德琪医药科技
ANTENGENE CORPORATION

Clinical Trial Protocol

Product Name:	ATG-010 (Selinexor)
Study Protocol No:	ATG-010-MM-001
Protocol Title:	An Open-Label, Single-Arm Clinical Study of ATG-010 Plus Low-Dose Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma Previously Treated with Immunomodulatory Agent and Proteasome Inhibitor
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Sponsor Name/Address:	Zhejiang Antengene Pharmaceuticals Co., Ltd. Room 315, Building 4, Life Science Industrial Park, 398 Mahuan Road, Lihai Town, Binhai New City, Shaoxing, Zhejiang Province, P.R. China

Confidentiality Information

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Protocol Synopsis

Study Title:
An Open-Label, Single-Arm Clinical Study of ATG-010 Plus Low-Dose Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma Previously Treated with Immunomodulatory Agent and Proteasome Inhibitor

Indication

Relapsed/Refractory Multiple Myeloma Previously Treated with Immunomodulatory Agent and Proteasome Inhibitor

Objectives:

Primary Objective:
To evaluate the overall response rate (ORR) for treatment with ATG-010 plus low-dose dexamethasone in patients with relapsed/refractory multiple myeloma previously treated with immunomodulatory agent and proteasome inhibitor

Secondary Objectives:
To evaluate the following endpoints of ATG-010 in the study:

a. Efficacy
- Survival rate (SR) at 6 months, 9 months, and 12 months
- Time to Progression (TTP)
- Progression Free Survival (PFS)
- Duration of response (DOR)
- Clinical Benefit Rate (CBR)
- Disease Control Rate (DCR)
- Overall Survival (OS)
- Minimal Residual Disease (MRD)
- The effect of risk factor stratification on clinical efficacy

b. Safety and tolerability
c. Pharmacokinetics (PK) parameters

Background and Study Design Rationale

Background

Multiple myeloma (MM) is the second most common hematological malignancy (after non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. According to the literature, the reported annual incidence of MM in the United States (US) and the European Union (EU) is 4.5-7/100,000. Although MM is currently not a common hematological malignancy in Asia, the incidence is rapidly increasing. In China, according to the previous epidemiology study results, the incidence of MM was 0.6/100,000 in 2005. The mortality rate of MM in China was 0.6/100,000 in 2013. In addition, another large-scale retrospective study of MM patient in China indicated that Chinese patients were often at an advanced stage with more serious renal dysfunctions and bone destructions at the time of diagnosis compared to patients in Western countries.
In the past 20 years, new therapies, such as proteasome inhibitors (PI) and immunomodulatory agents (IMiD), have significantly improved the survival rate of MM patients. Despite the increased effectiveness of variety agents in clinical practice, nearly all MM patients will eventually become

refractory to the treatment or relapse with their diseases; and their disease characteristics obviouslypresent as drug resistance and disease progression. Therefore, there is an unmet medical need for therapies in patients with relapsed and/or refractory (RR) MM.

Study design rationale

ATG-010 (Selinexor) is an orally bioavailable, selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). In preclinical studies, ATG-010 and other SINE compounds have demonstrated anti-MM activity. The completed Phase 1 clinical study, single agent ATG-010 showed an overall response rate (ORR) of 5%, while the ORR was 32% in combination with low-dose dexamethasone. In a Phase 2b clinical study (Part 1 of STORM study), the clinical efficacy and safety of ATG-010 80 mg plus dexamethasone 20 mg orally twice weekly were evaluated in patients with RRMM. The target population had either quad-relapsed/refractory MM (patients who have received bortezomib, carfilzomib, lenalidomide, and pomalidomide before enrollment) or penta-relapsed/refractory MM (patients who have received bortezomib, carfilzomib, lenalidomide, pomalidomide, and anti-CD38 monoclonal antibodies before enrollment were refractory to treatment and relapsed before enrollment). The primary endpoint for this study was ORR to validate the efficacy of the ATG-010 in these patients with polylines of relapsed/refractory disease. The preliminary results for this Phase 2b study indicated an ORR of 25.4% in the target population. Relevant results show that the efficacy of ATG-010 combined with low-dose dexamethasone is encouraging in patients with RRMM who had previously received polyline therapies and had limited treatment options.
Based on the promising efficacy data observed from the STORM study in Western population of RRMM, the current study is planned to extend ATG-010 combined with low-dose dexamethasone to the treatment of RRMM patients in China, in order to validate the clinical efficacy and safety of ATG-010 in Chinese RRMM patients.

Study Design

This is a single-arm and open-label study. Approximately 82 patients will be enrolled in the study. The treatment regimen is ATG-010 80 mg plus dexamethasone 20 mg by oral, twice per week, 4 weeks per cycle. Clinical efficacy, safety and tolerability of ATG-010 will be evaluated. Blood samples from the 15 patients of enrolled will be collected for additional PK analysis.

Study Population

Inclusion Criteria:

Patients must meet all of the following inclusion criteria to be eligible to enroll in this study:

1. Aware and sign the informed consent form (ICF) voluntarily.
2. Age ≥ 18 years.
3. Patients with multiple myeloma must have previously received regimens with immunomodulatory agent (lenalidomide) and proteasome inhibitor (bortezomib), are refractory to both drugs, and are refractory or intolerant to the most recent line of therapy (Patients documented as intolerant are allowed to be screened only after discussing and obtaining an approval from Sponsor Medical Monitor). Refractory MM includes primary refractory (patients do not achieve minimal response (MR) or have disease progression during therapy) or secondary refractory patients have progression within 60 days after completion of therapy).

4. Any non-hematological toxicities (except for peripheral neuropathy as described in exclusion criterion #17) that are relevant to previous therapies must have resolved to ≤ Grade 2 prior to the first dose of study drug.
5. Adequate hepatic function: total bilirubin <2× upper limit of normal (ULN) (for patients with Gilbert's syndrome, a total bilirubin of <3× ULN is required), AST <2.5× ULN, and ALT <2.5× ULN.
6. Adequate renal function: estimated creatinine clearance ≥20 mL/min (calculated using the formula of Cockroft-Gault).
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2.
8. Measurable MM as defined by at least one of the following:
   a. Serum M-protein (by serum protein electrophoresis, SPEP) ≥5 g/L,
   b. 24 hours-Urinary M-protein excretion ≥0.2 g (200 mg),
   c. Serum free light chain (FLC) ≥100 mg/L with abnormal FLC ratio.
9. Adequate hematopoietic function (no platelet transfusions within 1 week, and no red blood cell transfusions within 2 weeks prior to screening examination):
   a. Hemoglobin level ≥80 g/L
   b. ANC ≥1000/mm^3 (1.0×10^9/L)
   c. Percentage of plasma cells in bone marrow <50%, platelet count ≥75,000/mm^3 (75×10^9/L); or percentage of plasma cells in bone marrow ≥50%, platelet count ≥50,000/mm^3 (50×10^9/L).
10. Female patients of childbearing potential must meet below two criteria:
    a. Female patients of childbearing potential must agree to use 2 methods of contraception acceptable by the study physician or complete sexual abstinence throughout the study, and for 3 months following the last dose of study treatment.
       i. Sexual abstinence: this method is acceptable when it is consistent with the patient's preference and daily lifestyle. Periodic abstinence (based on calendar, ovulation, symotmatic body temperature, or post-ovulation methods) is not acceptable.
       ii. Acceptable contraception methods include: oral contraceptives, injectable contraceptives, or implanted sex hormonal contraceptives, intrauterine contraceptive device, barrier contraceptivse with spermicide; or a sexual partner who is status post of a sterilization surgery and using at least one barrier contraceptive tool.
    b. Must have a negative serum pregnancy test at screening.
       Note: Female patients of childbearing potential refer to all women who have started menarche and are not in the postmenopausal period and have not had surgical sterilization (for example hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). Postmenopausal is defined as more than 12 consecutive months of amenorrhea for unspecified reasons. Women who are taking oral contraceptives or using mechanical contraceptive method such as intrauterine device are considered childbearing potential.
11. Male patients (including those who have received vasectomy) must agree to use a condom if sexually active with a female of child-bearing potential from the date of signing the informed consent form (ICF), throughout the study, and for 3 months without pregnancy plan following the last dose of study treatment.

Exclusion Criteria:

Patients who meet any of the following criteria will not be enrolled:

1. Asymptomatic (smoldering) MM.
2. Plasma cell leukemia.
3. Documented complicated with amyloidosis.
4. Central nervous system (CNS) involved MM.
5. Pregnancy or breastfeeding.
6. Prior to the first dose of study drug:
   a. Chemotherapy within 1 week (including steroid therapy in chemotherapy regimen);
   b. Radiation, immunotherapy or other anti-MM therapy within 4 weeks;
   c. Radio-immunotherapy within 6 weeks.
7. Graft versus host disease (after allogeneic stem cell transplantation).
8. Life expectancy of < 4 months.
9. Major surgery within 4 weeks prior to the first dose of study drug.
10. Patients with active, unstable cardiovascular diseases, meet any of the following:
    a. Symptomatic ischemia;
    b. Uncontrolled clinically-significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with first-degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) are allowed);
    c. Congestive heart failure (CHF) of New York Heart Association (NYHA) ≥ Grade 3;
    d. Acute myocardial infarction (AMI) within 3 months prior to the first dose of study drug.
11. Uncontrolled hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg).
12. Uncontrolled active infection requiring treatment within 1 week prior to the first dose of study drug.
13. Known HIV seropositive.
14. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen).
    Note: including HBsAg negative but hepatitis B cored (HBc) antibody positive with detectable hepatitis B virus deoxyribonucleic acid (HBV-DNA) level (the upper limit of normal for HBV-DNA testing is based on the test value of each center).
15. Prior malignancy that required treatment or has shown evidence of recurrence (except for skin basal-cell carcinoma and the following in-situ carcinoma: squamous cell carcinoma, bladder cancer in situ, endometrial cancer in situ, cervical cancer in situ/atypical hyperplasia, accidental histological finding of prostate cancer (TNM staging is T1a or T1b), or breast cancer in situ) within 5 years prior to the first dose of study drug.
16. Active GI dysfunction interfering with the ability to swallow tablets, or any GI dysfunction that could interfere with absorption of study treatment.
17. Grade ≥3 peripheral neuropathy, and Grade ≥2 painful neuropathy, within 3 weeks prior to the first dose of study drug.
18. Active psychiatric disorder, or organic disease which, in the opinion of the Investigator, is not suitable for the study.
19. Participation in another investigational anti-cancer clinical trial within 3 weeks or within 5

half-life ($T_{1/2}$) time periods prior to the first dose of study drug.

20. Receipt any following treatments prior to the first dose of study drug:
    a. Platelet infusion within 1 week;
    b. RBC transfusion within 2 weeks;
    c. Receipt of the following blood growth factors within 2 weeks: Granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), erythropoietin (EPO), megakaryocyte growth factor, and/or platelet stimulating factor.
21. Known intolerance to or contraindication for glucocorticoid therapy.
22. Prior exposure to a SINE compound, including ATG-010.

Study Duration

The enrollment period for this study is expected to be approximately 6 months. The study will end when all patients have completed 12 months of treatment visit/follow-up from the initiation of the study drug, or when the last patient has expired, has been lost to follow-up, or has withdrawn consent, whichever occurs first. After the completion of this study, the Sponsor will continue providing ATG-010 to patients with clinical benefits (per Investigators' judgment) as needed, and continue collecting actively reported safety data.

Study Drug, Dose and Administration:

ATG-010 will be given by oral administration at a fixed dose of 80 mg in combination with dexamethasone (20 mg) twice weekly for 4-week cycles. Try to take the medicine twice a week at a fixed time with dose interval of 48 hours (e.g., Monday and Wednesday or Tuesday and Thursday, etc). Dexamethasone 20 mg will be given with each dose of ATG-010. If some patients cannot tolerate dexamethasone 20 mg orally, the Investigator may decide to adjust the dexamethasone to a minimum of 10 mg for each dose in these patients. If patients still cannot tolerate this dose, a potential discontinuation or further dose reduction may be allowed by the Investigator after a discussion with the Sponsor's Medical Monitor. Dose modification of ATG-010 can be conducted based upon grade severity of the adverse events (AE) as per CTCAE version 4.03. If a patient experiences more than one AE, dose modification will be conducted based on the AE of highest severity. If drug-related toxicity requires a treatment delay of more than 28 days, the patient will be withdrawn from the study treatment. All dose modifications or treatment delays must be documented in the electronic case reporting form (eCRF) and reasons must be provided.

Concomitant medications

To minimize nausea, unless contraindicated, all patients should receive 5-hydroxytryptamine (5-HT3) antagonists (e.g., palonosetron or equivalent) before the first dose of ATG-010, and the specific medication frequency should be adjusted according to the actual symptoms of the patients. Alternative anti-emetic agents may be used if the patient does not tolerate 5-HT3 antagonists. Additional anti-nausea and anti-anorexia agents may be given as needed (per National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines® for Antiemesis, NCCN Clinical Practice Guidelines® for Palliative Care and Chinese Expert Consensus on Prevention and Treatment of Nausea and Vomiting Related to Anti-Cancer Drug Treatment ［2019 version］). Patients will also receive therapy as needed to mitigate ATG-010 side effects, as part of the best supportive care.
Blood product transfusions, antimicrobials, and growth factors including granulocyte

colony-stimulating factors (for neutropenia), erythropoietins (for anemia), and/or platelet-stimulating factors for (thrombocytopenia) as the best supportive care are also permitted.
Concurrent therapy with any other approved or investigational anti-cancer therapy is not allowed during study period. Patients are not allowed to participate in other clinical trials during the study.

Study Endpoints

Primary endpoint

Overall response rate (ORR): Proportion of patients who achieve stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR).

Secondary endpoints

a. Efficacy:

- Survival rate (SR) at 6 months, 9 months, and 12 months
- Time to progression (TTP): Duration from start of study treatment to time of disease progression
- Progression-free survival (PFS): Duration from start of study treatment to PD or death (regardless of cause), whichever comes first
- Duration of response (DOR): Duration from the first observation of at least PR to time of disease progression, or deaths due to disease progression, whichever occurs first
- CBR: Proportion of patients who achieve sCR, CR, VGPR, PR, or minimal response (MR)
- DCR: Proportion of patients who achieve sCR, CR, VGPR, PR, MR, or stable disease (SD; for a minimum of 12 weeks)
- OS (Kaplan-Meier estimatess)
- MRD in patients who achieve CR and sCR
- The effect of risk factors stratification based on fluorescence in situ hybridization (FISH) on clinical efficacy, including del 13, del 17p13, t(4;14), t(14;16), 1q21 amplification

b. Safety and tolerability

c. PK: including but not limited to ATG-010 C_{max} and t_{max}

Criteria for Treatment Discontinuation:

At the discretion of the Investigator, patient study treatment could be discontinued for any of the following reasons and the Investigator will make the decision after timely communication with the clinical trial monitor under specific circumstances:

- Disease progression,
- Intolerable AE(s),
- Patient decides to discontinue study therapy or withdraws consent,
- Inappropriate to continue study participation by the Investigator or significant protocol violation in the opinion of Investigator and Medical Monitor.

Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study by Investigator so that the follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the study. In this situation, the reason for discontinuation should be clearly documented by Investigator. Supportive clinical data are required when disease progression is confirmed. If the patient is removed from the study by request from Investigator, the reason for withdrawal should also be documented.

Statistical Summary

Primary analysis (including efficacy, safety, and PK) will be conducted at 3 months after the last patient enrollment. Supplementary efficacy and safety analysis will be conducted after the completion of the study.

An interim analysis will be performed when approximately 50 patients have completed the clinical efficacy evaluations to assess the distribution of the patients who had previously received RRMM treatment. During interim analysis, the clinical efficacy in patients who had previously received 3 types of drugs (at least an immunomodulatory [i.e., lenalidomide], at least a protease inhibitor [i.e., bortezomib], and at least an anti-CD38 antibody) should be analyzed, but the efficacy of whole population enrolled will not be analyzed.

Sample Size Justification

This is a bridging study. A sample size of 82 patients will allow 80% power to detect a statistical significance with the target ORR of 28% against the threshold ORR of 15% (one-sided α=0.025).

Efficacy Evaluation

The primary efficacy analysis will be based on the ORR (proportion of patients who achieve sCR, CR, VGPR, or PR) as assessed by an independent review committee (IRC) using the modified intent-to-treat (mITT) population, defined as patients who receive at least 1 dose of study treatment. Supportive analysis of ORR will be performed using the per-protocol (PP) population.

A PP population will consist of all patients in the mITT population who meet the following criteria:

- Have ATG-010 dosing compliance ≥ 70%,
- Have at least 1 complete post-baseline response assessment unless death or study withdrawal from the clinical trial,
- No major protocol violations that would compromise the assessment of efficacy. The list of major protocol violations that affect statistical analysis will be finalized before database lock.

Secondary efficacy endpoints include: PFS, TTP, CBR, DOR, etc. They will be assessed using the mITT and PP population. Time to failure event with censored value (including PFS, TTP, DOR) will be assessed for overall survival using Kaplan-Meier methods. The 95% confidence interval will be provided for ORR and CBR.

PK evaluation

The pharmacokinetic parameters of ATG-010 will be calculated from the plasma concentration data with non-compartment model. Descriptive statistics will be provided for all concentration data and PK parameters.

Safety Evaluation

Data from all patients who take at least one dose of study drug will be used for safety analysis of study drug. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be graded by CTCAE version 4.03 and AE frequency will be tabulated by MedDRA term and system organ class.

A patient that experiences the same AE more than once will be counted only once. Other safety assessments such as hematology and chemistry will also be analyzed in the safety population.

Table 1: Schedule of Assessments and Study Activities

Activity/Assessment	Screening	Cycle 1					Cycle 2				Cycles ≥ 3	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Survival Follow-up[15]
	Day -21 to Day -1	Day 1	Day 3	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	≤ 14 Days Post Last Dose	30 Days Post Last Dose	Every 3 moths
		-1 days	+ 1 days	±1 days	±1 days	±1 days	±2 days	±2 days	±2 days	±2 days	±2 days		+ 7 days	±14 days
Informed consent	X													
Inclusion/exclusion criteria	X													
Demographics	X													
Medical history[1]	X	X												
Patient height	X													
Patient weight	X	X		X	X		X		X		X	X		
Physical examination, including vital signs[2]	X	X		X	X		X		X		X	X		
ECOG scoring[3]	X						X				X	X		
Echocardiogram or MUGA[3]	X													
12 Lead ECG[3]	X											X		
Clinical Laboratory														
Urinalysis[3]	X											X		
Hematology[3]	X			X	X	X	X	X	X	X	X	X		
TSH[3]	X											X		
Complete serum chemistry[3]	X						X				X	X		
Limited serum chemistry				X	X				X					
Coagulation tests[3]	X											X		
HBV, HCV, HIV[4]	X						（X）				（X）			
Serum hCG pregnancy test[5]	X						X (D1 of each cycle only)				X (D1 of each cycle only)	X		
C-reactive protein	X						X				X	X		

Table 1: Schedule of Assessments and Study Activities (Continued)

Activity/Assessment	Screening	Cycle 1					Cycle 2				Cycles ≥ 3	End-of-Treatment (EoT) Visit [14]	Safety Follow-up Call	Survival Follow-up[15]
	Day -21 to Day -1	Day 1	Day 3	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	≤ 14 Days Post Last Dose	30 Days Post Last Dose	Every 3 moths
		-1 days	+ 1 days	±1 days	±1 days	±1 days	±2 days	±2 days	±2 days	±2 days	±2 days		+ 7 days	±14 days
Multiple Myeloma Assessments														
SPEP and serum protein immunofixation [6]	X	X					X				X	X		X
UPEP (24-hr urine for total protein) and urine protein immunofixation[6]	X	X					X				X	X		X
Quantitative Ig levels[6]	X	X					X				X	X		X
Serum FLC[6]	X	X			X		X		X		X	X		X
β2-microglobulin	X											X		
Skeletal survey[7]	X						(X)				(X)	X		(X)
Plasmacytoma assessment[8]	X						(X)				(X)	X		(X)
Bone marrow aspirate[9]	X						(X)				(X)			(X)
Bone marrow biopsy[10]							(X)				（X）			
Myeloma Assessment	X						X				X	X		（X）
PK Sampling[11]		X			X									
Study drug dosing		ATG-010 80 mg + dexamethasone 20 mg (both twice weekly), oral, 4-week a cycle												
Adverse events[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Telephone contact[13]			X										X	X
Antineoplastic therapy after EoT												X	X	X

(X) indicates that additional information is provided in the footnotes. Merged cells indicate that the procedure may be performed during either Screening or C1D1 visit prior the first dose of study drug.

Abbreviations: sCR = stringent complete response; CR= complete response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment; Ig = immunoglobulin; MM = multiple myeloma; MRD= minimal residual disease; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; CBC = complete blood count; FLC = free light chain.

1 Including details of all prior anti-myeloma therapies. Includes baseline symptoms as well as a detailed history of prior cancer therapies, especially MM therapies, including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

2 Complete physical examination (PE) during Screening and EoT visit. Limited PEs during the study should be symptom directed. All PEs include vital signs (blood pressure, pulse, respiratory rate, and body temperature).

3 The following procedures may be performed at Screening or prior the first dose of study drug on C1D1 visit and as shown in the Schedule during the study: ECOG score, echocardiogram or MUGA scan, 12-lead ECG, urinalysis, hematological tests, TSH, complete serum chemistry, coagulations tests, and infectious disease tests. ECG should be performed whenever there are clinical indications.

Hematology labs: Weekly for Cycles 1-2. During Cycle 1, hematology labs will be performed at each study site on Days 1, 8, and 15, and locally on Day 22; during Cycle 2, hematology labs will be performed at each study site on Days 1 and 15, and locally on Days 8 and 22. If the screening hematology test is performed within 5 days prior to Cycle 1 Day 1, it does not need to be repeated on Cycle 1 Day 1. If hematology test is required on Cycle 1 Day 1, it should be clarified that this hematology test result meets the protocol inclusion criteria before the first dose.

4 Viral serology is performed at Screening, including HBsAg, HBsAb, HBcAb, HBV-DNA (eg, negative for HBsAg and positive for HBcAb), HCVAb, HCV-RNA (eg, positive for HCVAb), and HIV. If HBsAg is negative but anti-HBc is positive at screening, HBV-DNA must be tested and then repeated once every subsequent cycle (i.e., every 4 weeks).

5 For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles ≥ 2 and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

6 Response criteria include SPEP, UPEP, serum and urine immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and must be taken on prior of the first dose of study drug. The assessments must be repeated on the first day of following cycle, at the time of disease progression or suspected response in order to confirm response. Note: For patients who achieve CR or sCR, as assessed by the local laboratory, portions of collected samples will be shipped to the central laboratory for further confirmation.

7 Skeletal survey to be performed using x-rays per institutional guidelines. If x-rays are used, they should include a lateral radiograph of skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. If clinically appropriate, MRI, CT, or PET/CT, with tumor measurements, may be

used instead of, or in addition to, x-rays. If bone lesions or plasmacytomas are observed at baseline, their number and size should be recorded in the CRF. Bone lesions and/or plasmacytomas seen at baseline using imaging should be assessed as clinically appropriate per Investigator's discretion during the study. Skeletal survey results will be judged by the radiologist at the local laboratory.

8 If plasmacytomas are detected at baseline by PE, they should be measured and recorded, and re-assessed during the PE on Day 1 of each cycle, EoT visit, and every 3 months (if clinically appropriate) during follow-up.

9 Bone marrow aspirates:

a. At Screening for karyotyping and FISH analysis to confirm diagnosis and classify MM sub-type (required per standard of care).
b. MRD analysis at response for CR, sCR, or potential CR in patients with FLC only or unequivocal immunofixation electrophoresis (IFE).
c. Efficacy assessment is performed according to the guidelines of the International Myeloma Working Group (IMWG).

10 Bone marrow biopsies:

a. Validation of CR and sCR by the central laboratory in accordance with the guidelines of the International Myeloma Working Group (IMWG) (the levels of SPEP, UPEP, FLC, and quantitative Ig should be confirmed as soon as they are known).

11 PK sampling timepoints refer to Section 9.5.1.

12 All serious adverse events that occur after patient signs the ICF (including prior to first dose) and the adverse events that occur after the first dose of (including serious adverse events).

13 Telephone call (or visit) with patient to evaluate supportive care medications, concomitant medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place on C1D3 (following administration of first dose of ATG-010 on C1D1). Survival follow up should be conducted via telephone call or in-person contact with the subject every 3 months until death or study discontinuation. MM disease status, survival, subsequent antineoplastic therapy, and drug-related SAE data will be collected at these phone calls/visits.

14 The end of treatment (EoT) visit is considered to be ≤14 days after the last medication, and if it is more than 14 days after the last medication, the EoT visit will be performed within 1 week when the Investigator judges that the subject has permanently terminated the study drug.

15 After treatment discontinuation, if possible, for patients who are not progressing, SPEP with serum immunofixation, UPEP (24 h) with urine protein immunofixation, serum FLC, and quantitative Ig levels should be performed every 3 months for 1 year to assess durability of response.

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Listing of Tables

List of Abbreviations

Abbreviations	Definitions
5-HT3	5 hydroxytryptamine
ACS	Acute cerebellar syndrome
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AML	Myeloid leukemia, acute
ANC	Absolute Neutrophil Count
aPTT	Activated partial prothrombin time
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase (SGOT)
AUC_{last}	Area under the curve from the time of first measurement to the time of last measurement
$AUC_{0-\infty}$	Area under the curve from time 0 to the last measurement
AV	Atrioventricular
bid	Twice daily
BMSC	Bone marrow stromal cells
BP	blood pressure
BSA	body surface area
BSC	Best support care
BUN	BUN
℃	Degrees Celsius
CBC	Complete blood count
CBR	Clinical Benefit Rate
CD	Cluster of differentiation
抗 CD38 mAb	Leukocyte-expressed monoclonal antibody against CD38 antigen
CD-ROM	Compact disc read-only memory
CFR	Code of Federal Regulations
CHF	Congestive cardiac failure
CI	confidence interval
CLL	Chronic lymphoid leukemia
Cm	Centimeter
C_{max}	Maximum serum concentration
CML	Chronic myelogenous leukaemia
CNS	central nervous system
CR	complete response
CRA	Clinical Research Associate
CRF	Case Report Form
CRM1	Chromosomal region maintenance 1
CSF	CSF
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
cyclo	amide
DCR	Disease Control Rate
Dex	Dexamethasone
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting Toxicity
DM	Diabetes
DNA	deoxyribonucleic acid
DOR	Duration of response
Dox	Doxorubicin
DSMC	Data and Safety Monitoring Committee

DT	Dexamethasone + Thalidomide
ECG	electrocardiogram
eCRF	Electronic case report form
eDC	Electronic Data Capture
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetra acetic acid
F%	Oral bioavailability
F	Degree Fahrenheit
FACT-G	Functional Assessment of Cancer Therapy (General)
FACT-MM	Functional Assessment of Cancer Therapy-Multiple Myeloma
FDA	Food and Drug Administration
FFPE	Formalin-fixed Paraffin Embedded
FISH	Fluorescence in situ hybridization
FLC	Free light chain (κ/λ ratio)
FLT3	Fms-like tyrosine kinase
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GGT	Gamma-glutamyl transaminase
GI	gastrointestinal
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
GRP	Growth regulator protein
GSH	Glutathione
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPLC/MS-MS	High performance liquid chromatography-tandem mass spectrometry
hr	Hours
IC50	Median inhibitory concentration (half maximal inhibitory concentration)
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IFNα	Interferon alpha
IFNγ	Interferon gamma
IgA	Immunoglobulin A
IgVH	Immunoglobulin heavy-chain gene variable region
IL-1α	Interleukin-1α
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
IMiD	Immunomodulatory agent
IMWG	International Myeloma Working Group
INR	International Normalized Ratio
IRC	Independent Review Committee
ISS	International Staging System
ITT	Intention-to-treat
IV	Intravenous
kg	Kilogram
KM	Kaplan-Meier

LAFB	Left anterior bundle branch block
LDH	Lactate Dehydrogenase
LMW	low-molecular weight
LOCSIII	Lens Opacities Classification System
m^2	Square meter
MAb	monoclonal antibody
MCP1	Monocyte chemotactic protein-1
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial Infarction
min	Minutes
miRNA	microRNA
mL	Millilitre
mITT	Modified intent-to-treat
MM	Multiple Myeloma
mmHg	millimeters of mercury
MTD	maximum tolerated dose
MR	Minimal response
mRNA	messenger ribonucleic acid
MUGA	multigated acquisition
5'NT	5'-nucleotidase
NAC	N-acetylcysteine
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NES	Nuclear export sequence
NHL	Non-Hodgkin's lymphoma
NK1R	Neurokinin 1 receptor
NPC	Nuclear pore complex
NPM1	Nucleophosmin
NYHA	New York Heart Association
OPG	Osteoprotegerin
ORR	Overall response rate
OS	Overall survival
PCR	PCR
PD	Disease progression
PDn	Pharmacodynamics
PE	Physical examination
PFS	Progression Free Survival
PI	Proteasome inhibitor (in the context of drug therapy)
PI	Principal Investigator (in the clinical context)
PK	pharmacokinetic
po	Oral
PP	per-protocol
PPI	Proton pump inhibitors
PR	partial response
prn	On demand
PT	Prothrombin time
qAM	Every morning
qd	Once daily
qhs	At bedtime
qid	4 times daily

QoL	quality of life
qRT-PCR	Real-time quantitative polymerase chain reaction
RBBB	Right bundle branch block
RBC	Red blood cell
RNA	ribonucleic acid
RP2D	Recommended Phase 2 dose
RPPA	Reverse phase protein array
RR	Resistant/refractory
RT	Richter transformation
SAE	Serious Adverse Event
SAM	S-adenosyl methionine
sCR	Stringent complete response
Sd	ATG-010 80 mg plus Dexamethasone 20 mg (“low-dose” dexamethasone)
SD	stable disease
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SINE	Selective inhibitor of nuclear export
SOC	Standard of Care (in the context of treatment)
SOC	System Organ Class (in the context of adverse events)
SOP	Standard operating procedure
SPEP	Serum protein electrophoresis
SR	survival rate
TEAE	Treatment-emergent AEs
TRAE	Treatment-related adverse event
tid	3 times daily
TK	Toxicokinetics
T_{max}	Time to maximum drug concentration
TNFα	Tumor necrosis factor α
TOI	Trial Outcome Index
TSH	Thyroid Stimulating Hormone
TSP	Tumor suppressor protein
TTP	Time to progression
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling
ULN	Upper Limit of Normal
UPEP	Urine protein electrophoresis
VEGFα	Vascular endothelial growth factor α
VGPR	Very good partial response
WBC	white blood cell
XPO1	Exportin 1

1. Overview

Multiple myeloma (MM) is the second most common hematological malignancy (following non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. Despite the significant increase in the efficacy of first-line drugs such as immunomodulatory agents and proteasome inhibitors, most patients will eventually relapse with their diseases and becomerefractory to the treatments, and their diseases are characterized by manifest resistance against all types of existing anti-MM therapies. In the United States alone, it is expected that about over 30,000 new cases will be diagnosed and there will be approximately 12,600 deaths due to MM in 2016 (ACS 2016), which indicates an unmet need for the new therapies of refractory MM that can improve the overall survival rate.

ATG-010 (Selinexor) is a selective inhibitor of nuclear export (SINE) compound that can bind and inactive Exportin 1 (XPO1), and thereby compeling the nuclear tto retain key tumor suppressor protein (TSP). The level of XPO1 protein is significantly elevated in MM, which leads to nuclear exclusioin of TSP, the glucocorticoid receptors (GR), and enhanced translation of certain oncogene mRNAs (Tai 2014). High-level TSP is retained in the nucleus for a short time by blocking XPO1, thus activating its cell cycle checkpoints and genomic survey function. This results in the death of almost all types of malignant tumor cells, whilst normal cells experience transient cell cycle arrest and recover after the export blockage is released. XPO1 also exports GR and thereby causing a decline in its transcriptional activity. In the presence of glucocorticoids in the body, XPO1 blocking may lead to nuclear accumulation and activation of GR. In addition, inhibition of XPO1 induces nuclear to trap cap-binding protein (eIF4E)-dependent oncogenic mRNAs, preventing these oncogenes from being translated into proteins in the cytoplasm. In this way, SINE causes a reduction in key oncoproteins such as c-Myc, cyclin D, hDM2, and others. Moreover, inhibition of XPO1 protein reactivates multiple TSP pathways and glucocorticoid signaling together with reduced translation of key oncoproteins. This makes SINE a noval treatment for tumors including those with a variety of genomic changes and drug resistance mechanisms.

Based on the data of the Phase 2b clinical trial (STORM) conducted in patients with MM refractory to five agents (lenalidomide, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 monoclonal antibody), on July 3, 2019, FDA approved selinexor (Xpovio$^{@}$) in combination with dexamethasone for the treatment of adult patients with relapsed or refractory MM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

The Phase 1 clinical trials with oral ATG-010 monotherapy have been conducted in advanced hematologic malignancies including MM, acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL), and chronic lymphocytic leukemia (CLL) (KCP-330-001)], in solid tumors (KCP-330-002), and in soft-tissue and bone sarcoma (KCP-330-003). So far, these studies have demonstrated an extensive antitumor activity of ATG-010. In addition, Phase 2 studies are now ongoing in patients with MM, AML, diffuse large B-cell lymphoma (DLBCL), Richter's syndrome, glioblastoma, gynecological malignancy, and dedifferentiated liposarcoma (DDLS). As of March 2019, more than 3,000 patients with advanced hematologic diseases and solid tumors worldwide have received ATG-010 treatment in clinical trials.

To date, the most common adverse events (AEs) of ATG-010 found in clinical studies are

thrombocytopenia, anorexia, fatigue, nausea, and vomiting. These adverse events can be resolved or eliminated by standard supportive care. Besides, the prevlence and intensity of these AEs are usually decreased after 4 to 8 weeks of treatment. ATG-010 treatment is not associated with clinically significant major organ toxicities. Moreover, no clinically relevant cumulative toxicity has been observed in patients with longterm ATG-010 treatment, this includes 28 patients who have received ATG-010 monotherapy for more than 1 year and 6 patients who have received ATG-010 monotherapy for more than 2 years. For more information, please refer to the current Investigator's Brochure (IB).

In a Phase 1 dose-escalation clinical study, ATG-010 has shown a durable, single-agent, anticancer activity in patients with a variety of RR hematological and solid tumor malignancies (including MM), at doses ≥ 6 mg/m^2 body surface area (BSA).

Since ATG-010 has been demonstrated to activate glucocorticoid signaling via its receptor, patients received low-dose dexamethasone (20 mg) therapy in the previous Phase 2b clinical study as to improve the tolerability of ATG-010 and increase efficacy benefits. In previous studies, dexamethasone has also been demonstrated to be an effective prophylactic treatment the aforementioned common adverse events of ATG-010. Therapy naive MM is particularly sensitive to glucocorticoids, but the clinical benefits of glucocorticoids decrease with the prolongedtreatment duration involving multi-drug combination therapies. ATG-010 in combination with dexamethasone can re-activate glucocorticoid receptor (GCR) signaling to produce a synergistic effect on the clinical treatment of MM. The current study will evaluate the efficacy and safety of ATG-010 plus dexamethasone in the treatment of Chinese patients with relapsed/refractory MM who have previously received regimens of lenalidomide (immunomodulatory agent) and bortezomib (proteasome inhibitor).

2. Multiple Myeloma

Multiple myeloma (MM) is a hematologic malignancy that is characterized by accumulation of monoclonal plasma cells in bone marrow, presence of monoclonal immunoglobulins or M-proteins in serum or urine, bone disease, impaired renal function, and immunodeficiency. MM is more common in elderly patients (the median age at the diagnosis of the disease is 65-70 years; only 2% of the patients are under the age of 40 years) (Raab 2009).

MM is the second most common hematological malignancy (following non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. Study suggests that, the median survival after diagnosis is 5.2 years with current standard of care (Kumar 2014).

Although the pathogenesis of MM is unknown, studies have found that, a variety of mutated genes, including NRAS, KRAS, TP53, and BRAF mutations, occur frequently in MM patients; These mutations are universally acknowledged as the causal drivers for other cancers (Lohr 2014). In addition, some risk factors may make patients more susceptible to this disease. MM is more common in the elderly ≥ 65 years, in males, and in those with a family history of MM. 50% of MM patients have the following gene and chromosome mutations, including mutation of immunoglobulin heavy chain gene locus on chromosome 14 q32, partial or complete loss of chromosome 13, and partial loss of chromosome 17 (Raab 2009; Kyle 2004).

The related diagnosis of MM is based on the disease's key characteristics, space-occupying lesion(s) in the bone marrow cavity, bone lesions, and production of paraproteins (Raab 2009; IMWG 2003). MM is staged by the β2-microglobulin level, which is directly related to the renal function, tumor mass, and albumin level (Greipp 2005). See Appendix 2 for the summary of staging.

In the past 20 years, due to the use of high-dose chemotherapy (i.e., alkylating agent) and autologous stem cell transplantation plus the developement and application of some new drugs including immunomodulatory agents (e.g., thalidomide, lenalidomide, and pomalidomide) and proteasome inhibitors (bortezomib and carfilzomib), the treatment of MM has been greatly improved. However, despite the increased efficacy of these drugs, majority of the patients develop highly drug resistance MM gradually, then they relapse and become refractory to treatments and eventually die from the disease. The epidemiological study showed that 12,500+ people in the United States died from MM in 2016 (ACS 2016), which indicates great unmet medical needs and the necessity for developing anti-MM agents with noval mechanisms.

3. Nuclear Export

3.1. Inhibiting XPO1 in Human Cancer

Many important tumor suppressor proteins (TSPs), including but not limited to TP53, FOXO3a, IκB, BRCA1, APC, PP2A, and Rb, have been identified in the pathogenesis of cancer. TSP mediates tumor suppressor pathways through a variety of functions, including identification of cell damage, cell cycle arrest until repair is made, and induction of irreparable apoptosis (*Brown 2011*). Similarly, for binding with glucocorticoids and nuclear localization, GCR is essential for its signaling.

The tumor suppression and anticancer activity of these TSPs and GCRs demands their presence in the nucleus. On the contrary, their ability to regulate the cellular process can be inactivated when exported to the cytoplasm by the nuclear export protein (XPO1), (*Xu 2010*), through which cancer cells can successfully escape from normal DNA damage control and antitumor treatment. For most TSPs and GCRs, XPO1 is the only known nuclear export protein. It should be noted that, XPO1 has been identified as a selective survival gene in MM by unbiased high-throughput short interfering RNAs (siRNA) screening (*Tiedemann 2012*) and is often overexpressed in MM (*Tai 2014*).

The blocking of XPO1 causes transient nuclear retention of TSP, GCR and other growth regulatory factors and thereby reconstructing their tumor suppressor effect and growth regulatory effects on cancer cells, which allows potential reversal of the mechanism that causes resistance to chemotherapy (this may make sense for combination therapies in the future) (*Lain 1999*).

Some growth-promoting (including oncogenes) messenger RNAs (mRNAs) are particularly exported from the nucleus through a “cap-binding complex” to the cytoplasm, where they are further translated into proteins (*Culjkovic 2013; Koehler 2007*). Several key MM genes including c-Myc, cyclin D1, and hDM2, etc. utilize this complex by binding to the protein eIF4E, and thereby exit the nucleus and then are effectively translated into proteins. Only XPO1 can make the cap-binding complex protein eIF4E exported out of the nucleus to the cytoplasm. As these proteins have an extremely short half-life, constant translation is required for maintaining their cellular levels. Inhibition on XPO1-mediated nuclear export can lead to a decline in the translation of these growth-promoting proteins, thereby significantly reducing their levels.

In normal cells, XPO1 inhibition can lead to transient cell cycle arrest without resulting in any cytotoxicity, and normal cell cycles can be restored after the inhibition is removed (*Lain 1999*; *van der Watt 2009*; *Gray 2007*).

Inthe early clinical trials, subjects experienced significant of weight loss, diarrhea, and marked fatigue and asthenia due to off-target effects of the drug; as a result, several attempts to develop such class of anticancer drugs all failed (*Mutka 2009*; *Newlands 1996*; *Roberts 1986*).

It is now fully recognized that, forced nuclear retention of TSP can block a great number of tumorigenic growth stimulation (and inflammation) pathways that maintain the phenotype of malignant tumors. Likewise, in the presence of glucocorticoids, nuclear retention of GR can restore its activity. Eventually, inhibition of eIF4E/XPO1-mediated mRNA export of oncoprotein can cause a decrease in its level. Since the restoration of TSP ±GR activity and tumorigenic signal reduction are essentially associated with any cancer, the inhibition of XPO1 has an anti-tumor activity against MM and many other malignancies (Table 2).

Table 2: Effects of XPO1 Inhibition on Oncogenic and Inflammatory Pathways

Pathway Affected	Effect of XPO1 Inhibition	References
XPO1 overexpression	XPO1 reduction	Walker 2013
Glucocorticoid receptor (GR) In activation (nuclear export)	Nuclear GR retention (in the presence of glucocorticoids) and re-activation	Chen 2014
p53 mutation	p73 activation, p21 activation	Ranganathan 2012
hDM2 (MDM2) activation	Nuclear p53 retention and activation, hDM2 protein reduction	Kojima 2013
c-Myc amplification	MYC protein reduction	Schmidt 2013
Cyclin D1 overexpression	Cyclin D1 reduction	Gao 2014
NPM1 mutation	Nuclear restoration of NPM1	Falini 2007
CEBPA down-regulation	Nuclear retention and activation	Ranganathan 2012
CDKN2A reduction	P53/p73 stabilization	Azmi 2013
Rb reduction	Rb low phosphorylation, p14/p16 elevation	Fragomeni 2013
FLT3 activation	FLT3 reduction	Ranganathan 2012
c-KIT activation	c-KIT reduction	Ranganathan 2012
NF-B activation	Nuclear retention and activation of IκB	Lapalombella 2012
PIK3 or AKT activation	FOXO1, -3, -4 activation	Lapalombella 2012
Survivin-cytoplasm	Nuclear retention of survivin	Altura 2003
Bcr-Abl activation	PP2A activation	Walker 2013

4. ATG-010 (Selinexor)

ATG-010 is an innovative, orally bioavailable, slowly reversible, potent selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). XPO1 is responsible for the unidirectional export of approximately 220 different cargo proteins out of the nucleus to the cytoplasm (*Xu et al., 2010*). The anti-tumor activity of SINE compound is mediated by a minimum of 3 distinct pathways, involving tumor suppressor proteins (TSP), oncoproteins, and glucocorticoid receptors (GCR).

First, SINE compounds induce the nuclear localization and functional activation of a variety of TSPs, thereby leading to rapid apoptosis of multiple myeloma (MM) (*ai et al., 2014*) and other malignant tumor cells. By forcing the nuclear localization and activation of TSP, all types of cells exposed to SINE compounds experience G1±G2 cell cycle arrest, and then 'genomic fidelity' check. Genomedamaged cells (i.e., malignant tumor cells) are induced to die both in vitro and in vivo. Normal cells with intact genome stay in reversible, transient cell cycle arrest until the blocking of XPO1 is relieved. The second antitumor effect of SINE compounds is mediated by the mRNA cap-binding protein eIF4E, which is also a cargo protein carried by XPO1. Among other functions, eIF4E is responsible for effective nuclear export and delivering several kinds of growth promoting (oncoprotein) mRNAs to the cytoplasmic ribosome for translation. By forcing the nuclear retention of eIF43 bonded to XPO1, SINE compounds reduce the synthesis of oncoprotein mRNAs by cytoplasmic ribosome including c-Myc, hDM2, cyclin D1, and Bcl-XL. Finally, in the presence of glucocorticoids, SINE compounds also enable restoration of anti-myeloma glucocorticoid receptor (GR) signaling; meanwhile, ATG-010 and other SINE compounds will not enhance the hyperglycemic effects of glucocorticoids. Therefore, by inhibiting the key nuclear/cytoplasmic control protein XPO1, the SINE compounds exhibit an extensive and intensive anticancer activity.

4.1. Preclinical Data

This section briefly summarizes previous preclinical data. For more information, please refer to the Investigator's Brochure.

According to in vitro experiment of continued (approximately 72 hours) exposure to ATG-010, ATG-010 promoted cancer cell apoptosis in a wide range of tumor-derived cell lines and patient samples in culture (including multi-drug resistant cancer). In addition, in the absence or presence of bone marrow stromal cells (BMSCs), ATG-010 was cytotoxic to both MM and CLL cells.

Animal model pharmacokinetic (PK) studies were conducted in mice, rats and monkeys. The results showed that, the exposure of ATG-010 was proportional to the dose and there was no accumulation. For more information, please refer to the latest Investigator's Brochure.

The in vivo effects of SINE compounds on MM have be evaluated in several studies. In MM1.S xenograft tumors, tumor volume significantly decreased (40%) after treatment with the SINE compound KPT-276, whereas tumor volume increased by 36% in the placebo-treated cohort (*Schmidt 2013*). KPT-276 was also active in the Vk*MYC mouse model of MM, which has a positive predictive value of 67% for the activity of single-agent compounds in clinical trials (*Schmidt 2013; Chesi 2012*).

4.1.1. ATG-010 Plus Dexamethasone Studies

In vitro studies, compared to either drug alone, ATG-010 and dexamethasonein combination have synergistic activity on reducing the viability of MM1.S human MM cells (*Chen 2014*). In the presence of glucocorticoids, enhanced GR nuclear localization with activated GCR mediated transcription is at least partly related to the synergistic cytotoxicity of this combination therapy (*Gao 2014*).

The enhanced activity of ATG-010 plus dexamethasone was also observed in two human MM xenograft models. Compared to ATG-010 alone, the addition of dexamethasone to ATG-010 enhanced the activity (86%).

Given all that above, in MM cytotoxicity assays, ATG-010 plus dexamethasone showed synergistic effect both in vitro and in vivo by enhancing GCR nuclear localization and amplifying GCR transcriptional activity. In summary, these studies proved that, SINE compounds are active anti-MM compounds that reduce cell viability, cause increased apoptosis and cell cycle arrest in vitro, and potently inhibit the growth of MM tumor in vivo, and such effects can be enhanced by their combination with dexamethasone.

4.2. Clinical Experience

A total of 686 MM patients received selinexor treatment in four clinical studies (KCP-330-001, -012, -017, and -023). Both selinexor alone and its combination with dexamethasone were evaluated (studies KCP-330-001 and KCP-330-012). Study KCP-330-017 is evaluating the combination of selinexor with various therapeutic MM drugs, including pomalidomide, lenalidomide, carfilzomib, bortezomib, and daratumumab. The primary objective is to evaluate the preliminary efficacy and safety, and determine the recommended phase 2 dose (RP2D). Study KCP-330-023 is evaluating and comparing the safety and efficacy of selinexor+bortezomib+low-dose dexamethasone (SVd) vs. bortezomib+low-dose dexamethasone (Vd). The preliminary efficacy and safety data of studies KCP-330-001 and KCP-330-012 are summarized below (both studies KCP-330-017 and -023 are still ongoing).

4.2.1. Efficacy Results of Study KCP-330-001

Study KCP-330-001 was a Phase I, open-label, parallel-group study, with dose escalation and dose expansion phase, to determine the MTD, to evalute preliminary safety and efficacy of different selinexor dose schedules (3-80 mg/m^2, 1 to 3 times per week).

The results showed that, for all patients with MM (regardless of selinexor dose; n = 81), the overall response rate (ORR) was 8.6% (95%CI: 4%, 17%), including 1 patient with stringent complete response (sCR; 1.2%) and 6 patients with partial response (PR; 7.4%). The best response in another 13 patients (16%) was minimal response (MR), and the clinical benefit rate (CBR) was up to 25%. 29 patients (35.8%) had stable disease (SD), 20 (24.7%) patients had progressive disease (PD), and 1 (1.2%) patient had clinical progression.

Among the 81 selinexor-treated MM patients, 25 received selinexor (45 or 60 mg/m^2, BIW) +dexamethasone (20 mg BIW). Within these 25 patients, the ORR was 24.0% (95%CI: 9%, 45%) and CBR was 32.0%, including 1 case of sCR, 5 PRs, and 2 MRs. Eight patients (32.0%) had SD, and 5 (20.0%) patients experienced PD. All responses ≥ PR occurred at the dose level of 45 mg/m^2

selinexor.

Dose of 60 mg/m^2 was poorly tolerated and made the duration of study treatment (median, 15.0 days) shorter than that of 45 mg/m^2 (median, 110.5 days). In the 45 mg/m^2 selinexor+20 mg dexamethasone group, the median time to disease relapse or progression was 180 days. Therefore, the RP2D of selinexor in MM was 45 mg/m^2 (about 80 mg) +20 mg dexamethasone BIW.

4.2.2. Efficacy Results of Study KCP-330-012 (STORM)

STORM was a Phase 2b, open-label, single-arm study of selinexor+low-dose dexamethasone (Sd) in patients with relapsed/refractory MM. In Part 1, patients must have been previously treated with lenalidomide, pomalidomide bortezomib, and carfilzomib; and were refractory to a PI, an immunomodulatory agent (IMiD), and glucocorticoids, and a subset of the patients also were refractory to the "quad" agents (quad-refractory) as well as to an anti-CD38 antibody (i.e. penta-refractory). Patients orally took 6 or 8 doses of selinexor 80 mg (BIW) and dexamethasone 20 mg BIW in each 28-day cycle. The primary objective was to determine the ORR per International Myeloma Working Group criteria and DOR, both of which was assessed by an Independent Review Committee (IRC).

In Part 2 of the STORM study, a total of 123 patients with RRMM received selinexor 80 mg plus dexamethasone 20 mg. In the modified intent-to-treat (mITT) efficacy population, 122 patients had an ORR of 26.2%, including 2 cases of sCRs (both assessed as MRD negative), 6 VGPRs, and 24 PRs, as assessed by the IRC per IMWG criteria. The median time to initial response was 4 weeks (range: 1 to 10 weeks). The median OS was 8.6 months, 15.6 months for patients with ≥ PR or ≥ MR (two groups), and 1.7 months for those with PD (or NE). The PFS and OS were 4.7 and 9.3 months, respectively. Of the 32.1% (25/78 cases) patients who achieved a response ≥ MR, the median OS was 11.4 months, compared to 5.8 months of those achieving SD, PD or NE.

Table 3: Overall Response Rate Assessed by IRC per IMWG Criteria in Different Subgroups of KCP-330-012 Study (Part 2 of STORM)

Subgroup Population (n)	Overall response rate n (%) 95%CI	Clinical Benefit Rate n (%) 95%CI
Prior anti-MM treatment		
Penta (BCLPD) refractory (n = 83)	21 (25.3) 16.4, 36.0	31 (37.3) 27.0, 48.7
Refractory to CLPD (n = 101)	26 (25.7) 17.6, 35.4	37 (36.6) 27.3, 46.8
Refractory to BCPD (n = 94)	25 (26.6) 18.0, 36.7	36 (38.3) 28.5, 48.9
Refractory to CPD (n = 117)	31 (26.5) 18.8, 35.5	45 (38.5) 29.6, 47.9
Other subgroup factors		
R-ISS stage I (n = 20)	7 (35.0) (15.4, 59.2)	10 (50.0) (27.2, 72.8)
R-ISS stage II (n = 78)	21 (26.9) (17.5, 38.2)	32 (41.0) (30.0, 52.7)
Prior anti-MM treatment		
R-ISS stage III (n = 23)	4 (17.4) (5.0, 38.8)	6 (26.1) (10.2, 48.4)
FLC MM (n = 35)	15 (42.9)	19 (54.3)

	26.3, 60.6	36.6, 71.2
Non-FLC MM (n = 87)	17 (19.5) 11.8, 29.4	29 (33.3) 23.6, 44.3
High-risk MM (n = 65)	12 (18.5) 9.9, 30.0	24 (36.9) 25.3, 49.8
Impaired renal function		
CrCL <40 (n = 14)	35.7	NA
CrCL 40 to <60 (n = 25)	16.0	NA
CrCL ≥ 60 (n = 82)	28.0	NA
Age		
≤60 years (n = 46)	21.7	NA
>60 to 70 years (n = 49)	28.6	NA
≥70 years (n = 27)	29.6	NA

Prior anti-MM treatment: B = bortezomib; C = carfilzomib; L = lenalidomide; P = pomalidomide; D = daratumumab; CrCL = creatinine clearance; FLC = free light chain; NA = not applicable; R-ISS = Revised International Staging System

4.2.3. Clinical Safety Results

The most common TEAEs in the study were low-grade and reversible events and/or responded to the supportive care and dose modification. The most common TEAEs (≥35%) included nausea (65.1%, 1352/2076 cases), fatigue (57.9%, 1203/2076 cases), thrombocytopenia (52.1%, 1082/2076 cases), anorexia (MedDRA "decreased appetite") (51.0%, 1058/2076 cases), anemia (42.3%, 879/2076 cases), vomiting (38.2%, 794/2076 cases), and diarrhea (36.0%, 747/2076 cases).

4.3. Potential Risk

On July 3, 2019, FDA granted accelerated approval to selinexor. Post-marketing experience will be provided in the periodic adverse drug reaction report. FDA approved selinexor in combination with dexamethasone for adult patients with RRMM who have received at least 4 lines of prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody.

This study will continue to evaluate the efficacy and safety of selinexor plus dexamethasone in Chinese patients with RRMM. Measures will be taken to guarantee the safety of patients participating in this trial, including formulating strict inclusion and exclusion criteria and closely monitoring subjects' AEs.

If a patient experiences an AE during the course of the clinical trial, the Investigator may adjust the study treatment according to the protocol. During the trial period, and within 30 days after the last dose of study treatment or prior to the initiation of another anti-cancer therapy, all AEs and serious adverse events (SAEs) will be recorded, whichever comes first.

The most common AEs possibly related to ATG-010 are nausea, fatigue, thrombocytopenia, anorexia, anemia, vomiting, and diarrhea. In fact, all these side effects can be effectively managed with the modified dose of the study drug and/or the supportive care initiated prior to the first dose. Overall, the most common laboratory abnormalities includ thrombocytopenia, hyponatremia, and decreased erythrocytes. The majority of these AEs were mild or moderate in severity. For more information,

please refer to the Investigator's Brochure.

Based on 3 reports, acute cerebellar syndrome (ACS) is assessed as a potential risk of selinexor. One adult patient who had previously received multiple therapies, had recurrent pancreatic cancer, and had baseline magnetic resonance imaging (MRI) evidence of cerebellar abnormality, experienced ACS. This patent received selinexor 145 mg, twice weekly (i.e., an extremely high dose that is no longer used). The other 2 cases of ACS occurred in pediatric patients with refractory AML. These patients also had baseline cerebellar abnormality and received selinexor treatment at extremely high doses (these doses are no longer recommended). Since these cases were reported in 2015, no new reports were found, and further studies on higher doses have been discontinued. In addition, using "cerebellar syndrome", to search the newly obtained safety data in the studies sponsored by Karyopharm Therapeutics Inc., no new ACS cases were found.

4.3.1. Reproductive Risks

Macroscopic and microscopic changes of reproductive organs were observed in the toxicology studies of ATG-010 in rats and monkeys, and the majority of these changes recovered or partially recovered during the recovery period. The long-term effects of these changes on the reproductive capacity are unknown. In addition, secondary developmental effects due to decreased maternal body weight were observed in a rat embryo-fetal development study. For more information, please refer to the Investigator's Brochure. Since it is unknown whether ATG-010 causes any reproductive toxicity in humansall patients must agree to take effective contraceptive measures during the study period and until 3 months after the end of study treatment.

5. Rationale

MM is the second most common hematological malignancy. The median survival after diagnosis with conventional therapy is 5.2 years (Kumar 2014). Although MM is highly treatable, but it cannot be cured with existing therapies. Common therapies include glucocorticoids, chemotherapy, proteasome inhibitors, immunomodulatory agents, stem cell transplant, and radiotherapy.

In preclinical studies, the anti-MM activity of ATG-010 has been demonstrated both in vitro and in vivo. The clinical outcomes of MM patients in studies KCP-330-001 and -012 are summarized in Section 4.2.

In the Phase 2b trial (KCP-330-012) mentioned above, the 123 RRMM patients who received selinexor 80 mg plus dexamethasone 20 mg in Part 2 had an ORR of 26.2%, including 2 cases of sCRs (both assessed as MRD negative), 6 cases of VGPRs, and 24 cases of PRs. Relevant results have showed that the efficacy of ATG-010 combined with low-dose dexamethasone is encouraging in patients with RRMM who have previously received multi-line therapies and have limited treatment options. Based on the promising efficacy data observed from the study in the Western population of RRMM, the current study is planned to extended ATG-010 combined with low-dose dexamethasone to the treatment of RRMM patients in China, in order to validate the clinical efficacy and safety of ATG-010 in Chinese RRMM patients.

The design of this study protocol is based on the initial treatment option for RRMM (i.e., lenalidomide and bortezomib), aiming to evaluate if ATG-010 provides such MM patients (i.e., second-line refractory MM patients) with a new effective treatment option.

5.1. Rationale for ATG-010 Dose Regimen

As of March 2019, more than 3000 patients with advanced cancer have received ATG-010 treatment in multiple clinical studies. In the previous clinical trial (KCP-330-001) and STORM study (KCP-330-012), patients who received ATG-010 45 mg/m^2 (about 80 mg) plus dexamethasone 20 mg (both twice weekly) treatment achieved persistent response without any clinically significant cumulative toxicity (see Section 4.2). The recommended initial dose of selinexor approved by FDA is 80 mg in combination with dexamethasone taken orally on Days 1 and 3 of each week. This study plans to reducing dose according to the package inserts approved by FDA.

Patients in this study will receive ATG-010 80 mg (45 mg/m^2 BSA) plus dexamethasone 20 mg dosed both twice weekly in 4-week cycles. For patients who are partially intolerant to glucocorticoids (determined by the Investigator), the minimum dose of dexamethasone allowed is 10 mg. If the patient still fails to tolerate this dose, drug discontinuation or further dose reduction may be allowed after the Investigator has a discussion with the Sponsor's Medical Monitor based on the specific situation.

6. Study Objectives and Endpoints

6.1. Objectives:

6.1.1. Primary Objective

To evaluate the overall response rate (ORR) for treatment with ATG-010 plus low-dose dexamethasone in patients with relapsed/refractory MM previously treated with lenalidomide and bortezomib regimens.

6.1.2. Secondary Objectives

To evaluate the followingendpoints of ATG-010 in the study:

a. Efficacy

- Survival rate (SR) at 6 months, 9 months, and 12 months
- Time to Progression (TTP)
- Progression Free Survival (PFS)
- Duration of response (DOR)
- Clinical Benefit Rate (CBR)
- Disease Control Rate (DCR)
- Overall Survival (OS)
- Minimal Residual Disease (MRD)
- The effect of risk factor stratification on clinical efficacy

b. Safety and tolerability

c. Pharmacokinetics (PK) parameters

6.2. Study Endpoints

6.2.1. Primary Endpoint

ORR: Proportion of patients who achieve sCR, CR, VGPR, or PR

6.2.2. Secondary Endpoints

a. Efficacy:

- SR at 6 months, 9 months, and 12 months
- TTP: Duration from start of study treatment to time of disease progression
- PFS: Duration from start of study treatment to PD or death (regardless of cause), whichever comes first
- DOR: Duration from the first observation of at least PR to time of disease progression, or deaths due to disease progression, whichever occurs first.
- CBR: Proportion of patients who achieve sCR, CR, VGPR, PR, or minimal response (MR)
- DCR: Proportion of patients who achieve sCR, CR, VGPR, PR, MR, or stable disease (SD; for a minimum of 12 weeks)
- OS (Kaplan-Meier estimates)
- MRD in patients who achieve CR and sCR
- The effect of risk factor stratification based on fluorescence in situ hybridization (FISH) on clinical efficacy, including del 13, del 17p13, t (4;14), t (14;16), 1q21 amplification

b. Safety and tolerability

c. PK: including but not limited to ATG-010 C_{max} and t_{max}

7. Study Design

7.1. Overview

This is a Phase 2, single-arm, open-label, multi-center study of Sd (ATG-010 80 mg plus dexamethasone 20 mg) in patients with refractory MM who have previously received regimens with immunomodulatory agent and protease inhibitor (i.e., patients with relapsed/refractory MM who have previously received glucocorticoids, lenalidomide, and bortezomib) (note: "refractory" refers to a treatment response rate ≤25%, disease progression during the treatment described above, or disease progression within 60 days following the completion of treatment). This study plans to enroll approximately 82 patients to evaluate the efficacy, safety, and tolerability of Sd, and evaluate the pharmacokinetics (PK) of ATG-010 in 15 patients of enrolled.

Patients will receive Sd treatment at dose of ATG-010 (80 mg) plus dexamethasone (20 mg) simultaneously twice weekly. The drugs should be taken twice each week at a fixed time (whenever possible), and the doses should be approximately 48 hours apart (e.g., Monday and Wednesday or Tuesday and Thursday, etc.). Each treatment cycle will last 4 weeks. Patients will receive the treatment until disease progression, death, toxicity that cannot be managed by the standard of care, or withdrawal of consent, whichever comes first.

Patients will also receive blood product transfusions, antimicrobial agents, and growth factors including granulocyte colony-stimulating factors (for neutropenia), erythropoietins (for anemia), and/or platelet-stimulating factors (for thrombocytopenia), as best supportive care.

Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to stay in the study, so that follow-up information on disease progression, other antitumor therapy, symptoms, and survival status can be obtained. Patients can also decide to withdraw consent and decline further participation in the trial at any time.

The Investigator must determine patient's main reason for discontinuing study treatment and record this information in the electronic Case Report Form (eCRF). Patients who discontinue the study treatment prematurely will not be eligible for re-initiating the study treatment in this study protocol at a later date.

7.2. Independent Review Committee

The Independent Review Committee (IRC) will review the disease assessment data and independently assess the disease response. Disease response assessed by IRC is the basis for the evaluation of primary endpoint.

The IRC membership, functions, and procedures (including resolving the disagreements with the Investigators regarding disease assessment) will be stipulated in the *IRC Charter*.

7.3. Study Stopping Rules

Under the prescribed conditions in Section 10, the entire study or treatment of individual patients may be stopped.

7.4. Study Endpoints

See Section 6 for the study objectives and endpoints.

7.5. End of Study

The end of study (EoS) occurs when all patients have completed 12 months of study visit/follow-up since the initiation of the study drug, or when the last patient has expired, has been lost to follow-up, or has withdrawn consent, whichever occurs first. After the completion of this study, the Sponsor will continue to provide ATG-010 to patients with clinical benefits as needed (per Investigators' judgment), and continue to collect safety data as reported.

8. Selection of Patients

8.1. Number of Patients

A total of 82 patients will be enrolled. See Section 7.1.

8.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible to enroll in this study:

1. Aware and sign the informed consent form (ICF) voluntarily.
2. Age ≥ 18 years.
3. Patients with multiple myeloma must have previously received regimens with immunomodulatory agent (lenalidomide) and proteasome inhibitor (bortezomib), are refractory to both drugs, and are refractory or intolerant to the most recent line of therapy (Patients documented as intolerant are allowed to be screened only after discussing and obtaining an approval from Sponsor Medical Monitor). Refractory MM includes primary refractory (patients do not achieve minimal response (MR) or have disease progression during therapy) or secondary refractory patients have progression within 60 days after completion of therapy).
4. Any non-hematological toxicities (except for peripheral neuropathy as described in exclusion criterion #17) that are relevant to previous therapies must have resolved to ≤ Grade 2 prior to the first dose of study drug.
5. Adequate hepatic function: total bilirubin <2× upper limit of normal (ULN) (for patients with Gilbert's syndrome, a total bilirubin of <3× ULN is required), AST <2.5× ULN, and ALT <2.5× ULN.
6. Adequate renal function: estimated creatinine clearance ≥20 mL/min (calculated using the formula of Cockroft-Gault).
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2.
8. Measurable MM as defined by at least one of the following:
   a. Serum M-protein (by serum protein electrophoresis, SPEP) ≥5 g/L,
   b. 24 hours-Urinary M-protein excretion ≥0.2 g (200 mg),
   c. Serum free light chain (FLC) ≥100 mg/L with abnormal FLC ratio.
9. Adequate hematopoietic function (no platelet transfusions within 1 week, and no red blood cell transfusions within 2 weeks prior to screening examination):
   a. Hemoglobin level ≥80 g/L
   b. ANC ≥1000/mm^3 (1.0×10^9/L)
   c. Percentage of plasma cells in bone marrow <50%, platelet count ≥75,000/mm^3 (75×10^9/L); or percentage of plasma cells in bone marrow ≥50%, platelet count ≥50,000/mm^3 (50×10^9/L).
10. Female patients of childbearing potential must meet below two criteria:

    a. Female patients of childbearing potential must agree to use 2 methods of contraception acceptable by the study physician or complete sexual abstinence throughout the study, and for 3 months following the last dose of study treatment.
       i. Sexual abstinence: this method is acceptable when it is consistent with the patient's preference and daily lifestyle. Periodic abstinence (based on calendar, ovulation, symotmatic body temperature, or post-ovulation methods) is not acceptable.
       ii. Acceptable contraception methods include: oral contraceptives, injectable

contraceptives, or implanted sex hormonal contraceptives, intrauterine contraceptive device, barrier contraceptivse with spermicide; or a sexual partner who is status post of a sterilization surgery and using at least one barrier contraceptive tool.

b. Must have a negative serum pregnancy test at screening.
Note: Female patients of childbearing potential refer to all women who have started menarche and are not in the postmenopausal period and have not had surgical sterilization (for example hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). Postmenopausal is defined as more than 12 consecutive months of amenorrhea for unspecified reasons. Women who are taking oral contraceptives or using mechanical contraceptive method such as intrauterine device are considered childbearing potential.

11. Male patients (including those who have received vasectomy) must agree to use a condom if sexually active with a female of child-bearing potential from the date of signing the informed consent form (ICF), throughout the study, and for 3 months without pregnancy plan following the last dose of study treatment.

8.3. Exclusion Criteria

Patients who meet any of the following criteria will not be enrolled:

1. Asymptomatic (smoldering) MM.
2. Plasma cell leukemia.
3. Documented complicated with amyloidosis.
4. Central nervous system (CNS) involved MM.
5. Pregnancy or breastfeeding.
6. Prior to the first dose of study drug:
   a. Chemotherapy within 1 week (including steroid therapy in chemotherapy regimen);
   b. Radiation, immunotherapy or other anti-MM therapy within 4 weeks;
   c. Radio-immunotherapy within 6 weeks.
7. Graft versus host disease (after allogeneic stem cell transplantation).
8. Life expectancy of < 4 months.
9. Major surgery within 4 weeks prior to the first dose of study drug.
10. Patients with active, unstable cardiovascular diseases, meet any of the following:
    a. Symptomatic ischemia;
    b. Uncontrolled clinically-significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with first-degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) are allowed);
    c. Congestive heart failure (CHF) of New York Heart Association (NYHA) ≥ Grade 3;
    d. Acute myocardial infarction (AMI) within 3 months prior to the first dose of study drug.
11. Uncontrolled hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg).
12. Uncontrolled active infection requiring treatment within 1 week prior to the first dose of study drug.
13. Known HIV seropositive.
14. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg

(HBV surface antigen).
Note: including HBsAg negative but hepatitis B cored (HBc) antibody positive with detectable hepatitis B virus deoxyribonucleic acid (HBV-DNA) level (the upper limit of normal for HBV-DNA testing is based on the test value of each center).

15. Prior malignancy that required treatment or has shown evidence of recurrence (except for skin basal-cell carcinoma and the following in-situ carcinoma: squamous cell carcinoma, bladder cancer in situ, endometrial cancer in situ, cervical cancer in situ/atypical hyperplasia, accidental histological finding of prostate cancer (TNM staging is T1a or T1b), or breast cancer in situ) within 5 years prior to the first dose of study drug.
16. Active GI dysfunction interfering with the ability to swallow tablets, or any GI dysfunction that could interfere with absorption of study treatment.
17. Grade ≥3 peripheral neuropathy, and Grade ≥2 painful neuropathy, within 3 weeks prior to the first dose of study drug.
18. Active psychiatric disorder, or organic disease which, in the opinion of the Investigator, is not suitable for the study.
19. Participation in another investigational anti-cancer clinical trial within 3 weeks or within 5 half-life ($T_{1/2}$) time periods prior to the first dose of study drug.
20. Receipt any following treatments prior to the first dose of study drug:
    a. Platelet infusion within 1 week;
    b. RBC transfusion within 2 weeks;
    c. Receipt of the following blood growth factors within 2 weeks: Granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), erythropoietin (EPO), megakaryocyte growth factor, and/or platelet stimulating factor.
21. Known intolerance to or contraindication for glucocorticoid therapy.
22. Prior exposure to a SINE compound, including ATG-010.

8.4. Screening Failures

An informed consent form will be signed; however, patients who fail to receive study treatment for any reason are defined as screen failure. For all screen failures, the Investigator will enter the screening number, patient's initials, and reason for screen failure into the electronic Case Report Form (eCRF). Screen-failure patients will be replaced. Screen-failure patients can be re-screened.

8.5. Study Patient Number

Each patient will be allocated with an exclusive study number, which will be used throughout the study. The patient number will not be re-allocated or re-used, regardless of the reason.

Screen-failure patients shall obtain the consent from the Sponsor Medical Monitor before re-screening. However, such patients will be allocated with a new patient number and marked it as re-screened.

9. Assessment Methods and Endpoints

9.1. Standard Study Assessments

All assessments should be carried out as described in Table 1.

9.1.1. Demographics

During the screening period, patients' demographic data will be collected. These data include the year of birth, age, gender, race, and ethnic group.

9.1.2. Medical History

Each patient's complete MM history and other important medical histories will be obtained. Medical history includes baseline symptoms, detailed history of prior MM therapies, and other prior anticancer therapies (i.e., transplant, chemotherapy, hormone therapy, immunotherapy, biotherapy, radiotherapy, and surgery) including the start and end dates, best efficacy, dates of disease progression (during or after therapy), and discontinuationsdue to intolerability or toxicity. Smoking history will be recorded. The Investigator should review these data prior to the dose on Cycle 1 Day 1.

9.1.3. Concomitant Medications

At each scheduled visit, each patient's concomitant medications will be recorded. Medication history should be detailedly recorded in the eCRF. Thereafter, at each study visit, patients will be asked whether they have used any other drugs other than the study drugs (from screening to the end of study). All concomitant medications and changes in medication including dietary supplements, over-the-counter, and oral herbal preparations should be recorded in the eCRF. There is no need to record routine anesthetics andcontrast agents that arerequired for diagnosis or surgical procedures.

Supportive care (e.g., appetite stimulants, antiemetics, and antidiarrheals, etc.) is encouraged (see Section 11.4.2).

9.1.4. Physical Examination

A complete physical examination (PE), including vital signs (blood pressure, pulse, respiratory rate, and body temperature), will be carried out during Screening and the EoT visit. All other PEs during the study should be symptom directed. Any significant findings existed before the informed consent is signed must be recorded on the medical history page of the patient's CRF. Significant new findingsincluding plasmacytomas which are benign or exacerbated after informed consent, must be recorded on the AE or plasmacytoma page of the patient's CRF.

Unless otherwise specified, PE includes the following items:

- Body height (without shoes), unit: centimeter (cm), measured only at Screening
- Body weight (with indoor clothing only, without shoes), unit: kilogram (kg)
- Body temperature
- Systolic blood pressure, diastolic blood pressure, and pulse
- Physical examination of the whole-body systems

Blood pressure information must be recorded in the source documents at the study site. Clinically relevant findings found after the initiation of treatment and complying with the definition of AE must be recorded in the AE eCRF.

9.1.5. ECOG Scoring

ECOG scoring (see Appendix 1) will be carried out at Screening, Day 1 of each cycle, and the EoT visit.

9.2. MM disease specific assessments

Patient response is assessed according to the procedures summarized in Table 4 and staged according to the IMWG response criteria summarized in Table 10 (Appendix 3). Disease response will be uniformly assessed by the independent IRC (Section 7.2).

According to IMWG, the quantitative Ig level measured by nephelometry can be used to replace the M-protein level measured by SPEP for patients with IgA or IgD myeloma. Besides, if a patient fails to provide the 24-hour urine sample after screening, the response profile will be confirmed per IMWG. At each study visit, all MM assessments specified in this study protocol should be carried out prior to dosing. If MM assessments are performed at unscheduled times, these results must be recorded as unscheduled visits in the eCRF. These assessments include SPEP, UPEP, serum FLC, β2 microglobulin, quantitative Ig, and serum/urine protein immunofixation.

The results of SPEP and serum protein immunofixation, quantitative Ig, serum FLC, and 24-hour UPEP with immunofixation must be recorded at each specified time point. A blood sample and a urine sample will be sent to the central laboratory at each time point. If the central laboratory results show achievement of CR or sCR, samples for subsequent MM disease assessment should be collected per IMWG and sent to the central laboratory for confirming the CR or sCR. At each time point, approximately 12.5 mL of blood and 24-hour urine should be collected and sent to the central laboratory. For detailed information, please refer to the Laboratory Manual.

No matter what kind of diagnosis is currently adopted (for example, 24-hour UPEP must be collected at each time point specified in the study protocol, even though SPEP, Ig, or FLC is currently adopted for the patient), all diseases assessment (SPEP, UPEP, FLC, quantitative Ig, and serum/urine protein immunofixation) should be performed.

Table 4: Special Assessments of MM

Procedure	Notes
SPEP and serum M-protein level determination	Per IMWG.
UPEP (24-hr urine for total protein) and urine M-protein level determination	Per IMWG. If a patient fails to provide the 24-hr urine sample, it should be recorded. Every effort should be made to collect 24-hr urine samples at the specified time points. The 24-hour urine sample collected must be performed with UPEP - other methods are not acceptable. UPEP must be performed at each time point specified in the study protocol, even if SPEP is adopted for the patient.
Serum FLC	Per IMWG.
Quantitative Ig level	Per IMWG. For IgA myeloma and IgD myeloma, quantitative Ig determination is preferred for disease assessment; the same variation rate should be adopted for serum M peaks. Only nephrlometryy can be used for response assessment, and SPEP and nephrlometry value cannot be used interchangeably. (Durie et al., 2006).
β2 microglobulin	For MM staging (Appendix 2), not for response assessment (for the local laboratory only)
Skeletal survey	Skeletal survey (by X-rays and/or other clinically appropriate imaging methods [MRI,

Procedure	Notes
	whole body CT, or PET/CT]) will be performed per Investigator's discretion within 45 days prior to C1 D1, and if clinically indicated, may be performed per Investigator's discretion during the study period. X-rays should include a lateral radiograph of skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. The results will be interpreted by the local laboratory. If lytic bone lesions or plasmacytomas are observed at Screening, their number and size should be recorded in the CRF. Bone lesions and/or plasmacytomas seen at baseline should be assessed during the study period by the same imaging method adopted at screening, with the assessment frequency determined per Investigator's discretion. • For patients without soft tissue plasmacytomas (i.e., bone lesions only), skeletal survey should be performed by X-rays or low-dose CT. Contrast radiography is not required. • For patients with soft tissue plasmacytomas, skeletal survey should be performed by X-rays or low-dose CT (contrast radiography not required) and MRI or CT or PET-/CT should be additionally performed, for which contrast enhancement is often required.
Clinical plasmacytoma	If detected by physical examination/palpation at screening, plasmacytomas should be counted and measured per IMWG guidelines, recorded, and later re-assessed and recorded during the symptom-directed physical examination.
Bone marrow (BM) aspirate	BM aspirate obtained at Screening will be used for MM (a) karyotyping and FISH analysis (performed in the central laboratory) to confirm diagnosis and classify MM sub-type. For patients with CR or sCR, BM aspirate will also be collected for exploratory MRD analysis (performed in the central laboratory). Efficacy assessment is performed according to the guidelines of the International Myeloma Working Group (IMWG) For detailed information, please refer to the Laboratory Manual. If clinically indicated, bone marrow core (trephine) biopsy will be performed to assess the response profile.
Bone marrow core (trephine) biopsy	This will be performed as soon as possible after confirmation of CR and sCR by serum and urine assessments (per IMWG). If serum and urine immunofixation is negative and any soft tissue plasmacytoma disappears, a tissue core biopsy must be performed to confirm CR and sCR. For detailed information, please refer to the Laboratory Manual.

9.2.1. Bone Marrow Aspirate for MM Diagnosis and Classification and Efficacy Evaluation

The 10 mL of bone marrow aspirate sample will be collected at Screening to assess type of MM and high-risk mutations (including del13, del(17p) translocation, t(14;16) translocation, t(4;14) translocation, and 1q21 amplification) in tumor cells. The central laboratory will perform FISH analysis to identify specific chromosome translocations at loci known to be rearranged in MM. For more information about these procedures, please refer to the Laboratory Manual.

9.2.2. Bone Marrow Aspirate for MRD Analysis

For patients who achieve CR or sCR, 5 mL of bone marrow aspirate sample will be collected at the time of response for exploratory minimal residual disease (MRD) analysis. For more information about these procedures, please refer to the Laboratory Manual.

9.2.3. Bone Marrow Biopsy for Efficacy Confirmation

This will be performed as soon as possible after confirmation of CR and sCR based on serum and urine assessments (per IMWG). If serum and urine immunofixation is negative and any soft tissue plasmacytoma disappears, a tissue core biopsy must be performed to confirm CR and sCR. For more information about these procedures, please refer to the Laboratory Manual.

9.3. Multiple Myeloma Response Criteria

In this study, response is assessed per IMWG criteria (Kumar 2016) All MM assessments must be carried out at each time point specified in this study protocol (Table 1).

Response will be assessed according to IMWG criteria for response assessment in MM (Appendix 3). The response must be confirmed using 2 consecutive samples. The time interval between samples can be discussed with Medical Monitor. Samples can be collected on the same day but must be analyzed independently.

- Complete Response (CR)
- Stringent Complete Response (sCR)
- Very Good Partial Response (VGPR)
- Partial Response (PR)
- Minimal Response (MR)
- Stable Disease (SD)
- Disease progression (PD)

9.4. Safety Evaluation

Investigators should closely monitor patient's vital signs (blood pressure, pulse, respiratory rate, and body temperature). During the trial, if the Investigator considers additional related examinations (e.g., ECG monitoring, pulmonary function monitoring) are required based on the patient's condition, such examinations should be performed according to the routine clinical practice at the study site. The most common AEs in existing clinical trials are mainly hematological, gastrointestinal and systemic symptoms (fatigue, decreased appetite, and weight loss). Monitoring and risk control should be strengthened during the clinical trial. Investigators should also closely monitor drug-related effects that may occur, and strengthen the assessment and monitoring of adverse reactions in immune system and pancreas. For the safety data of ATG-010, please refer to the Investigator's Brochure.

Safety evaluation will be performed at each visit. Procedures included in the safety evaluation are summarized as follows.

9.4.1. 12 Lead ECG

As shown in Table 1, standard 12-lead ECG will be performed. The Investigator will interpret ECG according to the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The date and time of ECG and parameters below should be recorded in the eCRF: heart rate, PR interval, QT interval, QRS interval, and corrected QT interval (QTc) calculated by Bazett's formula or Fridericia's correction formula (Bazett 1920, Fridericia 1920). If Bazett's correction formula is entered by the study site, Fridericia-corrected QTc interval (QTcF)

will be deduced using the following formula: QT/(RR^[1/3]), where, RR = 60/heart rate.

9.4.2. Clinical Laboratory Assessments

As shown in Table 1, the following clinical laboratory tests should be performed.

- Hematological tests, which contain complete blood count (CBC) and differential, including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count and absolute differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelet count.
- Serum chemistry (blood sample: serum)
  - Complete serum chemistry includes blood sodium, blood potassium, chloride, bicarbonate (HCO3-)*, blood urea nitrogen (BUN)/blood urea (Urea), creatinine, blood glucose, blood calcium, blood phosphorus, blood magnesium, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), lactate dehydrogenase (LDH), alkaline phosphatase, bilirubin total bilirubin, total protein, albumin, amylase, lipase**, creatine kinase, and uric acid.
  - Limited serum chemistry includes blood sodium, blood potassium, chloride, bicarbonate*, BUN/Urea, creatinine, blood glucose, ALT, AST, alkaline phosphatase, total bilirubin, and LDH, unless otherwise indicated clinically.
- Thyroid-stimulating hormone (TSH).
- Viral serology is performed at Screening, including HBsAg, HBsAb, HBcAb, HBV-DNA (eg, negative for HBsAg and positive for HBcAb), HCVAb, HCV-RNA (eg, positive for HCVAb), and HIV. If HBsAg is negative but anti-HBc is positive at screening, HBV-DNA must be tested and then every subsequent cycle (i.e., every 4 weeks).
- Coagulation parameters include prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT).
- Urinalysis includes bilirubin urine, glucose urine, urine occult blood/urine red blood cells, ketone bodies, pH, urine protein, urine specific gravity, and urobilinogen.

* Bicarbonate is optional in the absence of safety concerns. In the presence of safety concerns, study sites that are not eqippted bicarbonate testing can select venous blood carbon dioxide binding capacity or arterial blood gas analysis with similar clinical significance as an alternative test, or perform examination items that are considered appropriate and necessary by the Investigator.

** Study sites that are not equipped for lipase testing can accept test results from another hospital (any hospital certified by the Ministry of Health).

All the tests above will be analyzed by the local laboratory at each study site and the laboratory test reports will be provided to the Investigator. The Investigator or designee will review the laboratory results and assess the clinical significance of all abnormal values. Appropriate measures should be taken for any abnormal values of clinical significance, until the condition is stabilized or the laboratory test value returns to a level within the clinically acceptable range regardless of the relationship with the study drug) or baseline level. Any laboratory test value that remains to be abnormal at the EoT visit or any laboratory test value that is considered clinically significant should be followed up for 30 days or until the abnormality disappears or returns to the baseline level

according to the established medical standard. Toxicity will be assessed by adopting CTCAE v4.03.

9.4.3. Pregnancy Test

For females of childbearing potential; negative serum human chorionic gonadotropin (hCG) pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles ≥ 2 and at the EoT Visit (serum hCG).

Pregnancy testing may also be performed as clinically indicated during the study.

9.5. Pharmacokinetic

9.5.1. PK Sampling Points

Blood sampling (3 mL/sampling point) for PK analysis will be completed on Day 1 and Day 15 of Cycle 1, including a total of 26 sampling points. The specific time points are as follows:

Pre-dose: 0-10 min

Post-dose: 30 min ±5 min, 1 hour ±10 min, 1.5 hours ±10 min, 2 hours ±10 min, 3 hours ±10 min, 4 hours ±20 min, 5 hours ±20 min, 6 hours ± 20 min, 8 hours ±20 min, 10 hours ±20 min, 24 hours ±20 min, and 48 hours ±20 min.

Approximately 3 mL of whole blood will be collected at each sampling point and sent to the central laboratory for testing.

9.5.2. Pharmacokinetic Endpoints

PK blood samples will be collected from 15 patients enrolled. PK analysis of ATG-010 plasma level will be performed on the blood samples collected. The PK endpoints evaluated include but are not limited to the ATG-010 maximum serum concentration (C_{max}) and time to maximum serum concentration (t_{max}). See Section 13.3.5 for details.

10. Study Discountinuation Criteria

10.1. Premature Termination of Study

This study may be terminated for any reasons, including medical reasons or ethical reasons that affect the continued conduct of the study, or difficulty in recruiting patients, at the discretion of the Sponsor.

If a safety signal is identified, the Investigator/designee should notify the Sponsor (see Section 7.2). However, Sponsor should decide in conjunction with the regulatory authorities whether this trial should be modified or terminated. If this occurs Sponsor should notify the IRB/REB/EC and Investigators.

10.2. Premature Termination of Study by Individual Patients

Investigator may exclude a patient from study treatment at his/her discretion for any of the following reasons:

- Progressive disease defined per IMWG based on MM progression, including a confirmatory analysis for proving the progression. Progressive disease should be confirmed by the IRC before the study treatment is discontinued.
- Unacceptable AE or intolerance to study treatment.
- Patient decides to discontinue study treatment.
- Any medically applicable reason or major study protocol violation per Investigator discretion.

The reason for study termination must be clearly recorded in the source documents and study CRF including the reasons for patient consent withdrawal and Investigator's decision to terminate the patient's study participation.

Patients may discontinue study treatment for any reasons. Patients who elect to discontinue study treatment should be encouraged to stay in the study, so that follow-up information on disease progression and survival status can be obtained. However, patients can elect to withdraw consent and decline further participation in this trial.

11. Treatment

The dosage form to be adopted for ATG-010 study drug is an immediate-release coated tablet for oral administration. ATG-010 tablets are single strength (20 mg) tablets and are supplied in a billfold-sized blister package. Dexamethasone 20 mg will be given with each dose of ATG-010.

See Section 11.1.3 for more information.

11.1. Dosage and Administration

11.1.1. Dose Adjustment

Before any change to the dose, all dose modifications will be discussed/decided by the Investigator and the Sponsor's Medical Monitor.

11.1.2. Label

All drug packages will be labeled according to the requirements of current GCP and regulatory authorities. The drug label contains the drug name, storage conditions, and batch number, etc.

11.1.3. TREATMENT INFORMATION

Patients will take a fixed oral dose of ATG-010 80 mg plus dexamethasone (20 mg) twice weekly. The drugs should be taken twice each week at a fixed time (whenever possible), with a dose interval of approximately 48 hours (e.g., Monday and Wednesday or Tuesday and Thursday, etc.). Each treatment cycle will last 4 weeks. Patients are allowed to take the drugs home to administrate.

Patients who are partially intolerant to glucocorticoids (determined by the Investigator) are allowed to use the minimum dose of dexamethasone (10 mg). If any patient fails to tolerate this dose, drug discontinuation or further dose reduction may be allowed after the Investigator has a discussion with the Sponsor's Medical Monitor based on the specific situation. Dexamethasone will be provided in the form of tablet and can be taken home.

The drugs should be taken with at least 120 mL of liquid (water, milk, juice, etc.) within 30 minutes after solid food cousumption. For detailed information on the drug formulation, preparation and administration, please refer to Appendix 4.

ATG-010 tablets should be swallowed whole and shall not be crushed.

The Investigator or representative will assess the study treatment compliance at each patient's visit, and record it together with the patient with drug counts in the source documents. The date will be recorded according to the study drug schedule. Investigator or designee will compare the number of tablets dispensed against the number returned by the patient. Any deviations and missed doses should be recorded in the eCRF and drug accountability logs, so that they can be verified with the reasons. The Investigator/designee should make efforts to ensure full compliance with the dosing schedule and provide guidance to patients in a timely manner.

11.1.4. Dosage Adjustments in Patients with VGPR

In order to improve long-term disease control and tolerability, dose reduction in patients with a very good antitumor activity of ATG-010 is allowed by this study protocol. Therefore, for patients with

≥ VGPR lasting for ≥ 6 months and whom the Investigator believes may benefit from dose reduction, the following dose reductions may be considered after the Sponsor's Medical Monitor is consulted: (a) the dose of dexamethasone may be reduced by 40%, or (b) the dose of ATG-010 may be lowered by 1 level, or (c) the dosing frequency may be reduced to once weekly. Normally, dexamethasone should always be given on the day of ATG-010 dosing. Patients who receive dose reduction according to this protocol should have appropriate MM tumor assessment labs being monitored at least once every 2 weeks (e.g., FLC), so that the dose may be re-escalated to their initial dose when evidence of disease progression appears. These monitoring studies may be done at local laboratories.

11.1.5. Guidelines for Dose Reduction due to Toxicity

Toxicity will be graded according to CTCAE v4.03 criteria; these grades of severity are applicable to the treatment adjustments described below.

If two or more toxicities occur at the same time, dose modification will be determined based on the highest grade of severity.

As described in each section of applicability to the specific toxicities, re-escalation of study drug dose is allowed. If the treatment is delayed by more than 28 days due to drug-related toxicity, patient's study protocol treatment may be canceled.

All dose modifications or treatment delays must be documented in the electronic case reporting form (eCRF) and corresponding reasons must be provided.

According to the observationsfrom the ongoing Phase 1 study in patients with advanced hematologic malignancies and solid tumors, ATG-010 has a very wide therapeutic range with activities from approximately 6 mg/m^2 to ≥60 mg/m^2. Therefore, in order to ensure the best specific anti-tumor activity and tolerability in patents, dose reduction and/or modification of schedule are allowed, as shown in Table 5 and Table 6. Patients should also be actively treated with supportive care to reduce toxicities.

For all grade ≥3 hematological and non-hematological AEs that are unrelated to ATG-010, after discussion with the Sponsor's Medical Monitor and at the discretion of the Investigator, the dose of ATG-010 may be maintained if the patient can continue the oral administration.

Table 5: Pre-specified Dose/Schedule Modification for AEs Related to Study Drug

	Dosage Level(s)	**ATG-010 Dose Administered**
Starting dose	**0**	**80 mg BIW (total dose: 160 mg per week)**
Dose reduction	-1	100 mg QW
	-2	80 mg QW
	-3*	60 mg QW

* If the Investigator believes further dose reduction could still benefit the patient, a decision can be made through discussion with the Sponsor 's Medical Monitor.

Table 6: Guidelines for Supportive Care and Dose Modification

Please pay attention to the following suggestions:

- For all hematological or non-hematological AEs unrelated to ATG-010, the dose of

ATG-010 may be maintained per the Investigator's discretion after the Sponsor's Medical Monitor is consulted.

- For all AEs related to ATG-010, if stable disease is maintained ≥4 weeks by the prescribed dose reduction/interruption in Table 6, dose re-escalation may be considered after approval by the Sponsor'sMedical Monitor.

Adverse Reaction [a]	Occurrence, count	Action
Hematological adverse reactions		
Thrombopenia		
Platelets count 25,000 to < 75,000/m^3	Any	• Lower the dose of ATG-010 by 1 level (see Table 5).
Platelets count 25,000 to < 75,000/m^3, with concomitant hemorrhage	Any	• Interrupt ATG-010. • After recovery from hemorrhage, lower the dose by 1 level and re-initiate ATG-010 administration (see Table 5).
Platelet count < 25,000/m^3	Any	• Interrupt ATG-010. • Monitor platelet count, until it is restored to a level of at least 50,000/m^3. • Lower the dose by 1 level and re-initiate ATG-010 administration (see Table 5).
Neutropenia		
Absolute neutrophil count 0.5 to 1.0 × 10^9/L, without fever	Any	• Lower the dose of ATG-010 by 1 level (see Table 5).
Absolute neutrophil count < 0.5 × 10^9/L or febrile neutropenia	Any	• Interrupt ATG-010. • Continuously monitoring neutrophil count, until it is restored to ≥1.0 × 10^9/L. • Lower the dose by 1 level and re-initiate ATG-010 administration (see Table 5).
Anaemia		
Hemoglobin < 8.0 g/dL	Any	• Lower the dose of ATG-010 by 1 level (see Table 5). • Blood transfusion and/or adopting other therapies in clinical guidelines.
Life-threatening consequences (urgent intervention indicated)	Any	• Interrupt ATG-010. • Continuously monitor hemoglobin, until it is restored to a level ≥ 8 g/dL. • Lower the dose by 1 level and re-initiate ATG-010 administration (see Table 5). • Blood transfusion and/or adopting other therapies in clinical guidelines.
Non-hematological adverse reactions		
Hyponatremia		
Sodium level ≤ 130 mmol/L	Any	• Interrupt ATG-010 and give appropriate supportive care. • Continuously monitor sodium level, until it is restored to ≥ 130 mmol/L. • Lower the dose by 1 level and re-initiate ATG-010 administration (see Table 5).
Fatigue		
Grade 2 (lasting more than 7 days) or grade 3	Any	• Interrupt ATG-010. • Continuously monitor, until fatigue is resolved to grade 1 or baseline level. • Lower the dose by 1 level and re-initiate ATG-010 administration (see Table 5).
Nausea and vomiting		
Grade 1 or 2 nausea (oral intake reduced without manifest body weight loss, dehydration, or malnutrition), *or*, grade 1 or 2	Any	• Continue ATG-010 administration, and initiate additional anti-nausea administration.

Adverse Reaction [a]	Occurrence, count	Action
vomiting (not more than 5 times per day)		
Grade 3 nausea (insufficient oral intake of energy or liquid), *or*, grade 3 or above vomiting (not less than 6 times per day)	Any	• Interrupt ATG-010. • Continuously monitor, until nausea or vomiting is resolved to grade 2 or below or baseline level. • Initiate additional anti-nausea administration. • Lower the dose by 1 level and re-initiate ATG-010 administration (see Table 5).
Diarrhea		
Grade 2 (daily defecation increased by 4 to 6 times compared to baseline)	First time	• Continue ATG-010 administration, and give supportive care.
	Second and subsequent	• Lower the dose of ATG-010 by 1 level (see Table 5). • Give supportive care.
Grade 3 and above (daily defecation increased by 7 or more times compared to baseline; hospitalization indicated)	Any	• Interrupt ATG-010 and give supportive care. • Continuously monitor, until diarrhea is resolved to grade 2 or below or baseline level. • Lower the dose by 1 level and re-initiate ATG-010 administration (see Table 5).
Weight loss and anorexia		
Body weight decreased by 10% to < 20%, *or*, anorexia with manifest weight loss or malnutrition	Any	• Interrupt ATG-010 and give supportive care. • Continuously monitor body weight, until it is restored to more than 90% of baseline body weight. • Lower the dose by 1 level and re-initiate ATG-010 administration (see Table 5).
Other non-hematological adverse reactions		
Grade 3 or 4 (life-threatening)	Any	• Interrupt ATG-010. • Continuously monitor until the reaction is resolved to grade 2 or below, lower the dose by 1 level and re-initiate ATG-010 administration (see Table 5).

11.1.5.1. ATG-010 Dose Reduction due to Decreased Glomerular Filtration Rate

ATG-010 is not mainly eliminated by kidney; therefore, there is no need to change the dose of ATG-010 in the presence of kidney dysfunction; however, creatinine clearance must be >20 mL/min, otherwise ATG-010 plus low-dose dexamethasone treatment cannot be initiated. If creatinine clearance is decreased during the treatment period and is considered unrelated to ATG-010, the dose of ATG-010 may be maintained, but patient's condition must be closely monitored. If creatinine clearance is decreased to < 20 mL/min, it is considered to be related to ATG-010, and then the dose of ATG-010 should be lowered by 1 level. If creatinine clearance is restored to >20 mL/min and stays at this level for 4 weeks, the dose of ATG-010 can be restored to the previous level. If dialysis is given during the ATG-010 plus low-dose dexamethasone treatment period, ATG-010 plus low-dose dexamethasone must be given after dialysis.

11.1.5.2. Adjustment of ATG-010 Dose in the Presence of Infection

Any patient with grade ≥ 3 infection should interrupt ATG-010, until the infection is clinically resolved or the patient is clinically stable, and then ATG-010 administration can be re-initiated by lowering 1dose level. If the Investigator assesses that the infection is unrelated to the study drug and decide the administration of study drug can be continued, this decision should be made per discussion with the Sponsor's Medical Monitor.

Dexamethasone should be adjusted according to the guidelines of the medical institution, with

adrenal suppression being taken into account. Missed doses shall not be made up. While re-initiating ATG-010 regimen, patients can continue long-term treatment with antibiotics or other antimicrobial agents per the Investigator's discretion.

11.1.5.3. Cases not Requiring ATG-010 Dose Reduction

Below are exceptional cases to the dose modification guidelines. There is no need to interrupt ATG-010 in the following cases:

- Any grade of alopecia
- Electrolyte or serum analyte (e.g., urate) abnormalities that can be reversed by standard intervention

11.1.5.4. Dose Modification to Missed Dose or Vomiting

Note: A maximum of 2 ATG-010 doses can be given per week.

Missed Dose

If a dose is missed, the treatment schedule of the week should be modified to adapt to the 2 doses of the week, and 2 consecutive doses should be at least 36 hours apart.

If this dose must be skipped (for example, per attending doctor's advice), the next dose should be taken according to the treatment schedule. The dosing interval should not be less than 36 hours, and all missed doses and delayed doses should be recorded.

Vomited Dose

If vomiting occurs ≤ 1 hour after dosing, another dose should be taken. If vomiting occurs > 1 hour after dosing, the patient will be regarded as having taken a full dose.

11.2. Study Drug Storage

ATG-010 tablets should be stored in a safe area with access only to the study site personnel pharmacists or designees, at a temperature no more than 30℃ (i.e., room temperature or refrigerating temperature). Room temperature storage is preferred. The tablets should not be frozen. Study sites need to record the temperature of the storage place for the study drugs.

ATG-010 tablets (20 mg) are supplied in plastic blister packs with an aluminum foil lid. For detailed information on the preparation, storage, stability, and administration of ATG-010, see Appendix 4.

Dexamethasone tablets should be stored according to the suggestions in the package inserts.

11.3. Study drug Accountability

The Investigator or designee must record the count and dispensing of study treatment drugs in the drug record log. Patients need to return all unused study treatment drugs and packages on a regular basis, at the end of study, or upon discontinuation of study treatment. During study site visits and at the completion of study, Clinical Research Associate (CRA) should check the drug count periodically.

During the course of the study and at study close out, the Investigator should return all used and

unused study treatment drugs as well as a copy of the completed drug record log to the Sponsor.

ATG-010 shall not be used for any purposes outside the scope of this study protocol, nor shall it be transferred or licensed to any party not participating in this clinical study. The data of ATG-010 are proprietary confidential information, and the Investigator should keep it in this way.

The Investigator or a responsible party designated by the Investigator must carefully record the inventory and disposition of unused materials.

Before being used or returned to Antengene or destroyed by the designee, all drug supplies provided by Antengene must be stored in an appropriate safe place with limited access. The drug supplies must be counted and verified at the study site before being returned. Study sites need to maintain a temperature log of the storage place for the study drugs.

11.4. Concomitant therapies

11.4.1. 5-HT3 Antagonists Required

Unless contraindicated, all patients should receive 5-hydroxytryptamine (5-HT3) antagonists (e.g., palonosetron or equivalent) before the first dose of ATG-010 to minimize nausea. Alternative antiemetic agents may be used if the patient does not tolerate 5-HT3 antagonists.

11.4.2. Supportive Care

During the period of participatioing in this clinical trial, supportive measures should be taken to ensure the best medical care for patients. It is advised that patients maintain sufficient intake of liquids and calories during the course of treatment. Intravenous fluids therapy may be considered for patients at risk of dehydration. Patients will also receive blood product transfusions, antimicrobials, and growth factors including granulocyte colony-stimulating factors (for neutropenia), erythropoietins (for anemia,) and/or platelet-stimulating factors (for thrombocytopenia) as the best supportive treatment.

In addition to dexamethasone included in the standard treatment plan and required 5-HT3 prophylaxis (Section 11.4.1), the following supportive care (including anti-nausea/antiemetic therapy), antacids (proton pump inhibitors [PPIs] and/or H2 blockers), and other therapies may also be given:

- Appetite stimulants: Megestrol acetate, at a dose of 80-400 mg per day.
- Centrally acting preparations: Olanzapine, 2.5-5.0 mg per night by oral is recommended.
- Neurokinin 1 receptor antagonists (NK1R antagonists): Aprepitant or equivalent may be considered, covering selected patients with severe nausea and vomiting.

Additional anti-nausea and anti-anorexia agents may be given as needed (per National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines® for Antiemesis, NCCN Clinical Practice Guidelines® for Palliative Care and Chinese Expert Consensus on Prevention and Treatment of Nausea and Vomiting Related to Anti-Cancer Drug Treatment (2019 version)).

11.4.3. Infection

In patients with fever or other signs of systemic infection, appropriate broad-spectrum intravenous

antibiotics and antifungals should be initiated immediately.

11.4.3.1. Other Glucocorticoid Side Effects

The management of common glucocorticoid side effects has been detailedly recorded. In this study, it is strongly recommended to actively use proton pump inhibitors (PPIs), anti-hypertensives, and other preparations, so that the combined use of dexamethasone plus ATG-010 can be continued.

Patients with documented osteopenia or osteoporosis should continue to use dexamethasone with ATG-010 according to the requirements of this study. Standard precautionary measures should be formulated, for example, use of bisphosphonates, unless contraindicated.

11.4.4. Concomitant Medications and Therapies

Concomitant medications refer to any prescription drugs or over-the-counter preparations for prophylactic or therapeutic purposes, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations. Patients can continue taking baselines drugs previously taken. All concomitant medications must be recorded in the eCRF (except for diagnostic or surgical preparations). Any diagnostic, therapeutic or surgical procedures performed during the study period should be recorded, including the dates, operating procedures, and any clinical findings (if applicable).

11.4.4.1. Concomitant Medications Allowed

Concomitant medications can be used for managing symptoms, AEs, and intermittent diseases, and if medically necessary, can be used as standard of care. Medications for treating concomitant diseases such as diabetes mellitus, hypertension, and etc. are allowed.

11.4.5. Restricted Medications

Medication: Theoretically, ATG-010 interacts with glutathione (GSH); therefore, the use of acetaminophen (Paracetamol) plus ATG-010 was limited in previous ATG-010 studies. However, no significant clinical or laboratory abnormalities were found by the ongoing clinical safety evaluation on the combined use of these drugs [up to 1 g of acetaminophen and up to 55 mg/m^2 (about 80-100 mg) of ATG-010]. Accordingly, there is no longer any restrictions on the combined use of acetaminophen or acetaminophen-containing drug with ATG-010, except that acetaminophen must not exceed a total daily dose of 1 g on the dosing days of ATG-010.

Diet: There is no dietary restriction in this study. Patients should maintain sufficient intake of calories and liquids.

11.4.6. Prohibited Medicines

Concurrent therapy: Concurrent therapy with any anticancer therapy drugs other than the study drugs is not allowed. Other investigational drugs shall not be used during the study. Any immunosuppressant use during the study period must be confirmed by the Medical Monitor.

Medication: In this study, patients shall not use any drugs containing glutathione (GSH), S-adenosyl methionine (SAM), or N-acetylcysteine (NAC), since they may

promote ATG-010 metabolism. See Appendix 5 for the list of representative drugs. In this study, patients must report all prescription and over-the-counter drugs to the doctor.

11.4.7. Contraception Requirements

During the study period, patients shall not get pregnant or father a child, since the study treatmenst in this study will affect the fetus. Women shall not breastfeed during the study period. Patients should be aware of that contraceptive measures must be taken while on the study; this is extremely important. Female patients of childbearing potential must agree to use 2 contraceptive methods (1 highly effective contraceptive method and 1 effective contraceptive method) and have a negative serum pregnancy test at Screening. Male patients, if sexually active with females of childbearing potential, must adopt an effective barrier method of contraception. Highly effective contraceptive methods include:

1. Hormonal contraceptives (e.g., compound oral contraceptives, contraceptive patch, vaginal ring, injectable contraceptives, and implantable contraceptives)
2. Contraceptive ring or intrauterine device
3. Vasectomy or tubal ligation

Effective contraceptive methods include:

1. Barrier contraception (e.g., male condom, female condom, cervical cap, contraceptive diaphragm, and contraceptive sponge)

It should be particularly noted that,

- A barrier method of contraception itself alone cannot be used as highly effective contraception.
- Correct use of contraceptive diaphragm or cervical cap, including use of spermatocide, is one kind of barrier method of contraception.
- Cervical cap and contraceptive sponge are not very effective in parous women.
- Use of spermatocide alone is not an appropriate barrier mehod of contraception.
- Male condom plus cervical cap, contraceptive diaphragm or sponge with spermatocide (double-barrier method of contraception) is acceptable, but not a highly effective contraception.
- Male condom and female condom shall not be used simultaneously, otherwise they may be teared up or damaged.

In other words, the following contraceptive requirements should be met:

1. Permanently surgically sterilized or post-menopausal sex partner
2. Complete (real) sexual abstinence (when satisfying patient's preference and daily lifestyle) is an acceptable method of contraception. Note: Periodic abstinence (e.g., calendar method, ovulation period method, symptothermal method, and post-ovulatory contraception) and coitus interruptus are not acceptable.

Acceptable contraceptive methods must be explained to potential male and female patients. atients must agree to use the contraceptive methods described above throughout the study period and for 3 months after the last dose of study treatment, otherwise they will not be eligible for participating in this study.

For more safety information about pregnancy, please see Section 4.31.

11.4.8. Radiation Therapy

If clinically indicated, palliative radiotherapy for non-target lesion(s) are permitted, however, the study drugs should be held for ≥1 day prior to initiation of palliative radiotherapy and ≥1 day after each dose of palliative radiotherapy. ATG-010 treatment shall not be terminated solely due to palliative radiotherapy.

11.5. Treatment Compliance

Investigator or other study personnel should supervise the study drug treatment administered in the study site and guide patients on study drug self-administration. Patients will be asked to bring their study drug packages at each visit, and their compliance with the study drug intake specified in the protocol will be checked by tablet count.

After discussing with the patient and drug counting staff, the study personnel will record the compliance of study drug. The Investigator or designee will assess the compliance of study drug and record it in the source documents. The date will be recorded according to the study drug schedule. The Investigator or designee will count the number of dispensed tablets against the number of tablets returned by patient. Any dose deviations and missed doses will be recorded in the eCRF and drug accountability log to confirm the corresponding reason.

12. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical study subject administered with a certain pharmaceutical product, irrespective of its causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

It is expected that, clinically significant symptoms and signs associated with disease progression will be reported as AE; however, disease progression that is asymptomatic or confirmed by examinations only does not neede to be reported as an AE.

All SAEs will be recorded since the subject signs the informed consent form. AEs will be recorded after the use of study drug till 30 days after the last dose. Any SAE learned by the Investigator at any time thereafter and suspected to be related to the study drug will also be recorded.

Any abnormal laboratory finding or test result (e.g., PE, ECG, Echo, vital signs, etc.) occurring during treatment, if clinically significant (i.e., meeting any one or more of the following conditions), should be recorded as a single diagnosis on the AE page of the eCRF.

1. Is accompanied by clinical symptoms
2. Leads to a change of study drug (e.g., dose modification, interruption, or permanent discontinuation)
3. Requires a change of concomitant therapy (e.g., addition, interruption, termination, or any other changes of concomitant medications, therapies or treatment).

Investigator is responsible for recording all AEs occurring during the study period. Patients will be asked a non-directive question, for example, “Since our last inquiry/since the last visit, have you experienced any new symptoms or are there any changes in the symptoms?” AE should be reported on the corresponding page of the eCRF.

The actual grade and duration of AE should be reported.

The severity/intensity of AE will be graded based on subject’s symptoms per current Common Terminology Criteria for Adverse Events (CTCAE, v4.03).

AEs that are not included in the CTCAE will be assessed according to the following criteria:

- Grade 1 = transient or mild discomfort; activity not limited; no medical intervention/therapy required;
- Grade 2 = mild-to-moderate or moderate limitation in activity, some assistance possibly required; no or minimal medical intervention/therapy required;
- Grade 3 = moderate to marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible;
- Grade 4 = Life threatening - extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable;
- Grade 5 = death - the event results in death.

The term “severe” is used to describe the severity of AE; the event itself may have little clinical significance (e.g., “severe” headache). This is different from “serious”. The seriousness of AE is based on its outcome and is usually associated with events posting a threat to patient’s life or functions.

Investigator will make judgments on the correlation between AE and study drug, as shown in Table 7 below.

Table 7: Classification of AEs Listed Per Causal Relationship

Not Related	The event is not temporally associated with the study treatment, or by providing any other drug, therapeutic intervention, or underlying disease that can fully explain the event, the assessment of causality rules out the possibility of a reasonable causal relationship.
Related	The temporal association between the event and study treatment constitutes a definite causal relationship, and compared to any other drug, therapeutic intervention, or underlying disease, the event may be more reasonably explained by the exposure to study treatment.

12.1. Serious Adverse Event

A serious adverse event (SAE) refers to any untoward medical occurrence that at any dose (including those after the signing of ICF and prior to dosing):

- Results in death
- Is life-threatening (patient is at immediate risk of death at the time the event occurs)
- Requires hospitalization (official hospitalization for medical reason) or prolongation of existing hospitalization
- Results in permanent or significant disability/incapability
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

TEAE-unrelated hospitalizations due to elective procedures or other medical procedures during treatment will not be regarded as SAEs.

Sudden death and death unexplained should be reported as an SAE.

Progression of malignancy (including lethal outcomes) during the study period or within the safety reporting period should not be reported as an SAE.

Hospitalizations due to the following events will not be regarded as SAEs:

- Routine treatment or monitoring of the indications studied, is not related to any conditions aggravated.
- Blood or platelet transfusion for routine treatment of the indications studied; however, hospitalization or prolongation of existing hospitalization due to complications of transfusion should still be reported as an SAE.
- Procedures related to study protocol/disease-related examinations (e.g., surgery, scan, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolongation of existing hospitalization due to complications of these procedures should still be reported as an SAE.
- Hospitalization or prolongation of existing hospitalization for technical, practical or social reasons in the absence of an AE.

- Pre-defined procedures (i.e., scheduled prior to initiation of study treatment); must be recorded in the source documents. However, hospitalization or prolongation of existing hospitalization due to complications should still be reported as an SAE.
- Elective treatment for an existing sickness that is unrelated to the indications studied.

12.1.1. Follow-up of AE and SAE

All AEs occurring during the study period should be followed up according to the Good Clinical Practice, until the events are resolved, stabilized, or judged as no longer clinically significant, or until the patient is medically stable or the event is a chronic disease. Any AE assessed as study drug-related must be followed up until it is resolved or stabilized.

12.1.2. Post-study AE and SAE

The Investigator should follow up all unresolved events until the event is resolved, the patient is lost to follow-up, or there is another explanation for the AE. At the last scheduled visit, the Investigator should instruct each patient to report any subsequent events that the patient or the patient'spersonal physician believes to bereasonably related to participation in this study.

Before the end of the study, the Investigator should notify the Antengene Pharmacovigilance Department (see Section 12.1.3.1) of any death or AE that occur at any time after a patient has discontinued or terminated participation in the study and that may be reasonably related to this study.

After the end of the study, the Investigator should notify Antengene or its designee of any death or AE that occur at any time after a patient has discontinued or terminated participation in the study and that may be reasonably related to this study. If the Investigator becomes aware of the development of cancer or a congenital anomaly in the subequently conceied offspring of a patient who ha participated in this study, Antengene should also be notified.

12.1.3. Report of Serious Adverse Events

12.1.3.1. Reporting Requirements

For any SAE in any patient, the Principal Investigator or designated study site personnel must report to the Antengene Pharmacovigilance Department (within 24 hours following initial awareness of the event or awareness of the follow-up information), relevant regulatory authorities, and relevant ethics committee. The study sites will be asked to provide the following information:

- Study Protocol No
- Study site and/or Investigator number
- Demographic data
- Brief description of the event
- Date and time of onset (if applicable)
- Date and time of resolution (if applicable), if the event is resolved
- Current status, if the event is not resolved yet
- Any concomitant therapy and medication
- Investigator's assessment on the correlation between the SAE and investigational product
- Event outcome, if available

All other Investigators participating in the ongoing study drug clinical study will submit the copies of these reports to their Institutional Review Board (IRB) Ethics Committee (EC) after receiving them, if applicable. According to the standard operating procedures and the policies of IRB/EC, the Investigator will report all the SAEs to IRB/EC. Adequate records must be kept to demonstrate that IRB/EC has been properly notified.

12.2. Overdosage

Overdose refers to the intentional or unintentional administration of study drug to a study patient using a dose level higher than that is allocated to that individual patient per the study protocol. In the event of drug overdose, the Investigator and Antengene should be notified immediately, and the patient's AEs should be closely monitored. The patient should receive symptomatic treatment as appropriate, and the overdose event and related AEs and/or treatment should be recorded in the patient's medical record. In addition to recording the overdose in the patient's medical record, the event must be reported to the Antengene Pharmacovigilance Department using the Overdose/Medication Error Report Form. Any AE or SAE due to overdose observed will be handled as described in Section 12.2 (if applicable).

Because ATG-010 is metabolized via GSH binding, it is predicted that hepatic GSH depletion may occur in the case of overdose. Therefore, in patients with abnormal liver function test, use of supportive measures such as SAM 400 mg by oral administration, 1-4 times/day, or other drugs that can replace GSH, should be considered.

Medication errors, and administrations of study drug outside the predictable range of the study protocol, including drug misuse and abuse, must also be reported to the Antengene Pharmacovigilance Department using an Overdose/Medication Error Report Form.

12.3. Pregnancy

Pregnancy itself will not be regarded as an AE, unless it is reasonably believed that the investigational drug may interfere with the effectiveness of contraceptive medication.

Each pregnancy in any patient treated with ATG-010 or patient's partner should be reported to Antengene within 24 hours following the awareness of the event. The pregnancy should be followed up to find out the outcome, including natural or voluntary termination of pregnancy, delivery details, and presence or absene of any birth defects, congenital anomalities, or maternal and/or newborn complications. Pregnancy must be followed up and recorded, even if the patient withdraws from or completes the study.

It is advised that male patients should avoid to father a chhild within 3 months from termination of ATG-010 treatment. There is currently no information about the effects of ATG-010 on reproductive capacity, pregnancy, or subsequent fetal development.

Any pregnancy found within the period from the start of study medication to 3 months post study medication should be reported to the Investigator and the Sponsor.

13. Statistical considerations

13.1. Overall Considerations

13.1.1. Statistics and Analysis Plan

This section describes the statistical analyses to be used for evaluating the efficacy and safety endpoints of this trial. For the analysis details, please refer to the Statistical Analysis Plan (SAP).

Listings of appropriate disposition, demographic, baseline, efficacy and safety parameters will be generated. For categorical variables, the number and percentage of patients in each parameter category (including the missing data category), as well as two-sided 95% confidence interval (CI) as appropriate, will be presented in the form of summary table. For continuous variables, the number of patients, mean, median, standard deviation (SD), minimum, and maximum values will be provided. Time to event data will be summarized by Kaplan-Meier (KM) method, using 25th, 50th (median), and 75th percentiles with two-sided 95% CIs, and percentage of censored observations.

Primary analysis (including efficacy, safety, and PK evaluations) will be conducted at 3 months after the last patient enrollment, and supplementary efficacy and safety analysis will be conducted after the end of the study.

An interim analysis will be performed when approximately 50 patients have completed the clinical efficacy evaluations to assess the distribution of the patients who had previously received RRMM treatment. During the interim analysis, the clinical efficacy in patients who had previously received 3 classes of drugs (at least an immunomodulatory [i.e., lenalidomide], at least a protease inhibitor [i.e., bortezomib], and at least an anti-CD38 antibody) should be analyzed, but the efficacy for whole population enrolled will not be analyzed.

13.1.2. Sample Size Determination

This trial is a bridging clinical study to evaluate the clinical efficacy of ATG-010 plus low-dose dexamethasone in Chinese patients with relapsed/refractory MM.

A sample size of 82 subjects with relapsed/refractory MM who have previously been treated with immunomodulatory agent and proteasome inhibitors (i.e., including lenalidomide and bortezomib) will allow for detecting a statistical significance of the target ORR of 28% against the threshold ORR of 15%, with power of 80% (one-sided α=0.025).

13.1.3. Patient Disposition

A summary of patient disposition will be provided, including the number of patients in each analysis population, the number of patients with unevaluable disease per IMWG criteria, the number of patients censored at each of PFS and OS analyses, the number of lost to follow-up patients, the number of patients who discontinued before completing the study, and the reasons for discontinuation.

13.1.4. Blinding and Randomization

This is an open-label, single-arm study, therefore blinding and randomization are not applicable.

13.1.5. Dose Adjustment

Dose modifications that occured during the first treatment cycle and throughout the entire clinical study process will be analyzed. Meanwhile, an exploratory analysis of the effects of dose modification on efficacy may be performed.

13.2. Analytical Dataset

13.2.1. Analysis Population

13.2.1.1. Modified Intent-to-treat (mITT) Population

The modified intent-to-treat (mITT) population will include patients who received at least one dose of study treatment. This population will be used for efficacy analysis.

13.2.1.2. Per Protocol Population

The Per Protocol (PP) population will include all patients in the mITT population who meet the following criteria:

- Have an ATG-010 compliance ≥ 70%,
- Have at least 1 complete post-baseline response assessment, unless died or withdrew from study before that.
- Have no major protocol deviation that would comprimise the efficacy evaluation. The list of major protocol deviations affecting statistical analysis will be finalized before database lock.

Major protocol deviations and their impact on efficacy evaluation will be determined independent of knowledge of treatment response before database lock and study analyses. This population will be used for supportive efficacy analysis; however, if there are significant differences between the results of this population and those obtained in the mITT population, the efficacy evaluation will take these differences into account.

13.2.1.3. Safety Population

The safety population will include patients who have received at least one dose of study treatment.

13.2.1.4. Subgroup Efficacy Analyses

Subgroup comparisons of special interest will be assessed according to the Statistical Analysis Plan (SAP).

13.3. Data Analysis and Presentation

The disposition of patients participating in this clinical study, and the demographic and baseline characteristics, efficacy and safety data described in the section below will be presented in the form of summary tables. All relevant data collected via the eCRF and labs will be provided in the patient data listings.

13.3.1. Demographic Characteristics

The demographic characteristics of mITT, PP, and safety populations will be summarized, including gender, race, ethnicity, and age at the time of informed consent. For gender and race, summary

statistics will include the number and percentage of patients within each category. The race category is a classification recorded in the database. For age at the time of informed consent, the mean, median, minimum, maximum, and standard deviation of each patient population will be provided.

13.3.2. Baseline Characteristics and Medical History

Baseline characteristics includeperformance status, duration from initial diagnosis, response to prior therapy, types of prior therapy, and body height/body weight. Baseline data will be tabulated using the summary statistics for the mITT, PP, and safety populations; formal hypothesis testing will not be performed.

Baseline medical history and physical examination results for the same analysis populations will be presented in summary tables.

13.3.3. Primary Endpoint

The primary efficacy endpoint of ORR (proportion of patients who achieve PR, VGPR, CR, or sCR) based on mITT population and response assessment by IRC will be analyzed. For the hypothesis tesing of the target ORR of 28% against the threshold ORR of 15%, a two-sided 95% confidential interval of the ORR will be provided. A lower bound of this interval >15% will indicate statistical significance of the test. ORR will also be analyzed based on the response assessments made by Investigator.

13.3.4. Secondary Endpoints

The following secondary efficacy endpoints for the mITT and PP populations will be analyzed separately.

- Survival rate (SR) at 6, 9, and 12 months
- Duration of response (DOR) = Duration from the first observation of at least partial response (PR) to time of disease progression (PD] or death due to PD, whichever comes first. DOR for death due to any reasons other than PD will be censored.
- Clinical benefit rate (CBR) = CBR+minimal response [MR], and duration of clinical benefit (duration from the first observation of at least MR to PD or death due to PD, whichever comes first). Duration of clinical benefit for death due to any reasons other than PD will be censored.
- Disease control rate (DCR) = CBR+stable disease [SD; for at least 12 weeks])
- Progression-free survival (PFS) = Duration from start of study treatment to PD or death [irrespective of cause of death], whichever comes first)
- Time to progression (TTP) = Duration from start of study treatment to time of PD
- Overall survival (OS) = Duration from start of study treatment to death

The Kaplan-Meier (KM) method will be used to analyze the time to event endpoints (including duration of response, PFS, TTP, and OS), including the median estimate, 25th and 75th percentiles, and two-sided 95% CIs. The CBR and DCR will be summarized using two-sided 95% confidence intervals.

In addition, the following secondary endpoints of safety and tolerability will be analyzed using the Safety Analysis Set.

- Safety and tolerability will be analyzed per National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.
- The ATG-010 PK profile of this patient population will be described.
- Cytogenetic and fluorescence in situ hybridization (FISH) prognostic markers, including chromosomal aberrations [e.g., del17p, t(4;14), t(14;16), del13] and other cytogenetic categories of MM.

13.3.5. Pharmacokinetic

Plasma analysis will be performed using validated High-Performance Liquid Chromatography-Tandem Mass Spectrometry (HPLC/MS-MS) to determine the blood concentration of ATG-010. The drug concentrations will be used to plot tables and graphs for each subject's drug concentration-time data and average drug concentration-time data. The following PK parameters of ATG-010 will be obtained by analyzing effective blood drug concentration data:

- Maximum drug concentration (C_{max}, observed value)
- Time to maximum drug concentration (T_{max}, observed value)
- Areas under the drug concentration-time curve from time 0 to the last measurable concentration and to infinity ($AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$, respectively)
- Terminal elimination half-life ($T_{½}$)
- Plasma clearance (CL)
- Volume of distribution (Varea)

13.3.6. Safety Data

Safety analysis will be performed on the total patient population receiving any dose of study treatment, and the results will be listed. Each patient's original dose level will be used for safety analysis; in the primary safety analysis, dose escalation or reduction will not be independently classified. An additional exploratory assessment of the effects of dose modification on safety may be performed.

13.3.6.1. Adverse Event

AEs will be coded per Medical Dictionary for Regulatory Activities (MedDRA) and presented in tables and listings per MedDRA System Organ Class (SOC) and Preferred Term (PT).

Events deemed to be treatment-emergent will be included in AE analysis, where "treatment-emergent" refers to any AE or exacerbation of a pre-existing disease that emergesonor after the first dose of study treatment or within 30 days after last dose of study treatment, or any event that emerges prior to the end of study and is considered drug-related by the Investigator. AEs with partial dates available will be assessed using the existing date information to determine if they are treatment-emergent; AEs with dates completely missing will be assumed as treatment-emergent. No formal hypothesis testing will be performed on the incidence rates of AEs.

AEs will be summarized per patients' incidence rates; therefore, each patient will be counted only once for a given AE (Preferred Term) in any listing. The number and percentage of patients with any treatment-emergent adverse event (TEAE) will be summarized per treatment group, and stratified per SOC and Preferred Term. The number and percentage of patients with TEAE that is assessed as at least possibly related to treatment by the Investigator will also be listed. The number and percentage

of patients with any Grade ≥3 TEAE will be listed in the same way.

The Investigator will assess the causal relationship between an AE and the study drug as not related or related. If a patient experiences the same AE repeatedly, events with the highest severity and/or with a strong causal relationship with treatment will be used for the purpose of tabulations.

All SAEs reported will be listed.

All AEs (emerging during and after treatment) will be presented in the individual patient data listings and will be classified per treatment, patient, and study day. In addition, individual patient listings will be provided for the following events: deaths, SAEs, and AEs leading to withdrawal.

13.3.6.2. Laboratory Data

Clinical laboratory test values will be presented using traditional units of International System of Units (SI). For various clinical laboratory parameters (including hematology, clinical chemistry, coagulation, and urinalysis), the actual value and change from baseline (Day 1, prior to first dose of study drug) to each on-study assessment will be summarized. In the presence of duplicate values, the last non-missing value of each study date/time will be used. If Day 1 data of a pre-defined patient/parameter are not available, the baseline values will be replaced with the screening values.

Severity of selected clinical laboratory measures (e.g., measures with corresponding CTCAE grading) will be determined per CTCAE v4.03 criteria. Laboratory values at CTCAE Grade ≥3 will be presented in data listings. Shift tables will be generated to list the changes from baseline to worst on-study value and from baseline to last on-study value relative to CTCAE classification.

13.3.6.3. Vital Signs, Physical Examination and ECOG Performance Status

For vital signs, the actual value and change from baseline (Day 1) to each study assessment will be summarized. Shift tables will be generated to list the changes from baseline to worst on-study value and to last on-study ECG performance status. The individual patient listing of all vital sign measurements and ECOG performance status scores will be presented in data listings.

The physical examination results at Screening and changes in the physical examination results during the study will be summarized. All physical examination results will be presented in the individual patient data listings.

13.3.6.4. ECG Results

ECG results, including heart rate and PR, QRS, QT, and QTc (calculated by Fridericia's correction formula) intervals, will be summarized in a descriptive manner. If Bazett's correction formula is already entered by the study site, Fridericia-corrected QTc interval (QTcF) will be deduced using the following formula: QT/(RR^[1/3]), where, RR=60/heart rate. Actual values and changes from baseline will be reported at each study visit.

Each patient's ECG data will be provided in a data listing.

13.3.6.5. Concomitant meds

Concomitant medications used will be included in the individual patient data listings.

13.3.7. Missing Data Handling Procedures

The missing data handling procedures will be performed following the SAP.

13.4. Changes in Study Conduct or Planned Analyses

All deviations from the original statistical analysis plan will be recorded and presented in the final clinical study report.

14. Regulatory Considerations

14.1. International Conference on Harmonization – Good Clinical Practices

The study conduct, assessment and recording procedures defined in this study protocol are designed to ensure the study is conducted by Antengene, authorized representatives, and Investigators in compliance with the Good Clinical Practice (GCP) in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines E6 and the general ethical principles in the Declaration of Helsinki. The study will be implemented after approval by IRB/EC. Investigator will implement all aspects of this study in accordance with the applicable laws of the country or region in which related regulatory authorities are located.

14.2. Investigator's Responsibilities

Investigator's responsibilities are stipulated in ICH GCP guidelines and local laws and regulations. Antengene staff or authorized representatives will assess and approve Investigators, while investigators will be responsible for choosing the study personnel.

Investigators should ensure that all personnel assisting in the study work have a full understanding of the study protocol, amendments, study treatment, and study-related responsibilities and functions. Investigators should be responsible for keeping the list of other qualified personnel assisting Investigators and delegated with important study-related responsibilities.

Investigators are responsible for keeping the records of all subjects who have signed informed consent forms (ICF) and accepted for study screening. For screen-failure subjects, the reason must be recorded in their source documents.

Investigators or designated personnel must be present during the monitoring period to check data, solve queries, and facilitate direct access to view subjects' records (e.g., medical records, outpatient medical records, inpatient medical records, and study-related medical records) as to complete the source data verification. Investigators must ensure CRFs are filled and the queries are resolved in a timely andaccurate CRF manner.

14.3. Subject Information and Informed Consent

Investigator must obtain the informed consent of legal representative before performing any study-related procedures.

The record of informed consent performed before the study subject enters the study and the process of obtaining informed consent should be kept in the subject's source documents, including relevant dates. The original copy of ICF signed and dated by the study subject and the personnel explaining the ICF before the subject enters the study must be kept in the Investigator's study file, with a copy provided to the subject. In addition, if the study protocol is amended and the amendment has an impact on the content of informed consent, the ICF must be modified accordingly. After the study protocol is amended, subjects participating in the study must agree to sign the modified ICF. The original copy of modified ICF signed and dated by the study subject and the personnel explaining the ICF must be kept in the Investigator's study file, with a copy provided to the subject.

14.4. Confidential

Antengene confirm that subjects have the right to prevent privacy violations and will follow the requirements of ICH and other local regulations (whichever is the strictest). Antengene requests Investigators to allow the representatives of Antengene and if necessary, representatives of regulatory authorities to inspect and/or copy any study-related medical records according to local laws.

Direct access to medical records should be exempted or authorized outside the ICF signed by subjects, and Investigator is responsible for obtaining such a written permission from appropriate individuals.

14.5. Protocol Amendment

Any amendment of this study protocol must be approved by Antengene Clinical Study Physician/Medical Monitor. An amendment will be submitted to IRB/EC for written approval. A written approval must be obtained before the amended study protocol is implemented. The Investigator's name, study protocol number, study title, and amendment number (if applicable) should be detailed in the signed written approval letter from IRB/EC. Administratively, an amendment involving logics only does not require approval from IRB/IEC, but should be submitted to IRB/EC for information purpose.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Prior to the start of the study , the study protocol, ICF, and any other appropriate documents will be submitted to IRB/EC, and a cover letter or form will be attached simultaneously to list the submitted documents, their issue dates, and study sites (or jurisdictional area or region, depending on the situation) to be approved. Where appropriate, the documents will also be submitted to regulatory authorities according to local laws.

Antengene or authorized representative shall not provide Investigators with IP until all the ethical and legal documents required for study initiation are received. These documents must contain a list of IRB/EC members and their occupation and qualification. IRB/EC shall not disclose the name, occupation or qualification information of IRB/EC committee members, and they should issue a statement to certify that the composition of IRB/EC complies with GCP requirements. For example, this list can be replaced with the IRB General Guarantee Numbers.

The study protocol title, number, amendment number (if applicable), study sites (or jurisdictional area or region, , depending on the situation), and other documents reviewed should be mentioned in the official approval letter from IRB/EC. The approval letter must indicate the date the decision is made and must be officially signed by the committee members of IRB/EC. All ethical and legal requirements must be met before the first subject is enrolled in the study.

All subsequent study protocol amendments must be notified to IRB/EC and regulatory authorities (if applicable) according to local laws. Any amendment must be assessed to determine whether an official approval is required and whether the ICF should be amended accordingly.

Investigators must properly keep all records of communication with IRB/EC and all records of communication between coordinating Investigators and IRB/EC. This requirement also applies to any communication between Investigators (or coordinating Investigators, if applicable) and regulatory authorities.

14.7. Continuously Providing Information to Institutional Review Board/Independent Ethics Committee

If requested by law or IRB/EC, Investigator must submit the following information to IRB/EC:

- Provide the information of serious or unexpected AE as soon as possible;
- Periodic report on study progress;
- Study protocol deviations or any situation that may involve increased subject risks.

14.8. End of Study

Antengene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature termination of study will be properly recorded according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

In addition, Investigator or Antengene has the right to terminate a study site from participating in the study work at any time during the study period for medical or administrative reasons, for example:

- Unsatisfied subject enrollment;
- Non-compliance with GCP requirements;
- Inaccurate or incomplete collection on data;
- Falsified records;
- Non-compliance with requirements of study protocol.

15. Data Processing and Records Keeping

15.1. Data/Documents

Investigators must ensure that records and documents related to study conduct and study drug dispensing are complete, accurate, archived, and properly kept. Examples of source documents include: hospital records; clinic and outpatient medical records; laboratory test sheets; memos; subject diaries or assessment lists; dispensing records; recorded data from automatic instrument; certified photocopies or transcripts; microfilms; X-ray film results and reports; records kept by pharmacy and laboratory, and CRF copies or CD-ROMs.

15.2. Data Management

In this clinical trial, data will be collected through CRF and will be entered into the clinical database according to the standard operating procedures (SOP) of Antengene or authorized representative. These data will be electronically verified using the programed edit check method specified by the clinical team. Any data discrepancies identified will be notified to the clinical team and if necessary, study site personnel. The database will be modified accordingly after these problems are solved. All changes to the data will be tracked through internal audit trail system.

15.3. Study-related Records Keeping

Essential documents will be kept by Investigators for at least 2 years after the marketing application of the ICH region is eventually approved, or there is no more pending or expected marketing authorization in the ICH region, or at least 2 years after the clinical development of the IP is officially discontinued. Investigators must keep these documents according to the time requirement described above or per local laws or (whichever is longer). Essential documents include but are not limited to:

- ICFs signed by all subjects;
- A list of subject identification codes, screening record form (if applicable), and enrollment record form;
- All communication records between the Investigator and IRB/EC;
- A list of IRB/EC members;
- All communication records of between the Investigator and Antengene and its authorized representative;
- Lists of other qualified personnel assisting the investigator, and delegates with important study-related responsibilities by Investigator, and their responsibilities in the study, curriculum vitae, and signature;
- Copies of a CRF (e.g., paper version) and modification records of all subjects;
- IP accountability records;
- Records of any body fluid or tissue sample;
- All other source documents (subject records, hospital records, laboratory test records, etc.);
- All other documents listed in Section 8 of ICH GCP Consensus Guideline (Essential Document for Conduct of a Clinical Trial).

If the Investigator wishes to assign essential documents to others for storage, transfer the documents to other place, or is not able to preserve keep the documents within a specific period of time,

Antengene must be notified. Investigator must obtain a written approval from Antengene before destroying any record. If the Investigator is not able to fulfill this obligation, he/she must apply for Antengene's permission to arrange a replacement. Details about this arrangement should be recorded.

If the relevant health department requests to access the study documents, all documents requested should be provided. Investigators/hospitasl should take action to prevent accidental or premature destroying of these documents.

15.4. Information Disclosure

All information provided to Investigators by Antengene or its designee will be kept strictly confidential. No disclosure is allowed unless it is compliant with the release right granted to the Investigator in the clinical trial agreement.

No information about the study or its progress will be disclosed to any personnel not participating in this study other than Antengene or its authorized representative, or be kept confidential to IRB or similar committees, unless required by law.

15.5. Reporting and Release of Study Documents

Antengene will publish the results of this study in peer-reviewed medical publications or journals, and may also use the study findings for educational purposes. In addition, Antengene may submit this study and its results upon the request of the local health department to include this study in all appropriate health department’s reserch registries, and may publish this study on theresearch registry website of the health department. Antengene will choose the first author based on several considerations, including but not limited to the study participation, subject enrollment, contribution to study protocol formulation and, analysis, writing of manuscript, relevant abstracts, and performance in the study.

16. Quality Control and Quality Assurance

Antengene or authorized representative will carefully monitor all aspects of the study to ensure compliance with applicable government regulations and current GCP, standard operating procedures.

16.1. Study Monitoring and Source Data Verification

Antengene ensures that appropriate monitoring procedures will be adopted before, during, and after study conduct. Review all aspects of the study with the Investigator and study personnel during the study initiation visit and/or Investigator meetings. Antengene representative will review the study protocol, CRF, informed consent process, records storage, and AE/SAE reporting, and other aspects with the Investigator before subject enrollment. Monitoring includes study site visits, and any proper communications by mail, e-mail, fax or phone with the Investigator and study personnel. During the monitoring visit, Antengene representative will check/inspect the facility, study drug storage area, CRF, subject source documents, and all other study documents according to the study monitoring plan.

The accuracy of data will be checked during source data verification, i.e., directly comparing the data recorded in the CRF with appropriate source documents. Any discrapancies identified will be checked by the Investigator and/or study personnel. For any necessary modification, a query will be generated directly in the CRF to the Investigator and/or study personnel. The informed consent, compliance with inclusion/exclusion criteria, as well as SAE documents and appropriate records will be verified according to the monitoring procedures. Other monitoring may also be required in a specialized study monitoring plan.

16.2. Auditing and Inspection

In addition to routine monitoring procedures, Antengene also has an internal GCP quality assurance team. The representative of this team will audit clinical study activities according to the SOP of Antengene or its authorized representative to assessstudy compliance per GCP and regulations.

Investigators are requested to permit IRB/IEC, regulatory authorities (e.g., National Medical Products Administration of China), and company's authorized representatives to have direct access to study conducting facilities, source documents, CRF, and applicable supporting records of subject participation, so that auditing and inspection can be carried out. Investigators should always be present during auditing and/or inspection. Whenever a regulatory authority contacts an Investigator and requests an inspection, the Investigator should notify Antengene immediately.

17. References

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Appendix 1. Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria

Table 8: Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria

ECOG performance status score	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Time in bed <50%. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about >50% of waking hours
3	Time in bed >50%. Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Origin: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.*Am J Clin Oncol*.1982;5:649-655)

Appendix 2. International Staging System for MM

Table 9: International Staging System for MM

Phase	Characteristics
Stage I	β2-microglobulin <3.5 mg/L, albumin ≥3.5 g/dL
Stage II	β2-microglobulin <3.5 mg/Land albumin <3.5 g/dL, or β2-microglobulin 3.5-5.5 mg/L irrespective of the serum albumin
Stage III	β2-microglobulin ≥5.5 mg/L

Origin: Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*.2005;23:3412-3420

Appendix 3. International Myeloma Working Group Response Criteria, Myeloma

Table 10: International Myeloma Working Group Response Criteria (Kumar 2016)

Standard IMWG Response Criteria[1, 2, 3]	
Response subcategory	**Response criteria**
Complete Response (CR)	Negative IFE of serum and urine, disappearance of any soft tissue plasmacytomas (SPD), and <5% plasma cells in bone marrow aspirates
Stringent Complete Response (sCR)	CR as defined above plus normal FLC ratio [4] and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells [5])
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by IFE but not on electrophoresis, or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours
Partial Response (PR)	≥50% reduction of serum M-protein plus reduction in 24-hour urine M-protein by ≥90% or to <200 mg per 24 hours. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum FLCs are also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%. In addition to the above criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required [6]
Minimal Response (MR)	≥25% but <49% reduction of serum M-protein, and reduction in 24-h urine M-protein by 50-89%. In addition to the above criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required [6]
Stable Disease (SD)	Not recommended for use as an indicator of response; stability of disease is best described by providing the TTP estimates. Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive of Disease (PD) [7,8]	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in any one or more of the following criteria. Serum M-protein with an absolute increase ≥ 0.5 g/dL; Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL Urine M-protein (absolute increase must be ≥200 mg/24 hr); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable FLC levels, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be >10%); Appearance of new lesions, ≥50% increase from nadir in SPD [6] of >1 lesion, or a ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of TTP or PFS but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD[6] of the measurable lesion. Hypercalcemia (>11 mg/dL); Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-

	myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma. Hyperviscosity related to serum paraprotein
Relapse from CR (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see above)
Relapse from MRD Negative (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

Abbreviations: ASCT = autologous stem cell transplantation; CR = complete response; CRAB features: calcium elevation, kidney failure, anemia, lytic bone lesion; CT = computed tomography; DOR = duration of response; FDG = fluorodeoxyglucose; FLC = free light chain; hr = hour; Ig = immunoglobulin; IMWG = International Myeloma Working Group; MM = multiple myeloma; MR = minimal response; MRD = minimal residual disease; MRI = magnetic resonance imaging; NGF = next-generation flow cytometry; NGS = next-generation sequencing; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; SD = stable disease; SPD = sum of products of two longest perpendicular diameters; TTP = time to progression; VGPR = very good partial response.
Source: Kumar, 2016

[1] All response categories require two consecutive assessments made at any time before the institution of any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (e.g., after induction therapy, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected CR. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG-PET if imaging MRD-negative status is reported.

[2] According to IMWG, the quantitative Ig level measured by turbidimetry can be used to replace SPEP in determining the conventional M-protein measure of patients with IgA or IgD myeloma. In addition, according to IMWG, response can be confirmed if the patient fails to provide 24-h urine sample collection after the screening activities. See the section "Practical considerations for application of IMWG consensus criteria" in the guidelines (Page e340; Kumar, 2016)

[3] Derived from international uniform response criteria for MM. (*Durie 2011*). MR definition and clarifications derived from Rajkumar (*Rajkumar 2011*). When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the CR criteria listed previously. VGPR in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response criteria. Bone marrow assessments do not need to be confirmed. Each category, except for SD, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as DOR.

[4] All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

[5] Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

[6] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

[7] Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and PFS, patients who have achieved a CR and

are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a CR or relapse from MRD should be used only when calculating disease-free survival.

[8] In the case where a value is felt to be a spurious result per Investigator's discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value.

For questions about the interpretation of these criteria, please refer to the section "Practical considerations for application of IMWG consensus criteria" of the guidelines.
(Page e340, *Kumar 2016*).

Appendix 4. ATG-010 (SELINEXOR) Preparation and Administration

Description of ATG-010

ATG-010 is a selective inhibitor of nuclear export (SINE) ATG-010 blocks nuclear export specifically by binding to the exportin XPO1.

Chemical name: (*Z*)-3-{3-[3,5-bis(trifluoromethyl)phenyl]-1H-1,2,4-triazol-1-yl}-*N'*-(pyrazin-2-yl) acrylohydrazide

Molecular formula: $C_{17}H_{11}F_6N_7O$

Molecular weight: 443.31

Dose Formulation

ATG-010 will be supplied and administered in the form of 20 mg immediate-release coated tablet.

Storage and Stability

ATG-010 tablet (20 mg) will be supplied in plastic blister packs with aluminum foil lid and packed in children-resistant secondary cartons. ATG-010 should be stored in a locked safe area with access to study site pharmacists or designees, at a storage temperature ≤ 30°C (86°F). Room temperature storage is recommended, and refrigeration is allowed. Tablets shall not be frozen.

Management

The preparation, handling, and safe disposal of chemical drugs should be done in an independent protected environment by qualified personnel familiar with procedures for minimizing self and environmental overexposure.

Availability

ATG-010 is an investigational product that will be provided free of charge by Antengene.

Preparation

No special preparation is required ATG-010 tablet formulation shall not be crushed.

Administration

ATG-010 will be taken orally as tablet. ATG-010 should be swallowed with at least 120 mL of liquid (water, milk, juice, etc.) within 30 minutes after intake of solid food.

Patients in this study will receive ATG-010 80 mg (45 mg/m2 BSA) plus dexamethasone (20 mg), twice weekly in four-week cycles.

Accountability

Investigator, or responsible party designated by Investigator must keep detailed records of drug inventory and disposal using the drug accountability record form or other similar drug accountability documents.

Destruction and Recovery

At the end of the study, unused ATG-010 supplies should be destroyed according to the policy of related institution. The destruction will be recorded in the drug accountability record form or other appropriate documents.

Appendix 5. Products Containing Glutathione (GSH), S-adenosyl Methionine (SAM), or N-acetylcysteine (NAC) (List of Representatives)

Table 11: Products Containing Glutathione (GSH), S-adenosyl Methionine (SAM), or N-acetylcysteine (NAC) (List of Representatives)

Glutathione (GSH)		**N-acetylcysteine (NAC)**		**S-adenosyl Methionine (SAM)**	
Product Name	**Ingredient**	**Product Name**	**Ingredient**	**Product Name**	**Ingredient**
Glutathione	Glutathione	Antidote to acetaminophen overdose	Acetylcysteine	SAM-e Complete	S-adenosyl-methionine
L-glutathione	L-glutathione	Cerefolin NAC: medical food for age-related memory loss	L-methylfolate, Vitamin B12 N-acetylcysteine	SAMe	S-adenosyl-L-methionine
Glutathione reduced	Glutathione	NAC	N-acetylcysteine	Double-strength SAMe 400	S-adenosyl-methionine
Reuced glutathione with α-lipoic Acid	Setria L-glutathione	N-A-C Sustain	N-acetyl-L-cysteine		
Glutathione, cysteine & C	Glutathione, L-cysteine, Vitamin C	Best NAC detox regulators	N-acetylcysteine		
(Mega-) Liposomal Glutathione	Glutathione				
Lypospheric GSH	Glutathione				
Ivory Caps Skin Enhancement Formula	Glutathione				