CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-803-02-13

Protocol Title: A Study of ALT-803 in Patients with Relapsed or Refractory Multiple Myeloma

Date of Protocol:
Version# 01 January 7, 2014

Sponsor Contact:

Altor BioScience
CORPORATION

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SYNOPSIS

Sponsor: Altor Bioscience Corporation

Protocol#: CA-ALT-803-02-13

Study Drug Name: Not applicable

Study Treatment

Active agents: ALT-803, a "recombinant human super agonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D:IL-15RαSu/IgG1 Fc complex)

Study Type: Interventional

Study Phase: Ib/II

Protocol Title: A Study of ALT-803 in Patients with Relapsed or Refractory Multiple Myeloma

Objectives: To evaluate the safety and tolerability of escalating doses, identify the Maximum Tolerated Dose level (MTD) or Minimum Efficacious Dose (MED) and designate a dose level for Phase II study (RP2D) of ALT-803 in patients with relapsed or refractory multiple myeloma.

To evaluate the effect of ALT-803 on the peripheral absolute lymphocyte counts (ALC) and white blood cell (WBC) counts, the number and phenotype of peripheral blood T (total and subsets) and NK cells.

To estimate the anti-tumor activity of ALT-803 by radiologic or pathologic disease response, progression free survival, and overall survival in treated patients.

To characterize the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α, of ALT-803 in treated patients.

Study Design: This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-803 in patients with relapsed or refractory multiple myeloma.

The study includes a dose escalation phase to determine the MTD or MED using a modified classic (3+3) dose escalation design and to designate a dose level for the Phase II expansion phase (RP2D) and a two-stage expansion phase at the RP2D using a Simon two-stage design. In Phase I, five dose levels will be evaluated. A step-down dose level (cohort# -1) will be provided in the event of encountering DLT in two patients at the planned initial dose level. In the absence of unacceptable toxicity or disease progression, each enrolled patient will receive up to four 6-week study treatment cycles, each consisting of a 4-week treatment period and a 2-week rest period. In each cycle, patients will receive four doses of ALT-803 by intravenous injection weekly for 4 weeks followed by a 2-week rest period. Patients with sufficient recovery of toxicities from the previous treatment cycles will be eligible to continue study treatment. After receiving two treatment cycles, patients who have at least stable disease assessed at week 11-12 may receive up to two additional study treatment cycles followed by reassessment for continued tumor response.

The study will be conducted in conformity with Good Clinical Practice (GCP).

Treatments: The study treatment plan for each enrolled patient includes up to four 6-week study treatment cycles. In each cycle, patients will receive four weekly doses of ALT-803 by intravenous injection followed by a 20-day rest period. The rest period may be extended to include up to four additional weeks if necessary. Patients who do not experience or who sufficiently recover from toxicities of the previous treatment cycles will be eligible to continue the treatment included in the study treatment plan.

Treated patients will have up to two anti-tumor evaluation visits. Patients who receive at least three study drug doses during the first 2-cycle treatment period will be evaluated for anti-tumor response during week 11-12. Patients who have at least stable disease from the first anti-tumor evaluation and who meet other criteria to continue study treatment will receive up to two additional study treatment cycles, with the same treatment schedule and at the same dose level as the first two cycles, followed by reassessment for continued tumor response.

The study treatment and response evaluation schedule is illustrated below:

Treatment Cycle	Cycle #1				REST	Cycle #2				Response Evaluation	Cycle #3				REST	Cycle #4				Response Evaluation
Treatment Week	1	2	3	4	5-6	7	8	9	10	11-12	13	14	15	16	17-18	19	20	21	22	23-24
Treatment Day	1	8	15	22	23-42	43	50	57	64	65-84	85	92	99	106	107-126	127	134	141	148	149-168
Dose#	1	2	3	4	Rest weeks	5	6	7	8		9	10	11	12	Rest weeks	13	14	15	16	
Response Evaluation										X										X
ALT-803	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	

There are no restrictions on further therapies, such as chemotherapy, radiation therapy or surgery to be used after the protocol-specified therapy. Clearly, post-study treatments could be of significant clinical benefit in selected patients, and these patients will be followed for outcome.

Enrolled patients will receive the study treatment at qualified cancer treatment centers with adequate diagnostic and treatment facilities to provide appropriate management of therapy and complications. ALT-803 will be administered by intravenous infusion into a central or peripheral vein under the supervision of a qualified physician experienced in the use of biologic anti-cancer agents.

Dose Escalation Phase: A modified 3 + 3 design will be used for identifying a tolerable dose for phase II studies by monitoring patients for DLTs to determine the MTD and for identifying an efficacious dose by monitoring patients' ALC and WBC count to determine the MED during the DLT observation period. The dose escalation phase is concluded when either the MTD or the MED is determined. A dose level (RP2D) will then be designated for Phase II study. There are five escalating dose levels of ALT-803 and a step-down cohort (-1) with a lower dose level of ALT-803 in the event that unexpected toxicity is encountered at the initial dose level.

Below are the planned dose levels of the study drug during the dose escalation phase of the study.

Cohort	ALT-803 Dose (µg/kg)	Number of patients
-1	0.5	3 to 6
1 (initial)	1	3 to 6
2	3	3 to 6
3	6	3 to 6
4	10	3 to 6
5	20	3 to 6

Dose limiting toxicity (DLT) is defined as follows: any study drug related toxicity that is of Grade 3 and does not resolve to Grade 1 or lower within a week despite the use of medical intervention or that is of Grade 4, with exceptions described in the study protocol.

The DLT Observation Period is defined as the duration of the first treatment cycle.

Maximum Tolerated Dose level (MTD) is defined as a dose level at which <2 out of 6 patients experienced DLT and that is one level below a dose that was not tolerated.

Minimal Efficacious Dose (MED) is defined as a dose level which produces an ALC ≥25,000/µL sustained for 14 days or a total WBC ≥35,000/µL sustained for 14 days among 2/3 or 4/6 of patients. For safety, we have also defined an "exceeding MED" as the occurrence of ALC ≥35,000/µL or WBC ≥50,000/µL sustained for 14 days.

Expansion Phase

The two-stage expansion phase at the MTD or the MED level will be conducted using an optimal Simon's two-stage design. Objective response (OR) (defined as complete response (CR) + partial response (PR)) will be evaluated and set thresholds of lack of efficacy (OR rate (ORR) = 10%) and an efficacy level of interest (ORR = 30%) will be selected.

Stopping Rules:

Patient enrollment will be temporarily suspended based on occurrence of any of the following events, and the study committee, including the sponsor, the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

During the dose escalation phase of the study,

- If the maximum planned dose level has been reached, but neither the MTD nor MED can be determined.

- If de-escalation occurs and the step-down dose level cannot be designated as the MTD or MED.

Any time during the expansion phase of the study,

- More than 33% of patients experience a possible, probable or definite study drug related DLT.
- Favorable anti-tumor response data collected from enrolled patients.

At any time during the study,
The study committee may meet to discuss how to proceed with the study and may make any or all of the following recommendations for further patient enrollment:

- Downward adjust the study drug dose.
- Adjust the study drug dosing schedule.
- Recommend more effective pre-therapy, intra-therapy and post-therapy side effect mitigation interventions.
- Correct protocol technical errors that caused unnecessary dose omissions or premature treatment discontinuations. After correction of protocol errors, the DSMB may meet to re-evaluate the safety profile of the study treatment and recommend how to proceed with the study, if necessary.

Evaluations: Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug. The anti-tumor response will be evaluated at week 11-12 and week 23-24 from the start of study treatment. All patients who receive at least 3 doses of the study drug ALT-803 will be included in the anti-tumor response evaluation.

Population: Patients of 18 years of age and above with relapsed or refractory multiple myeloma. Patients also need to have adequate cardiac, pulmonary, liver and kidney functions and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

Sample Size: A total of up to 30 assessable patients will be accrued to the dose escalation phase of the study (Phase Ib). Anticipated enrollment to this phase is 18 patients. Up to an additional 23 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 41 assessable patients will be enrolled to complete the study. Assuming a 20% rate of ineligible or non-assessable cases, a total of up to 50 patients may be accrued to the study.

Primary Endpoints

For Phase Ib only (1) Determination of the MTD or MED and designation of the recommended dose level (RP2D) for Phase II study of ALT-803 in patients with relapsed or refractory multiple myeloma.

For Phase Ib & II (2) Safety profile of ALT-803 in treated patients.
(3) Disease response rate of treated patients.

Secondary

Endpoints

(1) Evaluation of the effect of ALT-803 on the peripheral ALC and WBC counts, the number and phenotype of peripheral blood T (total and subsets) and NK cells in treated patients.
(2) Duration of response in treated patients.
(3) Progression free survival of treated patients.
(4) Overall survival of treated patients.
(5) Characterization of the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α, of ALT-803 in treated patients.

Pharmacokinetics & Biomarkers:

Fresh blood samples will be collected to assess immune cell levels and phenotype, and serum samples for pharmacokinetics, immunogenicity of the study drug ALT-803, and the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α after ALT-803 administration in treated patients. Blood samples for pharmacokinetic analysis will be taken on the first day of ALT-803 administration in the first study treatment cycle. Venous blood will be obtained at Time 0 (before the start of infusion), at 30 minutes, and 2, 4, 6 and 24 hours from Time 0 for the assessment of ALT-803 serum concentrations. Non-compartmental and compartmental analyses will be conducted. In addition, the same blood samples collected for PK analysis will be used to assess the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α. Fresh blood samples for immune cell levels and phenotype testing will be collected before the start of first and fourth dose of study drug infusion in each treatment cycle. Bone marrow samples will be collected for future analysis of molecular markers associated with responses or resistance to ALT-803 in patients with relapsed or refractory multiple myeloma.

Monitoring Tests:

Blood samples for standard chemistry and CBC with differential will be obtained at screening, on each study drug infusion day, and at follow-up visits. Blood samples for immunogenicity testing for anti-ALT-803 antibodies will be collected prior to dosing on the first ALT-803 infusion day and at weeks 7 and 12 from the initial dose of study treatment. Blood and urine samples will be collected on each follow-up visit for response assessment.

Response Assessment:

There are at least two response assessments for treated patients: the first assessment during week 11-12 and the second assessment during week 23-24 from the start of study treatment. After completion of the first two cycles of study treatment, patients who have received at least 3 doses of study drug will have the first response assessment. After completion of the two additional cycles of study treatment, patients, regardless of the number of additional study drug doses received, will have the second response assessment. Response assessments will be carried out according to the new International Uniform Response Criteria for Multiple Myeloma proposed by the International Myeloma Working Group. Baseline evaluations should be performed up to 14 days before study treatment starts.

Progression & Survival

Assessment: Progression-free survival, overall survival, and duration of response of all treated patients will be assessed every three months during year 1 and then every 6 months during years 2 and 3 from the start of study treatment, or through the point designated as the end of the study follow up.

Adverse Events: All patients will be monitored and evaluated for clinical toxicities during the treatment period and queried at each follow-up visit for Adverse Events (AEs). Patients may volunteer information concerning AEs. All adverse events will be graded by using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), and logged in the patient Case Report Form. The study centers should report all Serious Adverse Events (SAEs) and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) no more than 24 hours after learning of the event. The sponsor will use the information to manage and coordinate the dose escalation, cohort expansion and patient enrollment. The sponsor will then inform all of the participating clinical sites of the current dose level and the number of patients to be enrolled at that level, or of any patient enrollment suspension via phone, fax or email within 24 hours of learning of the event. The study centers should report all other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related AEs that are both serious and unexpected will be reported to the FDA in an expedited manner in accordance with 21 CFR §312.32.

Statistical Plan: For each cohort, all AEs will be tabulated and examined and all safety, pharmacokinetic and tumor response data will be evaluated. For estimation of duration of response and progression free survival, the Kaplan-Meier method will be used. *P*-values of ≤ 0.05 (two-sided) will be considered to indicate statistical significance.

8. STUDY CALENDAR, CLINICAL PROCEDURES & TESTS

8.1 Study calendar

TESTS & PROCEDURES	SCREEN/ BASELINE[1]	TREATMENT CYCLE #1				REST	TREATMENT CYCLE #2				1ST RESPONSE ASSESSMENT	TREATMENT CYCLES #3 AND #4	2ND RESPONSE ASSESSMENT	FOLLOW-UPS					
Study Month		1					2				3	4-5	6	9	12	18	24	30	36
Study Week		*1*	*2*	*3*	*4*	*5-6*	*7*	*8*	*9*	*10*	*11-12*	*13-22*	*23-24*	*Any day during the month*					
Study Day		1	8	15	22	23-42	43	50	57	64	65-84	85-148	149-168						
Tolerance Window		*+/- 2 days*				*23-42*	*+/- 2 days*				*Any day*		*Any day*						
Medical history	X					R E S T P E R I O R						Follow Institution's standard of care (SOC) policy. If performed, follow the same schedule as in the first two cycles of study treatment.							
Serum pregnancy test[2]	X																		
Complete physical exam	X	X					X				X		X						
Vital signs, Weight, Height[3], Cardiac & Lung function monitoring	X	X	X	X	X		X	X	X	X	X		X						
Concurrent medication	X	X	X	X	X		X	X	X	X	X		X						
Adverse event assessment[4]	X	X	X	X	X		X	X	X	X	X		X						
CBC with Differential	X	X	X	X	X		X	X	X	X	X		X						
Blood Chemistry	X	X	X	X	X		X	X	X	X	X		X						
EKG	X	X[5]					X												
PFT only when clinically indicated	X																		
Response evaluation[6]											X		X						
Serum quantitative immunoglobulins	X										X		X						
SPEP	X										X		X						
UPEP-random	X										X		X						
SIFE	X										X		X						
UIFE -random	X										X		X						
Serum FLC assay[6.1]	X										X		X						
Bone marrow plasma cell percentage[6.2]	X										X		X						
Bone marrow immunohistochemistry or immunofluorescence[6.3]											X		X						
Soft tissue plasmacytomas assessment[6.4]											X		X						
Disease & survival follow-up/post-therapies[7]														X	X	X	X	X	X
Immune cell levels & phenotype[8,11]		X[8]			X[8]		X[8]			X[8]									
PK[x], IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α[9,11]		X[9]																	
Immunogenicity tests[10, 11]		X[10]					X				X								
Study drug (ALT-803)		**a1**	**a2**	**a3**	**a4**		**a5**	**a6**	**a7**	**a8**		**Follow the same schedule as in the first 2 cycles of study treatment**							

[1]Screening/baseline evaluations are performed ≤ 14 days prior to start of therapy. If the patient's condition is deteriorating, ECOG status and laboratory evaluations should be repeated within 48 hours prior to initiation of study treatment infusion. [2]Pregnancy test is for women with childbearing potential only. [3]Vital signs (especially blood pressure), clinical status and laboratory tests should be reviewed before start of therapy. Vital signs will be evaluated at 15, 30, 60 and 120 minutes and then hourly post infusion until discharge (or at completion of dose monitoring) from the clinic, and body weight before infusion on drug infusion day. [4]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [5]If the screening EKG was performed within 14 days prior to start of study treatment, the EKG is not required. [6]Disease response and progression assessment will be evaluated using the new International Uniform Response Criteria for Multiple Myeloma proposed by the International Myeloma Working Group. [6.1]Only when serum and urine M-protein are unmeasurable. [6.2] Only when serum and urine M-protein and serum FLC are unmeasurable and bone marrow plasma cell percentage > 30% at baseline. [6.3]Only when sCR is to be determined. [6.4]Only when present at baseline, and to confirm CR or PR by X-rays, MRI or CT scans. [7]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [8]Fresh blood samples for immune cell levels & phenotype testing will be collected before dosing. [9]Collect blood samples at Time 0 (before drug infusion), at 30 min (+/- 5 min), 2 hour (+/- 15 min), 4 hour(+/- 30 min), 6 hour (+/- 60 min) , 24 hour (+/- 6 hour)- from Time 0. IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α assays are performed using the same samples and at the same schedule as PK. [10]Use the sample collected before dosing for PK test. [11]Residual samples may be used by Sponsor for research studies of other biomarkers. [x]The last PK sample will be collected on the next day.

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Date of Protocol:
Version# 01 January 7, 2014
Version# 02 February 3, 2014

Sponsor Contact:

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SYNOPSIS

Sponsor: Altor Bioscience Corporation

Protocol#: CA-ALT-803-02-13

Study Drug Name: Not applicable

Study Treatment

Active agents: ALT-803, a "recombinant human super agonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D:IL-15RαSu/IgG1 Fc complex)

Study Type: Interventional

Study Phase: Ib/II

Protocol Title: A Study of ALT-803 in Patients with Relapsed or Refractory Multiple Myeloma

Objectives: To evaluate the safety and tolerability of escalating doses, identify the Maximum Tolerated Dose level (MTD) or Minimum Efficacious Dose (MED) and designate a dose level for Phase II study (RP2D) of ALT-803 in patients with relapsed or refractory multiple myeloma.

To evaluate the effect of ALT-803 on the peripheral absolute lymphocyte counts (ALC) and white blood cell (WBC) counts, the number and phenotype of peripheral blood T (total and subsets) and NK cells.

To estimate the anti-tumor activity of ALT-803 by radiologic or pathologic disease response, progression free survival, and overall survival in treated patients.

To characterize the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α, of ALT-803 in treated patients.

Study Design: This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-803 in patients with relapsed or refractory multiple myeloma.

The study includes a dose escalation phase to determine the MTD or MED using a modified classic (3+3) dose escalation design and to designate a dose level for the Phase II expansion phase (RP2D) and a two-stage expansion phase at the RP2D using a Simon two-stage design. In Phase I, five dose levels will be evaluated. A step-down dose level (cohort# -1) will be provided in the event of encountering DLT in two patients at the planned initial dose level. In the absence of unacceptable toxicity or disease progression, each enrolled patient will receive up to four 6-week study treatment cycles, each consisting of a 4-week treatment period and a 2-week rest period. In each cycle, patients will receive four doses of ALT-803 by intravenous injection weekly for 4 weeks followed by a 2-week rest period. Patients with sufficient recovery of toxicities from the previous treatment cycles will be eligible to continue study treatment. After receiving two treatment cycles, patients who have at least stable disease assessed at week 11-12 may receive up to two additional study treatment cycles followed by reassessment for continued tumor response.

The study will be conducted in conformity with Good Clinical Practice (GCP).

Treatments: The study treatment plan for each enrolled patient includes up to four 6-week study treatment cycles. In each cycle, patients will receive four weekly doses of ALT-803 by intravenous injection followed by a 20-day rest period. The rest period may be extended to include up to four additional weeks if necessary. Patients who do not experience or who sufficiently recover from toxicities of the previous treatment cycles will be eligible to continue the treatment included in the study treatment plan.

Treated patients will have up to two anti-tumor evaluation visits. Patients who receive at least three study drug doses during the first 2-cycle treatment period will be evaluated for anti-tumor response during week 11-12. Patients who have at least stable disease from the first anti-tumor evaluation and who meet other criteria to continue study treatment will receive up to two additional study treatment cycles, with the same treatment schedule and at the same dose level as the first two cycles, followed by reassessment for continued tumor response.

The study treatment and response evaluation schedule is illustrated below:

Treatment Cycle	Cycle #1				REST	Cycle #2				Response Evaluation	Cycle #3				REST	Cycle #4				Response Evaluation
Treatment Week	1	2	3	4	5-6	7	8	9	10	11-12	13	14	15	16	17-18	19	20	21	22	23-24
Treatment Day	1	8	15	22	23-42	43	50	57	64	65-84	85	92	99	106	107-126	127	134	141	148	149-168
Dose#	1	2	3	4	Rest weeks	5	6	7	8		9	10	11	12	Rest weeks	13	14	15	16	
Response Evaluation										X										X
ALT-803	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	

There are no restrictions on further therapies, such as chemotherapy, radiation therapy or surgery to be used after the protocol-specified therapy. Clearly, post-study treatments could be of significant clinical benefit in selected patients, and these patients will be followed for outcome.

Enrolled patients will receive the study treatment at qualified cancer treatment centers with adequate diagnostic and treatment facilities to provide appropriate management of therapy and complications. ALT-803 will be administered by intravenous infusion into a central or peripheral vein under the supervision of a qualified physician experienced in the use of biologic anti-cancer agents.

Dose Escalation Phase: A modified 3 + 3 design will be used for identifying a tolerable dose for phase II studies by monitoring patients for DLTs to determine the MTD and for identifying an efficacious dose by monitoring patients' ALC and WBC count to determine the MED during the DLT observation period. The dose escalation phase is concluded when either the MTD or the MED is determined. A dose level (RP2D) will then be designated for Phase II study. There are five escalating dose levels of ALT-803 and a step-down cohort (-1) with a lower dose level of ALT-803 in the event that unexpected toxicity is encountered at the initial dose level.

Below are the planned dose levels of the study drug during the dose escalation phase of the study.

Cohort	ALT-803 Dose (µg/kg)	Number of patients
-1	0.5	3 to 6
1 (initial)	1	3 to 6
2	3	3 to 6
3	6	3 to 6
4	10	3 to 6
5	20	3 to 6

Dose limiting toxicity (DLT) is defined as follows: any toxicity that is not clearly unrelated to drug administration that is of Grade 3 and does not resolve to Grade 1 or lower within a week despite the use of medical intervention or that is of Grade 4, with exceptions described in the study protocol.

The DLT Observation Period is defined as the duration of the first treatment cycle.

Maximum Tolerated Dose level (MTD) is defined as a dose level at which <2 out of 6 patients experienced DLT and that is one level below a dose that was not tolerated.

Minimal Efficacious Dose (MED) is defined as a dose level which produces an ALC ≥25,000/µL sustained for 14 days or a total WBC ≥35,000/µL sustained for 14 days among 2/3 or 4/6 of patients. For safety, we have also defined an "exceeding MED" as the occurrence of ALC ≥35,000/µL or WBC ≥50,000/µL sustained for 14 days.

Expansion Phase

The two-stage expansion phase at the MTD or the MED level will be conducted using an optimal Simon's two-stage design. Objective response (OR) (defined as complete response (CR) + partial response (PR)) will be evaluated and set thresholds of lack of efficacy (OR rate (ORR) = 10%) and an efficacy level of interest (ORR = 30%) will be selected.

Stopping Rules:

Patient enrollment will be temporarily suspended based on occurrence of any of the following events, and the study committee, including the sponsor, the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

During the dose escalation phase of the study,

- If the maximum planned dose level has been reached, but neither the MTD nor MED can be determined.

- If de-escalation occurs and the step-down dose level cannot be designated as the MTD or MED.

Any time during the expansion phase of the study,

- More than 33% of patients experience a possible, probable or definite study drug related DLT.
- Favorable anti-tumor response data collected from enrolled patients.

At any time during the study,
The study committee may meet to discuss how to proceed with the study and may make any or all of the following recommendations for further patient enrollment:

- Downward adjust the study drug dose.
- Adjust the study drug dosing schedule.
- Recommend more effective pre-therapy, intra-therapy and post-therapy side effect mitigation interventions.
- Correct protocol technical errors that caused unnecessary dose omissions or premature treatment discontinuations. After correction of protocol errors, the DSMB may meet to re-evaluate the safety profile of the study treatment and recommend how to proceed with the study, if necessary.

Evaluations: Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug. The anti-tumor response will be evaluated at week 11-12 and week 23-24 from the start of study treatment. All patients who receive at least 3 doses of the study drug ALT-803 will be included in the anti-tumor response evaluation.

Population: Patients of 18 years of age and above with relapsed or refractory multiple myeloma. Patients also need to have adequate cardiac, pulmonary, liver and kidney functions and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

Sample Size: A total of up to 30 assessable patients will be accrued to the dose escalation phase of the study (Phase Ib). Anticipated enrollment to this phase is 18 patients. Up to an additional 23 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 41 assessable patients will be enrolled to complete the study. Assuming a 20% rate of ineligible or non-assessable cases, a total of up to 50 patients may be accrued to the study.

Primary Endpoints

For Phase Ib only (1) Determination of the MTD or MED and designation of the recommended dose level (RP2D) for Phase II study of ALT-803 in patients with relapsed or refractory multiple myeloma.

For Phase Ib & II (2) Safety profile of ALT-803 in treated patients.
(3) Disease response rate of treated patients.

Secondary

Endpoints

(1) Evaluation of the effect of ALT-803 on the peripheral ALC and WBC counts, the number and phenotype of peripheral blood T (total and subsets) and NK cells in treated patients.
(2) Duration of response in treated patients.
(3) Progression free survival of treated patients.
(4) Overall survival of treated patients.
(5) Characterization of the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α, of ALT-803 in treated patients.

Pharmacokinetics & Biomarkers:

Fresh blood samples will be collected to assess immune cell levels and phenotype, and serum samples for pharmacokinetics, immunogenicity of the study drug ALT-803, and the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α after ALT-803 administration in treated patients. Blood samples for pharmacokinetic analysis will be taken on the first day of ALT-803 administration in the first study treatment cycle. Venous blood will be obtained at Time 0 (before the start of infusion), at 30 minutes, and 2, 4, 6 and 24 hours from Time 0 for the assessment of ALT-803 serum concentrations. Non-compartmental and compartmental analyses will be conducted. In addition, the same blood samples collected for PK analysis will be used to assess the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α. Fresh blood samples for immune cell levels and phenotype testing will be collected before the start of first and fourth dose of study drug infusion in each treatment cycle. Bone marrow samples will be collected for future analysis of molecular markers associated with responses or resistance to ALT-803 in patients with relapsed or refractory multiple myeloma.

Monitoring Tests:

Blood samples for standard chemistry and CBC with differential will be obtained at screening, on each study drug infusion day, and at follow-up visits. Blood samples for immunogenicity testing for anti-ALT-803 antibodies will be collected prior to dosing on the first ALT-803 infusion day and at weeks 7 and 12 from the initial dose of study treatment. Blood and urine samples will be collected on each follow-up visit for response assessment.

Response Assessment:

There are at least two response assessments for treated patients: the first assessment during week 11-12 and the second assessment during week 23-24 from the start of study treatment. After completion of the first two cycles of study treatment, patients who have received at least 3 doses of study drug will have the first response assessment. After completion of the two additional cycles of study treatment, patients, regardless of the number of additional study drug doses received, will have the second response assessment. Response assessments will be carried out according to the new International Uniform Response Criteria for Multiple Myeloma proposed by the International Myeloma Working Group. Baseline evaluations should be performed up to 14 days before study treatment starts.

Progression & Survival

Assessment: Progression-free survival, overall survival, and duration of response of all treated patients will be assessed every three months during year 1 and then every 6 months during years 2 and 3 from the start of study treatment, or through the point designated as the end of the study follow up.

Adverse Events: All patients will be monitored and evaluated for clinical toxicities during the treatment period and queried at each follow-up visit for Adverse Events (AEs). Patients may volunteer information concerning AEs. All adverse events will be graded by using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), and logged in the patient Case Report Form. The study centers should report all Serious Adverse Events (SAEs) and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) no more than 24 hours after learning of the event. The sponsor will use the information to manage and coordinate the dose escalation, cohort expansion and patient enrollment. The sponsor will then inform all of the participating clinical sites of the current dose level and the number of patients to be enrolled at that level, or of any patient enrollment suspension via phone, fax or email within 24 hours of learning of the event. The study centers should report all other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related AEs that are both serious and unexpected will be reported to the FDA in an expedited manner in accordance with 21 CFR §312.32.

Statistical Plan: For each cohort, all AEs will be tabulated and examined and all safety, pharmacokinetic and tumor response data will be evaluated. For estimation of duration of response and progression free survival, the Kaplan-Meier method will be used. *P*-values of ≤ 0.05 (two-sided) will be considered to indicate statistical significance.

8. STUDY CALENDAR, CLINICAL PROCEDURES & TESTS

8.1 Study calendar

TESTS & PROCEDURES	SCREEN/ BASELINE[1]	TREATMENT CYCLE #1				REST	TREATMENT CYCLE #2				1ST RESPONSE ASSESSMENT	TREATMENT CYCLES #3 AND #4	2ND RESPONSE ASSESSMENT	FOLLOW-UPS					
Study Month		1					2				3	4-5	6	9	12	18	24	30	36
Study Week		*1*	*2*	*3*	*4*	*5-6*	*7*	*8*	*9*	*10*	*11-12*	*13-22*	*23-24*	*Any day during the month*					
Study Day		1	8	15	22	23-42	43	50	57	64	65-84	85-148	149-168						
Tolerance Window		*+/- 2 days*				*23-42*	*+/- 2 days*				*Any day*		*Any day*						
Medical history	X					R E S T P E R I O R						**Follow Institution's standard of care (SOC) policy. If performed, follow the same schedule as in the first two cycles of study treatment.**							
Serum pregnancy test[2]	X																		
Complete physical exam	X	X					X				X		X						
Vital signs, Weight, Height[3], Cardiac & Lung function monitoring	X	X	X	X	X		X	X	X	X	X		X						
Concurrent medication	X	X	X	X	X		X	X	X	X	X		X						
Adverse event assessment[4]	X	X	X	X	X		X	X	X	X	X		X						
CBC with Differential	X	X	X	X	X		X	X	X	X	X		X						
Blood Chemistry	X	X	X	X	X		X	X	X	X	X		X						
EKG	X	X[5]					X												
PFT only when clinically indicated	X																		
Response evaluation[6]											X		X						
Serum quantitative immunoglobulins	X										X		X						
SPEP	X										X		X						
UPEP-random	X										X		X						
SIFE	X										X		X						
UIFE -random	X										X		X						
Serum FLC assay[6.1]	X										X		X						
Bone marrow plasma cell percentage[6.2]	X										X		X						
Bone marrow immunohistochemistry or immunofluorescence[6.3]											X		X						
Soft tissue plasmacytomas assessment[6.4]											X		X						
Disease & survival follow-up/post-therapies[7]														X	X	X	X	X	X
Immune cell levels & phenotype[8,11]		X[8]			X[8]		X[8]			X[8]									
PK[x], IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α[9,11]		X[9]																	
Immunogenicity tests[10, 11]		X[10]					X				X								
Study drug (ALT-803)		**a1**	**a2**	**a3**	**a4**		**a5**	**a6**	**a7**	**a8**		**Follow the same schedule as in the first 2 cycles of study treatment**							

[1]Screening/baseline evaluations are performed ≤ 14 days prior to start of therapy. If the patient's condition is deteriorating, ECOG status and laboratory evaluations should be repeated within 48 hours prior to initiation of study treatment infusion. [2]Pregnancy test is for women with childbearing potential only. [3]Vital signs (especially blood pressure), clinical status and laboratory tests should be reviewed before start of therapy. Vital signs will be evaluated at 15, 30, 60 and 120 minutes and then hourly post infusion until discharge (or at completion of dose monitoring) from the clinic, and body weight before infusion on drug infusion day. [4]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [5]If the screening EKG was performed within 14 days prior to start of study treatment, the EKG is not required. [6]Disease response and progression assessment will be evaluated using the new International Uniform Response Criteria for Multiple Myeloma proposed by the International Myeloma Working Group. [6.1]Only when serum and urine M-protein are unmeasurable. [6.2] Only when serum and urine M-protein and serum FLC are unmeasurable and bone marrow plasma cell percentage > 30% at baseline. [6.3]Only when sCR is to be determined. [6.4]Only when present at baseline, and to confirm CR or PR by X-rays, MRI or CT scans. [7]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [8]Fresh blood samples for immune cell levels & phenotype testing will be collected before dosing. [9]Collect blood samples at Time 0 (before drug infusion), at 30 min (+/- 5 min), 2 hour (+/- 15 min), 4 hour(+/- 30 min), 6 hour (+/- 60 min) , 24 hour (+/- 6 hour)-from Time 0. IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α assays are performed using the same samples and at the same schedule as PK. [10]Use the sample collected before dosing for PK test. [11]Residual samples may be used by Sponsor for research studies of other biomarkers. [x]The last PK sample will be collected on the next day.

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-803-02-13

Protocol Title: A Study of ALT-803 in Patients with Relapsed or Refractory Multiple Myeloma

Date of Protocol:

Version# 01	January 7, 2014
Version# 02	February 3, 2014
Version# 03	February 5, 2014

Sponsor Contact:

Altor BioScience CORPORATION

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SYNOPSIS

Sponsor: Altor Bioscience Corporation

Protocol#: CA-ALT-803-02-13

Study Drug Name: Not applicable

Study Treatment

Active agents: ALT-803, a "recombinant human super agonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D:IL-15RαSu/IgG1 Fc complex)

Study Type: Interventional

Study Phase: Ib/II

Protocol Title: A Study of ALT-803 in Patients with Relapsed or Refractory Multiple Myeloma

Objectives: To evaluate the safety and tolerability of escalating doses, identify the Maximum Tolerated Dose level (MTD) or Minimum Efficacious Dose (MED) and designate a dose level for Phase II study (RP2D) of ALT-803 in patients with relapsed or refractory multiple myeloma.

To evaluate the effect of ALT-803 on the peripheral absolute lymphocyte counts (ALC) and white blood cell (WBC) counts, the number and phenotype of peripheral blood T (total and subsets) and NK cells.

To estimate the anti-tumor activity of ALT-803 by radiologic or pathologic disease response, progression free survival, and overall survival in treated patients.

To characterize the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α, of ALT-803 in treated patients.

Study Design: This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-803 in patients with relapsed or refractory multiple myeloma.

The study includes a dose escalation phase to determine the MTD or MED using a modified classic (3+3) dose escalation design and to designate a dose level for the Phase II expansion phase (RP2D) and a two-stage expansion phase at the RP2D using a Simon two-stage design. In Phase I, five dose levels will be evaluated. A step-down dose level (cohort# -1) will be provided in the event of encountering DLT in two patients at the planned initial dose level. In the absence of unacceptable toxicity or disease progression, each enrolled patient will receive up to four 6-week study treatment cycles, each consisting of a 4-week treatment period and a 2-week rest period. In each cycle, patients will receive four doses of ALT-803 by intravenous injection weekly for 4 weeks followed by a 2-week rest period. Patients with sufficient recovery of toxicities from the previous treatment cycles will be eligible to continue study treatment. After receiving two treatment cycles, patients who have at least stable disease assessed at week 11-12 may receive up to two additional study treatment cycles followed by reassessment for continued tumor response.

The study will be conducted in conformity with Good Clinical Practice (GCP).

Treatments: The study treatment plan for each enrolled patient includes up to four 6-week study treatment cycles. In each cycle, patients will receive four weekly doses of ALT-803 by intravenous injection followed by a 20-day rest period. The rest period may be extended to include up to four additional weeks if necessary. Patients who do not experience or who sufficiently recover from toxicities of the previous treatment cycles will be eligible to continue the treatment included in the study treatment plan.

Treated patients will have up to two anti-tumor evaluation visits. Patients who receive at least three study drug doses during the first 2-cycle treatment period will be evaluated for anti-tumor response during week 11-12. Patients who have at least stable disease from the first anti-tumor evaluation and who meet other criteria to continue study treatment will receive up to two additional study treatment cycles, with the same treatment schedule and at the same dose level as the first two cycles, followed by reassessment for continued tumor response.

The study treatment and response evaluation schedule is illustrated below:

Treatment Cycle	Cycle #1				REST	Cycle #2				Response Evaluation	Cycle #3				REST	Cycle #4				Response Evaluation
Treatment Week	1	2	3	4	5-6	7	8	9	10	11-12	13	14	15	16	17-18	19	20	21	22	23-24
Treatment Day	1	8	15	22	23-42	43	50	57	64	65-84	85	92	99	106	107-126	127	134	141	148	149-168
Dose#	1	2	3	4	Rest weeks	5	6	7	8		9	10	11	12	Rest weeks	13	14	15	16	
Response Evaluation										X										X
ALT-803	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	

There are no restrictions on further therapies, such as chemotherapy, radiation therapy or surgery to be used after the protocol-specified therapy. Clearly, post-study treatments could be of significant clinical benefit in selected patients, and these patients will be followed for outcome.

Enrolled patients will receive the study treatment at qualified cancer treatment centers with adequate diagnostic and treatment facilities to provide appropriate management of therapy and complications. ALT-803 will be administered by intravenous infusion into a central or peripheral vein under the supervision of a qualified physician experienced in the use of biologic anti-cancer agents.

Dose Escalation Phase: A modified 3 + 3 design will be used for identifying a tolerable dose for phase II studies by monitoring patients for DLTs to determine the MTD and for identifying an efficacious dose by monitoring patients' ALC and WBC count to determine the MED during the DLT observation period. The dose escalation phase is concluded when either the MTD or the MED is determined. A dose level (RP2D) will then be designated for Phase II study. There are five escalating dose levels of ALT-803 and a step-down cohort (-1) with a lower dose level of ALT-803 in the event that unexpected toxicity is encountered at the initial dose level.

Below are the planned dose levels of the study drug during the dose escalation phase of the study.

Cohort	ALT-803 Dose (µg/kg)	Number of patients
-1	0.5	3 to 6
1 (initial)	1	3 to 6
2	3	3 to 6
3	6	3 to 6
4	10	3 to 6
5	20	3 to 6

Dose limiting toxicity (DLT) is defined as follows: any toxicity that is not clearly unrelated to drug administration that is of Grade 3 and does not resolve to Grade 1 or lower within a week despite the use of medical intervention or that is of Grade 4, with exceptions described in the study protocol.

The DLT Observation Period is defined as the duration of the first treatment cycle.

Maximum Tolerated Dose level (MTD) is defined as a dose level at which <2 out of 6 patients experienced DLT and that is one level below a dose that was not tolerated.

Minimal Efficacious Dose (MED) is defined as a dose level which produces an ALC ≥25,000/µL sustained for 14 days or a total WBC ≥35,000/µL sustained for 14 days among 2/3 or 4/6 of patients. For safety, we have also defined an "exceeding MED" as the occurrence of ALC ≥35,000/µL or WBC ≥50,000/µL sustained for 14 days.

Expansion Phase

The two-stage expansion phase at the MTD or the MED level will be conducted using an optimal Simon's two-stage design. Objective response (OR) (defined as complete response (CR) + partial response (PR)) will be evaluated and set thresholds of lack of efficacy (OR rate (ORR) = 10%) and an efficacy level of interest (ORR = 30%) will be selected.

Stopping Rules:

Patient enrollment will be temporarily suspended based on occurrence of any of the following events, and the study committee, including the sponsor, the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

During the dose escalation phase of the study,

- If the maximum planned dose level has been reached, but neither the MTD nor MED can be determined.

- If de-escalation occurs and the step-down dose level cannot be designated as the MTD or MED.

Any time during the expansion phase of the study,

- More than 33% of patients experience a possible, probable or definite study drug related DLT.
- Favorable anti-tumor response data collected from enrolled patients.

At any time during the study,
The study committee may meet to discuss how to proceed with the study and may make any or all of the following recommendations for further patient enrollment:

- Downward adjust the study drug dose.
- Adjust the study drug dosing schedule.
- Recommend more effective pre-therapy, intra-therapy and post-therapy side effect mitigation interventions.
- Correct protocol technical errors that caused unnecessary dose omissions or premature treatment discontinuations. After correction of protocol errors, the DSMB may meet to re-evaluate the safety profile of the study treatment and recommend how to proceed with the study, if necessary.

Evaluations: Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug. The anti-tumor response will be evaluated at week 11-12 and week 23-24 from the start of study treatment. All patients who receive at least 3 doses of the study drug ALT-803 will be included in the anti-tumor response evaluation.

Population: Patients of 18 years of age and above with relapsed or refractory multiple myeloma. Patients also need to have adequate cardiac, pulmonary, liver and kidney functions and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

Sample Size: A total of up to 30 assessable patients will be accrued to the dose escalation phase of the study (Phase Ib). Anticipated enrollment to this phase is 18 patients. Up to an additional 23 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 41 assessable patients will be enrolled to complete the study. Assuming a 20% rate of ineligible or non-assessable cases, a total of up to 50 patients may be accrued to the study.

Primary Endpoints

For Phase Ib only (1) Determination of the MTD or MED and designation of the recommended dose level (RP2D) for Phase II study of ALT-803 in patients with relapsed or refractory multiple myeloma.

For Phase Ib & II (2) Safety profile of ALT-803 in treated patients.
(3) Disease response rate of treated patients.

Secondary

Endpoints

(1) Evaluation of the effect of ALT-803 on the peripheral ALC and WBC counts, the number and phenotype of peripheral blood T (total and subsets) and NK cells in treated patients.
(2) Duration of response in treated patients.
(3) Progression free survival of treated patients.
(4) Overall survival of treated patients.
(5) Characterization of the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α, of ALT-803 in treated patients.

Pharmacokinetics & Biomarkers:

Fresh blood samples will be collected to assess immune cell levels and phenotype, and serum samples for pharmacokinetics, immunogenicity of the study drug ALT-803, and the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α after ALT-803 administration in treated patients. Blood samples for pharmacokinetic analysis will be taken on the first day of ALT-803 administration in the first study treatment cycle. Venous blood will be obtained at Time 0 (before the start of infusion), at 30 minutes, and 2, 4, 6 and 24 hours from Time 0 for the assessment of ALT-803 serum concentrations. Non-compartmental and compartmental analyses will be conducted. In addition, the same blood samples collected for PK analysis will be used to assess the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α. Fresh blood samples for immune cell levels and phenotype testing will be collected before the start of first and fourth dose of study drug infusion in each treatment cycle. Bone marrow samples will be collected for future analysis of molecular markers associated with responses or resistance to ALT-803 in patients with relapsed or refractory multiple myeloma.

Monitoring Tests:

Blood samples for standard chemistry and CBC with differential will be obtained at screening, on each study drug infusion day, and at follow-up visits. Blood samples for immunogenicity testing for anti-ALT-803 antibodies will be collected prior to dosing on the first ALT-803 infusion day and at weeks 7 and 12 from the initial dose of study treatment. Blood and urine samples will be collected on each follow-up visit for response assessment.

Response Assessment:

There are at least two response assessments for treated patients: the first assessment during week 11-12 and the second assessment during week 23-24 from the start of study treatment. After completion of the first two cycles of study treatment, patients who have received at least 3 doses of study drug will have the first response assessment. After completion of the two additional cycles of study treatment, patients, regardless of the number of additional study drug doses received, will have the second response assessment. Response assessments will be carried out according to the new International Uniform Response Criteria for Multiple Myeloma proposed by the International Myeloma Working Group. Baseline evaluations should be performed up to 14 days before study treatment starts.

Progression & Survival

Assessment: Progression-free survival, overall survival, and duration of response of all treated patients will be assessed every three months during year 1 and then every 6 months during years 2 and 3 from the start of study treatment, or through the point designated as the end of the study follow up.

Adverse Events: All patients will be monitored and evaluated for clinical toxicities during the treatment period and queried at each follow-up visit for Adverse Events (AEs). Patients may volunteer information concerning AEs. All adverse events will be graded by using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), and logged in the patient Case Report Form. The study centers should report all Serious Adverse Events (SAEs) and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) no more than 24 hours after learning of the event. The sponsor will use the information to manage and coordinate the dose escalation, cohort expansion and patient enrollment. The sponsor will then inform all of the participating clinical sites of the current dose level and the number of patients to be enrolled at that level, or of any patient enrollment suspension via phone, fax or email within 24 hours of learning of the event. The study centers should report all other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related AEs that are both serious and unexpected will be reported to the FDA in an expedited manner in accordance with 21 CFR §312.32.

Statistical Plan: For each cohort, all AEs will be tabulated and examined and all safety, pharmacokinetic and tumor response data will be evaluated. For estimation of duration of response and progression free survival, the Kaplan-Meier method will be used. *P*-values of ≤ 0.05 (two-sided) will be considered to indicate statistical significance.

8. STUDY CALENDAR, CLINICAL PROCEDURES & TESTS

8.1 Study calendar

TESTS & PROCEDURES	SCREEN/ BASELINE[1]	TREATMENT CYCLE #1				REST	TREATMENT CYCLE #2				1ST RESPONSE ASSESSMENT	TREATMENT CYCLES #3 AND #4	2ND RESPONSE ASSESSMENT	FOLLOW-UPS					
Study Month		1					2				3	4-5	6	9	12	18	24	30	36
Study Week		*1*	*2*	*3*	*4*	*5-6*	*7*	*8*	*9*	*10*	*11-12*	*13-22*	*23-24*	*Any day during the month*					
Study Day		1	8	15	22	23-42	43	50	57	64	65-84	85-148	149-168						
Tolerance Window		*+/- 2 days*				*23-42*	*+/- 2 days*				*Any day*		*Any day*						
Medical history	X					R E S T P E R I O R						**Follow Institution's standard of care (SOC) policy. If performed, follow the same schedule as in the first two cycles of study treatment.**							
Serum pregnancy test[2]	X																		
Complete physical exam	X	X					X				X		X						
Vital signs, Weight, Height[3], Cardiac & Lung function monitoring	X	X	X	X	X		X	X	X	X	X		X						
Concurrent medication	X	X	X	X	X		X	X	X	X	X		X						
Adverse event assessment[4]	X	X	X	X	X		X	X	X	X	X		X						
CBC with Differential	X	X	X	X	X		X	X	X	X	X		X						
Blood Chemistry	X	X	X	X	X		X	X	X	X	X		X						
EKG	X	X[5]					X												
PFT only when clinically indicated	X																		
Response evaluation[6]											X		X						
Serum quantitative immunoglobulins	X										X		X						
SPEP	X										X		X						
UPEP-random	X										X		X						
SIFE	X										X		X						
UIFE -random	X										X		X						
Serum FLC assay[6.1]	X										X		X						
Bone marrow plasma cell percentage[6.2]	X										X		X						
Bone marrow immunohistochemistry or immunofluorescence[6.3]											X		X						
Soft tissue plasmacytomas assessment[6.4]											X		X						
Disease & survival follow-up/post-therapies[7]														X	X	X	X	X	X
Immune cell levels & phenotype[8,11]		X[8]			X[8]		X[8]			X[8]									
PK[x], IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α[9,11]		X[9]																	
Immunogenicity tests[10, 11]		X[10]					X				X								
Study drug (ALT-803)		**a1**	**a2**	**a3**	**a4**		**a5**	**a6**	**a7**	**a8**		**Follow the same schedule as in the first 2 cycles of study treatment**							

[1]Screening/baseline evaluations are performed ≤ 14 days prior to start of therapy. If the patient's condition is deteriorating, ECOG status and laboratory evaluations should be repeated within 48 hours prior to initiation of study treatment infusion. [2]Pregnancy test is for women with childbearing potential only. [3]Vital signs (especially blood pressure), clinical status and laboratory tests should be reviewed before start of therapy. Day 1 for the 1st patient of each cohort will have vital signs evaluated at 15, 30, 60 and 120 min then hourly for 6 hours post infusion and every 3 hours thereafter until discharge (24 hrs). Vital signs for the rest of the study visits and all visits for subsequent patients will be evaluated at 15, 30, 60 and 120 min and then hourly post infusion until discharge (or at completion of dose monitoring) from the clinic. Body weight will be collected before infusion on each drug infusion day for all patients. [4]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [5]If the screening EKG was performed within 14 days prior to start of study treatment, the EKG is not required. [6]Disease response and progression assessment will be evaluated using the new International Uniform Response Criteria for Multiple Myeloma proposed by the International Myeloma Working Group. [6.1]Only when serum and urine M-protein are unmeasurable. [6.2] Only when serum and urine M-protein and serum FLC are unmeasurable and bone marrow plasma cell percentage > 30% at baseline. [6.3]Only when sCR is to be determined. [6.4]Only when present at baseline, and to confirm CR or PR by X-rays, MRI or CT scans. [7]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [8]Fresh blood samples for immune cell levels & phenotype testing will be collected before dosing. [9]Collect blood samples at Time 0 (before drug infusion), at 30 min (+/- 5 min), 2 hour (+/- 15 min), 4 hour (+/- 30 min), 6 hour (+/- 60 min) , 24 hour (+/- 6 hour)- from Time 0. IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α assays are performed using the same samples and at the same schedule as PK. [10]Use the sample collected before dosing for PK test. [11]Residual samples may be used by Sponsor for research studies of other biomarkers. [x]The last PK sample will be collected on the next day.

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-803-02-13

Protocol Title: A Study of ALT-803 in Patients with Relapsed or Refractory Multiple Myeloma

Date of Protocol:

Version# 01	January 7, 2014
Version# 02	February 3, 2014
Version# 03	February 5, 2014
Version# 04	May 16, 2014

Sponsor Contact:

Altor BioScience CORPORATION

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SYNOPSIS

Sponsor: Altor Bioscience Corporation

Protocol#: CA-ALT-803-02-13

Study Drug Name: Not applicable

Study Treatment

Active agents: ALT-803, a "recombinant human super agonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D:IL-15RαSu/IgG1 Fc complex)

Study Type: Interventional

Study Phase: I/II

Protocol Title: A Study of ALT-803 in Patients with Relapsed or Refractory Multiple Myeloma

Objectives: To evaluate the safety and tolerability of escalating doses, identify the Maximum Tolerated Dose level (MTD) or Minimum Efficacious Dose (MED) and designate a dose level for Phase II study (RP2D) of ALT-803 in patients with relapsed or refractory multiple myeloma.

To evaluate the effect of ALT-803 on the peripheral absolute lymphocyte counts (ALC) and white blood cell (WBC) counts, the number and phenotype of peripheral blood T (total and subsets) and NK cells.

To estimate the anti-tumor activity of ALT-803 by radiologic or pathologic disease response, progression free survival, and overall survival in treated patients.

To characterize the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α, of ALT-803 in treated patients.

Study Design: This is a Phase I/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-803 in patients with relapsed or refractory multiple myeloma.

The study includes a dose escalation phase to determine the MTD or MED using a modified classic (3+3) dose escalation design and to designate a dose level for the Phase II expansion phase (RP2D) and a two-stage expansion phase at the RP2D using a Simon two-stage design. In Phase I, five dose levels will be evaluated. A step-down dose level (cohort# -1) will be provided in the event of encountering DLT in two patients at the planned initial dose level. In the absence of unacceptable toxicity or disease progression, each enrolled patient will receive up to four 6-week study treatment cycles, each consisting of a 4-week treatment period and a 2-week rest period. In each cycle, patients will receive four doses of ALT-803 by intravenous injection weekly for 4 weeks followed by a 2-week rest period. Patients with sufficient recovery of toxicities from the previous treatment cycles will be eligible to continue study treatment. After receiving two treatment cycles, patients who have at least stable disease assessed at week 11-12 may receive up to two additional study treatment cycles followed by reassessment for continued tumor response.

The study will be conducted in conformity with Good Clinical Practice (GCP).

Treatments: The study treatment plan for each enrolled patient includes up to four 6-week study treatment cycles. In each cycle, patients will receive four weekly doses of ALT-803 by intravenous injection followed by a 2-week rest period. The rest period may be extended to include up to four additional weeks if necessary. Patients who do not experience or who sufficiently recover from toxicities of the previous treatment cycles will be eligible to continue the treatment included in the study treatment plan.

Treated patients will have up to two anti-tumor evaluation visits. Patients who receive at least three study drug doses during the first 2-cycle treatment period will be evaluated for anti-tumor response during week 11-12. Patients who have at least stable disease from the first anti-tumor evaluation and who meet other criteria to continue study treatment will receive up to two additional study treatment cycles, with the same treatment schedule and at the same dose level as the first two cycles, followed by reassessment for continued tumor response.

The study treatment and response evaluation schedule is illustrated below:

Treatment Cycle	Cycle #1				REST	Cycle #2				Response Evaluation	Cycle #3				REST	Cycle #4				Response Evaluation
Treatment Week	1	2	3	4	5-6	7	8	9	10	11-12	13	14	15	16	17-18	19	20	21	22	23-24
Treatment Day	1	8	15	22	23-42	43	50	57	64	71-84	85	92	99	106	107-126	127	134	141	148	155-168
Dose#	1	2	3	4	Rest weeks	5	6	7	8		9	10	11	12	Rest weeks	13	14	15	16	
Response Evaluation										X										X
ALT-803	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	

There are no restrictions on further therapies, such as chemotherapy, radiation therapy or surgery to be used after the protocol-specified therapy. Clearly, post-study treatments could be of significant clinical benefit in selected patients, and these patients will be followed for outcome.

Enrolled patients will receive the study treatment at qualified cancer treatment centers with adequate diagnostic and treatment facilities to provide appropriate management of therapy and complications. ALT-803 will be administered by intravenous infusion into a central or peripheral vein under the supervision of a qualified physician experienced in the use of biologic anti-cancer agents.

Dose Escalation Phase: A modified 3 + 3 design will be used for identifying a tolerable dose for phase II studies by monitoring patients for DLTs to determine the MTD and for identifying an efficacious dose by monitoring patients' ALC and WBC count to determine the MED during the DLT observation period. The dose escalation phase is concluded when either the MTD or the MED is determined. A dose level (RP2D) will then be designated for Phase II study. There are five escalating dose levels of ALT-803 and a step-down cohort (-1) with a lower dose level of ALT-803 in the event that unexpected toxicity is encountered at the initial dose level.

Below are the planned dose levels of the study drug during the dose escalation phase of the study.

Cohort	ALT-803 Dose (µg/kg)	Number of patients
-1	0.5	3 to 6
1 (initial)	1	3 to 6
2	3	3 to 6
3	6	3 to 6
4	10	3 to 6
5	20	3 to 6

Dose limiting toxicity (DLT) is defined as follows: any toxicity that is not clearly unrelated to drug administration that is of Grade 3 and does not resolve to Grade 1 or lower within a week despite the use of medical intervention or that is of Grade 4, with exceptions described in the study protocol.

The DLT Observation Period is defined as the duration of the first treatment cycle.

Maximum Tolerated Dose level (MTD) is defined as a dose level at which <2 out of 6 patients experienced DLT and that is one level below a dose that was not tolerated.

Minimal Efficacious Dose (MED) is defined as a dose level which produces an ALC ≥25,000/µL sustained for 14 days or a total WBC ≥35,000/µL sustained for 14 days among 2/3 or 4/6 of patients. For safety, we have also defined an "exceeding MED" as the occurrence of ALC ≥35,000/µL or WBC ≥50,000/µL sustained for 14 days.

Expansion Phase

The two-stage expansion phase at the MTD or the MED level will be conducted using an optimal Simon's two-stage design. Objective response (OR) (defined as complete response (CR) + partial response (PR)) will be evaluated and set thresholds of lack of efficacy (OR rate (ORR) = 10%) and an efficacy level of interest (ORR = 30%) will be selected.

Stopping Rules:

Patient enrollment will be temporarily suspended based on occurrence of any of the following events, and the study committee, including the sponsor, the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

During the dose escalation phase of the study,

- If the maximum planned dose level has been reached, but neither the MTD nor MED can be determined.

- If de-escalation occurs and the step-down dose level cannot be designated as the MTD or MED.

Any time during the expansion phase of the study,

- More than 33% of patients experience a possible, probable or definite study drug related DLT.
- Favorable anti-tumor response data collected from enrolled patients.

At any time during the study,
The study committee may meet to discuss how to proceed with the study and may make any or all of the following recommendations for further patient enrollment:

- Downward adjust the study drug dose.
- Adjust the study drug dosing schedule.
- Recommend more effective pre-therapy, intra-therapy and post-therapy side effect mitigation interventions.
- Correct protocol technical errors that caused unnecessary dose omissions or premature treatment discontinuations. After correction of protocol errors, the DSMB may meet to re-evaluate the safety profile of the study treatment and recommend how to proceed with the study, if necessary.

Evaluations: Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug. The anti-tumor response will be evaluated at week 11-12 and week 23-24 from the start of study treatment. All patients who receive at least 3 doses of the study drug ALT-803 will be included in the anti-tumor response evaluation.

Population: Patients of 18 years of age and above with relapsed or refractory multiple myeloma. Patients also need to have adequate cardiac, pulmonary, liver and kidney functions and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

Sample Size: A total of up to 30 assessable patients will be accrued to the dose escalation phase of the study (Phase I). Anticipated enrollment to this phase is 18 patients. Up to an additional 23 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). An estimated total of approximately 41 assessable patients will be enrolled to complete the study. Assuming a 20% rate of ineligible or non-assessable cases, an estimated total of up to 50 patients may be accrued to the study.

Primary Endpoints

For Phase I only (1) Determination of the MTD or MED and designation of the recommended dose level (RP2D) for Phase II study of ALT-803 in patients with relapsed or refractory multiple myeloma.

For Phase I & II (2) Safety profile of ALT-803 in treated patients.
(3) Disease response rate of treated patients.

Secondary Endpoints

(1) Evaluation of the effect of ALT-803 on the peripheral ALC and WBC counts, the number and phenotype of peripheral blood T (total and subsets) and NK cells in treated patients.
(2) Duration of response in treated patients.
(3) Progression free survival of treated patients.
(4) Overall survival of treated patients.
(5) Characterization of the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α, of ALT-803 in treated patients.

Pharmacokinetics & Biomarkers: Fresh blood samples will be collected to assess immune cell levels and phenotype, and serum samples for pharmacokinetics, immunogenicity of the study drug ALT-803, and the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α after ALT-803 administration in treated patients. Blood samples for pharmacokinetic analysis will be taken on the first day of ALT-803 administration in the first study treatment cycle. Venous blood will be obtained at Time 0 (before the start of infusion), at 30 minutes, and 2, 4, 6 and 24 hours from Time 0 for the assessment of ALT-803 serum concentrations. Non-compartmental and compartmental analyses will be conducted. In addition, the same blood samples collected for PK analysis will be used to assess the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α. Fresh blood samples for immune cell levels and phenotype testing will be collected before the start of first and fourth dose of study drug infusion in each treatment cycle. Bone marrow samples will be collected for future analysis of molecular markers associated with responses or resistance to ALT-803 in patients with relapsed or refractory multiple myeloma.

Monitoring Tests: Blood samples for standard chemistry and CBC with differential will be obtained at screening, on each study drug infusion day, and at follow-up visits. Blood samples for immunogenicity testing for anti-ALT-803 antibodies will be collected prior to dosing on the first ALT-803 infusion day, at week 7 and at the first assessment during week 11-12 from the initial dose of study treatment. Blood and urine samples will be collected on each follow-up visit for response assessment.

Response Assessment: There are at least two response assessments for treated patients: the first assessment during week 11-12 and the second assessment during week 23-24 from the start of study treatment. After completion of the first two cycles of study treatment, patients who have received at least 3 doses of study drug will have the first response assessment. After completion of the two additional cycles of study treatment, patients, regardless of the number of additional study drug doses received, will have the second response assessment. Response assessments will be carried out according to the new International Uniform Response Criteria for Multiple Myeloma proposed by the International Myeloma Working Group. Baseline evaluations should be performed up to 14 days before study treatment starts.

Progression &

Survival Assessment: Progression-free survival, overall survival, and duration of response of all treated patients will be assessed every three months during year 1 and then every 6 months during years 2 and 3 from the start of study treatment, or through the point designated as the end of the study follow up.

Adverse Events: All patients will be monitored and evaluated for clinical toxicities during the treatment period and queried at each follow-up visit for Adverse Events (AEs). Patients may volunteer information concerning AEs. All adverse events will be graded by using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), and logged in the patient Case Report Form. The study centers should report all Serious Adverse Events (SAEs) and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) no more than 24 hours after learning of the event. The sponsor will use the information to manage and coordinate the dose escalation, cohort expansion and patient enrollment. The sponsor will then inform all of the participating clinical sites of the current dose level and the number of patients to be enrolled at that level, or of any patient enrollment suspension via phone, fax or email within 24 hours of learning of the event. The study centers should report all other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related AEs that are both serious and unexpected will be reported to the FDA in an expedited manner in accordance with 21 CFR §312.32.

Statistical Plan: For each cohort, all AEs will be tabulated and examined and all safety, pharmacokinetic and tumor response data will be evaluated. For estimation of duration of response and progression free survival, the Kaplan-Meier method will be used. *P*-values of ≤ 0.05 (two-sided) will be considered to indicate statistical significance.

8. STUDY CALENDAR, CLINICAL PROCEDURES & TESTS

8.1 Study calendar

TESTS & PROCEDURES	SCREEN/ BASELINE[1]	TREATMENT CYCLE #1				REST	TREATMENT CYCLE #2				1ST RESPONSE ASSESSMENT	TREATMENT CYCLES #3 AND #4	2ND RESPONSE ASSESSMENT	FOLLOW-UPS					
Study Month		1				2	2 - 3				3	4-5	6	9	12	18	24	30	36
Study Week		*1*	*2*	*3*	*4*	*5-6*	*7*	*8*	*9*	*10*	*11-12*	*13-22*	*23-24*	± *1 week*					
Study Day		1	8	15	22	23-42	43	50	57	64	71-84	85-148	155-168						
Tolerance Window		*+/- 2 days*				*23-42*	*+/- 2 days*				*Any day*		*Any day*						
Medical history	X											**Follow Institution's standard of care (SOC) policy. If performed, follow the same schedule as in the first two cycles of study treatment.**							
Serum pregnancy test[2]	X																		
Complete physical exam	X	X					X				X		X						
Vital signs, Weight, Height[3], Cardiac & Lung function monitoring	X	X	X	X	X		X	X	X	X	X		X						
Concurrent medication	X	X	X	X	X		X	X	X	X	X		X						
Adverse event assessment[4]	X	X	X	X	X		X	X	X	X	X		X						
CBC with Differential[13]	X	X	X	X	X	R	X	X	X	X	X		X						
Blood Chemistry[13]	X	X	X	X	X		X	X	X	X	X		X						
EKG	X	X[5]				E	X												
PFT only when clinically indicated	X					S													
Response evaluation[6]						T					X		X						
Serum quantitative immunoglobulins	X										X		X						
SPEP	X					P					X		X						
UPEP-random	X										X		X						
SIFE	X					E					X		X						
UIFE -random	X					R					X		X						
Serum FLC assay[6.1]	X										X		X						
Bone marrow plasma cell percentage[6.2]	X					I					X		X						
Bone marrow immunohistochemistry or immunofluorescence[6.3]						O					X		X						
Soft tissue plasmacytomas assessment[6.4]						D					X		X						
Disease & survival follow-up/post-therapies[7]														X	X	X	X	X	X
Immune cell levels & phenotype[8,11]		X[8]			X[8]		X[8]			X[8]									
PK[12], IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α[9,11]		X[9]																	
Immunogenicity tests[10, 11]		X[10]					X				X								
Study drug (ALT-803)		**a1**	**a2**	**a3**	**a4**		**a5**	**a6**	**a7**	**a8**		**Follow the same schedule as in the first 2 cycles of study treatment**							

[1]Screening/baseline evaluations are performed ≤ 14 days prior to start of therapy. If the patient's condition is deteriorating, ECOG status and laboratory evaluations should be repeated within 48 hours prior to initiation of study treatment infusion. [2]Pregnancy test is for women with childbearing potential only. [3]Vital signs (especially blood pressure), clinical status and laboratory tests should be reviewed before start of therapy. Day 1 for the 1st patient of each cohort will have vital signs evaluated at 15, 30, 60 and 120 min then hourly for 6 hours post infusion and every 3 hours thereafter until discharge (24 hrs). Vital signs for the rest of the study visits and all visits for subsequent patients will be evaluated at 15, 30, 60 and 120 min and then hourly post infusion until discharge (or at completion of dose monitoring) from the clinic. Body weight will be collected before infusion on each drug infusion day for all patients. [4]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [5]If the screening EKG was performed within 14 days prior to start of study treatment, the EKG is not required. [6]Disease response and progression assessment will be evaluated using the new International Uniform Response Criteria for Multiple Myeloma proposed by the International Myeloma Working Group. [6.1]Only when serum and urine M-protein are unmeasurable. [6.2] Only when serum and urine M-protein and serum FLC are unmeasurable and bone marrow plasma cell percentage > 30% at baseline. [6.3]Only when sCR is to be determined. [6.4]Only when present at baseline, and to confirm CR or PR by X-rays, MRI or CT scans. [7]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [8]Fresh blood samples for immune cell levels & phenotype testing will be collected before dosing. [9]Collect blood samples at Time 0 (before drug infusion), at 30 min (+/- 5 min), 2 hour (+/- 15 min), 4 hour (+/- 30 min), 6 hour (+/- 60 min) , 24 hour (+/- 6 hour)- from Time 0. IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α assays are performed using the same samples and at the same schedule as PK. [10]Use the sample collected before dosing for PK test. [11]Residual samples may be used by Sponsor for research studies of other biomarkers. All attempts will be made to collect research samples but missed samples will not be considered a protocol deviation.

[12]The last PK sample will be collected on the next day. [13]Safety labs can be drawn within 24 hours of scheduled dose.

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-803-02-13

Protocol Title: A Study of ALT-803 in Patients with Relapsed or Refractory Multiple Myeloma

Date of Protocol:

Version# 01	January 7, 2014
Version# 02	February 3, 2014
Version# 03	February 5, 2014
Version# 04	May 16, 2014
Version# 05	December 17, 2015

Sponsor Contact:

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SYNOPSIS

Sponsor: Altor Bioscience Corporation

Protocol#: CA-ALT-803-02-13

Study Drug Name: Not applicable

Study Treatment

Active agents: ALT-803, a "recombinant human super agonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D:IL-15RαSu/IgG1 Fc complex)

Study Type: Interventional

Study Phase: I/II

Protocol Title: A Study of ALT-803 in Patients with Relapsed or Refractory Multiple Myeloma

Objectives: To evaluate the safety and tolerability of escalating doses, identify the Maximum Tolerated Dose level (MTD) or Minimum Efficacious Dose (MED) and designate a dose level for Phase II study (RP2D) of ALT-803 in patients with relapsed or refractory multiple myeloma.

To evaluate the effect of ALT-803 on the peripheral absolute lymphocyte counts (ALC) and white blood cell (WBC) counts, the number and phenotype of peripheral blood T (total and subsets) and NK cells.

To estimate the anti-tumor activity of ALT-803 by radiologic or pathologic disease response, progression free survival, and overall survival in treated patients.

To characterize the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ, MCP-1 and TNF-α, of ALT-803 in treated patients.

Study Design: This is a Phase I/II, open-label, multi-center, competitive enrollment, and dose-escalation study of ALT-803 in patients with relapsed or refractory multiple myeloma.

The study includes a dose escalation phase to determine the MTD or MED using a modified classic (3+3) dose escalation design and to designate a dose level for the Phase II expansion phase (RP2D) and a two-stage expansion phase at the RP2D using a Simon two-stage design. In Phase I, seven cohorts will be evaluated. A step-down dose level (cohort# -1) will be provided in the event of encountering DLT in two patients at the planned initial dose level. In the absence of unacceptable toxicity or disease progression, each enrolled patient will receive up to four 6-week study treatment cycles, each consisting of a 4-week treatment period and a 2-week rest period. In each cycle for cohort 1, 2, 3 and 4, patients will receive four doses of ALT-803 by intravenous (IV) injection weekly for 4 weeks followed by a 2-week rest period. In each cycle for cohort 5, 6and 7 patients will receive four doses of ALT-803 by subcutaneous (SubQ) injection weekly for 4 weeks followed by a 2-week rest period. Patients with sufficient recovery of toxicities from the previous treatment cycles will be eligible to continue study treatment. After receiving two treatment cycles, patients who have at least stable

disease assessed at week 11-12 may receive up to two additional study treatment cycles followed by reassessment for continued tumor response.

The study will be conducted in conformity with Good Clinical Practice (GCP).

Treatments: The study treatment plan for each enrolled patient includes up to four 6-week study treatment cycles. In each cycle for cohort 1, 2, 3 and 4 patients will receive four weekly doses of ALT-803 by intravenous injection followed by a 2-week rest period. In each cycle for cohort 5, 6 and 7 patients will receive four doses of ALT-803 by subcutaneous injection weekly for 4 weeks followed by a 2-week rest period. The rest period may be extended to include up to four additional weeks if necessary. Patients who do not experience or who sufficiently recover from toxicities of the previous treatment cycles will be eligible to continue the treatment included in the study treatment plan.

Treated patients will have up to two anti-tumor evaluation visits. Patients who receive at least three study drug doses during the first 2-cycle treatment period will be evaluated for anti-tumor response during week 11-12. Patients who have at least stable disease from the first anti-tumor evaluation and who meet other criteria to continue study treatment will receive up to two additional study treatment cycles, with the same treatment schedule, route of administration, and at the same dose level as the first two cycles; followed by reassessment for continued tumor response.

The study treatment and response evaluation visits are illustrated below (refer to study calendar for all study visits):

Treatment Cycle	Cycle #1				REST	Cycle #2				Response Evaluation	Cycle #3				REST	Cycle #4				Response Evaluation
Treatment Week	1	2	3	4	5-6	7	8	9	10	11-12	13	14	15	16	17-18	19	20	21	22	23-24
Treatment Day	1	8	15	22	23-42	43	50	57	64	71-84	85	92	99	106	107-126	127	134	141	148	155-168
Dose#	1	2	3	4	Rest weeks	5	6	7	8		9	10	11	12	Rest weeks	13	14	15	16	
Response Evaluation										X										X
ALT-803	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	

There are no restrictions on further therapies, such as chemotherapy, radiation therapy or surgery to be used after the protocol-specified therapy. Clearly, post-study treatments could be of significant clinical benefit in selected patients, and these patients will be followed for outcome.

Enrolled patients will receive the study treatment at qualified cancer treatment centers with adequate diagnostic and treatment facilities to provide appropriate management of therapy and complications. ALT-803 will be administered by intravenous infusion for cohort 1, 2, 3 and 4 into a central or peripheral vein under the supervision of a qualified physician experienced in the use of biologic anti-cancer agents. ALT-803 will be administered by subcutaneous injection for cohort 5, 6 and 7 under the supervision of a qualified physician experienced in the use of biologic anti-cancer agents.

Dose Escalation Phase:

A modified 3 + 3 design will be used for identifying a tolerable dose for phase II studies by monitoring patients for DLTs to determine the MTD and for identifying an efficacious dose by monitoring patients' ALC and WBC count to determine the MED during the DLT observation period. The dose escalation phase is concluded when either the MTD or the MED is determined. A dose level (RP2D) will then be designated for Phase II study. There are seven cohorts of ALT-803 and a step-down cohort (-1) with a lower dose level of ALT-803 in the event that unexpected toxicity is encountered at the initial dose level.

Below are the planned dose levels and respective route of administration for the study drug during the dose escalation phase of the study.

Cohort	ALT-803 Dose (µg/kg)	Route	Number of patients
-1	0.5	IV	3 to 6
1 (initial)	1	IV	3 to 6
2	3	IV	3 to 6
3	6	IV	3 to 6
4	10	IV	3 to 6
5	10	SubQ	3 to 6
6	15	SubQ	3 to 6
7	20	SubQ	3 to 6

Dose limiting toxicity (DLT) is defined as follows: any toxicity that is not clearly unrelated to drug administration that is of Grade 3 and does not resolve to Grade 1 or lower within a week despite the use of medical intervention or that is of Grade 4, with exceptions described in the study protocol.

The DLT Observation Period is defined as the duration of the first treatment cycle.

Maximum Tolerated Dose level (MTD) is defined as a dose level at which <2 out of 6 patients experienced DLT and that is one level below a dose that was not tolerated.

Minimal Efficacious Dose (MED) is defined as a dose level which produces an ALC ≥25,000/µL sustained for 14 days or a total WBC ≥35,000/µL sustained for 14 days among 2/3 or 4/6 of patients. For safety, we have also defined an "exceeding MED" as the occurrence of ALC ≥35,000/µL or WBC ≥50,000/µL sustained for 14 days.

Expansion Phase

The two-stage expansion phase at the MTD or the MED level will be conducted using an optimal Simon's two-stage design. Objective response (OR) (defined as complete response (CR) + partial response (PR)) will be evaluated and set

thresholds of lack of efficacy (OR rate (ORR) = 10%) and an efficacy level of interest (ORR = 30%) will be selected.

Stopping Rules: Patient enrollment will be temporarily suspended based on occurrence of any of the following events, and the study committee, including the sponsor, the Data Safety Monitoring Board, and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

During the dose escalation phase of the study,

- If the maximum planned dose level has been reached, but neither the MTD nor MED can be determined.
- If de-escalation occurs and the step-down dose level cannot be designated as the MTD or MED.

Any time during the expansion phase of the study,

- More than 33% of patients experience a possible, probable or definite study drug related DLT.
- Favorable anti-tumor response data collected from enrolled patients.

At any time during the study,
The study committee may meet to discuss how to proceed with the study and may make any or all of the following recommendations for further patient enrollment:

- Downward adjustment of the study drug dose.
- Adjust the study drug dosing schedule.
- Recommend more effective pre-therapy, intra-therapy, and post-therapy side effect mitigation interventions.
- Correct protocol technical errors that caused unnecessary dose omissions or premature treatment discontinuations. After correction of protocol errors, the DSMB may meet to re-evaluate the safety profile of the study treatment and recommend how to proceed with the study, if necessary.

Evaluations: Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug. The anti-tumor response will be evaluated at week 11-12 and week 23-24 from the start of study treatment. All patients who receive at least 3 doses of the study drug ALT-803 will be included in the anti-tumor response evaluation.

Population: Patients of 18 years of age and above with relapsed or refractory multiple myeloma. Patients also need to have adequate cardiac, pulmonary, liver and kidney functions and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

Sample Size: A total of up to 42 assessable patients will be accrued to the dose escalation phase of the study (Phase I). Anticipated enrollment to this phase is 24 patients. Up to an additional 23 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). An estimated total of approximately 47 assessable patients will be enrolled to complete the study. Assuming a 20% rate of ineligible

or non-assessable cases, an estimated total of up to 57 patients may be accrued to the study.

Primary Endpoints

For Phase I only

(1) Determination of the MTD or MED and designation of the recommended dose level (RP2D) for Phase II study of ALT-803 in patients with relapsed or refractory multiple myeloma.

For Phase I & II

(2) Safety profile of ALT-803 in treated patients.
(3) Disease response rate of treated patients.

Secondary Endpoints

(1) Evaluation of the effect of ALT-803 on the peripheral ALC and WBC counts, the number and phenotype of peripheral blood T (total and subsets) and NK cells in treated patients.
(2) Duration of response in treated patients.
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(4) Overall survival of treated patients.
(5) Characterization of the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ, MCP-1 and TNF-α, of ALT-803 in treated patients.

Pharmacokinetics & Biomarkers:

Fresh blood samples will be collected to assess immune cell levels and phenotype. Serum samples will be collected for pharmacokinetics and immunogenicity of the study drug ALT-803. The same serum samples collected for PK analysis will be used to assess the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ, MCP-1, and TNF-α. Non-compartmental and compartmental PK analyses will be conducted. Bone marrow samples will be collected for future analysis of molecular markers associated with responses or resistance to ALT-803 in patients with relapsed or refractory multiple myeloma.

Monitoring Tests:

Blood samples for standard chemistry and CBC with differential will be obtained at screening, on each study treatment day, and at follow-up visits. Blood samples for immunogenicity testing for anti-ALT-803 antibodies will be collected prior to dosing on the first ALT-803 treatment day, at week 7 and at the first assessment during week 11-12 from the initial dose of study treatment. Blood and urine samples will be collected on each follow-up visit for response assessment.

Response Assessment:

There are at least two response assessments for treated patients: the first assessment during week 11-12 and the second assessment during week 23-24 from the start of study treatment. After completion of the first two cycles of study treatment, patients who have received at least 3 doses of study drug will have the first response assessment. After completion of the two additional cycles of study treatment, patients, regardless of the number of additional study drug doses received, will have the second response assessment. Response assessments will be carried out according to the new International Uniform Response Criteria for

Multiple Myeloma proposed by the International Myeloma Working Group. Baseline evaluations should be performed up to 28 days before study treatment starts.

Progression & Survival Assessment: Progression-free survival, overall survival, and duration of response of all treated patients will be assessed every three months during year 1 and then every 6 months during years 2 and 3 from the start of study treatment, or through the point designated as the end of the study follow up.

Adverse Events: All patients will be monitored and evaluated for clinical toxicities during the treatment period and queried at each follow-up visit for Adverse Events (AEs). Patients may volunteer information concerning AEs. All adverse events will be graded by using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), and logged in the patient Case Report Form. The study centers should report all Serious Adverse Events (SAEs) and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) no more than 24 hours after learning of the event. The sponsor will use the information to manage and coordinate the dose escalation, cohort expansion, and patient enrollment. The sponsor will then inform all of the participating clinical sites of the current dose level and the number of patients to be enrolled at that level, or of any patient enrollment suspension via phone, fax, or email within 24 hours of learning of the event. The study centers should report all other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related AEs that are both serious and unexpected will be reported to the FDA in an expedited manner in accordance with 21 CFR §312.32.

Statistical Plan: For each cohort, all AEs will be tabulated and examined and all safety, pharmacokinetic and tumor response data will be evaluated. For estimation of duration of response and progression free survival, the Kaplan-Meier method will be used. *P*-values of ≤ 0.05 (two-sided) will be considered to indicate statistical significance.

8. STUDY CALENDAR, CLINICAL PROCEDURES & TESTS

8.1 Study calendar

TESTS & PROCEDURES	SCREEN/ BASELINE[1]	TREATMENT CYCLE #1									REST	TREATMENT CYCLE #2				1ST RESPONSE ASSESSMENT	TREATMENT CYCLES #3 AND #4	2ND RESPONSE ASSESSMENT	FOLLOW-UPS					
Study Month		1									2	2 - 3				3	4-5	6	9	12	18	24	30	36
Study Week		*1*				*2*	*3*	*4*			*5-6*	*7*	*8*	*9*	*10*	*11-12*	*13-22*	*23-24*	± *1 week*					
Study Day		1	2	3	4	8	15	22	23	25	23-42	43	50	57	64	71-84	85-148	155-168						
Tolerance Window		*+/- 2 days*									*23-42*	*+/- 2 days*				*+/- 7 days*		*+/- 7 days*						
Medical history	X																							
Serum pregnancy test[2]	X																							
Complete physical exam	X	X										X				X	**Follow Institution's standard of care (SOC) policy. If performed, follow the same schedule as in the first two cycles of study treatment.**	X					
Vital signs, Weight, Height[3], Cardiac & Lung function monitoring	X	X				X	X	X				X	X	X	X	X		X						
Concurrent medication	X	X				X	X	X				X	X	X	X	X		X						
Adverse event assessment[4]	X	X				X	X	X				X	X	X	X	X		X						
CBC with Differential[12]	X	X				X	X	X				X	X	X	X	X		X						
Blood Chemistry[12]	X	X				X	X	X			R	X	X	X	X	X		X						
EKG	X	X[5]									E	X												
PFT only when clinically indicated	X										S													
Response evaluation[6]											T					X		X						
Serum quantitative immunoglobulins	X															X		X						
SPEP	X															X		X						
UPEP-random	X										P					X		X						
SIFE	X															X		X						
UIFE -random	X										E					X		X						
Serum FLC assay[6.1]	X										R					X		X						
Bone marrow plasma cell percentage[6.2]	X															X		X						
Bone marrow immunohistochemistry or immunofluorescence[6.3]											I					X		X						
Soft tissue plasmacytomas assessment[6.4]											O					X		X						
Disease & survival follow-up/post-therapies[7]											D								X	X	X	X	X	X
Immune cell levels & phenotype[8,11]		X[8]	X	X[13]	X			X[8]	X	X		X[8]			X[8]									
PK, IL-2, IL-4, IL-6, IL-10, IFN-γ, MCP-1 TNF-α[9,11]		X[9]	X	X[13]	X																			
Immunogenicity tests[10, 11]		X[10]										X				X								
Study drug (ALT-803)		**a1**				**a2**	**a3**	**a4**				**a5**	**a6**	**a7**	**a8**		**Follow the same schedule as in the first 2 cycles**							

[1]Screening/baseline evaluations are performed ≤ 28 days prior to start of therapy. If the patient's condition is deteriorating, ECOG status and laboratory evaluations should be repeated within 48 hours prior to dosing. [2]Pregnancy test is for women with childbearing potential only. [3]Vital signs (especially blood pressure), clinical status and laboratory tests should be reviewed before start of therapy. Day 1 for the 1st patient of cohort 1, 2, 3 and 4 will have vital signs evaluated at 15, 30, 60 and 120 min then hourly for 6 hours post infusion and every 3 hours thereafter until discharge (24 hrs). Vital signs for subsequent patients and dosing visits in cohort 1, 2, 3 and 4 and for all dosing visits in cohort 5, 6 and 7, vital signs will be evaluated at 15, 30, 60 and 120 min and then hourly post treatment until discharge (or at completion of dose monitoring) from the clinic. Body weight will be collected before treatment on each treatment day for all patients. [4]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [5]If the screening EKG was performed within 28 days prior to start of study treatment, the EKG is not required. [6]Disease response and progression assessment will be evaluated using the new International Uniform Response Criteria for Multiple Myeloma proposed by the International Myeloma Working Group. [6.1]Only when serum and urine M-protein are unmeasurable. [6.2] Only when serum and urine M-protein and serum FLC are unmeasurable and bone marrow plasma cell percentage > 30% at baseline. [6.3]Only when sCR is to be determined. [6.4]Only when present at baseline, and to confirm CR or PR by X-rays, MRI or CT scans. [7]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [8]Fresh blood samples for immune cell levels & phenotype testing will be collected before dosing. [9]Collect blood samples at Time 0 (before treatment), at 30 min (+/- 5 min), 2 hour (+/- 15 min), 4 hour (+/- 30 min), 6 hour (+/- 60 min) , 24 hour (+/- 6 hour)- from Time 0. IL-2, IL-4,

IL-6, IL-10, IFN-γ, MCP-1 and TNF-α assays are performed using the same samples as PK. [10]Use the sample collected before dosing for PK test. [11]Residual samples may be used by Sponsor for research studies of other biomarkers. All attempts will be made to collect research samples but missed samples will not be considered a protocol deviation. [12]Safety labs can be drawn within 72 hours of scheduled dose. [13]The Cycle 1 Day 3 visit is optional if patient is available.