For patients without any measurable lesion, follow-up with PET/CT will be performed until radiological confirmation of CR or progression if the patient hasn't reached CR in the first 24 weeks. Additional PET/CT will be performed if follow-up enhanced CT reveals residual lesion or suspected progression.

If contrast media for CT can be injected when PET/CT is performed and meet requirements on PET/CT and contrasted CT, additional enhanced CT can be skipped. View *Central Radiology Manual* for details.

Apart from subjects who discontinue treatment due to radiological disease progression, tumor assessment should be performed at pre-specified regular time points until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first.

Pharmacokinetics and Immunogenicity:

Samples will be analyzed for serum CS1001 concentrations and anti-drug antibody (ADA) using a validated immunoassay. The neutralizing antibody of CS1001 will be tested as needed if the neutralizing antibody assay method is established.

Statistical Methods:

Population:

Efficacy analysis set (EAS) consists of all subjects who receive any dose of CS1001 and have the disease under study confirmed by central pathology.

Safety analysis set (SAS) consists of all subjects who receive any dose of CS1001.

Primary efficacy analyses:

The primary efficacy endpoint is ORR assessed by IRRC, defined as the proportion of subjects who achieve CR or PR as the best overall response in all subjects with evaluable or measurable lesions in EAS.

The 95% confidence interval (CI) of ORR will be calculated using the exact binomial (Clopper-Pearson) method to evaluate the precision of the ORR estimate.

The statistical analysis will be performed by 24 weeks after the first dose of last subject.

Secondary efficacy analyses:

Proportions of subjects who achieve CR, PR, SD, and PD per IRRC evaluation and their 95% CIs will be summarized. This analysis will be performed in EAS subjects with evaluable or measurable lesion at baseline judged by IRRC. Proportions of subjects with responses per investigator's evaluation and their 95% CIs will be summarized. This analysis will be performed in EAS subjects with evaluable or measurable lesion at baseline judged by investigators.

Duration of response (DoR) is defined as the time from the date of the first documented CR or PR (whichever comes first) to the date of the first documented disease progression or death, whichever comes first. DoR will be evaluated in subjects with objective responses per investigator's or IRRC's assessment, respectively.

Time to response (TTR) is defined as the time from the date of the first study dose to the date of the first documented CR or PR, whichever comes first. TTR will only be evaluated for subjects who achieve ORR. TTR will be summarized according to the investigator's and IRRC's assessment, respectively.

Kaplan-Meier method will be used to analyze DoR; KM plots will be provided. DoR analysis will only be performed in subjects with objective responses.

Exploratory efficacy analyses:

Progression-free survival (PFS) is defined as the time from the date of the first study dose to the date of first documented disease progression or death, whichever comes first.

Overall survival (OS) is defined as the time from the date of the first study dose to the date of death irrespective of its cause.

Kaplan-Meier method will be used to analyze PFS and OS.

Sample size:

The primary efficacy endpoint is ORR assessed by IRRC according to Criteria for Response Assessment of Lymphoma: Lugano 2014 Classification. [redacted]

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Pharmacokinetic analysis:

Descriptive statistics will be summarized for the serum concentration of CS1001 for blood samples taken at pre-specified time points.

Safety analysis:

All adverse events will be described according to MedDRA and graded according to the NCI CTCAE v4.03. All adverse events that occurred during or after investigational product administration will be

summarized by NCI CTCAE grade. Besides, SAEs, severe AEs (Grade 3, 4, or 5 events), drug-related AEs, and AEs causing discontinuation of or changes in investigational product administration will each be summarized. Multiple occurrences of the same event will only be counted once for the most severe event. The proportion of subjects with at least one AE will be reported.

All deaths that occur during the study or within the follow-up period after the last dose/discontinuation of investigational product will be reported.

Specific laboratory tests, vital signs, physical examinations, and 12-lead ECGs and their changes from baseline will be summarized. The values at baseline and each time point following baseline will be presented by crosstabs, when appropriate.

Immunogenicity:

Immunogenicity evaluation results will be reported for the following parameters. Number and percentage of subjects who have positive ADA at baseline; number and percentage of subjects with at least one positive ADA test result in any time point following the first dose of the investigational product; number and percentage of subjects who develop treatment-induced ADA any time after the first dose of the investigational product; number and percentage of subjects with treatment-enhanced ADA any time after the first dose of investigational product.

Biomarkers:

Biomarker measurements will be presented for available data. Graphical and/or tabular forms will be used to describe genetic aberrations and their relationship with the efficacy of anti-cancer treatment.

The statistical method will be described in detail in the statistical analysis plan.

SCHEDULE OF STUDY ACTIVITIES

Table 1 Schedule of Activities

Trial Period	**Screening**	**Treatment**						**Follow-up**		
Treatment cycles or visits	Screening	1	2	3	4	N	End-of-treatment Visit[1]	Safety follow-up[2]	Radiology follow-up[3]	Survival follow-up[4]
Time of visit and time window	Day -28 to Day -1	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	+7 days	After the last dose 30, 60, 90 days ± 3 days		After the last dose Every 12 weeks (± 7 days)
Study Procedures										
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics and medical history	X									
Prior medications and concomitant medications[5]	X	X	X	X	X	X	X	X		
Clinical procedures/assessments										
Adverse events[6]	X	X	X	X	X	X	X	X		

12-Lead ECG[7]	X						X	X		
Height, weight, and vital signs[8]	X	X	X	X	X	X	X	X		
Physical examination and ECOG performance status[9]	X	X	X	X	X	X	X	X		
Subsequent anti-cancer treatment									X	X
Survival status										X
Study treatment										
CS1001[10]		X	X	X	X	X				
Laboratory procedures/assessments (at study sites)										
Pregnancy test[11]	X						X	X		
Hematology, serum chemistry, urinalysis[12]	X		X	X	X	X	X	X		
Coagulation functions[13]	X									
Virology[14]	X									

Thyroid functions[15]	X			X		X	X	X		
EBV DNA[16]	X		X	X	X	X				
Laboratory procedures/assessments (performed by central laboratory)										
Central pathology[17]	X									
PK[18]		X	X	X	X	X	X	X		
ADA[19]		X	X	X	X	X	X	X		
Efficacy evaluation										
Radiology examinations[20]	X					X			X	
Bone marrow aspiration and biopsy[21]	X									
Sample collection for biomarkers										
Blood sample collection[22]	X									
Tumor tissue[23]	X									

1. End-of-treatment (EOT) follow-up: EOT date will be the decision-making date for discontinuing the study treatment by investigators. EOT visit should occur 0-7 days after the EOT date.

2. Safety follow-up: Safety follow-up visit should be conducted at 30, 60, 90 days (± 3 days) after the last dose of investigational product. If the EOT visit occurs in the time window of the first safety follow-up visit (30± 3 days), the same tests and examinations don't need to be repeated. It is recommended to complete all protocol required follow-up evaluations for the safety follow-up at 60 ± 3days and 90± 3 days after the last dose, or AEs and concomitant medications can be collected through phone call. Safety follow-up period refers to the 90 days after the last dose of the investigational treatment or the start of new anti-cancer treatment, whichever occurs earlier.
3. Radiology follow-up: Apart from subjects who discontinue treatment due to radiological disease progression, tumor assessment should be performed at pre-specified regular time points until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first.
4. Survival follow-up: Survival status will be assessed every 12 weeks by telephone after the last dose of investigational product.
5. Concomitant medications: All concomitant medications received from 30 days before the screening will be recorded until 90 days after the last dose of study treatment or the start of new anti-cancer treatment, whichever occurs first.
6. Adverse events (AEs): All AEs will be recorded from signing informed consent to 90 days after the last dose of investigational product or starting new anti-cancer therapy, whichever comes first. Thereafter only study treatment-related SAEs need to be recorded. AEs that occur after the safety follow-up visit can be recorded by telephone follow-up 60 days and 90 days after the last dose.
7. Electrocardiogram (ECG): ECG will be performed at screening, EOT visit, and safety follow-up visit. The frequency of ECGs may be increased if clinically indicated.
8. Height, weight, and vital signs: Height will only be measured at screening, weight at screening, EOT visit, and safety follow-up visit. Vital signs include temperature, pulse, respiratory rate, and blood pressure.
9. Physical examination and ECOG performance status: Overall physical examination will be performed at screening, EOT visit, and safety follow-up visit. The lymphoma-specific physical examination will be performed during the treatment period.
10. Study treatment: The study treatment is CS1001 1200 mg, IV, Q3W, administered on the first day of each cycle after completing all the clinical and laboratory procedures/assessments.
11. Pregnancy test: Blood human chorionic gonadotrophin test is performed as a pregnancy test only in women of childbearing potential at screening (within 7 days before the first dose), EOT visit, and safety follow-up visit. An additional urine pregnancy test may be performed if clinically indicated. A serum pregnancy test is needed if the urine test reveals a positive result.
12. Hematology, serum chemistry, and urinalysis: Hematology includes complete blood count with differentials and hemoglobin. Serum chemistry tests include blood urea/urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphate, fasting blood glucose, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total cholesterol, total protein, and albumin. Urinalysis includes specific gravity, pH, urine glucose, urine protein, urine casts, ketones, and blood cells. These tests will be performed at screening (within 7 days before the first dose of investigational product), 3 days before each dosing starting from Cycle 2, EOT visit, and safety follow-up visit.
13. Coagulation function: Coagulation function tests including PT, APTT, and INR will be performed at screening.

14. Virology: Tests for HBsAg, HCV antibody, and HIV antibody will be performed at screening. Subjects who are HBsAg positive must receive further HBV DNA test. Subjects who are HCV antibody positive must receive further HCV RNA test.
15. Thyroid function: Thyroid function test including free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) tests will be performed at screening (within 7 days before the first dose of investigational product), thereafter 3 days before investigational product administration every other cycle (Cycle 3, 5, 7 and so on), EOT visit and safety follow-up visit.
16. EBV DNA: EBV DNA test will be performed at screening and 3 days before each dosing starting from Cycle 2. For subjects who achieve radiological CR, the EBV DNA test will be performed every other cycle thereafter.
17. Central pathology: Stained tumor tissue sections and corresponding pathological report or unstained tumor tissue sections (or tissue block) must be collected at screening for central pathology review. Both fresh and archival biopsies are accepted and can be used by central pathology. Investigators may enroll subjects before obtaining the result of the central pathology review. For subjects whose diagnosis is not ENKTL per central pathology laboratory's evaluation, investigators in consultation with sponsor medical monitors will determine whether to continue or discontinue the subject from treatment. View *Central Pathology Manual* for detailed instructions.
18. Pharmacokinetics (PK): Blood samples will be collected within 60 minutes before infusion as pre-treatment samples at Cycle 1, 2, 3, 4, and 8, and within 30 minutes after infusion at Cycle 1 and 4 in the treatment period. Blood samples for PK testing will be collected at the EOT visit and safety follow-up visit at 30 days, and 90 days after the last dose of study treatment. View *Central Laboratory Manual* for detailed instructions.
19. Immunogenicity: Pre-treatment blood samples are collected (within 60 minutes before dosing) at Cycle 1, 2, 3, 4, and every 4 cycles thereafter (e.g., Cycle 8, 12, 16, and so on). Blood samples for ADA testing will be collected at the EOT visit and safety follow-up visit at 30 days, and 90 days after the last dose of study treatment. View *Central Laboratory Manual* for detailed instructions.
20. Radiology assessment: Efficacy evaluations will be performed by investigators and IRRC based on Lugano 2014 classification. Contrast-enhanced CT will be performed at screening and every 12 weeks after the first dose of investigational product. Examined sites include head and neck region (that must include nasal cavity, palatum durum, anterior cranial fossa, and nasopharynx), chest, abdomen, and pelvis. For subjects allergic to CT contrast media, enhanced MRI will be used as an alternative. Systemic PET/CT examination will be performed at screening, Week 12, and Week 24. Only enhanced CT will be used for follow-up after first radiological CR or Week 24, whichever comes first. For subjects without any measurable lesion, follow-up with PET/CT will be performed until radiological confirmation of CR or progression if the subject hasn't reached CR in the first 24 weeks. Additional PET/CT will be performed if follow-up enhanced CT reveals residual lesion or suspected progression. If contrast media for CT can be injected when PET/CT is performed and meet requirements on PET/CT and contrasted CT, additional enhanced CT can be skipped. View *Central Radiology Manual* for details. Apart from subjects who discontinue treatment due to radiological disease progression, tumor assessment should be performed at pre-specified regular time points until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first.
21. Bone marrow aspiration and biopsy: Bone marrow aspiration and biopsy should be performed at screening for all subjects. Subjects with positive bone marrow aspiration/biopsy result or indeterminate overall bone marrow assessment at screening will undergo bone marrow aspiration and biopsy when achieving CR/CMR based upon radiology for confirmation. Immunohistochemistry (IHC) analyses should be performed under a microscope no matter bone marrow involves or not（Suggest detecting CD56、TIA-1、CD3、GrB、perforin, and EBER hybridization in situ, etc.).

22. Blood sample for biomarker testing: A total amount of 2 mL whole blood sample will be collected as germline control in whole-exome sequencing for tumor tissue. The whole blood can be collected at screening or retrospectively after study entry. View *Central Laboratory Manual* for details.
23. Tumor tissue for biomarker testing: Seven (7) unstained Formalin-Fixed, Paraffin-Embedded (FFPE) tumor tissue slides should be collected at screening for whole-exome sequencing of tumor tissue. If samples are not available at screening, a retrospective collection of 7 archival FFPE tumor tissue slides is allowed. View *Central Laboratory Manual* for details.

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1. INTRODUCTION

1.1 DISEASE OVERVIEW

ENKTL is a subtype of mature T cell and NK cell lymphomas. Its incidence varies by geography, higher in Asia than in Europe and North America (22% vs. 5% in mature T cell and NK cell lymphoma, respectively)[2, 3]. In a multi-center pathology classification survey of 10,002 lymphoma patients in 2012 in China, ENKTL accounted for about 6% of all lymphomas and 28% of all mature T cell and NK cell lymphomas[4]. Anthracycline-based chemotherapy is not recommended as the high expression of multidrug-resistant p-glycoprotein in ENKTL. Current systemic chemotherapy regimens for ENKTL are asparaginase-based regimens, including SMILE, AspMetDex, and P-Gemox, etc. The ORR and CR of first-line treatment are approximately 80% and 50%, respectively[5]. High-dose chemotherapy combined with autologous or allogeneic hematopoietic stem cell transplantation is used as consolidation/intensification therapy or second-line salvage therapy but not considered as a standard of care, because of the limited data.

There has not been any large prospective randomized control trial of medical treatment specifically targeting at R/R ENKTL population. A portion of R/R ENKTL patients enrolled in clinical studies for salvage combination chemotherapy have not received asparaginase in the first-line therapy and were treated with the asparaginase-based regime as salvage therapy, who have a better clinical outcome than those who have relapsed or are refractory after receiving asparaginase-based therapy. For now, the salvage combination chemotherapy showed significant toxicity and did not improve the OS significantly, with the median OS being less than 6.4 months[6-8]. As a targeted therapy, chidamide, a histone deacetylase inhibitor, has also been approved to treat R/R peripheral T-cell lymphoma (including R/R ENKTL) in China. It is reported to have a manageable safety profile and a CR rate of 6.3% (1/16) and an ORR of 18.8% (3/16) in the pivotal phase II trial[1]. And the post-marketing real-world data showed a CR rate of 6.1% (2/33) and an ORR of 15.2% (5/33)[9]. Furthermore, a phase II clinical study of anti-CD38 antibody daratumumab in R/R ENKTL reported an ORR of 25% (8/32) and a CR rate of 0%. The median duration of response (DoR) was short (55 days) and the survival benefit was limited (median OS: 130 days)[10]. In summary, there is a significant unmet medical need for patients with R/R ENKTL.

EBV infection is a primary mechanism and characteristic of ENKTL, which is highly correlated with tumor burden and its response to treatment[11, 12]. EBV infection induces immune tolerance of ENKTL by upgrading PD-L1 expression in tumor cells[13, 14]. Around 80% of ENKTL tumor cells express PD-L1[15]. All of these studies have provided a theoretical foundation for treating ENKTL by inhibiting the PD-1/PD-L1 pathway.

A small retrospective study published in Blood in February 2017 reported the results of pembrolizumab treatment in 7 R/R ENKTL patients after failure of asparaginase-based chemotherapy. Five patients achieved CR (including1 patient had pseudo-progression before achieving CR) and 2 achieved PR. The 5 CR patients were still in remission at a 6-month follow-up, indicating durable response and good tolerability with PD-1/PD-L1 inhibition[16]. Another retrospective study reported pembrolizumab treatment in 7 R/R ENKTL patients. Two patients achieved CR and 2 patients achieved PR[17]. A French study was conducted in 13 R/R ENKTL patients failing asparaginase-based chemotherapy. Three patients achieved CR, and 1 achieved PR[18]. A single-center retrospective study in Korea reported the outcome of 14 R/R ENKTL patients treated with pembrolizumab. Five patients achieved CR and 1 patient achieved PR[19]. Sintilimab, an anti-PD1 antibody developed in China, was explored in 28 R/R ENKTL patients failing asparaginase-based

regimens in a multicenter, single-arm, phase II trial (ORIENT-4). The CR rate and ORR were 7.1% (2/28) and 53.6% (15/28), respectively. Median DoR was 4.1 months[8]. Although the data of pembrolizumab in the treatment of R/R ENKTL were from small retrospective case studies, and no anti-PD1 antibody (including pembrolizumab and sintilimab) was approved in the treatment of R/R ENKTL, compared with other drugs, the anti-PD-1 antibody is demonstrated to be an effective treatment with mild adverse effects in R/R ENKTL. All of these data suggest great potential of significant efficacy and better tolerance of anti-PD-1 monoclonal antibody in R/R ENKTL patients who have failed multiple treatment lines.

In summary, R/R ENKTL is a rare disease that lacks effective therapy. Existing clinical data showing the efficacy of anti-PD-1 monoclonal antibody in R/R ENKTL indicate inhibiting the PD-1/PD-L1 pathway to be a potentially effective treatment for R/R ENKTL.

1.2 MECHANISM OF ACTION

Immune checkpoints are a group of immunosuppressive molecules. Their physical function is to prevent normal cells from damage or injury by modulating the intensity and extent of immune reaction. While tumor cells often utilize this feature of immune checkpoints to avoid the attack by immune cells. Clinically validated immune checkpoints include CTLA-4 and PD-1/PD-L1, in which PD-1/PD-L1 has greater clinical potential because of its favorable safety and wide indication.

PD-L1 is primarily expressed on the surface of tumor cells and antigen-presenting cells and is the main ligand of T-cell inhibitory receptor PD-1[20]. The binding of PD-L1 expressed on tumor cells and PD-1 on T cells triggers a signaling cascade that inhibits T cell proliferation and cytokine secretion by activated T cells, reduces the activity of T cells, and decreases the killing of tumor cells by T cells. Drugs that block the interaction between PD-1 and PD-L1 may restore T cell activity and its ability to kill tumor cells[21].

Up to 20 March 2020, the anti-PD-L1 monoclonal antibodies approved by the Food and Drug Administration (FDA) include atezolizumab, avelumab, and durvalumab. Anti-PD-1 monoclonal antibodies approved by the FDA include pembrolizumab, nivolumab, and cemiplimab. The indications include advanced urothelial carcinoma, advanced non-small cell lung cancer (NSCLC), advanced melanoma, relapsed or refractory classical Hodgkin lymphoma, advanced renal cell carcinoma, and advanced head and neck squamous cell carcinoma, etc. Besides, many more indications are in the phase of pivotal registration trials or submission for approval. The approval of these drugs demonstrates the key position of PD-1/PD-L1 immune checkpoint inhibitors in cancer immunotherapy. The PD-L1 inhibitors approved in China are durvalumab and atezolizumab. The New Drug Application of CS1001 for the treatment of stage IV NSCLC has been accepted by China Center for Drug Evaluation in Nov 2020. The PD-1 inhibitors approved in China include pembrolizumab, nivolumab, toripalimab, sintilimab, camrelizumab, and tislelizumab. The indications are unresectable stage III NSCLC, small cell lung cancer, unresectable or metastatic melanoma, relapsed or refractory classical Hodgkin lymphoma, advanced NSCLC, and recurrent or metastatic head and neck squamous cell carcinoma, etc. However, there has not been any PD-1/PD-L1 inhibitors approved for the treatment of ENKTL worldwide. The significance of actively developing these inhibitors is to offer patients with advanced cancer more and better treatment options.

1.2.1 Pre-Clinical Studies

1.2.1.1 Pharmacodynamic Studies

The in vitro activity of CS1001 was examined by various methods at both protein and cell levels. The results showed that CS1001 effectively bound to PD-L1 protein expressed on the cell surface, blocked PD-L1/PD-1 ligation, and effectively induced the proliferation of CD4+ T lymphocytes and the production of interferon-γ (IFN-γ) and interleukin-2 (IL-2). In addition, CS1001 employs IgG4 isotype and lacks antibody-dependent cellular mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC), thus avoids direct damaging of PD L1(+) immune cells. In addition, in an in vitro assay, CS1001 in combination with a Poly ADP-ribose polymerase (PARP) inhibitor IMP4297 enhanced T cell-mediated tumor killing compared to IMP4297 or CS1001 alone.

Furthermore, the in vivo efficacy of CS1001 in inhibiting tumor growth was demonstrated in the subcutaneous MC38-B7H1 murine colon carcinoma (murine MC38 cells expressing human PD L1) in PD-1 humanized mouse (Biocytogen's B-hPD-1 mouse) model. When combined with lenvatinib (VEGFR1/2/3 inhibitor), CS1001 can enhance the tumor growth inhibition compared to each of the monotherapy agents in subcutaneous MC38-B7H1 murine colon carcinoma (murine MC38 cells expressing human PD-L1) in PD-1 humanized mouse (Biocytogen's B-hPD-1 mouse) model.

1.2.1.2 Pharmacokinetic Studies

Cynomolgus monkeys were given a single intravenous injection of CS1001 at 10, 30, 90 mg/kg, respectively, and pharmacokinetic (PK) characteristics and anti-drug antibody (ADA) were evaluated. No significant PK differences were found between male and female cynomolgus monkeys; serum concentration at time 0 (C_0) of CS1001 increased in a dose-dependent manner in both genders as the dose increased from 10 mg/kg to 90 mg/kg and the ratio of area under the concentration-time curve from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-last}}$) increase was greater than the ratio of dose increase. ADA data showed that the number of monkeys which were ADA positive in the high-dose group (no ADA was observed in 90 mg/kg group) was lower than that in the low-dose group (ADA positive rate in the 10 mg/kg group was 22.2% for both male and female; ADA positive rate in the 30 mg/kg group was 22.2% for the male and 11.1% for the female).

The toxicokinetic analysis was incorporated into 29-day and 26-week monkey repeated dose toxicity studies. The results showed that all median time to maximum concentration appeared between 0.3-8.0 and 0.6-1.7 hours after administration for 29-day and 26-week studies, respectively. The systemic exposure increased in a dose-proportional manner and there were no significant gender differences. There was an increase in systemic exposure after repeated doses of CS1001, indicating the accumulation of drugs.

1.2.1.3 Safety Studies

Administration of CS1001 to cynomolgus monkeys by a single intravenous infusion at dose levels of 100, 300, or 1000 mg/kg followed by a 14-day observation period was well tolerated and did not result in any treatment-related effects on mortality, clinical signs, body weight, food consumption, or gross pathology. Under the conditions of the study, the maximum tolerated dose (MTD) was $\geqslant$ 1000 mg/kg.

Administration of CS1001 to cynomolgus monkeys at dose levels of 30, 75, or 200 mg/kg once weekly for 29 days (a total of 5 doses) followed by a 4-week recovery period was well tolerated and did not result in any treatment-related effects on mortality, clinical signs, body

weight, food consumption, local irritation, body temperature, clinical pathology, safety pharmacology, immunology, or pathology. Consequently, under the conditions of the study, the no adverse effect level (NOAEL) was considered to be 200 mg/kg, the corresponding systemic exposure (expressed by C_{max} and observed area under the concentration-time curve from time 0 to 168 hours [AUC_{0-168h}]) on Day 22 were 15,100 μg/mL and 55,800 day•μg/mL in males, and 12,200 μg/mL and 51,800 day•μg/mL in females, respectively. No animals were detected as positive for the anti-CS1001 antibody during this study.

In a 26-week toxicity study, similar to the results of the 29-day study, the dose level of 200 mg/kg was well tolerated in cynomolgus monkeys and did not result in any test article related changes. No animals were detected as positive for the anti-CS1001 antibody during this study. Consequently, the NOAEL was 200 mg/kg, the corresponding systemic exposure (expressed by C_{max} and AUC_{0-168h}) on Day 176 was 14,600 μg/mL and 69,600-day•μg/mL.

In the *in vitro* hemolysis test, CS1001 at concentrations of 6 and 30.8 mg/mL did not show any hemolytic potential.

In the active systemic anaphylaxis test in guinea pigs, there were no test article-related changes in body weight and clinical signs during the induction and challenge phases. There were no unscheduled deaths during the study. CS1001 did not produce any indication of anaphylactic response.

An immunohistochemistry staining method was applied to determine the binding activity of CS1001 in normal fresh frozen human, monkey, and rat tissues. CS1001 had tissue cross activity in the human placenta.

1.2.2 Clinical Studies

The clinical program with CS1001 currently includes 10 ongoing trials in patients. Study CS1001-101, a Phase Ia/Ib, open-label, first-in-human (FIH) study conducted in Mainland China in patients with advanced solid tumors or lymphoma; CS1001-102, a Phase I, open-label, dose-escalation study of single-agent CS1001 conducted in the US in patients with advanced solid tumors; CS1001/Regorafenib-101, Phase Ib/II, multi-center and open-label study of CS1001 in combination with regorafenib in patients with advanced or refractory solid tumors; CS3008(BLU-554)-101, Phase Ib/II, multi-center, open-label, multi-dose study to evaluate CS1001 in combination with CS3008 (BLU 554) in patients with locally advanced or metastatic hepatocellular carcinoma (HCC); CS1001-201/202, Phase II, single-arm, multicenter studies conducted in patients with relapsed or refractory extranodal NK/T lymphoma and relapsed or refractory classical Hodgkin lymphoma, respectively; CS1001-301/302/303/304, Phase II, multicenter, randomized, double-blind study conducted in China in patients with locally advanced/unresectable non-small cell lung cancer (NSCLC), Stage IV NSCLC, gastric/gastro-esophageal junction (GC/GEJ) adenocarcinoma, and advanced esophageal squamous cell carcinoma (ESCC), respectively.

In Study CS1001-101 Ia, no DLT was observed in Study CS1001-101, and MTD was not reached. The recommended Phase II dose was determined as 1200 mg fixed-dose, once every 3 weeks (Q3W), and was continued its dose expansion in various tumor types in Phase Ib of the study and in Phase II and III trials. The details refer to the investigator's brochure (version 6.0, 10 July 2020).

1.2.3 Risk/Benefit Assessment

According to the mechanism of action of this investigational product and the clinical safety information of products with the same mechanism of action, expected possible adverse events in this trial are all kinds of inflammation caused by immune system activation, such

as pneumonitis, colitis, hepatitis, nephritis, and endocrine inflammation, etc. According to available clinical data of the investigational product, although the incidence of adverse effects is high, the drugs are well tolerated with only a small number of subjects discontinuing study due to adverse effects, and the majority of the adverse effects can well resolve after treatment. Early symptoms of immune-related adverse effects are quite heterogeneous. Therefore, investigators should pay special attention to early symptoms and signs of immune-related reactions to make accurate and timely judgments to dose modification and adequate intervention on time. Meanwhile, investigators should avoid enrolling patients with autoimmune diseases, which could get worse when the immune system is activated.

According to the clinical reports on pembrolizumab in treating R/R ENKTL, PD-1/PD-L1 pathway inhibition is shown to be an effective treatment with a manageable safety profile.

In summary, this trial is planned to evaluate the efficacy and safety of CS1001 monotherapy in R/R ENKTL.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary objectives	**Primary endpoints**
To evaluate the efficacy of CS1001 in subjects with R/R ENKTL;	Objective response rate (ORR) assessed by IRRC according to Lugano 2014 classification
Secondary objectives	**Secondary endpoints**
To evaluate the efficacy of CS1001 in subjects with R/R ENKTL;	ORR assessed by investigators; CRR, PRR, TTR, DoR assessed by IRRC and investigators;
To evaluate the safety of CS1001 in subjects with R/R ENKTL	Severity and frequency of AEs, and frequency of SAEs
To evaluate the PK of CS1001	To determine the peak and trough serum concentration of CS1001
To evaluate the immunogenicity of CS1001	Number and percentage of subjects who develop ADA
Exploratory objectives	**Exploratory endpoints**
To evaluate the progression-free survival (PFS) and overall survival (OS) of R/R ENKTL subjects	6-months PFS rate, 6-month OS rate
To evaluate genetic aberrations in R/R ENKTL by whole-exome sequencing test of tumor tissues	The association between genetic aberrations and efficacy

3. STUDY DESIGN

3.1 OVERALL DESIGN

This study is a single-arm, multicenter, Phase II trial to evaluate CS1001 monotherapy in R/R ENKTL. This study consists of three periods: screening, treatment, and follow-up period.

- The screening period consists of 28 days before the first dose of investigational product.
- Treatment period: enrolled subjects will receive investigational product CS1001 1200 mg intravenous infusion every 21 days up to 2 years until disease progression, intolerance, consent withdrawal, death, or other reasons specified in the protocol. Lugano 2014 classification (Appendix 13.1) will be used for efficacy assessment in the treatment period.
- Following study treatment discontinuation or two years of treatment, whichever comes first, subjects will enter into the follow-up period.

The Schedule of study activities is shown in Table 1.

3.1.1 Screening

Subjects must sign the informed consent and complete the screening visit to determine whether they are eligible for study enrollment.

Stained tumor tissue sections and corresponding pathological reports or unstained tumor tissue sections (or tissue block) must be collected at screening for central pathology review. Both fresh and archival biopsies are accepted and can be used by central pathology. Investigators may enroll subjects before obtaining the result of the central pathology review.

Seven (7) unstained FPPE tumor slides should be collected at screening for whole-exome sequencing of tumor tissue. A total amount of 2 mL whole blood should be collected at screening as germline control of whole-exome sequencing. If the tumor tissue and whole blood samples were not available at screening, retrospective collections of 7 archival FFPE tumor tissue slides and collection of 2 mL whole blood are allowed for whole-exome sequencing.

The baseline tumor assessment will be completed within 28 days before the enrollment.

3.1.2 Treatment Period

All of the laboratory tests and vital sign measurements should be performed within 72 hours before dosing at each cycle. (For Cycle 1, pregnancy test, hematology, serum chemistry, urinalysis, and thyroid function can be assessed 7 days before dosing. AEs will be recorded at each visit.

All subjects will receive CS1001 1200 mg once every 3 weeks up to 2 years until disease progression, intolerable to study treatment, consent withdrawal, death, or other reasons specified in the protocol.

Efficacy will be assessed according to Lugano 2014 classification.

Blood samples for pharmacokinetic and immunogenicity assays are collected at the time points specified in Table 1.

Subjects must receive end-of-treatment (EOT) visit when permanently discontinue the study treatment. (The EOT date will be the decision making date for discontinuing the study treatment by investigators.)

3.1.2.1 Treatment Beyond Disease Progression

For subjects who have PD according to Lugano 2014 classification, if it is suspected by the investigator as pseudo-progression, treatment may continue until confirmation of PD with repeated imaging at least 4 weeks later (or preferred at the next scheduled regular imaging time point). But all of the following criteria must be met to continue the treatment:

a. Absence of clinically significant symptoms and signs of PD (including worsening laboratory values)
b. Stable ECOG PS performance
c. Absence of rapid progression of disease or PD at critical anatomical sites that necessitates urgent medical intervention

In special situations, a subject with disease progression confirmed by radiology or other clinical examinations who will possibly benefit from further investigational treatment may continue the treatment at the discretion of the investigator in consultation with the sponsor.

Written consent from the subject must be obtained before any treatment beyond disease progression (including suspected pseudo-progression and confirmed disease progression).

3.1.2.2 Study Discontinuation Criteria for Clinical Deterioration

Clinical events considered by the investigator as a result of disease progression that will probably not recover even if treatment continues will be judged to be a clinical deterioration. The subject will be determined to continue or discontinue treatment by the investigator in consultation with the medical monitor, and the process will be recorded in the study file.

3.1.3 Follow-up

Following study treatment discontinuation or two years of treatment, whichever comes first, subjects will enter into the follow-up period, which consists of three parts:

- Safety follow-up: A safety follow-up visit should be conducted 30, 60, 90 days after the last dose of the investigational product. Safety follow-up period refers to the 90 days after the last dose of the investigational treatment or the start of new anti-cancer treatment, whichever occurs earlier.
- Tumor assessment follow-up: For all subjects other than those who discontinue treatment due to radiological disease progression, tumor assessment should be performed at pre-specified regular time points until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first.
- Survival follow-up: Subjects will receive a follow-up visit every 12 weeks after the last dose of investigation product and survival data collection will continue until lost to follow-up, death, consent withdrawal, or the end of the study, whichever comes first. Telephone follow-up is acceptable.

AEs that occur during the follow-up period will be reported as per Section 7.

3.1.4 End of Study

The date of the end of the study is defined as the date of the last follow-up. The final analysis for the primary endpoint will be conducted up to 24 weeks after enrollment of the last subject. The study will continue until the last data point of the last subject has been collected (when the last subject completes the safety follow-up). The study can be terminated at any time by the sponsor.

3.1.5 Treatment Beyond End of Study

Subjects with clinical benefit (without disease progression and with good tolerance) when they have been on CS1001 treatment for 2 years or this clinical study ends may continue

treatment with the investigational product. These subjects must provide written ICF and be willing and able to continue to follow all study procedures in order to remain on treatment. The investigational product may be offered in another extension study or by means determined by the sponsor.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Single-Arm Design

Given the rarity of R/R ENKTL and the lack of standard of care after the failure of asparaginase-based treatment, there is a significant unmet medical need in this population. Existing clinical data showing the efficacy of anti-PD-1 monoclonal antibody in R/R ENKTL demonstrates the potential of inhibition of the the PD-1/PD-L1 pathway as an effective treatment for R/R ENKTL. Therefore, this trial is designed as a single-arm study.

3.2.2 Rationale for Primary Endpoint Analysis for Treatment of Up to 24 Weeks

According to data reported for pembrolizumab, the response was primarily achieved at 6-12 weeks of treatment. It's expected that each of the disease responses will be observed by 24 weeks after each of the subjects receives the drug. ORR analysis will be performed up to 24 weeks after the first dose in the last subject. The efficacy and safety will be evaluated via ORR in combination with PFS, DoR, and will use historical data as the reference.

3.2.3 Rationale for Setting ORR as the Primary Endpoint with Historical Control

In a report of pembrolizumab in 7 patients with R/R ENKTL who failed prior asparaginase-based regimen, 5 patients achieved CR and 2 patients achieved PR. The 5 CR patients were still in remission at a 6-month follow-up[16]. Another study of pembrolizumab in 7R/R ENKTL patients reported that 2 patients achieved CR and 2 patients achieved PR [17]. A French study was conducted in 13 R/R ENKTL patients failing asparaginase-based chemotherapy. Three patients (3/13, 23%) achieved CR, and one (1/13,8%) achieved PR[18]. A single-center retrospective study in Korea reported the outcome of 14 R/R ENKTL patients treated with pembrolizumab, with a CR rate of 35.7% (5/14) and ORR of 42.9% (6/14)[19]. These results indicated anti-PD-1/PD-L1 pathway inhibition could lead to a durable objective response, which correlates with clinical benefit. Therefore, ORR is used as the primary endpoint in this trial. While the ORR was encouraging, these were small retrospective case studies, and pembrolizumab is not approved for this indication. So, these data were not appropriate to be referenced as historical control. As a targeted therapy, chidamide has been approved to treat R/R peripheral T-cell lymphoma (including R/R ENKTL) in China. For the R/R ENKTL indication, it is reported to have a CR rate of 6.3% (1/16) and an ORR of 18.8% (3/16) in the pivotal phase II trial[1]. Taking into consideration of chidamide registration study ORR in R/R ENKTL, the historical control is proposed as 20% in this study.

3.2.4 Rationale for Treatment Beyond Disease Progression

Clinical data of other immune checkpoint inhibitors showed that a minority of subjects may derive clinical benefit from treatment beyond initial progression (manifesting as enlarged original lesion or occurrence of a new lesion) that occurs before clinical objective response and/or stable disease in some patients[22]. Currently, two mechanisms are believed to be responsible for this phenomenon. Firstly, intra-tumor inflammation aggravation may lead to an increase in tumor masses as manifested by an enlarged measurable lesion or new, visible unmeasurable lesion. Secondly, the anti-tumor immune response occurs at a later time in some patients who have a smaller tumor-inhibitory effect than the tumor growth kinetics in

the early stage. Therefore, for the subjects on CS1001 treatment who are considered to have clinical benefit and are well tolerated to the investigational product, they are allowed to continue treatment despite initial PD assessed by the investigator according to Lugano 2014 classification.

3.2.5 Rationale for Exploratory Biomarker Investigation

Few clinical trials investigated anti-PD-1/PD-L1 monoclonal antibody treatment in ENKTL patients, and biomarkers for predicting whether ENKTL patients can benefit from anti-PD-1/PD-L1 monoclonal antibody have not been reported yet. ENKTL-associated genetic aberration data such as single nucleotide variation, nucleotide insertion, and deletion can be found by whole-exome sequencing assay on tumor tissues. By matching the featured genetic aberrations and the efficacy of CS1001 in patients with ENKTL, we may find genetic aberrations that are associated with the efficacy of anti-PD-L1 monoclonal antibodies. These genetic aberrations may be used as biomarkers to guide patient selection and predict CS1001 efficacy in clinical practice.

4. STUDY POPULATION

It's planned to enroll approximately 80 subjects with R/R ENKTL in this trial.

The detailed inclusion and exclusion criteria are listed below.

4.1 Inclusion Criteria

1. Subjects who are willing to participate in this trial; fully understand and are fully informed of this trial, and are able to provide written ICF; are willing and able to follow all study procedures.
2. Subjects are ≥ 18 years and ≤ 75 years of age on the day of signing informed consent.
3. Subjects must have a histologically confirmed ENKTL at the study site. Both nasal and non-nasal ENKTL are allowed.
4. Subjects must have relapsed or refractory ENKTL failing asparaginase-based chemotherapy or chemoradiotherapy. (Relapse: disease progression after response to the last treatment; refractory: no response to the last treatment.)
5. ECOG PS of 0 or 1.
6. Life expectancy ≥ 12 weeks.
7. Subjects must have at least one evaluable or measurable lesion per Lugano 2014 classification [An evaluable lesion is a lymph node or extranodal lesion with radioactive uptake higher than liver on ^{18}FDG/PET and with typical lymphoma characteristic on PET and/or CT; Measurable lesion: the longest diameter (LDi) is of > 15 mm for nodal lesion or >10 mm for extranodal lesion (if the only measurable lesion has received prior radiotherapy, the subject must have evidence of radiological progression after radiotherapy), and concurrent elevated uptake of ^{18}FDG]. Absence of measurable lesion with diffuse ^{18}FDG uptake increase in the liver should be ruled out first.
8. Subjects must provide stained tumor tissue sections and corresponding pathological reports or unstained tumor tissue sections (or tissue block) for central pathology review. Investigators may enroll subjects before the result of the central pathology review.
9. Subjects must have adequate organ function and bone marrow function without severe hematopoietic disorder, or heart, lung, liver or kidney dysfunction or immune deficiency (no blood transfusion, granulocyte colony-stimulating factor or other relevant medical supporting care within 14 days before the first dose of study treatment):
    a) Absolute neutrophil count ≥ 1.0×10^9 /L;
    b) Platelets ≥ 50×10^9 /L;
    c) Hemoglobin ≥ 8 g/dL;
    d) Creatinine clearance ≥ 40 mL/min (according to Cockcroft-Gault equation);
    e) Serum total bilirubin ≤ 1.5 × ULN, unless considered to be due to Gilbert's disease, where it must be ≤3 × ULN
    f) AST and ALT ≤ 2.5 × ULN;

g) Coagulation functions: INR ≤ 1.5 × ULN; PT and APTT ≤ 1.5 × ULN (unless the subject is on anti-coagulant; and PT and APTT at screening are as expected in patients on anti-coagulant).

10. Subjects with prior anti-cancer treatment can only be enrolled when the toxicity of prior anti-cancer treatment has recovered to baseline or ≤ Grade 1 according to CTCAE v4.03. For patients with irreversible Grade 2 toxicities (e.g. thrombocytopenia, anemia, neurotoxicity, alopecia, and hearing impairment) that is anticipated to be unlikely to worsen during study treatment, the subject can be enrolled after approval by the medical monitor of the sponsor.
11. WOCBP must have a negative serum pregnancy test ≤7 days before the first dose of investigational product. WOCBP or fertile men and their WOCBP partners must agree to use an effective contraceptive method from providing signed ICF through 6 months after the last dose of the investigational product (Refer to Section 4.1.5 for details).

4.2 Exclusion Criteria

1. Aggressive natural killer-cell leukemia or ENKTL patients who have any degree of leukemic involvement will be excluded.
2. Concomitant with hemophagocytic lymphohistiocytosis.
3. Current or historical primary central nervous system lymphoma (PCNSL) or secondary CNS involvement.
4. Prior allogeneic organ transplantation.
5. Allogenic hematopoietic stem cell transplantation (HSCT) ≤ 5 years before the first dose of investigational product. (Patients are permitted to enroll if they received allogenic HSCT more than 5 years before the first dose of investigational product and without any current graft-versus-host reaction.)
6. Current participation in another clinical study or use of any investigational drug within 4 weeks before the first dose of investigational product in this trial.
7. Autologous HSCT within 90 days before the first dose of CS1001.
8. Subjects with an active autoimmune disease that requires systemic treatment in the past two years. (Hormone replacement therapy is not considered as systemic therapy such as the patient has type I diabetes mellitus, hypothyroidism that can be managed with thyroid hormone replacement only, or adrenal insufficiency or pituitary insufficiency that requires a physiological dose of corticosteroid replacement.) Subjects are permitted to enroll if they have an autoimmune disease that didn't require any systemic treatment in the past two years.
9. Subjects received systemic corticosteroid or any other immunosuppressive therapy within 14 days before the first dose of the investigational product. [Subjects are permitted to use topical, ocular, intra-articular, intranasal and inhaled corticosteroids (with minimal systemic absorption); a short course (≤ 7 days) of corticosteroids for prophylaxis (e.g., hypersensitivity to contrast media) or for treatment of non-autoimmune conditions (e.g., delayed hypersensitivity caused by contacting allergens).]
10. A known additional malignancy within 5 years prior to the first dose of investigational product. Subjects with locally curable malignancies (including basal

cell carcinoma of skin, squamous cell carcinoma of skin, breast cancer in situ or cervical cancer in situ, etc.) that have undergone curative therapy are permitted to enroll.

11. Subjects who have had prior chemotherapy, immunotherapy, biological therapy (including cancer vaccine, cytokine therapy or growth factors to treat cancer) used as a systemic treatment for cancer, within 28 days before the first dose of investigational product.
12. Subjects who underwent a major surgical procedure within 28 days prior to the first dose of investigational product or radiotherapy within 90 days before the first dose of investigational product.
13. Any use of traditional Chinese medicines or herbal preparations with anti-tumor indications within 7 days before the first dose of investigational product.
14. Has received a live vaccine within 28 days before the first dose of investigational product. (Attenuated influenza vaccine is allowed.)
15. Known history of (HIV infection and/or acquired immune deficiency syndrome (AIDS).
16. Subjects at the active phase of chronic hepatitis B or with active hepatitis C. Subjects who are HBsAg positive or HCV antibody positive at screening must not be enrolled until further definitive testing with HBV DNA titers (≤ 2500 copies/mL or 500 IU/mL) and HCV RNA tests (≤ the lower limit of detection) can conclusively rule out the presence of active hepatitis B or C that requires treatment, respectively. Subjects that carry the hepatitis B virus, with stable hepatitis B (HBV DNA titer ≤ 2500 copies/mL or 500 IU/mL) after medical treatment or with cured hepatitis C are permitted to enroll.
17. History of interstitial lung disease (except for those induced by radiation therapies and are asymptomatic).
18. Active tuberculosis infection.
19. An active infection requiring systemic anti-infection therapy within 14 days before the first dose of investigational product.
20. Subjects who have received anti-PD-1, anti-PD-L1, or anti-CTLA-4 monoclonal antibody treatment.
21. Subjects with a known severe allergy to monoclonal antibodies (≥ Grade 3 per CTCAE v 4.03) or uncontrolled allergic asthma.
22. Women in pregnancy or lactation.
23. Subjects with active alcohol or drug dependence..
24. Subjects with uncontrollable concomitant diseases including but not limited to symptomatic congestive heart failure, uncontrolled hypertension, unstable angina, active gastrointestinal ulcer or hemorrhagic disorders.
25. Subjects with a history of psychiatric disease; or subjects with incapacity or limited capacity.
26. Underlying condition that in the investigator's opinion would increase the risk of investigational product administration or confound the assessment for its toxicity.
27. Subjects in the investigator’s opinion are not suitable for participating in this trial.

4.3 Discontinuation and Withdrawal

4.3.1 Discontinuation of Study Treatment

Subjects must discontinue study treatment if any of the following criteria are met:

1. Any AE that meets the treatment discontinuation criteria specified in the protocol (refer to Section 5.3).
2. Disease progression. (Subject who meets the criteria for treatment beyond progression may continue treatment until confirmation of progressive disease by tumor assessment. Refer to Section 3.1.2.1.)
3. Subjects who receive any prohibited treatment during the trial that compromises the assessment of safety and efficacy may be determined to discontinue study treatment by the investigator in consultation with the sponsor medical monitor.
4. Any intercurrent condition that compromises the subject's ability to continue study treatment.
5. Pregnancy of female subjects.
6. Subjects and/or their legal guardian who decide to discontinue the study treatment may inform the subject's doctor at any time and then discontinue study treatment. According to the Deceleration of Helsinki and other applicable regulatory requirements, all subjects have the right to withdraw from the study at any time and for any reason. The doctor and the study site must not hold bias in their future treatment.
7. Subject with poor compliance who doesn't receive treatment at the right dose and the right time despite the investigator’s effort in communication and coordination, which may lead to significant uncorrectable bias in the study results may be determined to discontinue study treatment by the investigator in consultation with the sponsor medical monitor.
8. Other conditions that make study treatment continuation inappropriate judged by the investigator.

In any case, the primary reason for study treatment discontinuation will be recorded in the original medical record. For subjects who discontinue study treatment for any reason, the investigator should try every effort to have the subject complete end of study visit if the subject has received at least one dose of the investigational product, and continue to follow up subjects with unresolved AE.

4.3.2 Follow-up After Discontinuation

Subjects who discontinue study treatment must be followed up. Outcome and/or survival follow-up data will be collected per protocol requirements until the subject dies or this study ends. Apart from subjects who discontinue treatment due to radiological disease progression assessed by imaging, tumor assessment should be performed at pre-specified regular time points until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first.

Study sites will contact subjects who are lost to follow-up, if possible, determine the reason for lost to follow-up, and rearrange follow-up visits. The date of contacting the subject and contact method will be recorded in the study file.

4.3.3 Consent Withdrawal

If a subject that requires study treatment discontinuation would continue the study, he/she must follow the follow-up procedures specified in the study protocol. The only exception

allowed is that the subject clearly withdraws the informed consent and himself/herself or other authorized personnel who provides this information cannot be contacted. The subject shall inform the investigator by a written notice about the decision to withdraw the consent to future follow-up, if possible. The investigator should record the details in the subject's medical record, including whether the consent withdrawal refers to study treatment discontinuation only or no more study procedures and/or post-discontinuation follow-up. Only data that allowed to be disclosed in compliance with legal and applicable regulatory requirements can be used for survival evaluation.

4.4 Definition of WOCBP

Women of childbearing potential (WOCBP) refer to women that have had menarche, haven't received any sterilization operation (such as hysterectomy or bilateral oophorectomy), and haven't reached menopause. Menopause is defined as amenorrhea for over 12 months without any biological or physiological cause in women aged >45 years. Furthermore, the documented follicular stimulating hormone (FSH) level of women aged <55 years must be > 40 mIU/mL to confirm menopause.

* The FSH level of women on hormone replacement therapy (HRT) may be artificially suppressed. These women may need a washout period to obtain a physiological FSH level. The duration of the washout period is determined by the type of HRT. Guidelines recommend the following duration of the washout period. Investigators should determine the washout period at their own discretion when testing for serum FSH levels. Women whose serum FSH level is > 40 mIU/mL at any time during the washout period can be considered as menopause.

- At least one week for vaginal contraception products (such as vaginal ring, contraceptive jelly, and gel)
- At least 4 weeks for transdermal products
- At least 8 weeks for oral contraceptive agents

May need at least 6 months for other parenteral products.

4.5 Definition of Effective Contraception

Subjects must be willing to use at least two methods of contraception; one is a highly effective method and the other highly or less effective method as listed below. If total abstinence is used as a highly effective method, other methods will not be needed.

Highly effective contraception methods

WOCBP subjects or WOCBP partners of male subjects may use hormonal methods of contraception, for example, compound oral contraceptives, vaginal ring, injections, implant, or intrauterine device. The female partners of male subjects enrolled in this study may use hormonal contraceptive pills as an acceptable method of contraception because they don't receive investigational product administration.

Intrauterine device

Tubal ligation

Vasectomy

Total abstinence*

* Total abstinence defined as total avoidance of heterosexual intercourse is an acceptable method of contraception for all investigational products. Female subjects must continue to receive a pregnancy test. When a subject is no longer in total abstinence, other acceptable highly effective methods of contraception must be considered.

Less effective contraception methods

Male condom that contains spermicide

Contraceptive diaphragm that contains spermicide

Cervical cap that contains spermicide

Vaginal sponge

Male condom that doesn't contain spermicide

WOCBP subject or WOCBP partner of a male subject takes pills that only contain progesterone

Female condom*

* Male condom and female condom should not be used at the same time.

5. STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCT

The investigational product in this protocol is CS1001, [redacted]

The investigational treatment regimen is CS1001, 1200 mg, IV infusion Q3W.

5.1.1 Dosage Form and Specifications

Dosage form: injection

Specifications: 90 mg/3 mL/vial and 600 mg/20 mL/vial

Excipients: histidine/histidine hydrochloride, mannitol, sodium chloride, Polysorbate 80; pH 5.5

Period of validity: 36 months, tentatively.

Storage condition: 2 ℃ to 8 ℃

5.1.2 Packaging and Labeling

CS1001 is for injection with specifications of 90 mg/3 mL/vial and 600 mg/20 mL/vial. All investigational products will be labeled in compliance with Good Clinical Practice (GCP) requirements. The label content will be designed according to the sponsor's standards. All drugs will be dispatched as the main trial-specific materials.

A uniform format will be applied to the drug labels. The labeling will contain the following information: protocol number, name of the investigational product (and "For clinical trial use" labeled), specification, storage, batch number, expiry date, and sponsor.

All the records of batch number and expiry date as well as labels for all investigational products will be kept in the study file.

5.1.3 Management of Investigational Product

The investigational product handling liability will be executed as per requirements in Appendix 13.3.

5.1.3.1 Dispensing of Investigational Products

The investigational product is provided by the sponsor, dispatched to the study sites as per the plan. The investigational product must be kept and dispensed by a designated person at the study site. The investigational product will be stored in a locked cabinet as required.

5.1.3.2 Storage of Investigational Product

The investigational product will be kept, handled, and dispensed by a designated person at the study site. The responsible person at the study site will confirm the receipt of investigational product in writing and use the investigational product within the framework specified in the protocol. An accurate record of the shipment, dispensing, and return of the investigational product will be maintained. Meanwhile, the sponsor will retrieve the packages of investigational product at the end of this trial. The storage temperature of investigational products will also be recorded in corresponding documents.

The investigational product will be dispensed by a member of the study team. The personnel should ensure and record the dispensing of the investigational product as planned; the quantity of dispensed and returned drugs and corresponding dates will be recorded in the source medical record.

5.1.3.3 Return of Investigational Product

The investigational product will be returned in the study. All unused and/or partially used investigational product(s) will be returned to and destroyed by a third party designated by the sponsor following the accountability work at the study site.

5.1.3.4 Destruction of Investigational Product

The investigational product will be destroyed at a third party designated by the sponsor. Study personnel should ensure, develop, and record an adequate process of investigational product handling in compliance with applicable regulations, guidelines, and policies. The investigational product will be destroyed per sponsor's approval.

5.1.4 Preparation and Administration

CS1001 is to be administered as an IV infusion in compliance with local clinical guidelines. (Infusion using a device through a 0.2 micrometer in-line or with an additional filter is recommended.) See the *Drug Handbook* for additional information on preparation and other special requirements.

Dilution:

- Dilute the total dose of CS1001 to be administered with 250 mL of sterile normal saline (0.9% sodium chloride solution).

Administration Instructions

- CS1001 is to be administered as an IV infusion, not an IV bolus injection.
- Ensure that the investigational product is clear, colorless, and free from any particulate matter on visual inspection.
- Withdraw a total of 40 mL (13.33 vials of 90 mg/3 mL/vial product, or 2 vials of 600 mg/20 mL/vial product) of CS1001 solution into a syringe. The solution of the two specifications should not be mixed for a single infusion. Inject CS1001 solution withdrawn into a 250-mL infusion bag of normal saline. Do not insert a syringe into a vial to withdraw investigational products more than once. Do not use a glass syringe to withdraw investigational products.
- Mix by **gently** inverting several times. Do not shake.
- Visually inspect the final solution. If the solution is not clear or the contents appear to contain precipitate, the solution should be discarded and record in the drug management log.
- Record time and dose (in mg) of CS1001 preparation in the preparation sheet.
- The investigational product is administered over 60 minutes. For subjects who have an infusion-related reaction, the infusion duration can be extended appropriately, according to Section 5.3.4. The infusion line should not be used for other medication infusions.
- The infusion line should undergo flush with sufficient normal saline at the end of the infusion.
- The investigational product is recommended to be administered to subject immediately after preparation, avoiding exposing the prepared solution under room temperature for more than the recommended ***6-hour limit***. In which, the 6 hours include the time for CS1001 storage under room temperature, solution storage in the infusion bag, and infusion time. If the administration of the prepared drug is to be postponed, it should be stored under refrigeration at 2 ℃ to 8 ℃ for no more than **24 hours**.

5.2 TREATMENT COMPLIANCE

The dosing of the investigational product will be monitored by the principal investigator or his/her assistant for ensuring treatment compliance. The exact time of dosing (starting and ending of infusion) and dose administered should be recorded. For infusion interruption, the cause of interruption should be recorded in eCRF.

5.3 INVESTIGATIONAL PRODUCT DOSING MODIFICATION

5.3.1 Overall Principle for Investigational Product Dosing Modification

The mechanism of CS1001 is to promote T-cell activation and proliferation. As a result, CS1001 may induce autoimmune hyperactivity which will further cause autoimmune diseases involving multiple organ systems. Immune-related AEs (irAEs), for example, pneumonitis, diarrhea/enterocolitis, renal impairment, rash, hepatitis, endocrine disorders, and peripheral or central neuropathy have occurred in the clinical use of other immune checkpoint inhibitors including ipilimumab, nivolumab, pembrolizumab, and atezolizumab. Once a subject develops any of the above AEs in this trial, the subject should be monitored for symptoms and signs. Appropriate tests and examinations may be conducted for differentiating etiology. If no other cause (for example disease progression, concomitant medication, or infection) is found while the subject requires corticosteroid and/or other immunosuppressive treatment, the AE is considered as related to the immune system hyperactivity caused by CS1001, and thus is an irAE. (This rule doesn't apply to endocrinology events, for example, hyperthyroidism/hypothyroidism, hypophysitis, type I diabetes mellitus, and adrenal insufficiency, which will still be considered as related to autoimmune hyperactivity caused by CS1001 treatment although they may not require immunosuppressive treatment). Identification, diagnosis, management, and dose modification for irAEs are detailed in Appendix 13.4.

5.3.2 Criteria for Dose Modification of Investigational Product

Dose increase or reduction of CS1001 is not permitted in this trial. The investigational product will be **withheld** for any of the following investigational drug-related adverse reactions:

1. Grade 2 pneumonitis
2. Grade 2 or 3 colitis; Grade 3 diarrhea or persistent Grade 2 diarrhea
3. Grade 2 hepatitis (elevation of ALT, AST, or total bilirubin levels)
4. Grade 2 hypophysitis without adrenal crisis
5. Grade 2 nephritis
6. Grade 3-4 hypothyroidism
7. Grade 3 hyperthyroidism lasting for 6 weeks or more despite proper management
8. Grade 3 dermatitis
9. Grade 2 neuromuscular toxicity
10. Grade 2 ocular toxicity
11. Other Grade 2 AEs (for example arthritis, pancreatitis, hemolytic anemia, adrenal insufficiency, myasthenic syndrome, and rhabdomyolysis)
12. Grade 4 hematologic toxicity
13. Any Grade 3 abnormal laboratory test results except for the following situations:
    - Grade 3 hematologic toxicity.

- Study treatment will be delayed when Grade 2 hepatitis occurs.

14. Any AE, abnormal laboratory test result, or intercurrent condition that in the investigator's opinion requires postponing study treatment.

Subjects may resume investigational treatment when the above AE(s) resolve(s) to Grade 0/1 or baseline and the dose of systemic corticosteroid for treating the AE(s) have been tapered to 10 mg daily prednisone equivalents or less.

The investigational treatment will not be resumed for dosing delay due to any cause for more than **9 weeks** (12 weeks after the last dose). (Subject may continue treatment if he/she still benefits clinically at the discretion of investigator in consultation with the sponsor's medical monitor.)

5.3.3 Criteria for Permanent Discontinuation of Investigational Treatment

The investigational product will be **permanently discontinued** after consultation with the sponsor's medical monitor for any of the following drug-related adverse events:

- Grade 3-4 pneumonitis
- Grade 4 colitis, recurrent Grade 3 colitis, or colitis with symptom suggestive of intestinal perforation
- Grade 3 hepatitis (elevation of ALT, AST, or total bilirubin levels)
- Grade 4 abnormal laboratory test results except for the following situations:

  –Grade 4 neutropenia lasting for ≤ 5 days

  –Grade 4 lymphocytopenia or leukopenia

  - Solitary Grade 4 electrolyte disorder/imbalance that can be corrected by electrolyte supplementation/adequate treatment in 72 hours without any clinical consequence.
- Grade 3-4 hypophysitis or adrenal crisis
- Grade 3-4 nephritis
- Grade 4 hyperthyroidism
- Grade 4 dermatitis
- Grade 3-4 neuromuscular toxicity
- Grade 3-4 ocular toxicity
- Other Grade 3-4 AEs (for example arthritis, pancreatitis, hemolytic anemia, adrenal insufficiency, myasthenic syndrome, and rhabdomyolysis) except for Grade 3/4 hypothyroidism
- Grade 4 infusion-related reactions

Permanent discontinuation of investigational product will be considered for recurrence of any of the following Grade≥2 irAEs: pneumonitis, ocular toxicity, cardiac toxicity, and at the discretion of the investigator.

For subjects who meet any of the above criteria although benefiting from investigational treatment, the sponsor's medical monitor and the investigator will discuss and make the final decision in the subject's best interest.

5.3.4 Infusion-Related Reaction

The symptoms of infusion-related reactions include fever, chills, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Subjects should be closely monitored for such reactions. Treatment modification for symptoms of infusion-related reactions due to CS1001 is presented in Table 2.

Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical care (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions in the study sites. Infusion of CS1001 will be discontinued in case of Grade ≥2 infusion-related, allergic, or anaphylactoid reactions. Subjects must be closely monitored for infusion-related reactions continuously for 2 hours after the first two doses of CS1001.

Table 2 Treatment Modification for Symptoms of Infusion-Related Reactions

CTCAE Grade	Treatment Modification for CS1001
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated.	CS1001 infusion rate is decreased by 50% and any worsening of the reaction is closely monitored until its resolution.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); treatment of prophylactic medications ≤24 hours.	CS1001 infusion is interrupted. Infusion is resumed at 50% of the previous rate once infusion-related reactions have resolved or decreased to Grade ≤1 in severity and any worsening is closely monitored.
Grade 3 Prolonged (e.g., not rapidly responsive to symptomatic treatment and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization for clinical sequelae or cause clinical consequences (for example kidney injury or pulmonary infiltration).	CS1001 infusion is immediately discontinued. Continuation of study therapy is at the discretion of the investigator.
Grade 4 Life-threatening consequences; urgent intervention (for example mechanical ventilation) indicated.	Subjects must permanently discontinue CS1001 treatment.

NSAIDs, non-steroidal anti-inflammatory drugs.

Once the CS1001 infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If the subject has a second infusion-related reaction (Grade ≥ 2) on the slower infusion rate, the infusion should be stopped, and the subject should be permanently discontinued from CS1001 treatment.

CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an antihistamine (e.g., diphenhydramine or equivalent), antipyretic (e.g., paracetamol or equivalent), and oral or IV corticosteroids, epinephrine, bronchodilators, and oxygen on demand. The subject should receive bedside monitoring until symptoms resolve. In the **following** cycles, subjects should

receive oral prophylactic treatment with an antihistamine (e.g., diphenhydramine or equivalent) and an antipyretic (e.g., paracetamol or equivalent) at least 30 minutes before the start of the infusion, and they should be closely monitored for clinical signs and symptoms of an infusion-related reaction.

CTCAE Grade 3 or 4 infusion reaction: Immediately stop the infusion. Proper medical management should be instituted immediately, per type and severity of the reaction. This includes but is not limited to oral or IV anti-histamine, anti-pyretic, corticosteroids, epinephrine, bronchodilators, and oxygen.

If a subject experiences a Grade 4 infusion-related reaction at any time, CS1001 must be discontinued permanently.

In the event of a Grade 3 infusion-related reaction, the continuation of study therapy is at the discretion of the investigator after consultation with the sponsor's medical monitor. If continued, the infusion time of CS1001 in the **next cycle** should be at least 2 hours. Subjects should receive oral prophylactic treatment with an anti-histamine (e.g., 50 mg diphenhydramine or equivalent) and an antipyretic (e.g., paracetamol, NSAIDs or equivalent) 30-60 minutes before the start of the infusion. Subjects should be closely monitored for clinical signs and symptoms of an infusion-related reaction.

5.4 CONCOMITANT THERAPY

5.4.1 Prohibited Therapy

Treatments that the investigator considers necessary for a subject's medical needs may be administered except for the following prohibited therapies. If any of the following therapies is required by a subject as per the investigator's assessment, the subject's eligibility for continuing investigational treatment will be determined at the investigator's discretion in consultation with the sponsor medical monitor.

1. Anti-tumor therapies: no other anti-tumor therapy than the investigational product is permitted. This includes but is not limited to chemotherapy, immunotherapy, biologically targeted therapy, and traditional Chinese medicines with anti-tumor indications; and radiation therapy.
2. Concurrent investigational agent (unapproved medications) other than CS1001.
3. Immunosuppressant (unless for treating AEs).
4. Systemic corticosteroids (of dose higher than 10 mg prednisone or equivalent per day), unless for conditions specified in Section 5.4.2 Item 2, or for treating AEs.
5. Live vaccines are prohibited during the study.
6. Other prohibited treatment as specified in the inclusion/exclusion criteria.

5.4.2 Permitted Therapy

1. Inactivated or attenuated influenza vaccine that doesn't require wash-out. The use of other inactivated or attenuated preventive vaccines will be determined according to the actual condition after discussion with the investigator and sponsor's medical monitor.
2. Topical, ophthalmic, intra-articular, and nasal and inhaled corticosteroids (with very little systemic absorption) are permitted. Adrenal replacement with $\leqslant$10 mg corticosteroid per day or equivalent is permitted. Short-course (<3 weeks) of corticosteroid as prophylaxis (for contrast allergy) or treatment for non-autoimmune diseases (for example delayed-type hypersensitivity caused by allergen contact).

3. Symptomatic and supportive treatment for AEs during the study treatment is permitted.
4. Other permitted treatment as specified in the inclusion/exclusion criteria.

6. STUDY PROCEDURES AND ASSESSMENTS

Study procedures and assessments should be performed at the planned time points (refer to Table 1). Refer to Section 6.1 for details.

Once a subject is included in this trial, the subject must be informed of the study's nature and procedures, and a signed, written informed consent must be obtained before any study-related procedure.

6.1 STUDY PROCEDURES

6.1.1 Screening

The screening period is from D-28 to D-1. The assessments to be completed during screening are listed in Table 3:

Table 3 Visit procedures in the screening phase

Items	Note
Study Management Procedures	
Inclusion/exclusion criteria	Assess the subject's eligibility according to the inclusion/exclusion criteria
Demographics and medical history	● Age, sex, ethnicity, smoking and alcohol use history ● Pathohistology, clinical stage, tumor-related symptoms
Prior medications and concomitant medications	● Treatment regimens with administration methods, starting time and ending time, best response and cause for discontinuation for prior local or systemic anti-cancer therapies ● Concomitant medications within 28 days before the first investigational product dosing
Clinical Procedures and Assessments	
Adverse events	AEs that occur after obtaining informed consent and before the administration of the investigational product
Electrocardiogram (ECG)	Standard 12-lead ECG will be used
Height, weight, and vital signs	The vital signs include temperature, blood pressure, pulse, and respiratory rate
Physical examination and ECOG performance status	● Conduct Physical examination ● Score ECOG PS
Laboratory Procedures/Assessments (at site)	
Pregnancy test	Blood human chorionic gonadotrophin test is performed as a pregnancy test within 7 days before the first dose of study treatment
Hematology, serum chemistry, urinalysis	Hematology, serum chemistry, and urinalysis tests are performed within 7 days before the first dose ● Hematology: complete blood count (CBC) and hemoglobin ● Serum chemistry: blood urea/urea nitrogen, creatinine, sodium,

Items	Note
	potassium, magnesium, chloride, calcium, phosphate, fasting glucose, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total cholesterol, total protein, and albumin ● Urinalysis: specific gravity, pH, glucose, protein, cast, ketones, and blood cells
Coagulation	PT, APTT, and INR
Virology	All subjects must receive anti-HIV antibody, HBsAg, and anti-HCV antibody tests ● Subjects with positive HBsAg must further undergo HBV DNA test ● Subjects with positive anti-HCV antibody must further undergo HCV RNA test
Thyroid function	Thyroid function tests including FT3, FT4, and TSH will be performed within 7 days before the first dose of study treatment
EBV DNA	Blood sample collection
Laboratory Procedures/Assessments (by central laboratory)	
Central pathology	Stained tumor tissue sections and corresponding pathological reports or unstained tumor tissue sections (or tissue block) must be collected at screening for central pathology review. Both fresh and archival biopsies are accepted and can be used by central pathology. Investigators may enroll subjects before obtaining the result of central pathology review
Efficacy Evaluation	
Radiology	● Baseline radiology assessment methods include contrast-enhanced CT [for head and neck region (that must include nasal cavity, palatum durum, anterior cranial fossa and nasopharynx), chest, abdomen, and pelvis; for patients allergic to CT contrast media, enhanced MRI will be used as an alternative] and systemic PET/CT ● Tumor assessment performed with the same machine and method in the same hospital within 28 days before the first dose can be used as the baseline tumor evaluation
Bone marrow aspiration and biopsy	Bone marrow aspiration and biopsy should be performed. Immunohistochemistry (IHC) analyses should be performed under a microscope no matter bone marrow involves or not (Suggest detecting CD56、TIA-1、CD3、GrB、perforin, and EBER hybridization in situ, etc.)
Sample Collection for Biomarkers	
Blood samples	Collect 2 mL of whole blood

Items	Note
Tumor tissue	Seven (7) unstained FFPE tumor tissue slides

6.1.2 Treatment Period

Subjects will receive CS1001 1200 mg IV infusion every 21 days (3 weeks ± 3 days). All visits will be conducted at the planned time points specified in the protocol.

The items to be completed during the treatment phase are listed in Table 4:

Table 4 Visit procedures in the treatment phase

Items	Note
Study Management Procedures	
Prior medications and concomitant medications	Concomitant medications are documented
Clinical Procedures and Assessments	
Adverse events	Adverse events are recorded
Height, weight, and vital signs	Vital signs only; within 3 days before dosing in each cycle starting from Cycle 2
Physical examination and ECOG performance status	Lymphoma-specific physical examination and ECOG performance status evaluation within 3 days before dosing in each cycle starting from Cycle 2
Laboratory Procedures/Assessments (at site)	
Hematology, serum chemistry, urinalysis	Within 3 days before dosing in each cycle starting from Cycle 2
Thyroid function tests	Within 3 days before dosing every other cycle starting from Cycle 3 (Cycles 3, 5, 7, and so on)
EBV DNA	Blood sample for EBV DNA test will be collected at each cycle starting from Cycle 2 and every other cycle after radiological CR
Laboratory Procedures/Assessments (by central laboratory)	
PK	● Blood samples will be collected within 60 minutes before dosing as pre-treatment samples at Cycles 1, 2, 3, 4, and 8, and within 30 minutes after completion of infusion at Cycles 1 and 4
ADA	● Pre-treatment blood samples are collected (within 60 minutes before dosing) at Cycle 1, 2, 3, 4 and every 4 cycles thereafter (e.g., Cycle 8, 12, 16, and so on)
Efficacy Evaluation	
Radiology	● Contrast-enhanced CT will be performed every 12 weeks after the first dose of investigational product. Examined sites include head

Items	Note
	and neck region (that must include nasal cavity, palatum durum, anterior cranial fossa, and nasopharynx), chest, abdomen, and pelvis. For patients allergic to CT contrast media, enhanced MRI will be used as an alternative. ● Systemic PET/CT examination will be performed at Week 12 and Week 24. Only enhanced CT will be used for follow-up after first radiological CR or Week 24, whichever comes first. For patients without any measurable lesion, follow-up with PET/CT will be performed until radiological confirmation of CR or progression if the patient hasn't reached CR in the first 24 weeks. ● Additional PET/CT will be performed if follow-up enhanced CT reveals residual lesion or suspected progression.
Bone marrow aspiration and biopsy	If bone marrow aspiration/biopsy was/were positive or overall bone marrow assessment was indeterminate at screening, bone marrow aspiration and biopsy should be performed when CR is achieved according to radiology. Immunohistochemistry (IHC) analyses should be performed under a microscope no matter bone marrow involves or not (Suggest detecting CD56、TIA-1、CD3、GrB、perforin, and EBER hybridization in situ, etc.)

6.1.2.1 End-of-Treatment Visit

The date of end-of-treatment (EOT) visit will be the decision making date for discontinuing the study treatment by investigators. EOT visit should be the EOT date + 7 days. The items to be completed at the EOT visit are listed in the table below:

Table 5 Procedures in the End-of-Treatment Visit

Items	Observation items
Study Management Procedures	
Prior medications and concomitant medications	Concomitant medications are documented
Clinical Procedures and Assessments	
Adverse events	Adverse events are recorded
Electrocardiogram (ECG)	ECG is performed
Height, weight, and vital signs	Height, weight, and vital signs are measured
Physical examination and ECOG performance status	Systemic physical examination and ECOG performance status evaluation is performed
Laboratory Procedures/Assessments (at site)	
Pregnancy test	Blood human chorionic gonadotrophin test is performed as a pregnancy test

Items	Observation items
Hematology, serum chemistry, urinalysis	Hematology, serum chemistry, and urinalysis tests are performed
Thyroid function tests	Thyroid function tests are performed
Laboratory Procedures/Assessments (by central laboratory)	
ADA	Blood sample for ADA test is collected
PK	Blood sample for PK test is collected

6.1.3 Follow-up Period

6.1.3.1 Safety Follow-up

Safety follow-up period refers to the 90 days after the last dose of the investigational treatment or the start of new anti-cancer treatment, whichever occurs earlier. The safety follow-up visit is at 30 days (± 3 days) after the last investigational treatment, which has the same items as the EOT visit (refer to Section 6.1.2.1). If the EOT visit occurs in the time window of safety follow-up visit, the same tests and examinations do not need to be repeated. It is recommended to complete all protocol required follow-up evaluations for the safety follow-up at 60± 3 days and 90± 3 days after the last dose, or AEs and concomitant medications can be collected through phone call. Concomitant medications are recorded until 90 days after the last dose or the start of new anti-cancer treatment, whichever occurs earlier.

6.1.3.2 Radiology Follow-up

Apart from subjects who discontinue treatment due to radiological disease progression, tumor assessment should be performed at pre-specified regular time points if possible until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first; follow up with subsequent anti-cancer treatment.

6.1.3.3 Survival Follow-up

Survival status and the following anti-cancer treatment will be assessed every 12 weeks by telephone after the last dose of investigational product.

6.1.4 Unplanned Visit

If an additional follow-up visit is needed, all procedures (including laboratory test results) taken by the investigator should be recorded in the source medical record and unplanned visit page in the eCRF.

6.2 SAFETY ASSESSMENTS

Vital signs, physical examinations, ECOG performance status, laboratory tests, frequency, and severity of AEs and SAEs will be evaluated for safety assessment.

AEs are coded according to PT and SOC in ICH MedDRA.

The safety of investigational products will be assessed according to CTCAE v4.03.

6.2.1 Vital signs

Vital signs include temperature, blood pressure, pulse, and respiratory rate. Additional vital sign monitoring will be performed at the discretion of the investigator according to standard practice or as clinically indicated.

6.2.2 Physical Examination and ECOG Performance Status

Physical examination includes height, weight, overall physical examination, and lymphoma-specific examination. Abnormal changes in the physical examination will be assessed by the investigator. Changes of clinical significance (CS) should be reported as AEs by the investigator.

6.2.3 Electrocardiogram (ECG)

An electrocardiograph will be used to record the 12-lead ECG. ECGs must be recorded after 5 minutes of rest in the supine position. ECG parameters including heart rate, PR interval, QRS interval, QT interval, QTc interval, QRS wave, and T wave evaluation, and investigator's evaluation on ECG should be recorded. Clinically significant ECG findings should be reported as AEs by the investigator.

6.2.4 Laboratory Tests

Blood and urine samples for laboratory tests will be collected as per this protocol.

Table 6 Laboratory tests

Tests	Items
Pregnancy test	Blood human chorionic gonadotrophin pregnancy test Urinary human chorionic gonadotrophin pregnancy test (as clinically indicated)
Hematology	Complete blood count (CBC) and hemoglobin
Serum chemistry	Blood urea/urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphate, glucose, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total cholesterol, total protein, and albumin
Urinalysis	Specific gravity, pH, glucose, protein, cast, ketones, and blood cells
Coagulation	PT, APTT, and INR
HBV, HCV, and HIV	Anti-HIV antibody, HBsAg, anti-HCV antibody, HBV DNA test (only for HBsAg positive subjects), HCV RNA test (only for anti-HCV antibody positive subjects)
Thyroid function	FT3, FT4, and TSH
EBV DNA	EBV DNA

For clinical laboratory test findings with unknown cause or unexpected results, if clinically significant judged by the investigator, the tests are recommended to be retaken in 24 hours and followed up until test results return to normal range and/or cause found. Clinically significant ECG findings should be reported as AEs by the investigator.

6.3 PATHOLOGICAL ASSESSMENTS

Stained tumor tissue sections and corresponding pathological reports or unstained tumor tissue sections (or tissue block) must be collected at screening for central pathology review. Both fresh and archival biopsies are accepted and can be used by central pathology.

Investigators may enroll subjects before obtaining the result of central pathology review. For subjects whose diagnosis is not ENKTL per central pathology laboratory's judgment, investigators in consultation with sponsor medical monitors will determine whether to continue or discontinue the subject from treatment. See *Central Pathology Manual* for detailed instructions.

In the screening and treatment periods, lesion biopsy may be performed at the discretion of the investigator for pathological examination to confirm radiological findings.

6.4 EFFICACY ASSESSMENTS

Efficacy evaluation will be performed by investigators and IRRC based on Lugano 2014 classification.

Contrast-enhanced CT will be performed at screening and every 12 weeks after the first dose of investigational product. Examined sites include head and neck region (that must include nasal cavity, palatum durum, anterior cranial fossa, and nasopharynx), chest, abdomen, and pelvis. For patients allergic to CT contrast media, enhanced MRI will be used as an alternative. Systemic PET/CT examination will be performed at screening, Week 12, and Week 24. Only enhanced CT will be used for follow-up after first radiological CR or Week 24, whichever comes first. For patients without any measurable lesion, follow-up with PET/CT will be performed until radiological confirmation of CR or progression if the patient hasn't reached CR in the first 24 weeks. Additional PET/CT will be performed if follow-up enhanced CT reveals residual lesion or suspected progression.

If contrast media for CT can be injected when PET/CT is performed and meet requirements for PET/CT and contrasted CT, additional enhanced CT can be skipped. See *Radiology Manual for Study Sites* for details.

Apart from subjects who discontinue treatment due to radiological disease progression, tumor assessment should be performed at pre-specified regular time points until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first.

Bone marrow aspiration and biopsy should be performed at screening. Subjects with positive bone marrow aspiration/biopsy result or indeterminate overall bone marrow assessment at screening will undergo bone marrow aspiration and biopsy when achieving CR/CMR based upon radiology. Immunohistochemistry (IHC) analyses should be performed under a microscope no matter bone marrow involves or not (Suggest detecting CD56、TIA-1、CD3、GrB、perforin, and EBER hybridization in situ, etc.).

6.5 PHARMACOKINETICS AND IMMUNOGENICITY

All subjects will receive pharmacokinetic and immunogenicity assessments Neutralizing antibody of CS1001 will be tested if the neutralizing antibody testing method is established.

Pharmacokinetics (PK): Blood samples will be collected within 60 minutes before infusion as pre-treatment samples at Cycle 1, 2, 3, 4, and 8, and within 30 minutes after infusion at Cycle 1 and 4 in the treatment phase. Blood samples for PK testing will be collected at the EOT visit, and safety follow-up visit at 30 days, and 90 days after the last dose of study treatment.

Immunogenicity: Pre-treatment blood samples are collected (within 60 minutes before dosing) at Cycle 1, 2, 3, 4, and every 4 cycles thereafter (e.g., Cycle 8, 12, 16, and so on). Blood samples for ADA testing will be collected at the EOT visit and safety follow-up visit at 30 days, and 90 days after the last dose of study treatment.

See Laboratory Manual for detailed instructions.

6.6 BIOMARKERS

The whole-exome sequencing of tumor tissue and immune repertoire test of peripheral monocytes will be performed if permitted by the Ethics Committee.

Whole exome sequencing of tumor tissue: seven (7) unstained FFPE tumor tissue slides should be collected at screening for whole-exome sequencing of tumor tissue; a total amount of 2 mL whole blood should be collected at screening as germline control of whole-exome sequencing.

If the tumor tissue and whole blood samples were not available at screening, retrospective collections of 7 archival FFPE tumor tissue slides and collection of 2 mL whole blood are allowed for whole-exome sequencing.

Subjects must provide tumor tissue and whole blood sample for biomarker analysis. However, if tumor tissue is not available or the subject is unwilling to participate in the biomarker study, the subject enrollment will be determined by the investigator in consultation with the sponsor's medical monitor.

7. REPORTING OF ADVERSE EVENTS

7.1 ADVERSE EVENTS

7.1.1 Definition of an Adverse Event

An AE is any untoward medical occurrence or any worsening of existing medical conditions after the subject signs the informed consent in a study, regardless of its relationship with the investigational treatment. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medication, whether or not related to the medication. An AE can also be a pre- or post-treatment complication resulting from protocol-specified procedure, overdose, drug abuse/misuse, or occupational exposure. Any occurrence with a worsening or changing nature in the study or resulting from participation is also considered as an AE. All AEs should be recorded on the Adverse Events page on the subject's eCRF. All AEs are graded according to CTCAE v4.03.

The following conditions are not considered as AEs:

- Pre-existing or detected disease, condition, or laboratory finding before the screening visit that doesn't get worse during the study;
- Occurrence without any untoward medical event (for example elective operation, hospitalization due to social reason or for personal convenience);
- Any clinically significant medical occurrence or laboratory finding occurs before the subject signing the informed consent and is unrelated to any protocol-defined procedure. This is considered as a preexisting occurrence and should be recorded in the Medical History page on eCRF.

7.1.2 Adverse Event Monitoring

In the whole study course, AEs will be closely monitored before and after medication administration and reported by the medical staff. Subjects receive a general physical examination, hematology, urinalysis, hepatic and renal function and chemistry tests, and 12-lead ECG before and after the trial treatment. Vital signs will be monitored at various time points before and after investigational product administration on the dosing day.

7.1.3 Recording of Adverse Events

All AEs (including clinical symptoms, signs, or conditions) will be recorded in the eCRF, regardless of their relationship with the investigational treatment.

Time Period for Collection of Adverse Events

Adverse events will be collected from the time of signature of informed consent, throughout the treatment period and including the safety follow-up period of 90 days after the last dose of investigational product or the start of new anti-cancer treatment, whichever occurs earlier. After the safety follow-up visit (30 ± 3 days after the last investigational treatment), AEs can be collected by telephone follow-up 60±3 days and 90±3 days after the last dose. SAEs during the safety follow-up period will also be reported to the sponsor within a prespecified time frame.

For subjects with treatment discontinuation for any reason but still in the trial:

- Ongoing AEs should be followed up with data collection in the survival follow-up period

- Investigational product-related SAEs will still be collected during the survival follow-up period and reported to the sponsor according to the standard time frame and process of SAE reporting

All deaths after disease progression and during the survival follow-up period will be collected and recorded in the eCRF.

Refer to Table **7** for details.

Table 7 Summary of Recording and Follow-up for Adverse Events and Deaths

	Treatment phase	Safety follow-up	Survival follow-up
Collection of all newly occurred AEs in eCRF	Yes	Yes	No
Collection of all ongoing AEs in eCRF	Yes	Yes	Yes
Collection of all drug-related SAEs in eCRF	Yes	Yes	Yes
Collection of all non-drug-related SAEs in eCRF	Yes	Yes	No

Any AE that is unresolved at the subject's last visit in the study will be followed up by the investigator, but without further recording in the eCRF. The sponsor retains the right to request additional information for any subject with ongoing AE(s) at the end of the study if judged necessary.

If an investigator learns of any SAE, including death, at any time after the subject has been discontinued from the study, and he/she considers there is a reasonable possibility that the event is related to the investigational product, the investigator should notify the sponsor.

Variables

The following variables will be collected for each AE:

- Diagnosis/description of AE
- The date when the AE started and stopped
- Change of CTCAE grade
- Whether the AE is serious or not
- Investigator causality attribution against the investigational product (yes or no)
- Investigator causality attribution against the investigational product
- Outcome

In addition, additional variables including intervention will be collected for SAEs.

It is important to distinguish between serious and severe AEs. Severity is to describe the intensity, while the definition of SAEs is listed in Section 7.2.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mile stroke but would be an SAE.

Events will be assessed and graded based upon the NCI CTCAE v4.03. For events of uncoded CTCAE grade, mild, moderate, and severe events will be converted to CTCAE level as recommended by the NCI CTCAE guideline. The latest version of CTCAE can be downloaded from the web of cancer treatment and evaluation plan (http://ctep.cancer.gov).

Causality Assessment

The investigator will assess the causal relationship between the investigational product and each event, and answer **'definitely related', 'possibly related', 'unlikely related', 'definitely unrelated' and 'not evaluable'** to the question 'Do you consider that there is a possibility that the event may have been caused by the investigational product?'

Refer to Section 7.3.1 for the causality assessment guideline.

Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by subjects or caregivers and AEs found through observation will be recorded in the eCRFs. The subject's symptoms and signs will be recorded in the Diagnosis record (if possible) during the collection of AEs. If the diagnosis is confirmed, however, with symptoms and signs that are unlikely to be caused by the diagnosis should be recorded separately.

Adverse Events Based on Laboratory Tests and Examinations

All results of the protocol mandatorily required laboratory tests, vital sign measurements, ECG and other safety assessments will be summarized in the Clinical Study Report (CSR). If a parameter is worsened than the baseline level and meets the SAE criteria, or it leads to subject withdrawal apart from disease progression (see Disease Progression), it will be reported as an AE.

Worsened laboratory test results, vital signs, ECG, or other safety assessments with accompanying clinical symptoms and signs should be reported as supplementary information while the signs or symptoms reported as an AE. Reporting investigators should use clinical terminology whenever possible instead of laboratory terminology (for example anemia instead of low hemoglobin level). Non-mandatory test result that worsens with no accompanying clinical sign or symptom should be reported as an AE.

Worsening of laboratory test which is unequivocally due to disease progression will not be reported as an AE.

A newly found abnormal clinical test finding during physical examination or test results worse than the baseline level will be reported as an AE.

Disease Progression

Disease progression can be considered as deterioration of the subject's condition attributable to the disease under study. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary tumor under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study. Refer to Section 7.5.2 for a detailed explanation.

New Cancers

The development of new cancer should be regarded as an AE, and under most circumstances, they meet at least one criterion of SAE. New primary cancers are those that are not the primary reason for the administration of the investigational product and have been identified

after the subject's inclusion in this study. Metastasis of the primary tumor is not considered new cancer.

Deaths

All deaths that occur during the study, or within the protocol-defined follow-up period after the administration of the last dose of the investigational product, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as an SAE.
- Where death is not clearly due to PD under study, the AE causing the death must be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. Every effort should be made to identify the cause of death. An autopsy may be helpful in the assessment of the cause of death, and if performed a copy of the autopsy results should be forwarded to the representative of the sponsor in an expedited way within the predetermined timeframe.

7.2 SERIOUS ADVERSE EVENTS

7.2.1 Definition of A Serious Adverse Event

According to the definition from ICH (International Council for Harmonisation), SAE is any adverse medical event that meets any of the following criteria:

- Results in death;
- Is life-threatening (Note: life-threatening in the context of an SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe);
- Requires in subject hospitalization or prolongation of existing hospitalization (except for hospitalization due to medical insurance reimbursement issue or hospitalization without approval by the study doctor);
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Other medically significant events.

These medically significant events that may not result in death, be life-threatening or require hospitalization may be considered serious when they jeopardize the participant and may require intervention to prevent one of the outcomes listed above. Medical and scientific judgment should be exercised in deciding whether the event should be reported in the light of expedited reporting rules. Examples of medically significant events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse. For the avoidance of doubt, infection resulting from drug deterioration is considered as a medically significant event and should be reported according to the expedited reporting rules.

The following hospitalizations that occur during the course of study should not be considered as SAEs:

- Admission into an emergency room, outpatient, or other departments for <24 hours and not hospitalized (unless is considered “medically significant event” or life-threatening event);
- Planned optional operation before ICF signing;
- Protocol-specified admission for medical/surgical treatment or monitoring;
- Admission for physical assessment;
- Admission for a Grade 1 AE, including overnight hospitalization due to non-medical reasons after investigational product administration;
- Hospitalization for changing living conditions, which doesn’t affect health conditions and doesn’t involve medical/surgical intervention (for example for homeless, financial difficulty, family reasons, or management need).

7.2.2 Serious Adverse Event Reporting

Any SAE occurring from the time of ICF signing to 90 days after the last dose of investigational product or the start of new anti-cancer therapy, whichever occurs earlier, must be reported to the designated representative of CRO or the sponsor **no later than 24 hours** when it gets learned of, regardless of causality with the investigational product. After the safety follow-up period, only treatment-related SAEs need to be recorded and reported.

Once an SAE occurs, the investigator should:

- Immediately take appropriate treatment measures for the subject and report to the sponsor as described above, and to drug regulatory authorities, health administrative authorities, and the Ethics Committee according to the local requirements.

  Complete the SAE module in the EDC system, after which an automated email will be sent to the designated sponsor representative. In case EDC is down, all applicable modules of the sponsor’s SAE form will be completed by the investigator/site staff. The investigator must assess the relationship of each SAE to each specific component of study treatment, complete and sign the SAE Report Form, and submit the completed form within 24 hours to the sponsor pharmacovigilance representative. Follow-up information is submitted in a new SAE report form and marked as the follow-up information of a previously reported SAE.

Any SAE that is unresolved at the end of study or subject withdrawal must be followed up until any of the following condition occurs:

- Event resolves; or
- Event stabilizes; or
- Event returns to baseline level (if baseline level available); or
- The event can be attributable to factors related with a medication other than the investigational product or unrelated with the investigator's behavior, or further information is unable to be obtained (when the subject or medical staff refuses to provide more information or when there’s evidence showing the subject is lost to follow-up despite every effort made).

7.3 ASSESSMENT OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or study doctor is responsible for the causality and severity assessments of AEs and SAEs, and the final review and confirmation of the accuracy of data and assessments.

Any non-clinically significant laboratory finding is not recorded as an AE or SAE. Clinically significant (documented as 'Abnormal finding with clinical significance') laboratory findings (for example clinical laboratory, hematology, or urinalysis) and any other abnormal assessment result (for example ECG and vital signs) must be recorded as an AE or SAE. Events in compliance with the definition of AE or SAE must be recorded as an AE or SAE. If the laboratory finding is a component of a syndrome, the syndrome or diagnosis (for example anemia) instead of the laboratory finding (decreased hemoglobin) should be recorded.

7.3.1 Causality Assessment

The investigator should determine the relationship between the AE and the investigational product based on the following criteria:

- **Definitely related:** there is a rational temporal relationship of the occurrence of an AE including clinical laboratory finding to the administration of the investigational product. The investigational product can explain the AE more than any other reason (for example the underlying disease, environmental or toxic factors, or other treatment received by the subject); the reaction after discontinuation of investigational treatment is clinically reasonable.
- **Possibly related:** there is a rational temporal relationship of the occurrence of an AE including clinical laboratory finding to the administration of the investigational product. The investigational product can explain the AE with equal rationality with any other reason (for example the underlying disease, environmental or toxic factors, or other treatment received by the subject); information on post-discontinuation reaction is unavailable or unclear.
- **Unlikely related:** other reasons (for example the underlying disease, environmental or toxic factors, or other treatment received by the subject) explain the AE (including laboratory findings) more than the investigational product
- **Definitely unrelated:** there is no rational temporal relationship of the occurrence of an AE to the administration of the investigational product. The AE has other more remarkable reasons (for example the underlying disease, environmental or toxic factors, or other treatment received by the subject).
- **Not determined:** the above information is not available and with no complementary data, making causality not determined.

Definitely related, possibly related, and not determined events are counted as related adverse events when statistical analyses for adverse events are performed.

7.3.2 Assessment of Severity

For any AE, whether it is fatal or life-threatening, whether it leads to persistent or permanent disability, requires or prolongs hospitalization, or causes congenital anomaly will be recorded and graded based upon CTCAE v4.03. For an AE that is related to abnormal laboratory test finding(s), the event will be graded according to the clinical severity of the underlying condition; the grade is not necessarily in line with the grade of laboratory test finding.

Intensity will be graded based upon the following rules:

Grade	Description

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
Grade 2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age appropriate instrumental activities of daily living*
Grade 3	Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self care activities of daily living**
Grade 4	Life-threatening consequences or urgent intervention indicated
Grade 5	Death related to adverse event

* Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, financial management, etc.

** Examples of self-care activities of daily living include bathing, dressing, and undressing, taking food, using the toilet, and taking medications, as performed by patients who are not bedridden.

7.4 HANDLING OF ADVERSE EVENTS

All clinical events and clinically significant laboratory AEs will be handled based upon the guideline in CTCAE v4.03.

The investigator will record AEs resulting from the treatment, remind the sponsor medical monitor to pay attention, and take appropriate actions in consultation with the sponsor's medical monitor. Subjects with AEs must be followed up regularly if possible, regardless of the AEs' relationship with the treatment, until resolution of the symptoms, all the abnormal laboratory values return to normal or baseline values or are confirmed irreversible, or the observed changes can be properly explained.

For Grade 3 or 4 laboratory test finding with clinical significance, the test should be repeated to confirm the finding, if possible. Every effort should be made to have the subject revisit the site within 3 days of obtaining the initial test result for repeating the test and taking appropriate actions.

7.5 REPORTING OF SPECIAL SITUATIONS

7.5.1 Definition of a Special Situation

Reporting of special situations includes reporting of a medication error, drug abuse, misuse, overdose, and pregnancy (regardless of its relationship with any AE). Reports of adverse infant reaction post breast milk exposure and Reports of adverse drug effects associated with product complaints or tip-offs due to occupational exposure are also included.

The Pregnancy Report is used to report any pregnancy after maternal or paternal exposure.

Medication error refers to any unintended error in the prescription, dispensing, or administration of medications made by healthcare providers, subjects, or consumers.

Drug abuse is defined as persistent or occasional intended overuse of medication by a subject.

Misuse is defined as intended, improper use of medication that is not in line with the protocol or prescribing information.

Medication overdose is defined as: occasional or intended use/injection of the investigational product in a dose exceeding the prescribed one. Overdose is defined as: the subject has taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol by 20%.

A product complaint is a complaint due to potential bias in the manufacturing, packaging, or distribution of medication.

7.5.2 Reporting of Special Situations

7.5.2.1 Reporting of Pregnancy

If any pregnancy occurs in a female subject in the course of the study, the investigational product should be discontinued immediately and report the pregnancy to the sponsor. Any pregnancy that occurs after the subject first agrees to participate (by signing the ICF) and during the clinical study (including post-treatment follow-up period and 6 months after the last dose) must be reported to the sponsor using the pregnancy report form by the investigational staff no later than 24 hours of when he/she becomes aware of it.

Pregnancy itself is not regarded as an AE. Induced abortion for pregnancy termination is unnecessary unless there's a medical reason. Early pregnancy termination (for example spontaneous abortion due to complication or other medical reasons, or therapeutic induced abortion) must be reported within 24 hours as an SAE. The medical reason during this course should be recorded as the AE term. Spontaneous abortion is always regarded and reported as an SAE. The subject will be appropriately monitored and taken care of until the end of pregnancy. However, subjective induced abortion for pregnancy termination without medical reason does not need to be reported as an SAE of pregnancy termination.

For male subjects, the pregnancy of their female partners must be reported as an SAE. Their partners will be monitored until the end of pregnancy. Refer to Section 4.1.5 for effective contraceptive measures.

7.5.2.2 Progression of Cancers

The progression of underlying malignancies will not be reported as an AE.

Hospitalization or death merely resulting from the progression of the underlying malignancies will not be reported as an SAE. If the symptom is not exclusively attributable to the underlying malignancy or the symptom is not an expected result of the progression of the investigational disease, the symptom will be reported as an AE.

Some subjects may experience deterioration of clinical symptoms. In this case, the subject's clinical symptom is a typical manifestation of PD but it's not supported by the change in tumor lesion size; or the disease progression is substantial enough that the investigator may consider it unnecessary to perform any further assessments of disease. And as such, clinical progression will be determined based upon the clinical symptom deterioration. Such cases are rare, and the investigator, therefore, should make every effort to record the objective progression of the underlying malignancy.

An AE that cannot be determined as exclusively resulting from the investigational product will be reported as an AE or SAE.

7.5.2.3 Reporting of Other Special Situations

All other special situations must be recorded by the investigator within 24 hours when he/she becomes aware of it. A special situation that constitutes an AE or SAE, will be reported as an AE or SAE. All reports must contain information regarding the involved investigational product, but not for the concomitant medications. Concomitant medications will not be reported unless it results in an AE. Any improper use of prohibited medication should not

be reported as ‘misuse’ but appropriately recorded as protocol deviation. All clinical sequelae related to these special situations should be reported as AEs using the AE report form. If a special situation results in an SAE, it should be reported using the SAE report form. The report will contain information regarding symptoms, signs, clinical intervention, and outcome.

Overdose

If an overdose occurs, symptomatic and supportive care should be given to the subject. If the dose of the investigational product exceeds that specified in the protocol and has an accompanying AE, the AE will be recorded using the Adverse Event Form. Any of the above situations leading to an SAE should be reported as an SAE.

7.6 LIVER FUNCTION TEST FINDINGS

If ALT or AST > 3 x ULN with elevation in total bilirubin (>2 x ULN), it will be considered as a marker of severe liver injury after ruling out Cholelithiasis or other clinical jaundices that may lead to bilirubin. Therefore, any of the following events must be reported as an AE by the investigator:

- During the course of treatment, ALT or AST > 3 x baseline level; or ALT or AST >2 x baseline level and total bilirubin > 2 x ULN (direct bilirubin 35%) in a subject with baseline transaminase elevation;
- ALT or AST > 3 x baseline level with clinical jaundice during the course of treatment.

The most appropriate diagnosis or clinical test finding (if diagnosis unestablished) will be recorded in the eCRF and reported to the sponsor within 24 hours when the investigator gets aware of it, whether it’s an SAE or not.

7.7 OTHER SAFETY CONSIDERATIONS

Any significant worsening of interim or final physical examination, ECG, or other safety assessments (no matter it's required by the protocol or not) must be recorded and reported.

8. STATISTICAL CONSIDERATIONS AND ANALYSIS PLANS

8.1 SAMPLE SIZE DETERMINATION

The primary efficacy endpoint is ORR assessed by IRRC according to Criteria for Response Assessment of Lymphoma: Lugano 2014 Classification.

8.2 SUMMARY OF CONDUCT OF STUDY

8.2.1 Analysis Sets

Efficacy analysis set (EAS) consists of all subjects who received at least one dose of investigational product and confirmed by central pathology.

Safety analysis set (SAS) consists of all subjects who received at least one dose of investigational product. The distribution of subjects, their demographics, other baseline characteristics, and the safety analyses will be based upon the SAS.

Pharmacokinetics analysis set (PKAS) consists of subjects who received at least one dose of investigational product and have available plasma drug concentration data.

Anti-drug antibody analysis set (ADAAS) consists of subjects who received at least one dose of investigational product and have available ADA data.

Biomarker analysis set (BAS) consists of subjects who received at least one dose of investigational product and have available biomarker data.

All analysis sets will be determined prior to database lock.

8.2.2 Demographics and Baseline

Patient demographics and baseline characteristics, for example, age, sex, baseline disease characteristics, ECOG PS, and prior anti-cancer treatment, will be summarized for the SAS. Baseline measurement refers to the last measurement obtained before the first dose of investigational product in a subject.

Continuous variables will be summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of patients in each category.

8.3 Efficacy Analyses

8.3.1 Primary Efficacy Endpoints

The primary efficacy endpoint, objective response evaluated by IRRC, refers to CR or PR determined by IRRC based upon Lugano 2014 classification. For subjects who fail to meet the above criteria or fail to receive any tumor assessment after baseline will be considered as non-responder.

ORR is the rate of objective responders. The population involved in the IRRC-ORR analysis are EAS subjects with evaluable or measurable lesion at baseline confirmed by IRRC.

The 95% confidence interval (CI) of ORR will be calculated using the exact binomial (Clopper-Pearson) method to evaluate the precision of the ORR estimate.

The statistical analysis will be performed by 24 weeks after the first dose of the last subject.

8.3.2 Secondary Efficacy Endpoints

Proportions of subjects who achieve CR, PR, SD, and PD per IRRC evaluation and their 95% CIs will be summarized. This analysis will be performed in EAS subjects with evaluable or measurable lesion at baseline judged by IRRC. Proportions of subjects with responses per investigator's evaluation and their 95% CIs will be summarized. This analysis will be performed in EAS subjects with evaluable or measurable lesion at baseline judged by investigators.

Duration of response (DoR) is defined as the time from the first documented CR or PR (whichever comes first) to the first documented disease progression or death, whichever comes first. DoR will be evaluated in subjects with objective responses per investigator's or IRRC's assessment, respectively. At analysis, subjects without event (disease progression or death) as of data cutoff will be censored at the date of "last tumor assessment". If no tumor assessment is performed after the first occurrence of CR or PR, DoR will be censored at the date when CR or PR first occurs. Kaplan-Meier method will be used to analyze DoR; the KM curve will be constructed.

Time to response (TTR) is defined as the time from the first study dose to the first documented CR or PR, whichever comes first. TTR will only be evaluated for subjects who achieve ORR. TTR will be summarized according to the investigator's and IRRC's assessments, respectively.

8.4 SAFETY ANALYSES

The safety analysis will be performed for the SAS population.

Descriptive statistics will be performed to summarize the exposure of the investigational product, which may contain number of cycles, administrations and dose levels, etc.

All adverse events will be described according to MedDRA and graded according to the NCI CTCAE v4.03. All adverse events that occurred during or after investigational product administration will be summarized by NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade 3, 4, or 5 events), drug-related AEs, and AEs causing discontinuation or dose modification of the investigational product will each be summarized. Multiple occurrences of the same event will be only counted once for the most severe event. The proportion of subjects with more than one adverse event will be reported.

All deaths that occur during the study or within the defined follow-up period after the last dose/discontinuation of investigational product will be reported.

Specific laboratory tests, vital signs, physical examinations, and 12-lead ECGs and their changes compared with baseline will be summarized. The values at baseline and each time point post-baseline will be presented by crosstabs, when appropriate.

8.5 PHARMACOKINETIC ANALYSES

Descriptive analysis will be performed for serum concentration of CS1001 in samples taken planned sampling time points. The data in this study will be pooled with that from other CS1001 trials to develop a population PK model. This model will be used to evaluate internal and external covariates and their influence on the PK of CS1001. Furthermore, the exposure-response analysis will be performed on specific efficacy and safety endpoints. Results of the above group PK and exposure-response analyses will be recorded in separate reports.

8.6 IMMUNOGENICITY ANALYSES

Immunogenicity evaluation results will be reported for the following parameters. Number and percentage of subjects who have positive ADA at baseline; number and percentage of subjects with at least one positive ADA test result in any time point following the first dose of the investigational product; number and percentage of subjects who develop treatment-induced ADA anytime after the first dose of the investigational product; number and percentage of subjects with treatment-enhanced ADA anytime after the first dose of investigational product. The treatment-induced ADA will also be analyzed by computing and reporting duration of an induced ADA response which will be classified as transient-positive ADA or persistent-positive ADA.

8.7 EXPLORATORY ANALYSES

Progression-free survival (PFS) and overall survival (OS) will be explored. PFS is defined as the time from the first study dose to the date of first documented disease progression or death, whichever comes first. The investigators and IRRC will assess the progression of disease based upon the Lugano 2014 classification. At the analysis, subjects without event (disease progression or death) will be censored at the date of "last tumor assessment". Subjects without tumor assessment after baseline will be censored at the date of the first dose. Six-month PFS rate refers to the proportion of subjects who are alive without any progression at 6 months after the first dose of investigational product. Six-month PFS rate will be calculated using the Kaplan-Meier method and the Greenwood formula was used to derive the variance regarding its 95% CI calculation.

OS is defined as the time from the first study dose to the date of death irrespective of its cause. Subjects without death reports as of data cutoff will be censored at the date of the last survival confirmation. Subjects without any data after baseline will be censored at the date of the first dose. The same analysis method is used for PFS.

Exploratory biomarker analysis will be performed to identify the relationship between tumor genetic aberrations and the efficacy of the investigational product. Subjects will be sub-grouped based upon their demographics (for example age, sex) and baseline characteristics (for example ECOG PS, prior treatment lines) for evaluating the consistency among all subgroups.

The consistency of ORR (yes or no) between IRRC evaluation and investigator's evaluation will also be assessed.

8.8 HANDLING OF MISSING DATA

Subjects without any assessment after baseline will be regarded as non-responders at ORR analysis.

Subjects without available data on the date of disease progression or death when calculating PFS will be censored at the date of the last tumor assessment. Subjects without any tumor assessment after the baseline will be censored at the date of the first dose.

Subjects without death report at OS analysis will be censored at the date of the last survival confirmation. For OS analysis, subjects without any data after baseline will be censored at the date of the first dose.

For DoR analysis, subjects without event (no disease progression or death) by database locking will be censored at the date of "last tumor assessment". If no tumor assessment is performed after the first occurrence of CR or PR, DoR will be censored at the date of the first occurrence of CR or PR first occurs.

9. ETHICAL CONSIDERATIONS

9.1 ETHICS COMMITTEE

Before initiating a trial, the clinical study protocol and informed consent form (ICF) are submitted to the Ethics Committee (EC) for review and approval. The Ethics Committee must be constituted in accordance with all applicable regulatory requirements and International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) guidelines.

The investigator will inform the EC of the progress of the trial in accordance with the requirements from the EC. All changes in the study activities and unanticipated questions involved in the subject's risks must be reported to the EC immediately. If the risk of participation in a study significantly outweighs the expected outcome, the investigators should inform the subjects and the EC about it. During the further review by the EC, the trial may be suspended unless this suspension jeopardizes the health of subjects. Investigators should also ensure all subjects should be informed about such risks.

The trial must not be changed before obtaining the approval from the EC unless it's necessary to eliminate immediate substantial harm to the human subjects.

9.2 ETHICS INSTRUCTIONS FOR THE STUDY

The study will be conducted in compliance with the ethical principles in the Declaration of Helsinki, the 18th World Medical Association (WMA) in Helsinki, Finland in June 1964, and the later amendments.

The conduct of this study will also comply with the Committee for Proprietary Medicinal Products (CPMP) guidance and ICH E6 GCP guidelines (CPMP/ICH/135/95).

As long as national laws are not violated, the ICH guidelines and other applicable international guidelines, recommendations, and requirements will be considered comprehensively to ensure the maximization of the subject's rights, safety, and health.

9.3 SUBJECT INFORMED CONSENT FORM

The investigator will give full and adequate oral and written information to each subject, their legal representative, or witness about the objectives, procedures, possible risk, and benefit of the study. Each subject must provide signed and dated informed consent before conducting any procedure specifically for the study. The ICF contains information about the purpose, procedures, possible risks and limitations of the trial, and specifically possible adverse effects of the investigational product and potential drug-drug interactions. Furthermore, the ICF also explains the range of insurance in the course of the study. Elements involved in the ICF are drawn up in accordance with ICH E6 GCP guidelines.

10. STUDY MANAGEMENT

10.1DATA MANAGEMENT

Data Management will be performed by the sponsor delegated CRO.

10.1.1 Completion and Submission of Case Report Forms

All eCRFs will be completed by the investigator or the designated personnel according to the original medical record. Changes to the data in eCRF will be recorded as audit tracking. The reason for changes, the name of the staff who makes the changes, and the time and date of changes will be recorded in the audit tracking log.

10.1.2 Data Entry and Modification

Before the initiation of a site or any data entry, the investigators and delegated site personnel will receive appropriate training and take proper safety measures.

The data entry in eCRF should be completed as soon as possible during or after each visit and kept updated to ensure the eCRF can reflect the latest status of the subject. Investigators should review data in the eCRF to verify they are authentic and accurate. Any assessment not conducted in the study or any information that is unavailable, inapplicable, or unknown should be recorded in the eCRF by the investigator.

The eCRF is only used as forms to collect data instead of the source documents unless otherwise specified. The source documents are subject-related documents used by the investigators or hospitals, which can prove the existence and eligibility of a subject. The source data include laboratory test results, ECG results, notes, dispensing log of the pharmacy and subject file, etc.

The investigator is responsible for maintaining all source documents and provide them to be reviewed by CRA at each visit. In addition, the investigator must submit the complete eCRF for all the subjects, regardless of their duration of study participation. All supportive documents (for example laboratory record or hospital record) submitted together with the eCRF must be verified carefully for the protocol number and subject number, and all personal information (including the subject's name) should be deleted or unidentifiable to protect the privacy of subjects.

eCRF records will be automatically appended with the identification of the creator, by means of their unique User ID. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate. The e-signing process will be done by entering the user ID and password. The system will automatically append the date and time of the signature. Investigators must not share user ID or password with others.

AEs and diseases will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-Drug).

To ensure the accuracy, completeness, and reliability of the data, the sponsor or the designated representative will take the following measures:

- Instructions for each site at the appropriate time.
- Initiation training for the investigators and coordinators (on the protocol, completion of eCRF, and study procedures).
- Routine site visits.

- Offer counseling service and maintain contact with the site staff by email, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computerized editing to check for errors in the data collection.
- Quality checks for the database.

Furthermore, the sponsor or the designated representatives may conduct periodic audits to subject data samples recorded by the site personnel with reference to the source documents. The sponsor or the authorized representatives and/or regulatory authority may perform audits at any time, which will be notified to the investigator beforehand.

To ensure the safety of participants and the accuracy, completeness, and reliability of the data, the laboratory test reports, clinical records, and subject's medical record will be kept in the subject's file as the source documents of this study by the investigator. The investigators allow the sponsor, regulatory authorities, and the Ethics Committees, if applicable, direct access to the source documents per request.

10.1.3 Data Review

The data management personnel will perform data, range, and logic reviews for all the ranges and interactions of each parameter in the eCRF. A computer program may be coded to conduct checks, identify the cause of errors, and correct them. The content of all errors and corrections will be filed for reference.

10.1.4 Archival

Important study documents will be archived in a secure way and ensured their accessibility when requested by a regulatory authority.

The archival of subject (hospital) files should comply with requirements of local regulations and be kept for the longest period allowed by the hospital and institutes. The investigator/institute must inform the sponsor of any changes to the archival arrangement (for example altered location or ownership).

The Investigator Site File (ISF) must not be destroyed without the sponsor's approval.

The investigator's contract will cover all applicable regulatory requirements related to the sites.

All trial data must be kept for at least 15 years after the study is completed.

1. Storage of trial records: the source documents will be kept in each site.
2. eCRF:
    a) eCRF will be completed in accordance with the GCP principles to ensure the accuracy of data.
    b) Delegated personnel will complete eCRF based upon the source record.
    c) Lastly, the PI will sign off the eCRF after review.

10.2INSPECTION PROCEDURES (QUALITY ASSURANCE)

The sponsor and investigators will fulfill their duties, strictly follow the study protocol, and adopt a standard operation procedure (SOP) to ensure quality control and quality assurance are performed for the study.

10.2.1 Routine Monitoring

The main responsibilities of a monitor are to supervise the process of the study and ensure that the study is conducted in compliance with the protocol and GCP principles, all records and reports are accurate and complete, and all the subjects sign ICF before entering the study. A monitor must report any occurrence inconsistent with the study protocol to the sponsor and responsible person for the project during the trial.

10.2.2 Audits and Inspections

A regulatory authority, an EC, and/or the sponsor may perform on-site audits or inspections at the site to ensure that the study process, completion of eCRF, and other reports are in compliance with the protocol, GCP, Declaration of Helsinki, and applicable regulatory requirements. The auditors/inspectors will conduct source data verification (SDV) to ensure the credibility of the data. Quality control will be performed at each stage of the study to ensure that the data are reliable and the whole study process is correct. The quality control will be performed in accordance with the Quality Management Manual of the sponsor. When an investigator receives notice of inspection from a regulatory authority, he/she should inform the sponsor immediately.

10.3STUDY MANAGEMENT AND MATERIALS

10.3.1 Data Collection

The participating doctors will record all major observations and findings in the subject's medical record, which include:

- Actual date of visits, and the scheduled date or visit.
- Notes on the general condition and subject's conditions, including major medical findings. The severity, frequency, duration of any reported AE, resolution to the AE, and investigator's assessment about the relationship between the reported AE and the investigational product.
- Changes to the concomitant medication or dosage.
- The signature or initials of the doctor.

In addition, any contact with the subject on the major clinical information through telephone or other measures should also be recorded in medical records (progress note) as stated above.

The data in the medical record (progress note) and other source documents will be transcribed into the appropriate sections in the eCRF in time.

Changes to the information in the medical record (progress note), eCRF, and other source documents will be signed and dated by the investigator or the designated personnel. If the cause of change is not clear, a short note should be made alongside the change.

10.3.2 Archival of Source Data and Records

The source documents include original observations and all activities of the clinical study. They include but are not limited to, medical records (progress notes), printouts, screening diaries, and data recorded by automated devices.

All source documents in this study will be maintained by the investigators, and authorized personnel is permitted access to these documents. The original, signed ICFs are stored together with the investigator's records, with a copy provided to the subject.

All data obtained from the study are the property of the CStone Pharmaceuticals (Shanghai) Co., Ltd., and CStone Pharmaceuticals (Suzhou) Co., Ltd.

The records will be stored in accordance with the latest version of ICH GCP guidelines. All necessary documents (including the subject records, source documents, eCRFs, and the investigational product dispensing and returning forms) must be kept.

All these necessary documents must be kept until 15 years after the approval of the investigational product. However, the relevant documents will be kept for a longer time if required by the regulatory authority or sponsor. The sponsor will inform the investigators of the duration requirements of document storage.

The investigator will not dispose of any document of this study without the written permission of the sponsor. The investigator will provide the sponsor with opportunities to collect relevant records. The investigator is responsible for ensuring the sufficiency and accuracy of the paper source documents for all reports of observations and data obtained during this trial. The sponsor, the designated representative, and regulatory authority may perform audits and inspections on these documents at any time.

If an investigator has position changes, withdraws from the study, or retires, the responsibility of maintaining records will be transferred to other study personnel with sub-responsibilities. This responsibility transfer must be notified and approved by the sponsor.

10.3.3 Confidentiality

Any subject's health-related data obtained during this trial will be confidential. A written agreement must be obtained before disclosing any data.

The investigators must ensure that subject's identity is not disclosed. The subject's name will not be used as an identifier in the eCRF and other documents submitted to the sponsor or the delegated CRO. In contrast, the enrollment No. of the subject will be used to ensure all of the study documents are confidential. This unique number will be used for the subject in the whole course of the study. The investigator will keep a separate log for each subject number.

To comply with the regulatory requirements and to ensure the safety of subjects, the sponsor, representative of the sponsor, CRO personnel, local study review committee, or regulatory authorities may inspect the subject's medical record due to its correlation with the study. The unique enrollment number of subjects on eCRF is the only means of subject identification. The full name of a subject, however, may be released to the drug administrative authority or other authorized government organizations or healthcare officers, if necessary, and designated personnel of the sponsor.

Documents (for example ICFs) not submitted to the sponsor or CRO will be held in strict confidentiality by the sponsor. But monitors from the sponsor or CRO and inspectors from a regulatory authority have the absolute privilege to review them. All documents in which a subject may be identified by his/her name must not leave the site, and the identity of subjects in all study-related publications will be kept confidential.

10.4APPLICATION PROCEDURES

10.4.1 Ethics Approval

According to national laws and regulations, CStone Pharmaceuticals (Shanghai) Co., Ltd., and CStone Pharmaceuticals (Suzhou) Co., Ltd., or the delegated agents will be responsible for obtaining approval of applicable regulatory authorities and the EC.

Any subject must not enter the trial before the approval of the regulatory authorities. A copy of the approval (if available according to local regulations) will be provided to the investigators and ECs.

10.4.2 Changes to the Protocol

According to ICH GCP E6 guidelines, an investigator must not deviate from or change the protocol before obtaining the written approval of the sponsor and EC, unless the protocol amendment is required to eliminate the immediate harm suffered by a subject, or it is a logistics or administrative change (for example altered monitor or telephone number).

Any change to the study protocol must be handled as a protocol amendment. Any potential revision must be approved by the sponsor. A written amendment must be submitted to the regulatory authorities and the responsible EC. The protocol amendment will not be executed before the approval of EC unless the change is required to eliminate the immediate harm suffered by a subject. In this case, the change must be communicated to the EC within 5 days of execution.

The regulatory authorities and ECs are to approve each protocol amendment except for the administrative change which is only to be communicated to but not approved by each regulatory authority or EC. Each approved amendment attached to the instructions on how to add it to the protocol will be distributed to all recipients of the original protocol.

If a protocol amendment changes the study design, procedures, and/or increases the subject's potential risks, judged by the local EC, investigators, and/or the sponsor, the current approved ICF will be revised. The regulatory authorities and ECs are to approve the revised ICF before the revised form is used. In this case, the enrolled subjects must resign a new ICF before further participating in the study.

10.4.3 Protocol Adherence and Deviations

Read through the whole study protocol and follow the instructions. A protocol deviation judged by the investigator or a reliable, well trained professional personnel (sub-investigator) designated by the investigator as a necessary immediate emergent intervention for the subject's protection, safety, and health considerations may be regarded as an exception.

However, the investigator or designated personnel must communicate any major protocol deviation due to an emergency, accident, or error to the medical monitor by telephone. And as such the decision regarding the subject's eligibility to further participate in the trial will be jointly determined and recorded by the investigator, sponsor, and medical monitor.

10.4.4 Publication of Study Results

Upon study completion, the study results may be co-submitted by the investigators and sponsor for publication. Investigators must commit that any data obtained under this protocol will not be submitted for publication without prior permission from CStone Pharmaceuticals (Shanghai) Co., Ltd., and CStone Pharmaceuticals (Suzhou) Co., Ltd.

10.4.5 Clinical Study Report

A final clinical study report (CSR) will be prepared in accordance with ICH E3. A final CSR will be prepared regardless of whether this study is completed or early terminated. The sponsor will provide a copy of the final CSR to all investigators for archival.

10.4.6 Insurance, Reimbursement, and Compensations

CStone Pharmaceuticals (Shanghai) Co., Ltd. and CStone Pharmaceuticals (Suzhou) Co., Ltd. will execute the policy regarding insurance for the study.

This is to prevent the situation when protocol deviation (especially unplanned dose, other methods of administration, other indications, or prolonged treatment period) is not covered by the subject's compulsory insurance.

10.4.7 Termination of Study

The sponsor may terminate the study when it's in the best interest of the subjects and due to medical or ethical considerations. The study may be terminated at any time upon agreement of investigators and the sponsor. CStone Pharmaceuticals (Shanghai) Co., Ltd., CStone Pharmaceuticals (Suzhou) Co., Ltd., the CROs, and investigators must ensure the full consideration about protecting subjects' rights at the study termination.

Reasons for study termination may include but are not limited to:

- Unanticipated, major or unacceptable risk occurred in enrolled subjects;
- The sponsor determines to suspend or stop the development of the investigational product.

10.4.8 Document Management at Sites

The investigator is responsible for securing the storage of site documents. The site documents may include, but are not limited to the following data:

1. Investigator's Brochure;
2. Current version of the approved protocol and every previous version of protocol;
3. Protocol amendments (if applicable);
4. Operation manuals (if applicable);
5. Current version of ICF (blank) and every previous version of ICF;
6. The curriculum vitae of the investigator and sub-investigators, a copy of their licenses (if required by law); the investigators must also complete all regulatory documents required by ICH GCP and local or national regulations;
7. EC approvals for the protocol, ICF, protocol amendments, and ICF revisions;
8. Key communications on the conduct of study among investigators, the ECs, and sponsor/CROs;
9. Laboratory accreditation certificates;
10. Monitoring log;
11. Record of investigational product management (including dispensing sheet, temperature record and accountability record, etc.);
12. Study staff delegation form.

11. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug Antibody
ADAAS	Anti-drug Antibody Analysis Set
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
auto-SCT	Autologous Stem Cell Transplantation
BAS	Biomarker Analysis Set
CDC	Complement Dependent Cytotoxicity
CMR	Complete Metabolic Response
CR	Complete Response/Remission
CRA	Clinical Research Assistant
CRO	Contract Research Organization
CRR	Complete Remission Rate
CS	Clinical Significance
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T Lymphocyte-Associated Antigen-4
DLT	Dose-Limiting Toxicity
DoR	Duration of Response
EBV	Epstein-Barr Virus
ECG	Electrocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
^{18}FDG/PET	^{18}F-Fluorodeoxyglucose/ Positron Emission Tomography
FFPE	Formalin-Fixed, Paraffin-Embedded
FT3	Free Triiodothyronine
FSH	Follicular Stimulating Hormone
FT4	Free Thyroxine
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
HSCT	Hematopoietic Stem Cell Transplantation
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
INR	International Normalized Ratio
irAE	Immune-related Adverse Event
IRRC	Independent Radiological Review Committee
IV	Intravenous
LDi	Longest Diameter
LY	Lymphocyte
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCS	No Clinically Significant

Abbreviation	Definition
NOAEL	No-Observed-Adverse-Effect-Level
NSAID	Nonsteroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly ADP-Ribose Polymerase
PCNSL	Primary Central Nervous System Lymphoma
PD-1	Programmed Death-1
PD-L1	Programmed Death Ligand 1
PET/CT	Positron Emission Tomography/Computed Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
PKAS	Pharmacokinetics Analysis Set
PR	Partial remission
PRR	Partial Remission Rate
PT	Prothrombin Time
PT	Preferred Term
RP2D	Recommended Phase II Dose
R/R ENKTL	Relapse or Refractory Extranodal Natural Killer / T cell lymphoma
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SD	Stable Disease
SDV	Source Data Verification
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid Stimulating Hormone

Abbreviation	Definition
TTR	Time to Response
ULN	Upper Limit of Normal
VEGFR	Vascular Endothelial Growth Factor Receptor
WOCBP	Women of Childbearing Potential

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13. APPENDICES

13.1 CRITERIA FOR RESPONSE ASSESSMENT OF LYMPHOMA: LUGANO 2014 CLASSIFICATION[1]

Response and Site	PET-CT-Based Response	CT-Based Response
CR	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
PR	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node ＞ 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by ＞ 50% in length beyond normal

New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
SD	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	＜ 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
PD	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: An individual node/lesion must be abnormal with: LDi ＞ 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions ＞ 2 cm In the setting of splenomegaly, the splenic length must increase by ＞ 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to ＞ 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline

		New or recurrent splenomegaly
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis (with an absolute increase of > 0.5 cm compared to the nadir value) A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measurable dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher
than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

[1]Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol 2014;32(27):3059-3068.

13.2 CRITERIA FOR ECOG PERFORMANCE STATUS ASSESSMENT

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

13.3 RESPONSIBILITY FOR MEDICATION MANAGEMENT

1. Each investigational product should have a label and package provided by CStone Pharmaceuticals (Shanghai) Co., Ltd. and CStone Pharmaceuticals (Suzhou) Co., Ltd. The sponsor will carry the qualification certificate, the inspection report of the investigational product and the investigational product to each site for handover procedure. The investigational product will be stored in a specific area;
2. A delegated personnel at the site will manage the investigational product, receive, dispense and return the medication by strictly following applicable SOPs and drug administrative requirements.
3. The investigational product is only for use in this trial, but not any other circumstance.
4. The transport, receiving, dispensing and return of the investigational product must be recorded by a delegated personnel. The use of investigational product will be carefully recorded in the Investigational Product Use Log, signed and dated by the operator.
5. The investigator must not destroy and package or label or the remaining unused medication without prior notification and permission of the sponsor.
6. When the trial ends, the investigational product will be destroyed at a third party designated by the sponsor. Study personnel should ensure, develop and record adequate process of investigational product handling in compliance with applicable regulations, guidelines and policies. The investigational product will be destroyed per sponsor’s approval.

13.4IMMUNE-RELATED ADVERSE REACTIONS MANAGEMENT GUIDANCE FOR INVESTIGATORS

Identification, diagnosis, management and dose modification for irAEs are detailed below:

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
Pneumonitis	Symptomatic: dyspnea, cough, pleuritic chest pain, hypoxia Asymptomatic: lung infiltrates that mimic severe bacterial pneumonia	• Radiographic imaging of chest • Tissue and lavage samples from bronchoscopy to rule out infectious pathogens and pathologic evaluation	Moderate (Grade 2): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1001 until resolved to ≤ Grade 1
			≥ Severe (Grade 3): high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics; in-subject hospitalization; consultation with a respiratory physician; additional immunosuppression with infliximab can be considered	Permanent discontinuation from the study treatment
Colitis	Watery diarrhea, mucus or blood in stool, abdominal pain, nausea/vomiting, dehydration, peritoneal signs, bowel perforation	• Stool cultures • Endoscopy or colonoscopy to rule out infection • Biopsy to rule out alternative etiology	≤ Grade 2 diarrhea: antidiarrheal medication, oral hydration, electrolyte supplement	Continue dosing
			Persistent Grade 2 diarrhea: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1001 until resolved to ≤ Grade 1

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
			≥ Severe (Grade 3) diarrhea: high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics; infliximab can be considered for steroid refractory diarrhea	Withhold CS1001 until resolved to ≤ Grade 1
			Recurrent severe (Grade 3) or life-threatening (Grade 4) diarrhea: high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics; infliximab can be considered for steroid refractory diarrhea; in-subject hospitalization	Permanent discontinuation from the study treatment
			If bowel perforation is suspected, steroid should be withheld and surgical opinion should be explored; in-subject hospitalization; Infliximab should not be administered	Permanent discontinuation from the study treatment
Hepatitis	Symptomatic: fever, fatigue, nausea, abdominal pain, jaundice, hepatomegaly Asymptomatic: elevation of liver function tests (hepatic transaminases, bilirubin)	• Chemistry: elevated levels of hepatic transaminases • Serologic testing: should be performed to rule out viral hepatitis (including hepatitis A and B), cytomegalovirus, and Epstein-Barr virus • Ultrasonograms of the liver • Biopsy or radiologic imaging to distinguish	• Moderate (Grade 2): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1001 until resolved to ≤ Grade 1

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
		from other etiologies of hepatic injury, such as neoplastic disease progression in the liver, infections, and effects of other medications or alcohol intake	• ≥ Severe (Grade 3): administration of high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone); if not improved after 48-72 hours, alternative immunosuppression agents (mycophenolate mofetil) should be considered; in-subject hospitalization; consultation with a hepatologist • Total serum bilirubin >3 times upper limit of normal	Permanent discontinuation from the study treatment
Hypophysitis	Headache refractory to nonsteroidal anti-inflammatory drugs or other analgesics; weakness; fatigue, weight gain or weight loss; changes in mood or behavior; hypotension; electrolyte disturbances; abdominal pain; loss of libido; adrenal crisis; hypogonadism	• Clinical chemistry tests • Endocrinologic laboratory test, ACTH, thyroid function test • Magnetic resonance imaging (MRI) of the brain: enlargement of the pituitary with variable contrast enhancement characteristics	Moderate (Grade 2) without adrenal crisis: high-dose corticosteroids (methylprednisolone 1 to 2 mg/kg/day or the equivalent); initiate appropriate hormone replacement therapy; consultation with an endocrinologist	Withhold CS1001 until resolved to ≤ Grade 1
			≥ Grade 3 or adrenal crisis: high-dose corticosteroids (methylprednisolone 1 to 2 mg/kg/day or the equivalent); consultation with an endocrinologist	Permanent discontinuation from the study treatment
Nephritis	Hematuria, peripheral edema, elevated serum creatinine	• Clinical chemistry tests • Urine test • Biopsy if necessary	Moderate (Grade 2): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1001 until resolved to ≤ Grade 1

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
			≥ Severe (Grade 3): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Permanent discontinuation from the study treatment
Hypothyroidism /hyperthyroidism	Typically asymptomatic and is identified by lab tests	Triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH) test results	Asymptomatic ≤ moderate (Grade 2) hypothyroidism: thyroxine replacement therapy	Continue dosing
			Asymptomatic ≤ moderate (Grade 2) hyperthyroidism: consider beta blockade	Continue dosing
			≥ Severe (Grade 3) hypothyroidism: replacement therapy	Withhold CS1001 until resolved to ≤ Grade 1 or baseline
			Severe (Grade 3) hyperthyroidism lasting ≥ 6 weeks despite active management: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1001 until resolved to ≤ Grade 1
			Life-threatening (Grade 4) hyperthyroidism	Permanent discontinuation from the study treatment
Dermatitis	Maculopapular rash or erythroderma, pruritus, skin ulceration, bullous dermatitis, Stevens-Johnson syndrome	• Unless an alternative etiology is identified, it should be considered immune-related • Pathologic evaluation of skin biopsy can be	≤ Moderate (Grade 2) (up to 30% of body surface area): topical corticosteroids and oral over-the-counter antihistamines and systemic corticosteroids if no improvement within 7 days	Continue dosing

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
		performed to rule out alternative etiology	Severe (Grade 3, > 30% of body surface area): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1001 until resolved to ≤ Grade 2
			Life-threatening (Grade 4, for example Stevens-Johnson syndrome, toxic epidermal necrosis, full-thickness dermal ulceration, necrosis or hemorrhage): high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone); in-subject hospitalization; consultation with a dermatologist	Permanent discontinuation from the study treatment
Neuromuscular toxicity	Peripheral sensory neuropathy, muscle weakness, Guilliain-Barre syndrome, transverse myelitis, myasthenia gravis	• Physical exam of sensory change, loss of deep-tendon reflexes • Neuroimaging, nerve conduction exam • Nerve/muscle biopsy	≤ Moderate (Grade 2): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1001 until resolved to ≤ Grade 1
			≥ Severe (Grade 3): high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone)	Permanent discontinuation from the study treatment

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
Ocular toxicity	Photosensitivity, pain or dryness of the eyes, blurred vision, uveitis, iritis, episcleritis	• Ophthalmic exam	≤ Moderate (Grade 2): topical steroids (1% prednisolone)	Withhold CS1001 until resolved to ≤ Grade 1; if not resolved ≤ Grade 1 within 14 days with topical steroids or initiation of systemic treatment, permanent discontinuation from the study treatment
			≥ Severe (Grade 3): high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone)	Permanent discontinuation from the study treatment
Other irAEs, such as arthritis, pancreatitis, hemolytic anemia, adrenal insufficiency, myasthenic syndrome, and rhabdomyolysis			Moderate (Grade 2)	Withhold CS1001 until resolved to ≤ Grade 1
			≥ Severe (Grade 3)	Permanent discontinuation from the study treatment

13.5PROTOCOL AMENDMENT

Major amendments in protocol Version 3.0

Section(s)	Title of section(s)	Amendment details	Amendment rationale
SYNOPSIS	Secondary endpoints	Move 6 month PFS and 6 month OS rate from secondary endpoints to exploratory endpoints, details refer to Protocol Amendment 3.0	In single-arm trials, time-to-event efficacy endpoints such as PFS and OS should be exploratory rather than secondary endpoints
	Secondary efficacy analyses		
	Exploratory endpoints		
	Exploratory efficacy analyses		
2．OBJECTIVES AND ENDPOINTS			
8.3.2	Secondary Efficacy Endpoints		
8.7	EXPLORATORY ANALYSES		
SYNOPSIS	Inclusion Criteria / Exclusion Criteria	Inclusion Criteria： “3. Subjects must have a histologically confirmed ENKTL at the study site。” is amended to “Subjects must have a histologically confirmed ENKTL at the study site. Both nasal and non-nasal ENKTL are allowed.” Add “ 6. Life expectancy ≥ 12 weeks.” “8. d) Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or creatinine clearance ≥ 40 mL/min (according to Cockcroft-Gault equation); e) Serum total bilirubin ≤ 1.5 × ULN;” is amended to“8. d) Creatinine clearance ≥ 40 mL/min (according to Cockcroft-Gault equation); e) Serum total bilirubin ≤	[redacted]
4.1/4.2	Inclusion Criteria / Exclusion Criteria		

		1.5 × ULN, unless considered to be due to Gilbert's disease, where it must be ≤3 × ULN;" Exclusion Criteria： “1.Aggressive natural killer-cell leukemia.” is amended to “1. Aggressive natural killer-cell leukemia or ENKTL patients who have any degree of leukemic involvement will be excluded.” “3. Primary central nervous system lymphoma (PCNSL) or secondary CNS involvement” is amended to “3. Current or historical primary central nervous system lymphoma (PCNSL) or secondary CNS involvement.” “10. A known other malignancy within the past 5 years. Subjects with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, breast cancer in situ, or cervical cancer in situ that have undergone curative therapy are permitted to enroll” is amended to “10. A known additional malignancy within 5 years piror to the first dose of investigational product. Subjects with locally curable malignancies (including basal cell carcinoma of skin, squamous cell carcinoma of skin, breast cancer in situ or cervical cancer in situ, etc.) that have undergone curative therapy are permitted to enroll” “23. Subjects with a known history of alcoholism or drug abuse.” is amended to “23. Subjects with active alcohol or drug dependence.” “25. Subjects with a history of psychiatric disease; subjects with incapacity or limited capacity” is amended to “25. Subjects with a history of	

		psychiatric disease; or subjects with incapacity or limited capacity.”	
SYNOPSIS	Primary efficacy analyses	“The statistical analysis will be performed by 24 weeks after the first dose of last subject. The median duration of follow-up of all responders since the time of first response is estimated to be around 23 months by that time, under an assumed enrollment rate of 1.5 subjects per month.” is amended to “The statistical analysis will be performed by 24 weeks after the first dose of last subject.”	Update statistical methods
8.3.1	Primary efficacy endpoints		
SYNOPSIS	Sample size	The primary efficacy endpoint is ORR assessed by IRRC according to Criteria for Response Assessment of Lymphoma: Lugano 2014 Classification. [redacted]	[redacted]
8.1	SAMPLE SIZE DETERMINATION		

		[redacted].	
SCHEDULE OF STUDY ACTIVITIES	Safety follow-up	"2. Safety follow-up：Adverse events (AEs) and concomitant medications can be collected by telephone follow-up at 60 days and 90 days after the last dose." is amended to"2. safety follow-up：It is recommended to complete all protocol required follow-up evaluations for the safety follow-up at 60 ± 3days and 90± 3 days after the last dose, or AEs and concomitant medications can be collected through phone call."	According to Protocol clarification letter dated 27 Jul 2020, clarify the safety follow-up
6.1.3.1	safety follow-up		
SCHEDULE OF STUDY ACTIVITIES	Central pathology	Add："Both fresh and archival biopsies are accepted and can be used by central pathology."	clarify the request of sample for central pathology
3.1.1	Screening		
6.1.1	Screening Central pathology		
6.3	PATHOLOGICAL ASSESSMENTS		
SCHEDULE OF STUDY ACTIVITIES	Bone marrow aspiration and biopsy	"21.Bone marrow aspiration and biopsy: Bone marrow aspiration and biopsy should be performed at screening for all subjects. Subjects with positive bone marrow aspiration/biopsy result at screening will undergo bone marrow aspiration and biopsy when achieving CR/CMR based upon radiology for confirmation." is amended to "21.Bone marrow aspiration and biopsy: Bone marrow aspiration and biopsy should be performed at screening for all subjects. Subjects with positive bone marrow aspiration/biopsy result or indeterminate overall bone marrow assessment at screening will undergo	Clarify that the bone marrow aspiration and biopsy should be performed when achieving CR/CMR, if the overall bone marrow assessment is indeterminate at screening
6.1.2	Treatment Period, Bone marrow aspiration and biopsy		
6.4	**EFFICACY ASSESSMENTS**		

		bone marrow aspiration and biopsy when achieving CR/CMR based upon radiology for confirmation."	
SCHEDULE OF STUDY ACTIVITIES	Blood sample/ tumor tissue for biomarker testing	"22.Blood sample for biomarker testing: A whole blood sample of 2 mL will be taken as genetic control in whole-exome sequencing for tumor tissue. View Central Laboratory Manual for details. Tumor tissue for biomarker testing: Seven (7) unstained tumor tissue sections are collected at screening for whole-exome sequencing of tumor tissue. View Central Laboratory Manual for details." is amended to "22.Blood sample for biomarker testing: A total amount of 2 mL whole blood sample will be collected as germline control in whole-exome sequencing for tumor tissue. The whole blood can be collected at screening or retrospectively after study entry. View Central Laboratory Manual for details. 23.Tumor tissue for biomarker testing: Seven (7) unstained Formalin-Fixed, Paraffin-Embedded (FFPE) tumor tissue slides should be collected at screening for whole-exome sequencing of tumor tissue. If no samples were collected at screening, a retrospective collection of 7 archival FFPE tumor tissue slides is allowed. View Central Laboratory Manual for details."	To clarity that the samples for biomarker testing can be retrospective collected in study period.
1.2.1.1	Pharmacodynamic Studies	Update the data of pharmacodynamic studies, details refer to Protocol Amendment 3.0	Data from pre-clinical pharmacodynamic studies were updated according to CS1001 IB v6.0.
1.2.2	Clinical Studies	Update the data of clinical studies, details refer to Protocol Amendment 3.0	Data from clinical studies were updated according to CS1001 IB v6.0.

3.1.1	Screening	"At the screening phase, tumor tissue (7 evaluable unstained sections) and 2 mL of whole blood as genetic control in whole exome sequencing for tumor tissue" is amended to: "Seven (7) unstained FPPE tumor slides should be collected at screening for whole-exome sequencing of tumor tissue. A total amount of 2 mL whole blood should be collected at screening as germline control of whole-exome sequencing. If the tumor tissue and whole blood samples were not available at screening, retrospective collections of 7 archival FFPE tumor tissue slides and collection of 2 mL whole blood are allowed for whole-exome sequencing"	To clarity that the samples for biomarker testing can be retrospective collected in study period.
3.1.5	Treatment Beyond End of Study	Add "These subjects must provide written ICF and be willing and able to continue to follow all study procedures for continuing treatment."	According to Protocol clarification letter dated 27 Jul 2020, clarify the treatment beyond end of study
[redacted]	[redacted]	[redacted]	[redacted]

		[redacted]”	
5.3.2	Criteria for Dose Modification of Investigational Product	Add“13.Any Grade 3 abnormal laboratory test result except for the following situations : – Grade 3 hematologic toxicity. – Study treatment will be delayed when Grade 2 hepatitis occurs. 14. Any AE, abnormal laboratory test result or intercurrent condition that in the investigator’s opinion requires postponing study treatment.”	Clarity the laboratory and other criteria for dose modification of investigational product
5.3.3	Criteria for Permanent Discontinuation of Investigational Treatment	Add “Grade 4 abnormal laboratory test result except for the following situations: –Grade 4 neutropenia lasting for ≤ 5 days –Grade 4 lymphocytopenia or leukopenia –Solitary Grade 4 electrolyte disorder/imbalance that can be corrected by electrolyte supplementation/adequate treatment in 72 hours without any clinical consequence.”	Clarity the laboratory and other criteria for permanent discontinuation of investigational product
6. 6	**Biomarkers**	“Whole exome sequencing of tumor tissue: seven (7) unstained tumor tissue sections are collected at screening for whole-exome sequencing of tumor tissue; 2 mL of whole blood collected as genetic control.” is amended to: “Whole exome sequencing of tumor tissue: seven (7) unstained FFPE tumor tissue slides should be collected at screening for whole-exome sequencing of tumor tissue; a total amount of 2 mL whole blood	To clarity that the samples for biomarker testing can be retrospective collected in study period.

		should be collected at screening as germline control of whole-exome sequencing. If the tumor tissue and whole blood samples were not available at screening, retrospective collections of 7 archival FFPE tumor tissue slides and collection of 2 mL whole blood are allowed for whole-exome sequencing."	
Throughout the document		Administrative changes: • Modifications to the heading and the texts • Abbreviation list update • Cross-reference update Typo and formatting update	To increase protocol clarity, consistency and readability

Major amendments in protocol Version 2.0

Section(s)	Title of section(s)	Amendment details	Amendment rationale
SYNOPSIS	Study design and methods	The flow-chart: "safety follow-up: 30 days after the last dose of study treatment" is amended to "safety follow-up:30, **60, 90** days after the last dose of study treatment，Safety follow-up period refers to the 90 days after the last dose of the investigational treatment or the start of new anti-cancer treatment, whichever occurs earlier."	To clarify the safety follow-up timeframe.
SYNOPSIS	Exclusion Criteria (number 13)		To clarify the criteria of Chinese

4.2		"13. Any use of traditional Chinese medicines or herbal preparations within 7 days prior to the first dose of investigational product." is amended to "13. Any use of traditional Chinese medicines or herbal preparations with anti-tumor indications within 7 days before the first dose of investigational product"	medicines or herbal preparations in prior treatment in exclusion criteria.
SYNOPSIS	[redacted]	[redacted]	[redacted]
SYNOPSIS	Statistical Methods	Update "Statistical Methods", detail refer to Protocol Amendment 2.0	Statistical methods were updated.
SCHEDULE OF STUDY ACTIVITIES	Safety follow-up (with footnote 2)	"safety follow-up: 30 days after the last dose of study treatment" is amended to "safety follow-up:30, **60, 90** days after the last dose of study treatment, Safety follow-up period refers to the 90 days after the last dose of the investigational treatment or the start of new anti-cancer treatment, whichever occurs earlier."	To clarify the safety follow-up timeframe.
SCHEDULE OF STUDY ACTIVITIES	Concomitant medications (with footnote 5)	"All concomitant medications received from 30 days prior to the screening will be recorded until safety follow up is completed" is amended to "All concomitant medications received from 30 days prior to the screening will be recorded until **90 days** after the last dose of study treatment or the start of new anti-cancer treatment, whichever occurs first"	According to Protocol clarification letter dated 17 Apr 2019, clarify the period for collection of concomitant medications.
SCHEDULE OF STUDY ACTIVITIES	PK (with footnote 18)	Add: "Blood samples for PK testing will be collected at the EOT visit, and safety follow-up visit at 30 days, and 90 days after the last dose of study treatment."	ADA sample should be always accompanying by PK sample simultaneously as reference of concentration data for justifying ADA result especially for negative result.
6.1.2.1	End-of-Treatment Visit		
6.5	Pharmacokinetics and immunogenicity		

SCHEDULE OF STUDY ACTIVITIES	ADA (with footnote 19)	"Blood samples for ADA testing will be collected at EOT visit and safety follow-up visit" is amended to "Blood samples for ADA testing will be collected at the EOT visit and safety follow-up visit at 30 days, and 90 days after the last dose of study treatment"	Add ADA follow-up visit to follow ADA until the serum titers revert to baseline
6.5	Pharmacokinetics and immunogenicity		
SCHEDULE OF STUDY ACTIVITIES	Hematology, serum chemistry and urinalysis	Delete "bicarbonate"	According to Protocol clarification letter dated 07 Dec 2018, delete the collection of bicarbonate value
6.1.1			
6.2.4			
SCHEDULE OF STUDY ACTIVITIES	Bone marrow aspiration and biopsy	"Bone marrow aspiration/biopsy should be performed at screening. Subjects with positive bone marrow aspiration/biopsy result at screening will undergo bone marrow aspiration/biopsy when achieving CR based upon radiology for confirmation. Flow cytometry or immunohistochemistry (IHC) analyses can be used per investigator's judgment if bone marrow involvement cannot be determined under microscope." is amended to "Bone marrow aspiration **and** biopsy should be performed at screening for all subjects. Subjects with positive bone marrow aspiration/biopsy result at screening will undergo bone marrow aspiration **and** biopsy when achieving CR/CMR based upon radiology for confirmation. Immunohistochemistry (IHC) analyses should be performed under microscope **no matter bone marrow involves or not (Suggest detecting CD56、TIA-1、CD3、GrB、perforin, and EBER hybridization in situ, etc.)**."	According to Protocol clarification letter dated 08 May 2018, clarify the requirements for bone marrow aspiration and biopsy
6.1.1			

1.1	DISEASE OVERVIEW	Update overview of indication, details refer to Protocol Amendment 2.0	Update the disease overview to provide more background information
1.2	MECHANISM OF ACTION	Update the information of approved anti-PD1/L1 antibody products, details refer to Protocol Amendment 2.0	Update the information about approved competitive products to provide more up-to-date information on the marketing status of these products
1.2.1.2	Pharmacokinetic Studies	Update the data of PK studies, details refer to Protocol Amendment 2.0	Data from pre-clinical PK studies were updated according to CS1001 IB v4.0.
1.2.1.3	Safety Studies	Update the data of safety studies, details refer to Protocol Amendment 2.0	Data from pre-clinical safety studies were updated according to CS1001 IB v4.0.
1.2.2	Clinical Studies	Update the data of clinical studies, details refer to Protocol Amendment 2.0	Data from clinical studies were updated according to CS1001 IB v4.0.
3.1.3	Safety follow-up	"A safety follow-up visit should be conducted 30 days after the last dose of the investigational product." is amended to "A safety follow-up visit should be conducted 30, **60, 90** days after the last dose of the investigational product. Safety follow-up period refers to the 90 days after the last dose of the investigational treatment or the start of new anti-cancer treatment, whichever occurs earlier."	To clarify the safety follow-up timeframe.
3.2.3	Rationale for Setting ORR as the Primary Endpoint	Update the rationale of ORR as primary endpoint	Update the references to support the selection of ORR as the primary endpoint
4.5	Definition of Effective Contraception	Add "If total abstinence was used as highly effective method, other methods were no needed."	According to Protocol clarification letter dated 17 Apr 2019, clarify the definition of effective contraception
5.4.2	Permitted Therapy	"Adrenal replacement with >10 mg corticosteroid per day or equivalent is permitted." is amended to	To correct a typo error.

		"Adrenal replacement with ≤10 mg corticosteroid per day or equivalent is permitted."	
6.1.2 6.4	Treatment Period EFFICACY ASSESSMENTS	"Bone marrow aspiration/biopsy should be performed at screening and when CR is achieved according to radiology. Flow cytometry or immunohistochemistry can be used per investigator's judgment if bone marrow involvement cannot be determined under microscope." is amended to "Bone marrow aspiration **and** biopsy should be performed. Immunohistochemistry (IHC) analyses should be performed under microscope **no matter bone marrow involves or not (Suggest detecting CD56、TIA-1、CD3、GrB、perforin, and EBER hybridization in situ, etc.)**"	According to Protocol clarification letter 08 May 2018, clarify the requirements for bone marrow aspiration and biopsy
6.1.3.1 7.1.3	Safety Follow-up Recording of Adverse Events	"Safety follow-up period refers to the 90 days after the last dose of the investigational treatment" is amended to "Safety follow-up period refers to the 90 days after the last dose of the investigational treatment or the start of new anti-cancer treatment, whichever occurs earlier." Add "Concomitant medications are recorded until 90 days after the last dose or the start of new anti-cancer treatment, whichever occurs first."	According to Protocol clarification letter dated 17 Apr 2019, clarify the collection period of concomitant medications and clarify the safety follow up period.
7.2.1	Definition of A Serious Adverse Event	"A SAE is defined as any adverse event that occurs from the time when subject signs the ICF to the time of end of post-treatment follow-up or PD (whichever occurs last), which meets any one of the following criteria:" is amended to "According to the definition from ICH (International Council for Harmonisation), SAE is any adverse medical event that meets any of the following criteria:"	According to the requirement of ICH guideline, update the definition of SAE
7.2.2	Serious Adverse Event Reporting	Update "Serious adverse event reporting"	According to Protocol clarification letter dated 17 Apr 2019, clarify the

			requirement of SAE reporting and update the information of pharmacovigilance
7.5.2.1	Reporting of Pregnancy	Add “However, subjective induced abortion for pregnancy termination without medical reason does not need to be reported as a SAE of pregnancy termination.”	Clarify the criterion for reporting of pregnancy
8.1, 8.3 and 8.9	Sample Size Determination (8.1); Efficacy Analyses (8.3); and Interim Analysis (8.9)	Update statistical considerations and analysis plans, details refer to Protocol Amendment 2.0	Update sample size determination and efficacy analyses sections. Remove Section 8.9 as no interim analysis will be performed.
8.6	Immunogenicity Anslysis	Add “The treatment-induced ADA will also be analyzed by computing and reporting duration of an induced ADA response which will be classified as transient-positive ADA or persistent-positive ADA.”	Clarify the analysis of transient-positive ADA or persistent-positive ADA
9.1	ETHICS COMMITTEE	“The EC is constituted in accordance with China Food and Drug Administration (CFDA) recommendations and ….” Is amended to “The Ethics Committee must be constituted in accordance with all applicable regulatory requirements and ….”	The constituent of EC need to meet the request of all applicable regulatory requirements
Throughout the document		Administrative changes: • Modifications to the heading and the texts • Abbreviation list update • Cross-reference update • Typo and formatting update	To increase protocol clarity, consistency and readability

Major amendments in protocol Version 1.1

Section	Title of section	Amendment details	Cause of amendment
1.2.2	Clinical Studies	“Up to now, no dose-limiting toxicity was observed in the dose-limiting toxicity study in a total of 6 subjects from 3 mg/kg and 10 mg/kg dose groups. The study showed overall good safety and tolerability” is amended to “To date (up to 13 February, 2018), no dose-limiting toxicity or treatment related serious adverse event was observed in the dose-limiting toxicity study in a total of 14 subjects from 4 groups including 3 mg/kg, 10 mg/kg, 20 mg/kg and 1200 mg fixed dose group. The study showed good overall safety and tolerability."	Data from phase I trial was updated.
3.1	Overall Design	“At the screening phase, tumor tissue (7 evaluable unstained sections) and 9 mL of peripheral blood will be collected for biomarker investigation.” is amended to “At the screening phase, tumor tissue (7 evaluable unstained sections) and 2 mL of whole blood as genetic control in whole exome sequencing for tumor tissue.”	The immune repertoire assay of peripheral monocytes is not required, and therefore there’s no need for taking peripheral blood sample of 7 mL.
3.1.2.1	Treatment Beyond Disease Progression	The following paragraphs are added: "In special situations, a subject with disease progression confirmed by radiology or other clinical examinations who will possibly benefit from further investigational treatment may continue the treatment at the judge of investigator in consultation with the sponsor. A written consent from the subject must be obtained before any treatment beyond progression (including suspected pseudoprogression and confirmed disease progression)."	According to feedback from investigators and clinical study results of drugs of a similar target, in special cases, a patient may continue to benefit from the investigational treatment despite disease progression confirmed by radiology or other clinical examinations. In the protocol, a written consent is required for a subject to receive treatment beyond definite disease progression.
4.1.1	Inclusion Criteria	“With disease progression as the best response to the last line of therapy, or progression following response or stable disease achieved after the last line of therapy” is amended to “relapse: disease progression after response to the last treatment; refractory: no response to the last treatment”.	According to input from clinicians and designs of similar studies, patients who are non-responders to the last treatment may be enrolled in the clinical trial.

7.1.3	Recording of Adverse Events	"…the safety follow-up period of 30 days after the last dose of investigational product" is amended to "...the safety follow-up period of 90 days after the last dose of investigational product. AEs that occur after the safety follow-up visit can be recorded by telephone follow-up 60 days and 90 days after the last dose."	Adverse effects of an anti-PD-L1 or anti-PD-1 drug are primarily immune related events that last longer period of time. Prolonged period for AE collection will improve the safety management for subjects. Method of AE collection after the safety follow-up visit is defined.
7.2.2	Serious Adverse Events Reporting	"Any SAE occurring from the time of ICF signing to 30 days after the last dose of investigational product…" is amended to "Any SAE occurring from the time of ICF signing to 90 days after the last dose of investigational product..."	To correct a clerical mistake. "90 days" is in line with note 6 of Schedule of Study Activities.
6.4	Efficacy Assessment	"Bone marrow aspiration/biopsy should be performed when CR is achieved according to radiology" is amended to "Bone marrow aspiration/biopsy should be performed at screening. Subjects with positive bone marrow aspiration/biopsy result at screening will undergo bone marrow aspiration/biopsy when achieving CR based upon radiology."	According to Lugano classification, only subjects with positive baseline bone marrow need to have bone marrow test when CR is achieved according to radiology evaluation.
6.4	Efficacy Assessment	The sentence "PET/CT should be performed first followed by enhanced CT at screening, week 12 and week 24" is deleted.	The "PET/CT first and then enhanced CT" rule only applies to the situation where PET/CT and enhanced CT are performed on the same day. According to feedback from clinicians, PET/CT and enhanced CT are performed on separate dates in most cases. Therefore this requirement is deleted from the protocol, while a new requirement stating that "if PET/CT and enhanced CT are to be performed on the same day, PET/CT should be performed first followed by enhanced CT" is added in the Radiology Manual provided to the sites.
13.1	Criteria for Response Assessment of Lymphoma: Lugano 2014 Classification	In the "PD-New lesions" part, "A new node > 1.5 cm in any axis" is amended to "A new node > 1.5 cm in any axis (with an absolute increase of > 0.5 cm compared to the nadir value)"	The radiology evaluation criteria is refined after agreement is achieved with the central radiologists.