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Protocol Title:	A phase 1 study of SEA-BCMA in patients with relapsed or refractory multiple myeloma
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PROTOCOL SYNOPSIS

Protocol Number SGNBCMA-001 **Version** Amendment 9, 03-Jun-2022 **Phase** Phase 1b	**Product Name** SEA-BCMA **Sponsor** Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

A phase 1 study of SEA-BCMA in subjects with relapsed or refractory multiple myeloma

Study Objectives

Primary

- Evaluate the safety and tolerability of SEA-BCMA monotherapy in subjects with relapsed or refractory multiple myeloma (RRMM)
- Identify the maximum tolerated dose (MTD) and/or optimal dose and schedule of SEA-BCMA monotherapy, and in combination with dexamethasone, in subjects with RRMM
- Evaluate the safety and tolerability of SEA-BCMA in combination with standard of care therapies in subjects with RRMM

Secondary

- Identify a recommended single-agent dose and schedule of SEA-BCMA
- Assess the pharmacokinetics (PK) of SEA-BCMA
- Assess the immunogenicity of SEA-BCMA
- Assess the antitumor activity of SEA-BCMA

Exploratory

- Assess incidence and level of B-cell maturation antigen (BCMA) expression in RRMM and relationship to clinical response to SEA-BCMA
- Assess the pharmacodynamic effects and biomarkers of response, toxicity, and resistance to SEA-BCMA
- Assess minimal residual disease (MRD) in subjects with very good partial response (VGPR) or better
- Assess impact of SEA-BCMA in combination with standard of care therapies on health-related quality of life (HRQoL) from the subject's perspective.

Study Population

Adults 18 years and older are eligible if they have a histologically confirmed diagnosis of multiple myeloma (MM), an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤1 and are a candidate for SEA-BCMA treatment in the opinion of the treating physician. In Part A, prior lines of therapy must include at least a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody. In Parts B and C, subjects must not have other therapeutic options known to provide clinical benefit in multiple myeloma available, must have received at least 3 prior lines of antimyeloma therapy, and must be refractory to at least 1 agent in each of the following classes: PI, IMiD, and an anti-CD38 antibody. In Part D, subjects must have received at least 3 prior lines of antimyeloma therapy, including a PI, IMiD, and an anti-CD38 antibody, and must have documented International Myeloma Working Group (IMWG) disease progression on or within 60 days of completion of their last treatment. There is no requirement for subject selection based on BCMA expression level.

Number of Planned Subjects

Up to approximately 131 subjects are expected to be enrolled in this study. This number is based on the following assumptions:

- Up to approximately 45 subjects will be evaluated in Part A (monotherapy dose- escalation and expansion; every 2 weeks [q2wk] dosing).
- Up to approximately 20 subjects will be evaluated in Part B (monotherapy intensive dosing; once weekly [q1wk] for 8 weeks, followed by q2wk dosing).
- Up to approximately 60 subjects total will be evaluated in the Part C dexamethasone combination therapy cohorts. Up to 20 subjects will be enrolled in cohort 1 (standard dosing SEA-BCMA). Up to 40 subjects will be enrolled in cohort 2 (intensive dosing SEA-BCMA): 20 subjects in each of up to 2 parallel dose levels.
- Up to approximately 6 DLT-evaluable subjects will be evaluated in the Part D pomalidomide and dexamethasone combination safety run-in cohort.

Study Design

This is a phase 1, open-label, multicenter, dose-escalation study designed to evaluate the safety, tolerability, and antitumor activity of SEA-BCMA monotherapy and combination in adults with RRMM. The study will be conducted in 4 parts:

- Part A: Monotherapy dose-escalation and expansion
  - Dose-escalation: Up to approximately 25 subjects will be treated with SEA-BCMA monotherapy q2wk to evaluate the safety and tolerability of SEA-BCMA, and to identify the MTD or optimal dose.
  - Expansion: Up to approximately 20 subjects will be treated with SEA-BCMA monotherapy at dose levels not exceeding the MTD or optimal dose to further characterize the safety and antitumor activity of SEA-BCMA.
- Part B: Monotherapy intensive dosing. Up to 20 subjects will be treated at the recommended dose in an expansion cohort testing weekly induction dosing (q1wk) of SEA-BCMA for 8 weeks, followed by q2wk maintenance dosing. This expansion cohort will begin with a 6-subject safety run-in with dose de-escalation permitted.
- Part C: Dexamethasone combination therapy cohorts. Up to approximately 60 subjects may be enrolled to evaluate the safety and antitumor activity of SEA-BCMA in combination with dexamethasone.
  - Cohort 1: The standard dosing combination cohort will combine dexamethasone with SEA-BCMA administered q2wk. This expansion cohort will begin with a 6-subject safety run-in with dose de-escalation permitted. Cohort expansion up to 20 subjects may occur, if permitted after completion of the safety run-in.
  - Cohort 2: The intensive dosing combination cohort will combine dexamethasone with SEA-BCMA administered q1wk for 8 weeks, followed by q2wk dosing. This expansion cohort will complete a 6-subject safety run-in at 800 mg SEA-BCMA intensive dosing (dose level –1) and, if deemed tolerable, will be followed by a 6-subject run in at 1600 mg SEA-BCMA intensive dosing. Cohort

expansion up to a total of 20 subjects may occur in each of up to 2 dose level cohorts, eg, 800 mg and 1600 mg SEA-BCMA dose levels, if permitted after completion of each safety run-in.

- Part D: Pomalidomide and dexamethasone combination therapy cohort. Up to 6 DLT evaluable subjects may be enrolled in this safety run-in cohort to evaluate the safety of SEA-BCMA administered q2wk in combination with pomalidomide and dexamethasone. Part D will be conducted in the US only.
    - Cohort 1: The standard dosing combination cohort will combine dexamethasone and pomalidomide with SEA-BCMA administered q2wk. This expansion cohort will begin with a 6-subject safety run-in with dose de-escalation permitted.

A Safety Monitoring Committee (SMC) consisting of the study medical monitor, drug safety representative, site investigators, and the study biostatistician will monitor the safety of subjects and make dosing recommendations throughout dose-escalation, dose-expansion, post-remission treatment, and combination therapy treatment. The SMC may recommend investigation of an intermediate dose level or an alternative dosing schedule if warranted by cumulative safety and PK/pharmacodynamic data.

The dose-escalation part of SEA-BCMA monotherapy will be conducted in up to approximately 25 subjects using the modified toxicity probability interval (mTPI) method (Ji 2010) to evaluate safety and tolerability, and to identify the MTD of SEA-BCMA. If the MTD is not reached, safety, PK, pharmacodynamic, and biomarker analyses, as well as preliminary antitumor activity, will be used to determine the optimal dose. De-escalation to a lower dose level may be performed at any time by the sponsor in consultation with the SMC. Intrasubject dose-escalation to a dose level shown to be safe may be permitted in the event that a subject has not experienced a Grade ≥2 adverse event (AE) while on study treatment, has received at least 1 cycle of SEA-BCMA at the current dose level, and achieves stable disease (SD) or better.

Investigational Product, Dose, and Mode of Administration

SEA-BCMA will be administered at the assigned dose and schedule by IV infusion.

Combination Products

Part C

Dexamethasone will be administered at a dose of 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle as an IV infusion or PO. On days when SEA-BCMA is to be administered, dexamethasone should be administered 1 to 3 hours prior to SEA-BCMA infusion.

Part D

Pomalidomide will be administered at a dose of 4 mg once daily on Days 1 to 21 of each 28-day cycle taken PO. On Cycle 1 Day 1, pomalidomide will be administered 1 to 3 hours prior to SEA-BCMA infusion.

Dexamethasone will be administered at a dose of 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle as an IV infusion or taken PO. On days when SEA-BCMA is to be administered, dexamethasone should be administered 1 to 3 hours prior to SEA-BCMA infusion.

Duration of Treatment

Subjects in all cohorts may continue on treatment until disease progression, unacceptable toxicity, withdrawal of consent, death, or study termination, whichever occurs first.

Efficacy Assessments

- Best response per the 2016 IMWG uniform response criteria (Kumar 2016)
    - MRD-negative (in subjects with complete response [CR])
    - Stringent complete response (sCR)
    - CR
    - VGPR
    - Partial response (PR)
    - Minimal response (MR)
    - SD
    - PD
- Duration of response

- Progression-free survival (PFS)
- Overall survival (OS)

Pharmacokinetic and Immunogenicity Assessments

Blood samples will be obtained for PK and immunogenicity evaluation at protocol-defined time points. Serum SEA-BCMA levels will be measured. In Parts C and D, additional PK samples will be collected and archived for possible analysis of concentrations of combination drugs. PK parameters to be estimated include maximum serum concentration and area under the serum concentration-time curve. Immunogenicity will be evaluated with measurements of antitherapeutic antibodies (ATA) in serum.

Pharmacodynamic Assessments

Peripheral blood and bone marrow (BM) aspirates and biopsies will be collected for pharmacodynamic biomarker assessments. Assessments performed with these samples may include, but are not limited to, myeloma cell monitoring and profiling, including expression of BCMA and assessments of immune cell populations. Additionally, BM samples may be analyzed to identify gene expression profiles, cytogenetic abnormalities, genetic mutations, and other tumor and tumor microenvironment-related biomarkers that may define disease risk profiles, predict response to SEA-BCMA, and clarify SEA-BCMA mechanisms of action. MRD may be analyzed in selected BM specimens using next generation sequencing (NGS). Plasma and serum will also be collected for quantification of biomarkers of drug activity, which may include serum free light chain (SFLC), cytokines/chemokines, soluble BCMA, and other soluble biomarkers.

Information from pharmacodynamic and biomarker assessments, including BCMA expression, will not be used for subject selection.

Qualitative Interviews

Up to a total of 10 subjects in Parts C and D will be interviewed within 1 cycle of their first objective response (PR or better) or within 1 cycle of ongoing SD in Cycle 4 (Part C only). See the Interview Guide for additional details.

Safety Assessments

Safety assessments will include the surveillance and recording of AEs, including serious adverse events (SAEs); recording of concomitant medications; and measurements of protocol-specified physical examination findings and laboratory tests. Safety will be monitored over the course of the study by the SMC.

Statistical Methods

For SEA-BCMA monotherapy in Part A, dose-escalation and identification of MTD will be guided by the mTPI method. The dose-limiting toxicity (DLT)-evaluable (DE) analysis set includes all treated subjects who either experienced a DLT or were followed for the full DLT evaluation period and did not receive prohibited treatment. The DE analysis set will be used for determination of the MTD. Safety and efficacy endpoints will be summarized with descriptive statistics. The All-Treated Subjects analysis set will include all subjects treated with any amount of SEA-BCMA. The efficacy-evaluable analysis set includes all treated subjects who had both a baseline and at least 1 evaluable postbaseline disease assessment according to the IMWG uniform response criteria (Kumar 2016), or per investigator claim of clinical progression.

Binomial exact 95% confidence intervals (CIs) for objective response rate (ORR) will be provided.

Assuming the observed ORR is between 30 to 70%, the 95% binomial exact CIs are summarized below.

ORR	95% CI (N=20)
30%	12%, 54%
40%	19%, 64%
50%	27%, 73%
60%	36%, 81%
70%	46%, 88%

Any expansion cohort may also be discontinued at any point at the discretion of the sponsor.

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ADC	antibody-drug conjugate
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
APRIL	A proliferation-inducing ligand
BAFF	B cell-activating factor
BCMA	B-cell maturation antigen
β-hCG	beta human chorionic gonadotropin
BM	bone marrow
C_{eoi}	concentration at the end of infusion
C_{max}	maximum observed concentration
C_{trough}	trough concentration
CAR	chimeric antigen receptor
CBC	complete blood count
CI	confidence interval
CR	complete response
CRF	case report form
CT	computed tomography
CYP	cytochrome P
DDI	drug-drug interaction
DE	DLT-evaluable
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescent in situ hybridization
FLC	free light chain
FSH	follicle-stimulating hormone
GFR	glomerular filtration rate
GSI	gamma-secretase inhibitor
HbA1c	hemoglobin A1c
HCV	hepatitis C-virus
HNSTD	highest non-severely toxic dose

HRQoL	health-related quality of life
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IHR	infusion/hypersensitivity reaction
IL	interleukin
IMiD	immunomodulatory imide drug
IMWG	International Myeloma Working Group
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
IUD	intrauterine device
IV	intravenous
MDRD	Modification of Diet in Renal Disease [study]
MedDRA	Medical Dictionary for Regulatory Activities
MIP	macrophage inflammatory protein
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NK	natural killer (cell)
NSG™	NOD scid gamma
OR	objective response
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PBMCs	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic
PO	orally (per os)
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
Pom/dex	pomalidomide in combination with low-dose dexamethasone
PPoS	predictive probability of success
PR	partial response
PT	prothrombin time

PTT	partial thromboplastin time
q1wk	once per week
q2wk	every 2 weeks
q4wk	every 4 weeks
QD	once a day
REMS	Risk Evaluation and Mitigation Strategy
RNA	ribonucleic acid
RRMM	relapsed or refractory multiple myeloma
sBCMA	soluble BCMA
sCR	stringent complete response
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SFLC	serum free light chain
SMC	Safety Monitoring Committee
SOC	standard of care
SPEP	serum protein electrophoresis
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
UPEP	urine protein electrophoresis
UPM	unit probability mass
US	United States
VGPR	very good partial response

1. INTRODUCTION

SEA-BCMA is a non-fucosylated monoclonal antibody directed against B-cell maturation antigen (BCMA), a cell surface receptor that is widely expressed on the surface of malignant plasma cells in subjects with multiple myeloma (MM). This phase 1 study is designed to establish the safety, tolerability, and antitumor activity of SEA-BCMA as monotherapy and in combination with standard of care (SOC) therapies in subjects with relapsed or refractory MM (RRMM).

A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the Investigator's Brochure (IB).

1.1. Multiple Myeloma

MM is a neoplastic disorder of clonally proliferating plasma cells in the bone marrow (BM), peripheral blood or other extramedullary sites. Malignant plasma cells exert a direct pathologic effect on the marrow microenvironment and adjacent skeletal bone, leading to anemia, osteolytic bone lesions, and hypercalcemia. In most cases, malignant plasma cells also produce an abnormal monoclonal immunoglobulin known as the M-protein, but in a minority, the myeloma cells produce only monoclonal free light chains (FLC). Abnormal levels of either M-protein or FLC can contribute to the clinical spectrum of disease that includes renal failure and an increased susceptibility to infections (Palumbo 2011; Rollig 2015; Kumar 2017).

Standard treatments for MM include combination regimens containing proteasome inhibitors (PIs) such as bortezomib and carfilzomib, and/or immunomodulatory drugs (IMiDs), such as lenalidomide and pomalidomide, together with corticosteroids, and also chemotherapy regimens incorporating alkylating agents such as melphalan and cyclophosphamide. Subjects who are free from significant comorbidities and considered eligible are often treated with myeloablative chemotherapy and/or radiation, followed by autologous stem cell transplant (ASCT) (Rollig 2015; Rajkumar 2016). More recently, daratumumab, a monoclonal antibody targeting the CD38 antigen, has been approved for the treatment of RRMM as monotherapy in fourth line and subsequently garnered approvals in various combination regimens in earlier lines of therapy.

Over the past 20 years, the overall survival (OS) of subjects with MM has increased considerably due to advances in treatment as well as improvement in supportive care (Kumar 2008). Despite recent advances in treatment options, to date MM remains an incurable disease managed with sequential lines of treatment that typically yield shorter durations of disease control with each subsequent relapse (Kumar 2004). In particular, frail subjects are facing unmet needs, given the toxicity profile of newer agents. The unmet medical need is even further pronounced in the late relapsed setting in subjects who are refractory to PIs, IMiDs, and anti-CD38 antibodies ("triple-class" refractory). In July of 2019, selinexor was granted accelerated approval by the FDA in combination with dexamethasone on the basis of 122 subjects with RRMM (fifth line or greater) treated on a phase 2b single-arm trial in which the objective response rate (ORR) was 26%, median progression-free survival (PFS) was 3.7 months, and median OS was 8.4 months (Chari 2019). In August of 2020, the BCMA-targeting ADC belantamab mafodotin received FDA accelerated approval in a similar population (fifth line or greater, triple-class refractory

RRMM) based on the results of an uncontrolled phase 2 trial in which the ORR was 31%, highlighting that an unmet medical need remains in this patient population. Subsequently, approvals of BCMA CAR-T therapies such as idecabtagene vileucel and ciltacabtagene autoleucel were approved on the basis of high ORR, although the toxicity profile of this form of cellular therapy limits its usage to subjects with sufficient underlying fitness.

1.2. BCMA

SEA-BCMA targets BCMA, an established plasmablast and plasma cell-specific protein that mediates cell proliferation and survival. BCMA is expressed at moderate to low levels on the majority of MM subject tumor cells (Novak 2004; Seckinger 2017). The ligands A proliferation-inducing ligand (APRIL) and B cell-activating factor (BAFF) bind to BCMA and mediate prosurvival cellular signals (Moreaux 2004; Novak 2004; O'Connor 2004).

Efforts are ongoing to optimize the effectiveness of therapeutic targeting of BCMA in MM. One such strategy is combination with gamma-secretase inhibitors (GSIs); inhibition of gamma-secretase prevents the cleavage of BCMA from the surface of plasma cells, leading to higher BCMA expression on target cells and reducing levels of soluble BCMA (Pont 2019). This combination strategy is particularly attractive in subjects who have failed prior BCMA-directed therapies, where downregulation of BCMA on plasma cells may be a mechanism of therapeutic escape (Timmers 2019).

1.3. SEA-BCMA

SEA-BCMA is a humanized non-fucosylated immunoglobulin G1 (IgG1) monoclonal antibody targeting BCMA. Based on preclinical data, SEA-BCMA acts through 3 mechanisms: 1) enhanced FcγRIII binding resulting in enhanced antibody dependent cellular cytotoxicity (ADCC), 2) antibody dependent cellular phagocytosis, and 3) blocking of BCMA mediated proliferative signaling. Preclinical data support this molecule as an active therapeutic with an acceptable safety margin.

1.4. Summary of Nonclinical Toxicology

Human peripheral blood mononuclear cells (PBMCs) co-cultured in vitro with BCMA-expressing myeloma cell lines and treated with SEA-BCMA displayed minimal cytokine activation. In PBMCs from donors with normal-affinity FcγRIII (representing approximately 90% of the target patient population), of 29 cytokines tested, SEA-BCMA induced a minimal change in interleukin (IL)-8 at 100 µg/mL (corresponding to the maximum observed concentration [C_{max}] of a dose of approximately 5 mg/kg). In PBMCs from donors with high-affinity FcγRIII (representing approximately 10% of the target patient population), SEA-BCMA induced minimal to moderate cytokine production. Of 29 cytokines evaluated, IL-8 and macrophage inflammatory protein (MIP)–1b were the only immune activating cytokines consistently induced by treatment with 100 µg/mL of SEA-BCMA. In addition, no proliferation of myeloma cells expressing BCMA was observed when treated with 100 µg/mL of SEA-BCMA.

The BCMA receptor in the cynomolgus monkey does not cross-react with SEA-BCMA; therefore, preclinical testing in this model is an indicator of safety only in the absence of target ligation. The highest non-severely toxic dose (HNSTD) in the cynomolgus monkey was 100 mg/kg every 3 weeks for 2 doses. No adverse effects were observed at this dose.

1.5. Summary of Preclinical Activity

SEA-BCMA shows activity in 7 of 7 tumor xenograft models tested, inducing tumor delays at doses as low as 0.03 mg/kg, and generating prolonged survival and durable complete regressions with repeat dosing. SEA-BCMA is active on tumor xenografts expressing as few as 2000 surface copies of BCMA antigen. Both effector function and ligand blocking contribute to overall in vivo activity. In the absence of effector cell recruitment, ligand blocking alone can induce prolonged durable regressions. Treatment of human PBMCs co-cultured in vitro with BCMA-expressing myeloma cells induces depletion of target MM cells. SEA-BCMA can bind MM cells in the presence of soluble BCMA, APRIL, and BAFF in vitro.

1.6. Rationale for Study

MM is considered an incurable disease. The most active available therapies for MM include PIs and IMiDs in combination with corticosteroids, anti-CD38 monoclonal antibody therapy, and high-dose alkylating agents and/or radiotherapy followed by consolidative ASCT for subjects considered eligible (Kumar 2017). Advances in therapy have enabled subjects to achieve responses of greater depth and duration, however most MM subjects relapse and many will become resistant to prior therapies. Subjects who experience superior outcomes are often those who achieved deeper remissions to earlier lines of therapy (Kumar 2016). Thus, there is a clear need for the development of new antimyeloma agents with novel mechanisms of action and the potential for inducing rapid and deep remissions.

Recent data demonstrate that a targeted therapeutic approach using naked monoclonal antibodies directed against either the CS–1 or CD38 antigens expressed on myeloma cells can be highly effective (Lokhorst 2015; Lonial 2015).

Multiple BCMA-targeted programs are currently in clinical development. This includes ADCs, BCMA-CD3 bispecific antibodies, and several BCMA CAR T programs. These clinical programs support BCMA as an attractive therapeutic target in MM. SEA-BCMA targets BCMA using an approach distinct from other clinical stage BCMA therapies. Preclinical testing of SEA-BCMA in human in vitro culture and in animals shows a favorable safety profile and promising antitumor activity.

It is appropriate to initially evaluate SEA-BCMA monotherapy dosed every 2 weeks (q2wk) in a patient population whose disease has relapsed or is refractory to SOC therapies, and for whom there remains no treatment options available that have been shown to provide clinical benefit. Based on the favorable safety profile and preliminary evidence of clinical activity observed during Part A (monotherapy dose-escalation and expansion), investigation of SEA-BCMA in combination with approved SOC agents is also warranted.

The immunospecificity and antitumor activity of SEA-BCMA have been demonstrated both in vitro and in vivo in BCMA-expressing MM models and support further investigation of its clinical utility. Safety, pharmacokinetic (PK), and pharmacodynamic data, as well as preliminary antitumor activity acquired in this trial will provide the basis for the development of SEA-BCMA as a treatment for MM.

1.6.1. Rationale for Study Design

This is a phase 1, dose-escalation study to evaluate the safety and tolerability of SEA-BCMA, and to estimate the maximum tolerated dose (MTD) and/or optimal dose in subjects with RRMM. Initial clinical development of SEA-BCMA will involve its evaluation in subjects with RRMM that have no other therapeutic options known to provide clinical benefit available and are candidates for SEA-BCMA treatment in the opinion of the treating physician. Prior therapies must include at least a PI, an IMiD, and an anti-CD38 antibody. Frontline and first relapse SOC treatments are expected to have failed in these subjects prior to enrollment. Because BCMA is a broadly expressed tumor antigen in subjects with MM (Section 1.2), initial selection of subjects based on BCMA expression will not be required, although the relationship between target expression and outcome will be explored in this phase 1 study.

Part A of the study will include dose-escalation in order to estimate the MTD and/or optimal dose of SEA-BCMA. Once dose-escalation is complete and safety of the drug is demonstrated, an expansion cohort of up to approximately 20 subjects will be enrolled to further evaluate the safety and antitumor activity of SEA-BCMA at the standard q2wk dosing schedule. The expansion cohort will allow for the collection of additional information about the safety, tolerability, and activity of SEA-BCMA. This information will be the basis for determining the recommended single-agent dose and schedule for SEA-BCMA. Because maintenance therapy has been shown to prolong remissions in subjects with MM, subjects will be permitted to continue on treatment until progressive disease (PD) or unacceptable toxicity, whichever occurs first. In addition, intrasubject dose-escalation to a dose level shown to be safe may be permitted in the event that a subject has not experienced a Grade ≥2 adverse event (AE) while on study treatment, has received at least 1 cycle of SEA-BCMA at the current dose, and achieves a response of stable disease (SD) or better.

The modified toxicity probability interval (mTPI) dose-escalation method was chosen for Part A dose-escalation because of potential advantages it has over the traditional “3+3” approach for dose finding. These advantages include the ability to estimate the MTD with higher accuracy, treating fewer subjects above the MTD thereby improving safety, and allowing for flexible cohort sizes (Ji 2010). The mTPI also uses information from all subjects treated at all dose levels for estimation of the MTD to improve accuracy of estimation.

1.6.2. Rationale for Intensive Dosing Schedule (Part B)

The major proposed mechanisms of action of SEA-BCMA (blocking of BCMA ligands binding and enhancement of ADCC) are expected to be enhanced by full saturation of membrane BCMA. This is complicated by the presence of circulating ligands such as APRIL, BAFF, and soluble BCMA, which may increase with higher levels of myeloma disease burden. A more

frequent initial dosing schedule may facilitate more consistent maintenance of target saturation throughout the dosing interval and initiate response. Thus, an intensive dosing schedule (once per week [q1wk] dosing for 8 weeks followed by q2wk dosing) of SEA-BCMA will be tested after the completion of dose-escalation at the standard q2wk schedule.

1.6.3. Rationale for Combination Therapy

Standard treatment for MM consists of combinations of therapies with distinct mechanisms of action. SEA-BCMA may provide additive or synergistic therapeutic effects when administered with SOC therapies.

1.6.3.1. Rationale for Dexamethasone Combination Therapy (Part C)

Corticosteroids have historically represented the backbone of SOC regimens across lines of therapy for MM (Burwick 2019); steroid treatment potentiates the efficacy of a variety of other antimyeloma classes of agents including IMiDs, monoclonal antibodies, and the XPO1 inhibitor selinexor. SEA-BCMA will be studied in combination with dexamethasone to determine whether coadministration of steroid therapy will augment the activity of SEA-BCMA.

1.6.3.2. Rationale for Pomalidomide and Dexamethasone Combination Therapy (Part D)

IMiDs such as lenalidomide and pomalidomide have long been a cornerstone of early lines of therapy for myeloma. IMiDs are known to enhance natural killer (NK) cell expansion and activity and potentiate ADCC when combined with monoclonal antibodies (Wu 2008), thus making IMiD regimens an attractive combination backbone for SEA-BCMA.

1.6.3.3. Patient Input Into Design

Patients were not involved in the design of this study.

1.7. Benefit-Risk Assessment

A brief summary of the expected benefits and risks are outlined below. More detailed information about the known and expected benefits and risks and reasonably expected AEs of SEA-BCMA may be found in the IB.

1.7.1. Risk Assessment

The nonclinical safety profile of SEA-BCMA has been evaluated in vitro and in vivo in the cynomolgus monkey model (Section 1.4), in which no adverse effects were observed at the HNSTD. Monoclonal antibodies have the potential to cause infusion-related reactions (IRRs); a premedication plan for IRRs is described in Section 5.5, and study stopping criteria include a provision that the entire study will be halted if Grade 4 or higher allergic reactions that cannot be controlled with standard treatments exceed 15% at any point during the trial.

1.7.2. Benefit Assessment

Subjects with RRMM who are eligible for this study have disease that has relapsed or is refractory to SOC therapies. BCMA is broadly expressed in MM. Based on the evidence of preclinical effectiveness and preliminary clinical evidence of monotherapy activity (Hoffman

2021), SEA-BCMA has the potential to become a new therapeutic option. Subjects may also derive other benefits from participating in this phase 1 trial because of the regimented routine that subjects undergo such as routine physical examinations, laboratory testing, and radiological examinations.

For patients with triple-class refractory RRMM, novel BCMA directed therapies which have either received recent Health Authority approval, or remain in late-stage development, may represent new therapeutic options. Although some of these agents may produce deep and durable remissions, multiple myeloma remains incurable. Thus, patients with triple-class refractory MM who have failed prior BCMA therapy represent a new area of high unmet medical need. Mechanisms of resistance to prior BCMA therapy are varied and remain under active investigation, but early studies suggest that loss of BCMA antigen expression at relapse is a rare phenomenon (Martin 2020). Additionally, loss of persistence of CAR-T cells, or intolerance of ADC toxicity, may also lead to treatment failure independent of BCMA expression. Recent data from the BCMA/CD3 bispecific antibody teclistamab demonstrated encouraging response rates in a cohort of patients who had received prior BCMA CAR-T or ADC therapy (Touzeau 2022). Thus, retreatment with another BCMA-targeted therapy lacking overlapping class-effect toxicity may be a promising therapeutic approach in heavily refractory patients, and therapy with prior BCMA-directed agents is permitted in Parts B and C of this study.

1.7.3. Overall Benefit-Risk Assessment

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with SEA-BCMA are justified by the anticipated benefits that may be afforded to subjects with RRMM.

2. OBJECTIVES

This study will evaluate the safety and antitumor activity of SEA-BCMA as monotherapy and in combination in subjects with RRMM. Specific objectives and corresponding endpoints are detailed in Table 1.

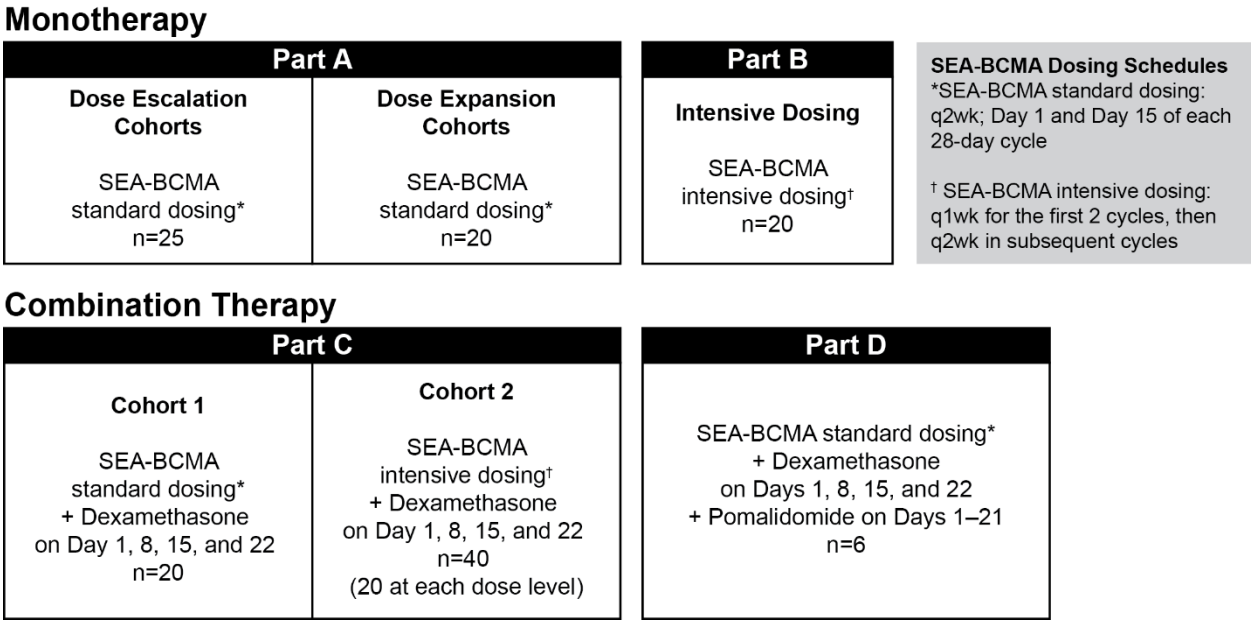
Table 1: Objectives and corresponding endpoints

Primary Objectives	Corresponding Primary Endpoint
Evaluate the safety and tolerability of SEA-BCMA monotherapy in subjects with relapsed or refractory multiple myeloma (RRMM) Identify the maximum tolerated dose (MTD) and/or optimal dose and schedule of SEA-BCMA monotherapy, and in combination with dexamethasone, in subjects with RRMM Evaluate the safety and tolerability of SEA-BCMA in combination with SOC therapies in subjects with RRMM	Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) Type, incidence, and severity of laboratory abnormalities Incidence of dose-limiting toxicities (DLTs)
Secondary Objectives	**Corresponding Secondary Endpoints**
Identify a recommended single-agent dose and schedule of SEA-BCMA Assess the pharmacokinetics (PKs) of SEA-BCMA Assess the immunogenicity of SEA-BCMA Assess the antitumor activity of SEA-BCMA	Incidence of DLTs, cumulative safety and activity by dose level and schedule Maximum serum concentration and area under the serum concentration-time curve Incidence of SEA-BCMA antitherapeutic antibodies (ATA) Best response per the International Myeloma Working Group (IMWG) uniform response criteria (Kumar 2016) Objective response rate (ORR) Duration of objective response (OR) and complete response (CR) Progression-free survival (PFS) Overall survival (OS)
Exploratory Objectives	**Corresponding Exploratory Endpoints**
Assess incidence and level of BCMA expression in RRMM and relationship to clinical response to SEA-BCMA Assess the pharmacodynamic effects and biomarkers of response, toxicity, and resistance to SEA-BCMA Assess minimal residual disease (MRD) in subjects with very good partial response (VGPR) or better Assess impact of SEA-BCMA in combination with SOC therapies on health-related quality of life (HRQoL) from the subject's perspective.	Characterization of BCMA expression on malignant plasma cells Exploratory biomarkers of SEA-BCMA mediated pharmacodynamic effects Rate of MRD clearance Descriptive outcomes of qualitative interviews Maximum serum concentration and area under the serum concentration-time curve

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

Figure 1: Study Design Schema



3.1.1. Part A: Monotherapy Dose-escalation and Expansion

3.1.1.1. Monotherapy Dose-Escalation Cohort

The monotherapy dose-escalation portion of the trial will be conducted in up to approximately 25 subjects using the mTPI method (Ji 2010) to evaluate safety and tolerability, and to identify the MTD of SEA-BCMA. If the MTD is not reached, safety, PK, and biomarker analyses, as well as preliminary antitumor activity, will be used to determine the optimal dose. The mTPI design uses a Bayesian statistical framework and a beta/binomial hierarchic model to compute the posterior probabilities of 3 intervals that reflect the relative distance between the toxicity rate of each dose level to the target DLT rate (see Appendix C). Using a target DLT rate of 25% with a 5% margin, the - 3 intervals will be (0%, 20%), (20%, 30%), and (30%, 100%), and the corresponding dosing decision rules would be:

1. Escalate if current DLT rate is most likely <20%
2. Continue if current DLT rate is most likely between 20 and 30%
3. De-escalate if current DLT rate is likely >30%

Dose finding decisions are shown in Table 2. E, S, and D represent escalating the dose, staying at the same dose, and de-escalating the dose, respectively. Decision DU means that the current dose level is unacceptable because of high toxicity and should be excluded from future dosing in the trial.

Enrollment in this study will occur on a cohort-by-cohort basis. Multiple cohorts may be treated at each dose level, with a maximum of 4 subjects treated per cohort. Decisions on

dose-escalation and subsequent cohort size will be made by the sponsor in consultation with the Safety Monitoring Committee (SMC) after completion of each cohort. Subjects in the current cohort must be observed for the full duration of the DLT period before the next cohort of subjects is enrolled. In addition, as a precaution, for the first 2 subjects in the study there will be a 72-hour observation period before the next subject can be dosed. At dose levels above Dose Level 1, a 24-hour observation period is required after the first subject receives their first dose of SEA-BCMA prior to dosing subsequent subjects at that dose level. At least 2 DLT-evaluable (DE) subjects will be treated per dose level until the first DLT is observed, then a minimum of 3 DE subjects per dose level will be required before escalation to all higher doses. Subjects who are considered not evaluable for DLT during Cycle 1 may be replaced. A minimum of 6 DE subjects will be observed at the estimated MTD before the MTD or optimal dose is determined. The MTD or optimal dose will be estimated based on data from all subjects across all evaluated doses.

De-escalation to a lower dose level may be performed at any time by the sponsor in consultation with the SMC. Intrasubject dose-escalation to a dose level shown to be safe may be permitted in the event that a subject has not experienced a Grade ≥2 AE while on study treatment, has received at least 1 cycle of SEA-BCMA at the current dose level, and achieves SD or better.

Table 2: Dose-finding spreadsheet for mTPI design

Number of DLTs	Number of DLT-evaluable subjects treated at current dose														
	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	E	E	E	E	E	E	E	E	E	E
2	DU	D	D	S	S	S	S	S	S	S	S	S	E	E
3		DU	DU	DU	D	S	S	S	S	S	S	S	S	S
4			DU	DU	DU	DU	DU	D	S	S	S	S	S	S
5				DU	DU	DU	DU	DU	DU	D	S	S	S	S
6					DU	DU	DU	DU	DU	DU	DU	DU	D	S
7						DU	DU	DU	DU	DU	DU	DU	DU	DU
8							DU	DU	DU	DU	DU	DU	DU	DU
9								DU	DU	DU	DU	DU	DU	DU
10									DU	DU	DU	DU	DU	DU
11										DU	DU	DU	DU	DU
12											DU	DU	DU	DU
13												DU	DU	DU
14													DU	DU
15														DU

D = de-escalate to the next lower dose, DLT = dose-limiting toxicity, DU = current dose is unacceptably toxic, E = escalate to the next higher dose, mTPI = modified toxicity probability interval, S = stay at the current dose

SEA-BCMA will initially be administered q2wk in 4-week cycles at the planned doses shown in Table 3; a dosing interval of every 4 weeks (q4wk) may be explored after consultation with the SMC. The SMC may also recommend investigation of intermediate dose levels, in which case the mTPI dose-escalation rules will continue to be applied.

Table 3: Dose-escalation schema

Dose Level[a]	Dose (mg)
1	100
2	200
3	400
4	800
5	1600

a The SMC may recommend investigation of intermediate dose levels based on emerging clinical data
SMC = Safety Monitoring Committee

3.1.1.2. Monotherapy Expansion Cohort

To further characterize the safety and antitumor activity of SEA-BCMA, an expansion cohort of up to approximately 20 subjects may be enrolled. The dose and schedule for the expansion cohort were determined by the sponsor in consultation with the SMC based on the cumulative safety and activity demonstrated during dose-escalation, which was completed without exceeding MTD at the doses tested.

3.1.2. Part B: Monotherapy Intensive Dosing

Part B will evaluate the safety and tolerability of SEA-BCMA dosed q1wk during an induction phase (for 8 doses during the first 2 cycles of therapy); following the completion of the 8 week induction phase, subjects who have not yet experienced confirmed disease progression may proceed to receive SEA-BCMA dosed q2wk during a maintenance phase (Cycle 3 and beyond, dosing at the recommended standard-schedule monotherapy expansion dose determined in Part A).

Part B will include a safety run-in at the recommended SEA-BCMA monotherapy expansion dose (1600 mg), administered on the intensive dosing schedule (Day 1, Day 8, Day 15, and Day 22 of Cycles 1 and 2, and Day 1 and Day 15 of subsequent cycles). DLTs will be evaluated in the first 6 subjects.

4. If 0 or 1 of the first 6 subjects experience DLT, the expansion cohort will proceed to enroll up to 20 total subjects with the recommendation of the SMC.
5. If ≥2 DLTs occur in the first 6 subjects, MTD will be considered exceeded and the dose of SEA-BCMA will be de-escalated to the next lower dose level (800 mg q1wk x 8 weeks during Cycles 1 and 2, followed by 1600 mg q2wk from Cycle 3 and beyond).
    - If 0 or 1 of the first 6 subjects at the lower dose level experience a DLT, the expansion cohort will proceed to enroll up to 20 total subjects at this dose level with the recommendation of the SMC.
    - If ≥2 DLTs occur in the first 6 subjects at the lower dose level, MTD will be considered exceeded, and the Part B Monotherapy Intensive Dosing cohort will be discontinued.

Subjects who are deemed not evaluable for DLT during dose finding will be replaced.

Table 4: Planned dose levels for Part B

Dose Level	Weekly Induction Dose, Cycles 1-2 (mg)	Biweekly Maintenance Dose, Cycles 3 and beyond (mg)
1	1600	1600
–1 (if Dose Level 1 is not tolerated)	800	1600

3.1.3. Combination Therapy Cohorts

To characterize the safety and tolerability of SEA-BCMA in combination regimens, subjects may be enrolled in each of the following combination therapy Parts/Dose Level Cohorts:

- Part C: Dexamethasone Combination Therapy Cohorts
    - Cohort 1: SEA-BCMA standard dosing (up to 20 subjects)
    - Cohort 2: SEA-BCMA intensive dosing (up to 40 subjects; up to 20 subjects may enroll in each of up to 2 dose level cohorts)

In addition, up to 6 DLT-evaluable subjects may be enrolled in the following combination therapy cohort safety run-in:

- Part D: Pomalidomide and Dexamethasone Combination Therapy Cohort
  - Cohort 1: SEA-BCMA standard dosing

3.1.3.1. Parts C and D: Combination Therapy Cohorts Safety Run-in

The Part C dexamethasone combination therapy cohorts and Part D Pom/dex combination therapy cohort will include 6-subject safety run-ins at each dose level tested.

3.1.3.2. Part C: Dexamethasone Combination Therapy Cohorts

Enrollment into dexamethasone combination therapy cohorts may be initiated upon identification of tolerable SEA-BCMA monotherapy doses and schedules as determined by the SMC.

- In Cohort 1
  - SEA-BCMA will be administered at 1600 mg (the recommended monotherapy expansion dose) on Day 1 and Day 15 of each 28-day cycle (standard dosing).
  - Dexamethasone will be administered on Day 1, Day 8, Day 15, and Day 22 of each 28-day cycle.
- In Cohort 2
  - SEA-BCMA will be administered
    - at 800 mg (one dose level below the recommended monotherapy expansion dose) on Day 1, Day 8, Day 15, and Day 22 of Cycles 1 and 2 (intensive dosing), AND
    - at 1600 mg (the recommended monotherapy expansion dose) on Day 1 and Day 15 of Cycle 3 and subsequent cycles
  - Dexamethasone will be administered on Day 1, Day 8, Day 15, and Day 22 of each 28-day cycle.

In Cohort 2, a 3-subject cohort will be evaluated at dose level –1 (Table 4) initially. If 2 or more DLTs occur among the first 3 subjects, then Cohort 2 will be discontinued. If 1 DLT occurs among the first 3 subjects, the cohort will be expanded to 6 subjects, and only escalated if there are fewer than 2 DLTs among the 6 subjects. If 0 DLTs occur among the first 3 subjects, the dose will be escalated to 1600 mg q1wk for 2 cycles and then 1600 mg q2wk from Cycle 3 and beyond, the 6-subject safety run-in rules outlined below will be applied, and 3 additional subjects will be treated at 800 mg to complete the 6-subject safety run-in.

In Cohort 1 and Cohort 2, DLTs will be evaluated in the first 6 subjects enrolled at each dose level tested, in each combination therapy cohort.

1. If 0 or 1 of the first 6 subjects experience DLTs, the expansion cohort will proceed to enroll up to 20 subjects with the recommendation of the SMC.
2. If ≥2 DLTs occur in the first 6 subjects, MTD for the combination will be considered exceeded and the dose of SEA-BCMA will be de-escalated to the next lower dose level.
   - If 0 or 1 of the first 6 total subjects at the lower dose level have experienced a DLT, the lower dose level will be declared MTD.

- If ≥2 DLTs occur in the first 6 total subjects at the lower dose level, MTD for the combination will be considered exceeded and the SMC will determine whether a further de-escalation will be tested, or if the combination cohort will be discontinued.

Subjects who are deemed not evaluable for DLT during dose finding will be replaced.

In Cohort 2, following completion of 6-subject safety run-in at both 800 mg and 1600 mg dose levels, up to 2 dose level cohorts may be explored in parallel by random allocation up to 20 subjects each, if both dose levels are deemed tolerable.

3.1.3.3. Part D: Pomalidomide and Dexamethasone Combination Therapy Cohort

Enrollment into the pomalidomide/dexamethasone combination therapy cohort may be initiated upon identification of tolerable SEA-BCMA monotherapy doses and schedules as determined by the SMC. Part D will be conducted in the US only.

- In Cohort 1
  - SEA-BCMA will be administered at 1600 mg (the recommended monotherapy expansion dose) on Day 1 and Day 15 of each 28-day cycle (standard dosing).
  - Dexamethasone will be administered on Day 1, Day 8, Day 15, and Day 22 of each 28-day cycle.
  - Pomalidomide will be administered on Days 1 to 21 of each of each 28-day cycle.

DLTs will be evaluated in 6 subjects enrolled at the 1600 mg dose level. The dose will be considered tolerable if ≤1 DLT is observed among the first 6 subjects. Further expansion in Part D will be contingent upon review of the data from the 6 subjects in Cohort 1 and a protocol amendment.

Subjects who are deemed not evaluable for DLT during dose finding will be replaced.

3.1.4. Duration of Treatment

Subjects in all cohorts may continue on treatment until disease progression, unacceptable toxicity, withdrawal of consent, death, or study termination, whichever occurs first.

3.1.5. Dose-Limiting Toxicity

The DLT-evaluation period is the first cycle of treatment. DLTs are graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03, and defined as any of the following events during the DLT-evaluation period:

- A delay of SEA-BCMA treatment by more than 7 days due to toxicity
- Any AE ≥ Grade 3, unless deemed by the SMC to be clearly unrelated to SEA-BCMA (in Parts A through D) except for the following AEs, which must meet these specified criteria to be considered a DLT:
  - Grade 4 neutropenia lasting more than 5 days

- Thrombocytopenia ≥ Grade 4, or Grade 3 thrombocytopenia with clinically significant bleeding
- Anemia ≥ Grade 4 unrelated to underlying disease
- Any Grade ≥3 tumor lysis syndrome, including associated laboratory evaluations, that is not successfully managed clinically and that does not resolve within 7 days without end organ damage
- Any ≥ Grade 4 IRRs or Grade 3 IRRs that do not resolve to ≤ Grade 2 within 24 hours with infusion interruption, infusion rate reduction, and/or standard supportive measures. In the event of a Grade 3 IRR in ≥20% of subjects (ie, 2 or more in the first 10 subjects), all subsequent subjects will require premedication and/or modification of infusion approach per the recommendation of the SMC. For subjects receiving premedication, any ≥ Grade 3 IRR will be considered a DLT.
- Any Grade ≥3 asymptomatic laboratory abnormality that does not resolve, with or without intervention, to ≤ Grade 1 or the baseline grade within 72 hours

- Any treatment-related death

3.1.6. Stopping Criteria

3.1.6.1. Enrollment Pause at the Cohort Level

If a subject's death is considered by the investigator, in consultation with the SMC, to be related to SEA-BCMA, enrollment will be paused within the applicable cohort until:

1. The case is reviewed by the investigator, the SMC, and the sponsor, and
2. The sponsor has notified applicable regulatory authorities of the outcome of the safety assessment and justification for restarting enrollment in the affected cohorts, and has received approval to resume, if required by local regulations.

3.1.6.2. Enrollment Halt for the Entire Study

Enrollment in the entire study will be halted by the sponsor if the overall benefit-risk balance is considered unfavorable.

The study will be halted if any of the following occur:

- Rate of on-study toxic deaths unrelated to underlying disease occurring within 30 days of dose exceeds 10% (initially, 2 or more out of up to 20 subjects; then 3 or more out of up to 30 subjects; 4 or more out of up to 40 subjects; etc.)
- Rate of Grade 4 nonhematologic toxicity unrelated to underlying disease exceeds 25% (initially, 5 or more out of up to 20 subjects; then 6 or more out of up to 24 subjects; then 7 or more out of up to 28 subjects; then 8 or more out of up to 32 subjects; then 9 or more out of up to 36 subjects; 10 or more out of up to 40 subjects; etc.)
- Rate of ≥ Grade 4 allergic reactions that cannot be controlled with standard treatments exceeds 15% (initially, 3 or more out of up to 20 subjects; then 4 out of up to 26 subjects; then 5 or more out of up to 33 subjects; 6 or more out of up to 40 subjects; etc.)

Stopping criteria will be continuously monitored throughout the study by the sponsor in consultation with the SMC, considering enrollment halt if the incidence and/or the severity of toxicity leads to a risk-benefit assessment that is unacceptable to the study population. The sponsor will consult the SMC to consider whether to allow subjects already receiving treatment to continue, to consider modifying the protocol to continue the trial, or to terminate the study.

If enrollment is halted due to safety concerns, enrollment can only be restarted after appropriate amendments and notifications to Regulatory Authorities, with approval to resume, if required by local regulations.

3.1.7. Retreatment

Retreatment with SEA-BCMA monotherapy or with SEA-BCMA and combination therapy is permitted with medical monitor approval, for subjects who achieve clinical benefit (defined as stabilization or improvement of disease-related symptoms as assessed by the investigator) objective response (OR) (a partial response [PR] or better) on study and then experience disease progression after discontinuing initial treatment with SEA-BCMA. Eligibility criteria in Section 4.1 and Section 4.2 must be re-evaluated before initiating retreatment. Subjects who discontinue SEA-BCMA treatment due to Grade ≥3 toxicity are not eligible for retreatment with SEA-BCMA. The retreatment dose level for each subject will not exceed the highest safe dose level and will be determined by the medical monitor and the site investigator.

3.1.8. End of Study

The study will be closed approximately 3 years after the last subject receives the last dose, or when no subjects remain in follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time (Section 10.3.2).

3.1.9. Safety Monitoring Committee

The SMC will monitor safety throughout the study. The SMC is composed of the study medical monitor, study biostatistician, drug safety representative, and study site investigators. The committee is tasked with monitoring the safety of subjects in this study, through regular or ad hoc meetings that include review of data pertaining to dose-escalation decisions and treatment-emergent toxicities.

At a minimum, SMC meetings will be held during Part A (monotherapy dose-escalation) and during dose finding in Part B (intensive dosing) and Parts C and D (combination therapy) cohorts after all subjects in a safety run-in cohort have completed the DLT evaluation period. The SMC will also meet quarterly throughout the study for cumulative subject data review.

3.1.9.1. Part A Dose-escalation Safety Monitoring

During monotherapy dose-escalation, the SMC will review clinical data from enrolled subjects for safety assessment and for DLT determination. The SMC will make recommendations on dose level and cohort size in conjunction with the mTPI decision rules chart. A maximum of 4 subjects are allowed per cohort, with multiple cohorts allowed at each dose level (ie, the SMC

may recommend subsequent enrollment of cohorts of 1, 2, 3, or 4 subjects depending on the number of DLTs observed and cumulative data review).

In addition to determination of DLTs and dose-escalation recommendations, the SMC may make one or more of the following recommendations during the study, as applicable:

- Recommendation or requirement of a premedication regimen as prophylaxis against IRRs
- Further evaluation of safety of SEA-BCMA at a given dose
- Evaluation of alternative approaches to SEA-BCMA infusion
- Evaluation of an intermediate SEA-BCMA dose level during dose-escalation
- Evaluation of longer (eg, q4wk) SEA-BCMA dosing intervals
- Consideration of postremission dosing (not exceeding tested dose levels deemed tolerable)
- The SEA-BCMA dose and dosing interval to be evaluated in the monotherapy expansion cohort based on activity and tolerability of dose levels during escalation
- The recommended single-agent dose and schedule for SEA-BCMA based on the safety and activity data

The process for dose-escalation decisions and dose-interval recommendations, and the roles and responsibilities of the SMC will be detailed in an SMC charter.

3.1.9.2. Parts B, C, and D Safety Monitoring

During dose finding safety run-in cohorts in Parts B, C, and D, the SMC will review clinical data from enrolled subjects for safety assessment and for DLT determination. The SMC will make recommendations on the SEA-BCMA dose.

In addition to determination of DLTs and dose recommendations for the combination, the SMC may make 1 or more of the following recommendations during the study, as applicable:

- Recommendation or requirement of a premedication regimen as prophylaxis against IRRs
- Further evaluation of safety of SEA-BCMA on intensive dosing schedule and/or in combination with dexamethasone
- Evaluation of alternative approaches to SEA-BCMA infusion
- Evaluation of an intermediate SEA-BCMA dose on intensive dosing schedule and/or in combination cohorts
- Consideration of postremission dosing (not exceeding tested dose levels deemed tolerable)
- The recommended dose and schedule for SEA-BCMA on intensive dosing schedule and/or in combination based on the safety and activity data

3.2. Method of Assigning Subjects to Treatment Groups

Subject allocation to a dose level will be determined by mTPI decision rules as illustrated in Table 2 and will occur upon approval of subject enrollment by Seagen or their designee.

The medical monitor will assess the safety of SEA-BCMA administration throughout the trial and, for safety reasons, may override the model's allocation of a subject to a particular dose level.

The study design allows for concurrent enrollment in multiple cohorts. If 2 or more expansion cohorts with identical eligibility criteria are open for enrollment concurrently, allocation will be determined by the sponsor or designee prior to informed consent.

3.2.1. Rationale for Selection of Doses

3.2.1.1. Monotherapy

For adult phase 1 studies of monoclonal antibodies, either body size-based dosing or fixed dosing may be considered. Based on an analysis of 12 mAbs, these 2 dosing approaches performed similarly across the mAbs in terms of their population and individual PK performances (Wang 2009). In addition, the PK variability of mAbs introduced by either dosing approach is moderate relative to the variability generally observed in pharmacodynamics, efficacy, and safety (Bai 2012). Available data from clinical trials and extensive population PK modeling of monoclonal antibodies in oncology also support use of fixed dosing for oncology indications (Hendrikx 2017). Fixed dosing could offer advantages in ease of dose preparation, and reduced chance of dosing errors. In addition, previous clinical trials of non-fucosylated and bivalent antibodies have utilized this approach during phase 1 with no significant safety concerns (Sehn 2012; Rosen 2017). Based on the predicted broad therapeutic window for SEA-BCMA, a fixed dosing strategy is used.

The monotherapy starting dose of 100 mg is based on a 1.25 mg/kg starting dose with a nominal subject weight of 80 kg. The starting dose was selected based on preclinical studies and PK/pharmacodynamic modeling and is expected to provide an adequate safety margin with the potential for clinical benefit. Data supporting the proposed starting dose include:

- Preclinical testing of SEA-BCMA in cynomolgus monkeys indicates a favorable safety profile at the proposed starting dose. The BCMA receptor in the cynomolgus monkey does not cross-react with SEA-BCMA; therefore, preclinical testing in this model is an indicator of safety in the absence of target ligation. The HNSTD in the cynomolgus monkey was 100 mg/kg for 2 doses administered at a 3 week interval. No adverse effects were observed at this dose. The proposed starting dose of 1.25 mg/kg is lower than 1/6 of the monkey HNSTD, using body surface area for animal-to-human dose conversion based on body weight, and represents an appropriately conservative starting dose.
- Human PBMCs co-cultured in vitro in the presence of BCMA-expressing myeloma cells and treated with SEA-BCMA displayed minimal cytokine activation. In PBMCs from donors with normal-affinity FcγRIII (representing approximately 90% of the target patient population), of 29 cytokines tested, SEA-BCMA induced a minimal change in IL-8 at 100 µg/mL (corresponding to the C_{max} of a dose of approximately 5 mg/kg). In PBMCs from donors with high-affinity FcγRIII (representing approximately 10% of the target patient population), SEA-BCMA induced minimal to moderate cytokine

production. Of 29 cytokines evaluated, IL-8 and MIP–1b were the only immune activating cytokines consistently induced by treatment with 100 µg/mL of SEA-BCMA. In addition, no proliferation of myeloma cells expressing BCMA was observed when treated with 100 µg/mL of SEA-BCMA.

- SEA-BCMA is active in 7 of 7 tumor xenograft models tested, with a lowest active dose of 0.03 mg/kg in the disseminated NCI-H929 luciferase tumor xenograft model in NSG mice. In some models, repeat dosing enables ligand blocking to contribute to antitumor activity. Soluble factors, including soluble BCMA, are predicted to impact SEA-BCMA binding to target cells below 20 µg/mL of antibody, which corresponds to the predicted C_{max} of a dose of approximately 1 mg/kg.
- Based on PK simulations, the proposed dosing interval of q2wk will achieve 99% target receptor occupancy over the dosing interval after 2 doses of 400 mg assuming a serum half-life of 21 days, or 800 mg assuming a serum half-life of 11 days. Ninety-nine percent receptor occupancy is desired because ligand blocking by SEA-BCMA is one mechanism contributing to its antitumor activity, and full receptor occupancy may be required for optimal activity. Alternative dosing intervals may be explored after consultation with the SMC.

The dose-escalation design is reasonable for a monoclonal antibody in which target expression is restricted to plasmablasts and plasma cells and is anticipated to have minimal potential for toxicity to other organs and tissues. Ninety-nine percent receptor occupancy over the dosing interval is expected to induce an optimal antitumor activity. Based on PK simulations, this will be achieved at doses ranging from 400 to 1600 mg. The proposed dose-escalation plan consists of 2-fold increases per dose level, enabling efficient escalation (2 to 3 dose-escalations) into a dose range where optimal antitumor activity is anticipated to be achieved. This plan will preserve safety while avoiding exposure of an excessive number of subjects to subtherapeutic doses.

Alternative dosing strategies, including intermediate doses or longer dosing intervals, may be explored upon the recommendation of the SMC following evaluation of PK, pharmacodynamics, safety, and activity from the available clinical data.

During Part A (monotherapy dose-escalation), 6 DE subjects were treated at the highest tested dose of 1600 mg q2wk. No DLTs were observed in these 6 subjects; based upon this and cumulative safety data from prior dose cohorts, the sponsor, in consultation with the SMC, deemed 1600 mg q2wk tolerable and selected this as the monotherapy expansion dose for the standard q2wk dosing schedule.

3.2.2. Combination Therapy

Dexamethasone and IMiDs such as pomalidomide play an important role in SOC combinations for MM. Thus, it is important to assess safety and activity of SEA-BCMA in combination with such agents. In Part C Cohort 1 and Part D, SEA-BCMA will be administered at the recommended monotherapy expansion dose of 1600 mg (Sections 3.1.1 and 3.1.2). In Part C Cohort 2, SEA-BCMA will be administered initially at dose level –1 (Table 4). In Part D,

pomalidomide and dexamethasone will be administered at their respective standard doses and schedules to ensure subjects receive the optimal doses.

3.2.3. Blinding and Unblinding

This is an open-label study.

4. STUDY POPULATION

Subjects must meet all of the enrollment criteria to be eligible for this study and prior to study drug administration (within 1 day of dosing) on Cycle 1 Day 1. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

To be eligible for retreatment as described in Section 3.1.7, subjects must meet all inclusion and exclusion criteria outlined in Section 4.1 and Section 4.2.

4.1. Inclusion Criteria

1. Diagnosis of MM requiring systemic therapy as defined by IMWG 2014 criteria (Kumar 2016).
2. Subjects must have MM that is relapsed or refractory and must be a candidate for SEA-BCMA treatment in the opinion of the treating physician.
    a. Part A: Subjects must not have other therapeutic options known to provide clinical benefit in MM available. Subjects' prior lines of therapy must include at least a PI, an IMiD, and an anti-CD38 antibody in any order during the course of treatment. Subjects who could not tolerate a PI, IMiD, or anti-CD38 antibody are allowed.
    b. Parts B and C: Subjects must not have other therapeutic options known to provide clinical benefit in MM available. Subjects must have received at least 3 prior lines of antimyeloma therapy and must be refractory to at least 1 agent in each of the following classes: PI, IMiD, and an anti-CD38 antibody.
    Prior BCMA-directed myeloma therapy, excluding prior treatment with SEA-BCMA, is permitted (eg, ADC, CAR-T cell therapy, or bispecific antibody targeting BCMA) provided that at least 3 months will have elapsed from the last dose of prior BCMA targeting therapy and Cycle 1 Day 1 of this study, and that the subject has recovered from any clinically significant toxicity of the prior BCMA-targeting therapy.
    c. Part D: Subjects must have received at least 3 prior lines of antimyeloma therapy, including a PI, IMiD, and an anti-CD38 antibody, and must have documented IMWG disease progression on or within 60 days of completion of their last treatment. Subjects with a history of ASCT are eligible if the date of transplant was at least 12 weeks prior to initiation of SEA-BCMA treatment. Part D will be conducted in the US only.
3. Measurable disease, as defined by one or more of the following:
    a. Serum monoclonal paraprotein (M-protein) level ≥0.5 g/dL; for IgA or IgD myeloma subjects, serum IgA or serum IgD ≥0.5 g/dL is acceptable
    b. Urine M-protein level ≥200 mg/24 hr
    c. Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio
4. Age 18 years or older.
5. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (see Appendix D for conversion of performance status using Karnofsky and Lansky scales, if applicable)

6. Life-expectancy of >3 months in the opinion of the investigator
7. The following baseline laboratory data (hematologic criteria must be met in the absence of growth factor or platelet transfusion support):
    a. Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 per the Modification of Diet in Renal Disease (MDRD) equation (Appendix I)
    b. Absolute neutrophil count ≥1000/μL
    c. Platelet count ≥75,000/μL
8. For Parts A, B, and C: Subjects of childbearing potential, as defined in Section 4.3, under the following conditions:
    a. Must have a negative serum or urine pregnancy test (minimum sensitivity 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 7 days prior to the first dose of SEA-BCMA. Subjects with false positive results and documented verification that the subject is not pregnant are eligible for participation
    b. Must agree not to try to become pregnant during the study and for at least 6 months after the final dose of any study drug administration
    c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 6 months after the final dose of any study drug
    d. If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix E) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of any study drug
9. For Parts A, B, and C: Subjects who can father children, under the following conditions:
    a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 6 months after the final dose of any study drug
    b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix E) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of any study drug
    c. If sexually active with a person who is pregnant or breastfeeding, must consistently use 1 of 2 contraception options (as defined in Appendix E) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study any drug.
10. For Part D, containing pomalidomide: Subjects of childbearing potential, as defined in Section 4.3.1 , under the following conditions:
    a. Must have 2 negative serum or urine pregnancy tests (minimum sensitivity 25 mIU/mL or equivalent units of hCG). One 10 to 14 days prior to start of the study drug and one 24 hours prior to the start of study drug
    b. Must agree not to try to become pregnant during the study and for at least 6 months after the final dose of any study drug administration

c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 6 months after the final dose of study drug. Must agree to not donate blood for at least 90 days following completion of study treatment
d. If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix F) for 4 weeks prior to the start of treatment with study drugs and continuing throughout the study and for at least 6 months after the final dose of any study drug

11. For Part D, containing pomalidomide: Subjects who can father children, under the following conditions:
    a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 6 months after the final dose of study drug. Must agree to not donate blood for at least 90 days following completion of study treatment
    b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, or a person who is pregnant or breastfeeding, must consistently use 2 highly effective methods of birth control (as defined in Appendix F), one of which must be a latex or synthetic condom, starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of any study drug.
12. For Part D, containing pomalidomide: must be willing and able to comply with the Pomalyst® Risk Evaluation and Mitigation Strategy (REMS) program. Part D will be conducted in the US only.
13. The subject must provide written informed consent.

4.2. Exclusion Criteria

1. Parts A and D: Prior exposure to any other BCMA-directed therapy
2. History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (eg, 5-year OS ≥90%), such as adequately treated carcinoma in situ of the cervix, nonmelanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.
3. Active cerebral/meningeal disease related to the underlying malignancy. Subjects with a history of cerebral/meningeal disease related to the underlying malignancy are allowed if prior central nervous system disease has been treated.
4. Any uncontrolled Grade 3 or higher (per the NCI-CTCAE, v. 4.03) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of SEA-BCMA. Routine antimicrobial prophylaxis is permitted.
5. Positive for hepatitis B by surface antigen expression. Active hepatitis C infection (positive by polymerase chain reaction or on antiviral therapy for hepatitis C within the last 6 months). Subjects who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.
6. Known to be positive for human immunodeficiency virus (HIV)

7. Subjects with previous allogeneic stem cell transplant (SCT)
8. Uncontrolled or severe cardiovascular or pulmonary disease determined by the investigator, including documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with congestive heart failure, Class III to IV, New York Heart Association (see Appendix G) within 6 months prior to their first dose of SEA-BCMA (Parts A, B, and C), or within 12 months prior to their first dose of SEA-BCMA (Part D)
9. For Part D containing pomalidomide: unable to tolerate thromboembolic prophylaxis while on study
10. Current therapy with other systemic antineoplastic or investigational agents
11. Chemotherapy, radiotherapy, biologics, investigational agents, and/or other antitumor treatment with immunotherapy that is not completed 4 weeks prior to first dose of SEA-BCMA, or 2 weeks if progressing and recovered from clinically significant toxicity associated with the treatment. CAR-T-cell therapy that is not completed 8 weeks prior to first dose of SEA-BCMA. Palliative radiotherapy to a single site of disease is allowed with the approval of the medical monitor.
12. Systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of enrollment. Inhaled or topical steroids and adrenal replacement steroid doses ≤10 mg daily prednisone equivalent are permitted. Refer to Section 5.6.2 for allowed use of intermittent high-dose corticosteroid treatment.
13. Subjects who are breastfeeding, pregnant, or planning to become pregnant from time of informed consent until 6 months after final dose of study drug administration.
14. Known hypersensitivity to any excipient contained in the drug formulation of SEA-BCMA.
15. Subjects with plasma cell leukemia (>2.0 × 10^9/L circulating plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or clinically significant amyloidosis.
16. Moderate or severe hepatic impairment, as indicated by any of the following:
    a. Serum total bilirubin >1.5 x upper limit of normal (ULN). For subjects with Gilbert's disease, total bilirubin >3 x ULN
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x ULN
17. Significant comorbid condition or disease which in the judgment of the investigator would place the subject at undue risk or interfere with the proper assessment of safety and toxicity of the study drug.
18. Part C and D only: Known intolerance to corticosteroids.
19. Part C and D only: Any uncontrolled psychoses.
20. Part D only: Prior history of hypersensitivity reaction of prior IMiD therapy (pomalidomide, thalidomide, or lenalidomide).

21. Part D only: Grade ≥2 peripheral neuropathy.
22. Part D: Subjects with gastrointestinal conditions that might predispose for drug intolerability or poor drug absorption (eg, inability to take oral medication, prior surgical procedures affecting absorption (eg, gastric bypass), malabsorption syndrome, and active peptic ulcer disease)

4.3. Childbearing Potential

Subjects of childbearing potential is anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

Females treated with hormone replacement therapy are likely to have artificially suppressed follicle-stimulating hormone **(**FSH) levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of hormone replacement therapy used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/mL at any time during the washout period, the subject can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other products may require a washout period as long as 6 months.

Subjects who can father children is anyone born male who has testes and who has not undergone surgical sterilization (eg, vasectomy followed by a clinical test proving that the procedure was effective).

4.3.1. Subjects Treated with Pomalidomide (Part D)

Women of childbearing potential, as defined by the Pomalyst REMS program, must also include all females who are menstruating, amenorrheic from previous medical treatments, under 50 years of age, and/or perimenopausal, and do not qualify for the category “females not of reproductive potential.”

Females not of reproductive potential, as defined by Pomalyst REMS program, include females who have been in natural menopause for at least 24 consecutive months, or who have had a hysterectomy and/or bilateral oophorectomy.

Part D will be conducted in the US only.

4.4. Removal of Subjects from Therapy or Assessment

Seagen or their designee must be notified if a subject is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the subject's medical records and case report form (CRF).

4.4.1. Discontinuation of Study Treatment

A subject's study treatment may be discontinued for any of the following reasons:

- PD
- AE
- Pregnancy
- Investigator decision
- Subject decision, non-AE
- Study termination by sponsor
- Other, non-AE

In Parts A and B (monotherapy), subjects who discontinue SEA-BCMA will be considered discontinued from study treatment. Subjects who discontinue from study treatment will remain on study for follow-up until withdrawal of consent, death, or study closure, whichever occurs first.

In Part C, subjects who discontinue SEA-BCMA and dexamethasone will be considered discontinued from study treatment. Subjects receiving dexamethasone who discontinue corticosteroid therapy may continue to receive SEA-BCMA as monotherapy with medical monitor approval. Subjects who discontinue SEA-BCMA will be considered discontinued from study treatment.

In Part D, subjects who discontinue SEA-BCMA, dexamethasone, and pomalidomide will be considered discontinued from study treatment. Subjects receiving dexamethasone who discontinue corticosteroid therapy may continue to receive SEA-BCMA and pomalidomide with medical monitor approval. Subjects who discontinue pomalidomide may continue to receive SEA-BCMA and dexamethasone with medical monitor approval. Subjects who discontinue SEA-BCMA will be considered discontinued from study treatment.

4.4.2. Subject Withdrawal from Study

Any subject may be discontinued from the study for any of the following reasons:

- Subject withdrawal of consent
- Retreatment
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

5. TREATMENTS

5.1. Treatments Administered

SEA-BCMA is a non-fucosylated monoclonal antibody directed against BCMA. Subjects will receive the investigational medicinal product SEA-BCMA as monotherapy or combination therapy (Section 3.1). Subjects in combination therapy cohorts will also receive dexamethasone or dexamethasone plus pomalidomide.

Guidance for intrasubject dose-escalation for subjects who have the potential to achieve greater benefit at a dose higher than the dose level assigned during dose-escalation is described in Section 5.2.3.

5.2. Investigational Product: SEA-BCMA

Detailed information describing the preparation, administration, and storage of SEA-BCMA is located in the Pharmacy Instructions.

5.2.1. Description

SEA-BCMA is a sterile, preservative-free, colorless to light yellow, clear to slightly opalescent solution with no visible particulate matter. SEA-BCMA is supplied by Seagen in single-dose glass vials. The drug product solution is diluted in sterile 0.9% sodium chloride injection, US Pharmacopeia, or equivalent, for IV administration.

SEA-BCMA drug product is labeled with a nominal content of 100 mg/vial. Each vial contains 110 mg of SEA-BCMA, which allows the label quantity to be withdrawn for use. SEA-BCMA drug product consists of SEA-BCMA (20 mg/mL), histidine, arginine, trehalose and polysorbate 80. The pH of the product is approximately 6.5.

5.2.2. Dose and Administration

SEA-BCMA will be administered at the assigned dose by IV infusion. SEA-BCMA must not be administered as an IV push or bolus. SEA-BCMA should not be mixed with other medications.

On Cycle 1, Day 1, subjects were closely observed in the clinic for at least 6 hours after completion of study treatment administration during dose-escalation. Vital signs will be collected as described in Section 6. Monitoring for subsequent cycles was considered upon review of safety data with the SMC. The observation period after completion of study treatment administration on Cycle 1, Day 1 is reduced to 2 hours during Part A monotherapy dose expansion and in all subsequent cohorts following review of data from the dose-escalation cohort, in which there were no instances of delayed-onset IRRs.

Infusion duration will vary depending on the method of infusion administration and the SEA-BCMA dose. Please refer to the Pharmacy Instructions for further details.

The initial approach to SEA-BCMA administration will be stepwise infusion. In a stepwise infusion, the infusion rate is increased at set time intervals until a defined maximum rate of infusion is reached. The first infusion of SEA-BCMA will be initiated at a rate of 50 mg/hour. If the first 30 minutes is well-tolerated, the rate will be incrementally increased (no greater than

2-fold increase in rate) every 30 minutes as tolerated until a maximum rate (400 mg/hour) is reached. With subsequent infusions, the infusion rate may be increased more rapidly in shorter time intervals; eg, after the first 15 minutes, the rate can be incrementally increased (no greater than 2-fold increase in rate) every 15 minutes as tolerated until the maximum rate is reached.

As clinical experience with stepwise infusions evolves, the maximum rate may be increased or decreased based on accumulating safety data and/or recommendations of the SMC. In addition, alternative approaches to SEA-BCMA administration may be evaluated to manage potential safety signals, including IRRs, as recommended by the SMC. These may include systematic implementation of the following strategies: extending the planned infusion duration, fixed-duration infusion (Section 5.2.2.1), administration at a fixed infusion rate (Section 5.2.2.2), divided-dose administration (Section 5.2.2.3), or a change in premedications (Section 5.6.1).

See the Pharmacy Instructions for additional details.

5.2.2.1. Fixed-Duration Infusion

If fixed-duration infusion is implemented, the SEA-BCMA infusion duration is defined by the sponsor. As clinical experience with SEA-BCMA infusion evolves, the infusion duration may be increased or decreased based on accumulating safety data and/or recommendations of the SMC.

In an individual subject, if the subject is unable to tolerate the infusion, the infusion duration may be increased; the infusion duration in subsequent infusions may also be increased per investigator discretion with medical monitor approval. Conversely, if a subject does not experience an IRR greater than Grade 1 with consecutive infusions, the infusion duration may be shortened (ie, administered at a faster rate) at the discretion of the investigator with medical monitor approval, the implementation of which may be dose-cohort specific.

5.2.2.2. Fixed Infusion Rate

If a fixed infusion rate is implemented, the dose is administered at a fixed rate rather than over a fixed time.

For example, for a fixed infusion rate of 50 mg/hour, a dose of 100 mg would be infused over 2 hours. As clinical experience with administration at a fixed infusion rate evolves, the rate may be increased, or decreased, based on accumulating safety data and/or recommendations of the SMC.

In an individual subject, if the subject is unable to tolerate the infusion rate, the infusion rate may be decreased in subsequent infusions per investigator discretion with medical monitor approval. Conversely, if an individual subject does not experience an IRR greater than Grade 1 with consecutive infusions, the infusion rate may be increased at the discretion of the investigator with medical monitor approval.

5.2.2.3. Divided-Dose Administration

If divided-dose administration is implemented, the dose is divided and administered separately within a time period. For example, the dose could be divided in 2 parts, in which the first 10% of

the dose is infused over approximately 45 minutes, followed by a 30-minute observation period as the subject remains in the infusion chair. If the investigator determines that the subject has tolerated the initial SEA-BCMA infusion, the remaining 90% is infused over approximately 45 minutes.

5.2.3. Dose Modifications

On a per-subject basis, lengthening of dosing intervals for toxicity, including DLT, may be allowed upon approval by the medical monitor. Subjects who experience DLT in Cycle 1 should not receive further treatment with SEA-BCMA unless clinical benefit is demonstrated with adequately managed toxicity and there is approval from the medical monitor. Examples of clinical benefit include an OR assessed by imaging, laboratory assessment, or physical examination; or SD and clinical improvement in disease-related symptoms per investigator. If clinical benefit is demonstrated, the dosing interval may be lengthened by 50 to 100% after discussion with the medical monitor. The type and severity of the AE observed will be taken into consideration to inform the decision. For subjects treated at the lowest dose level, the dosing interval may be lengthened, or the subject may be discontinued from treatment.

If a subject has a clinically significant, unresolved AE on the planned dosing day, the dose may be delayed for up to 7 days. Dosing delays due to other reasons or lasting >7 days must be discussed with the medical monitor (see Table 5); during the DLT period, subjects should not receive further treatment with SEA-BCMA unless clinical benefit is demonstrated with adequately managed toxicity and there is approval from the medical monitor. For subjects requiring a dose delay >7 days due to an unresolved AE, the dosing interval may be lengthened by 50 to 100% after discussion with the medical monitor.

In q2wk dosing, if a subject has a clinically significant, unresolved AE on Day 15 that prevents dosing, the Day 15 visit may be delayed for ≤7 days. On the seventh day, if a subject cannot receive the dose, the second dose of the cycle will be eliminated, the Day 15 visit will be skipped, and the Day 22 visit will be performed. If the Day 15 dose is delayed for ≤7 days, study assessments required for Day 15 to 28 will be delayed by the same number of days as the dose delay, and study drug administration for the next cycle will be delayed by at least the same number of days.

In intensive dosing weekly induction Cycles 1 and 2, if a subject has a clinically significant, unresolved AE that prevents dosing on Day 8, 15, or 22, the dose may be delayed for ≤3 days. On the third day, if a subject cannot receive the dose, the dose of SEA-BCMA will be eliminated and the corresponding visit will be skipped; dosing and visit schedule would resume the following week (eg, at Day 22, if Day 15 is skipped). However, if a Day 8, 15, or 22 dose is delayed for ≤3 days, subsequent study assessments within the same cycle will be delayed by the same number of days as the dose delay, and study drug administration for the next dose will be delayed by at least the same number of days.

During the DLT period (Cycle 1), growth factor and transfusion support is discouraged unless medically indicated; subjects who receive growth factor (eg, granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) or transfusion support (other than

red blood cell transfusions for MM-related anemia) during this period for reasons other than DLT may not be evaluable for DLT, except in Part D, where granulocyte colony-stimulating factor is permitted during Cycle 1 if given as primary or secondary prophylaxis in conjunction with pomalidomide. Consideration should be given for growth factor support for prophylaxis or treatment of cytopenias in subsequent cycles (Table 5). During dose-escalation, subjects with Grade 4 neutropenia must have a follow-up complete blood count (CBC) with differential obtained 5 days from the time of assessment for evaluation of DLT. In addition, subjects with Grade 3 asymptomatic laboratory abnormalities must have follow-up laboratory evaluation obtained 72 hours from the time of assessment for evaluation of DLT. Serum chemistry and CBCs should be collected minimally on a weekly schedule during dose delays resulting from toxicity.

Table 5 describes the recommended dose modifications for toxicity.

Table 5: Recommended dose modifications for toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nonhematologic (AE or laboratory abnormality)	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ Grade 1 or baseline[a], and then resume treatment at 50% of the SEA-BCMA dose	Discontinue study treatment
Hematologic (neutropenia, thrombocytopenia, and anemia)	Continue at same dose level	Continue at same dose level	First occurrence: Withhold dose until resolution to ≤ Grade 2 or baseline; for Grade 3 events, resume treatment at the same dose level; for Grade 4 events, either resume treatment at the same dose level after discussion with the medical monitor or discontinue treatment at the discretion of the investigator. Treatment delay of up to 7 days is permitted[a] Second occurrence: Withhold dose until toxicity is ≤ Grade 2 or baseline[a]. Either resume treatment at the same dose level with growth factor support after discussion with the medical monitor or discontinue study treatment at the discretion of the investigator	
Infusion-related reaction	See Section 5.7.1			

a Treatment delays of >7 days are to be discussed with the medical monitor.
AE = adverse event, BCMA = B-cell maturation antigen

Intrasubject dose-escalation may be permitted in the event that a subject has not experienced a Grade ≥2 AE while on study treatment, has received at least 1 cycle of SEA-BCMA at the current dose level, and achieves SD or better. Additional treatment cycles may be administered at 1 dose level below the currently enrolling dose level for dose-escalation (or at the MTD if it has been determined) at the discretion of the investigator and upon approval by the medical monitor.

5.2.4. Storage and Handling

Refrigeration should be set at 2 to 8 °C for storage of vials and solutions containing SEA-BCMA. The controlled location must be accessible only to the pharmacist, the investigator, or a duly designated person. SEA-BCMA does not contain preservatives; therefore, opened and reconstituted vials should be used as soon as possible. Please refer to the Pharmacy Instructions for further details on storage and handling.

Drug accountability procedures are provided in the Pharmacy Binder.

5.2.5. Packaging and Labeling

SEA-BCMA is supplied in clear glass vials. The clinical supplies for open-label studies are labeled as SEA-BCMA Injection. A sample label is provided in the Pharmacy Instructions.

5.2.6. Preparation

Recommended safety measures for handling and preparation include masks, protective clothing, gloves (double glove with nitrile gloves), and vertical laminar airflow safety cabinets.

Detailed drug preparation instructions are provided in the Pharmacy Instructions.

5.2.7. Continued Access to SEA-BCMA After the End of the Study

A subject deriving clinical benefit from SEA-BCMA at the time the study is completed may be permitted to continue to receive SEA-BCMA, provided the investigator considers it to be the subject's best treatment option and the study is not terminated due to safety concerns. Requests will be discussed on a subject-by-subject basis with the sponsor. If continued access to SEA-BCMA is permitted, sparse data may be collected to monitor the safety and tolerability of continued administration. Subjects will not receive SEA-BCMA beyond the protocol definition of end of treatment (EOT).

5.3. Dexamethasone

5.3.1. Description

Corticosteroids, including dexamethasone, are a key component of SOC combination regimens in MM (Burwick 2019). Dexamethasone induces apoptosis and suppresses protein synthesis in MM cell lines in vitro (Chauhan 2002; Burwick 2017). In clinical trials, dexamethasone has been shown to increase the activity of several classes of drugs, including alkylating agents, IMiDs, and PIs. In addition, dexamethasone is administered as premedication for monoclonal antibodies such as daratumumab and elotuzumab (Darzalex and Empliciti prescribing information).

5.3.2. Method of Procurement

In the US, dexamethasone will be sourced by study sites from commercial supply. In other countries, oral dexamethasone will be provided to the study sites by the sponsor or dexamethasone (oral or IV) will be sourced by study sites from commercial supply.

5.3.3. Dose and Administration

Dexamethasone will be administered on Days 1, 8, 15, and 22 of each 28-day cycle. Dexamethasone is administered as an IV infusion or PO at a dose of 40 mg. The dose of dexamethasone is 20 mg for subjects ≥75 years, or with BMI <18.5, or known to be intolerant of dexamethasone 40 mg. On days when SEA-BCMA is to be administered, dexamethasone should be administered 1 to 3 hours prior to the SEA-BCMA infusion.

5.3.4. Dose Modifications

Suggested dose modifications and supportive care by toxicity are listed in Table 6.

Table 6: Recommended dose modifications for dexamethasone-related toxicity

NCI-CTCAE Category	Toxicity	Recommended Dose Modification/Supportive Care
Gastrointestinal	Grade 1 to 2 dyspepsia, gastric or duodenal ulcer, gastritis requiring medical management	Treat with a proton pump inhibitor such as omeprazole. If symptoms persist, decrease dexamethasone dose by 50%.
	≥ Grade 3 requiring hospitalization or surgery	Hold dexamethasone until symptoms are adequately controlled. Then restart at 50% of current dexamethasone dose along with concurrent therapy with a proton pump inhibitor such as omeprazole. If symptoms persist, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	≥ Grade 3 edema limiting function and unresponsive to therapy or anasarca	Diuretics as needed and decrease dexamethasone dose by 25%. If symptoms persist, decrease dose to 50% of initial dose. If symptoms continue to persist, discontinue dexamethasone and do not resume.
Neurology/ Psychiatric	≥ Grade 2 confusion or mood alteration interfering with function	Hold dexamethasone until symptoms are adequately controlled. Restart at 50% of current dose. If symptoms persist, discontinue dexamethasone and do not resume.
Musculoskeletal	≥ Grade 2 muscle weakness, symptomatic and interfering with function but not interfering with activities of daily living	Decrease dexamethasone dose by 25%. If weakness persists, decrease to 50% of initial dose. If symptoms continue to persist, discontinue dexamethasone and do not resume.
	> Grade 2 muscle weakness, symptomatic and interfering with activities of daily living	Hold dexamethasone until muscle weakness is ≤ Grade 1 or baseline. Then decrease dexamethasone dose by 25% and resume. If weakness persists, decrease dose to 50% of initial dose. If symptoms continue to persist, discontinue dexamethasone and do not resume.
Metabolic[a]	≥ Grade 3 hyperglycemia	Treatment with insulin or oral hypoglycemic agents as needed. If symptoms persist, decrease dose by 25% decrements until levels are satisfactory.
Constitutional	≥ Grade 2 insomnia	Decrease dexamethasone dose by 50%.

a Subjects who enter the study with elevated hemoglobin A1c (HbA1c) (≥6.5%) or fasting glucose (≥126 mg/dL) at screening must be referred to an appropriate provider for glucose management prior to or within 1 week of starting study treatment in Cycle 1.

NCI-CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events

Adverse drug reactions to dexamethasone and dexamethasone infusion/hypersensitivity reactions (IHRs) should be managed according to the approved package insert.

5.3.5. Storage and Handling

Refer to the dexamethasone package insert for storage and handling requirements.

5.3.6. Packaging and Labeling

Dexamethasone is commercially available in the US.

5.3.7. Preparation

Dexamethasone should be prepared per the package insert.

5.4. Pomalidomide

5.4.1. Description

IMiD agents such as thalidomide, lenalidomide, and pomalidomide are commonly used in early lines of therapy for MM. IMiDs enhance NK cell expansion and activity and have been shown to potentiate ADCC when combined with monoclonal antibodies. Pomalidomide is a thalidomide analogue which is approved for the treatment of RRMM in subjects who have failed prior lenalidomide therapy.

5.4.2. Method of Procurement

In the US, pomalidomide will be sourced by study sites from commercial supply.

5.4.3. Dose and Administration

Pomalidomide will be administered once daily at a dose of 4 mg PO on days 1 to 21 of each 28-day cycle. On Cycle 1 Day 1, pomalidomide should be administered 1 to 3 hours prior to SEA-BCMA infusion, to allow for appropriate timing of PK analysis. Pomalidomide should subsequently be taken at approximately the same time each day, and without food (at least 2 hours before or 2 hours after each meal). The capsules should be swallowed whole with water and not opened, broken, or chewed.

5.4.4. Dose Modifications

Suggested dose modifications and supportive care by toxicity are listed in Table 7.

Table 7: Recommended dose modifications for pomalidomide-related toxicity

NCI-CTCAE Category	Toxicity	Recommended Dose Modification
Hematologic	Grade 4 thrombocytopenia, each occurrence	Withhold pomalidomide treatment and follow complete blood count weekly until thrombocytopenia improves to ≤ Grade 2, then resume pomalidomide at 1 mg less than previous dose PO daily[a].
	Grade 4 neutropenia or any grade febrile neutropenia, each occurrence	Withhold pomalidomide treatment and follow complete blood count weekly until neutropenia improves to ≤ Grade 2, then resume pomalidomide at 1 mg less than previous dose PO daily[a].
Gastrointestinal	Grade 1 or higher AST or ALT elevation, or elevation from baseline CTCAE grade	Withhold pomalidomide treatment until liver enzymes return to normal or baseline. Consider resuming pomalidomide at 1 mg less than previous dose[a].
Other	≥ Grade 3 nonhematologic toxicity	Withhold pomalidomide treatment and follow for improvement of toxicity to ≤ Grade 2, then resume pomalidomide at 1 mg less than previous dose PO daily. Permanently discontinue pomalidomide for angioedema, anaphylaxis, Grade 4 rash, skin exfoliation, bullae, or any other severe dermatologic reaction.

a If toxicities occur after dose reduction to 1 mg, discontinue pomalidomide.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CYP = cytochrome P, NCI-CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events, PO = taken orally

If necessary to coadminister strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4/5 and P-glycoprotein, consider reducing pomalidomide dose by 50%.

Dose modification guidance is based on pomalidomide prescribing information, which contains additional guidance on pomalidomide dosing.

5.4.5. Storage and Handling

Refer to the pomalidomide package insert for storage and handling requirements.

5.4.6. Packaging and Labeling

Pomalidomide is commercially available in the US.

5.4.7. Preparation

Pomalidomide should be prepared per the package insert.

5.5. Required Premedication and Postmedication for SEA-BCMA

In Parts B through D, routine premedication for infusion reactions must be administered prior to SEA-BCMA infusion per the following regimen, unless contraindicated or recommended otherwise by the SMC or medical monitor:

- Antipyretic + Antihistamine: administer approximately 45 to 90 minutes prior to SEA-BCMA infusion (required for all subjects for all doses during Cycle 1 and Cycle 2)
  - Acetaminophen, oral, 650 to 1000 mg
  - Diphenhydramine, oral or IV, 25 to 50 mg (or equivalent H1 blocker)

If no IRR is experienced during Cycle 1 or Cycle 2: one or both premedications may be omitted starting with Cycle 3 Day 1 dose.

If IRR occurs despite acetaminophen + antihistamine, treat with supportive care based on symptoms.

For monotherapy subjects (not receiving dexamethasone), add:

- Methylprednisolone, IV, 100 mg (or equivalent dosage intermediate to long-acting corticosteroid) as required premedication 1 to 3 hours prior to next SEA-BCMA infusion. If this infusion is tolerated without IRR, methylprednisolone dose may be reduced to 60 mg (or equivalent dosage of intermediate to long-acting corticosteroid), administered either oral or IV, prior to subsequent doses.
- Additional premedications (eg, H2 blockers or leukotriene inhibitors) may be considered.

For combination subjects (receiving dexamethasone), add:

- H2 blocker (famotidine 40 mg IV or equivalent) as required premedication 45 to 90 minutes prior to all subsequent SEA-BCMA doses
- Additional premedications (eg, leukotriene inhibitors) may be considered.

For management of IRRs, including recommended concomitant therapy, see Section 5.7.1.

There are no required postmedications for SEA-BCMA.

For Parts C and D, refer to the dexamethasone package insert for detailed information on premedication and postmedication.

5.6. Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent.

5.6.1. Required Concomitant Therapy

Required premedications (prior to study treatment) are described in Section 5.5. Based on emerging safety data, the SMC may modify concomitant therapy requirements.

For Part D, containing pomalidomide, subjects must receive thromboembolic prophylaxis per institutional guidelines or the investigator's discretion. Examples of commonly used thromboembolic prophylaxis medications include aspirin, low molecular weight heparin, and vitamin K antagonists.

5.6.2. Allowed Concomitant Therapy

During the DLT period (Cycle 1), growth factor and transfusion support is discouraged unless medically indicated; subjects who receive growth factor or transfusion support during this period for reasons other than DLT may not be evaluable for DLT, except for in Part D. After the DLT period, growth factors or transfusions may be administered according to the revised ASCO 2015

guidelines (Smith 2015) (see Table 5). Subjects may receive all other supportive treatments according to institutional standards.

Prophylactic treatment/measures are strongly recommended for subjects at risk for tumor lysis syndrome, per institutional standard (eg, treatment with allopurinol or rasburicase, as well as adequate hydration (Coiffier 2008).

Prophylactic anti-infective agents (antiviral, antifungal, or antibacterial) may also be administered according to institutional standard.

Allowed concomitant therapy to prevent or manage IRRs is described in Section 5.7 and 5.7.1.

Palliative radiotherapy to a single site of disease is allowed with the approval of the medical monitor.

Concomitant prednisone (or equivalent) may be used at a dose of ≤10 mg/day for noncancer-related AEs. The use of intermittent high-dose corticosteroid treatment to prevent or manage IRRs, other noncancer-related symptoms, or as premedication for radiocontrast for imaging or blood product transfusions is allowed.

Adjuvant therapy for other malignancies that have been definitively treated is allowed.

Routine prophylaxis with vaccines is permitted, including novel respiratory virus vaccines which are approved or available under Emergency Use Authorization; it is recommended that vaccines used do not contain live micro-organisms.

5.6.3. Prohibited Concomitant Therapy

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic antineoplastic therapy during the study, or within 28 days of first study drug dose administration (exceptions noted in Section 4.2 Numbers 10 and 11, and Section 5.6.2).

For Part D, containing pomalidomide, avoid coadministration of pomalidomide with strong inhibitors of CYP1A2 unless medically necessary. Coadministration of pomalidomide with drugs that are strong inhibitors of CYP1A2 (eg, ciprofloxacin, enoxacin and fluvoxamine) and CYP3A4/5 (eg, ketoconazole) or P-gp (eg, amiodarone) could increase pomalidomide exposure and should be avoided, unless medically necessary.

5.7. Management of Adverse Reactions

5.7.1. Management of SEA-BCMA Infusion Reactions

IRRs may occur during the infusion of monoclonal antibody therapies such as SEA-BCMA. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for IRRs.

During dose-escalation, additional mitigation strategies may be explored to manage IRRs. These may be implemented upon SMC recommendation, and may include but are not limited to any or all of the following:

- Slowing, interruption, or other adjustments in the administration of SEA-BCMA
- Potential premedication or postmedication for infusions, for example:
- Antihistamines, such as diphenhydramine 50 mg IV or equivalent and famotidine 40 mg IV or equivalent
- Antipyretics, such as acetaminophen 500 to1000 mg PO
- Antiemetics, such as ondansetron
- IV fluid support, such as normal saline
- Anti-rigor medication, such as meperidine
- Vasopressors
- Corticosteroids, such as hydrocortisone 100 mg IV or equivalent or methylprednisolone 40 mg IV or equivalent (for subjects not receiving dexamethasone as combination therapy)

Required premedication regimen for Parts B through D is provided in Section 5.5. Based on emerging safety data, the SMC may modify or omit the premedication regimen as per Section 3.1.9.2. Recommendations for the management of IRRs are detailed in Table 8. IRRs should be graded according to NCI-CTCAE, v. 4.03, guidelines and per Section 7.7.

Table 8: Management of infusion-related reactions

IRR Grade[a]			
Grade 1	Grade 2	Grade 3	Grade 4
Mild transient reaction; SEA-BCMA treatment interruption not indicated; intervention not indicated	SEA-BCMA treatment interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life threatening consequences; urgent intervention indicated
Treatment Recommendations			
Monitor vital signs more frequently until symptoms have resolved and subject is medically stable. Administer symptomatic treatment as medically indicated.	Hold SEA-BCMA treatment. Monitor vital signs more frequently until symptoms have resolved and subject is medically stable. Administer symptomatic treatment as medically indicated. If subject responds promptly and is medically stable in the opinion of the investigator, SEA-BCMA treatment may be continued at a slower rate.	Stop SEA-BCMA treatment. Institute additional medical management as indicated. Consider hospitalization.	Stop SEA-BCMA treatment immediately. Hospitalization.
Dose Modifications			
No intervention indicated.	Additional premedication with subsequent SEA-BCMA treatment per Section 5.5. Consider slower infusion rate. If recurrent after the above measures, consider dose reduction to 50% of current dose with medical monitor consultation.	Subjects with an IRR that resolves to baseline or Grade 1 or lower within approximately 2 hours after intervention may continue SEA-BCMA at 50% of the dose with additional premedications per Section 5.5. required prior to all subsequent doses, if approved by the medical monitor. OR Permanently discontinue from study treatment.	Permanently discontinue from study treatment.

a Per NCI-CTCAE version 4.03
BCMA = B-cell maturation antigen, IRR = infusion-related reaction, IV = intravenous, NCI-CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events, NSAIDs = Nonsteroidal anti-inflammatory drugs

If anaphylaxis occurs, administration of SEA-BCMA should be immediately and permanently discontinued.

All Grade 3 or 4 events of IRR (with onset during infusion or within ≤24 hr after infusion) or hypersensitivity reaction (with onset occurring >24 hr after infusion) must be reported to the sponsor or designee immediately, regardless of relationship to SEA-BCMA. All Grade 4 events are serious adverse events (SAEs) and are to be reported within the SAE reporting timeframe of 24 hours via the standard SAE forms (see Section 7.7.8).

Subjects in Part A experiencing a ≥ Grade 3 IRR or delayed hypersensitivity reaction must have an IHR visit and an IHR Follow-up visit for evaluation and collection of blood samples for analysis of the mechanism of action of the reaction.

5.8. Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents and the CRF. In the event of an overdose ≥10%, the site should notify the sponsor or designee as soon as they are aware of the overdose.

6. STUDY ACTIVITIES

6.1. Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.7.7). Any study protocol-related AE (defined in Section 7.7.1.1) as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

All procedures on dosing days must be performed predose within 1 day prior to study drug administration unless otherwise specified. Clinical laboratory assessments (serum chemistry panel, CBC with differential (manual differential if clinically indicated, see Section 7.7.11), urinalysis (with microscopy if results are abnormal), spot urine, physical exam, weight, and performance status may be performed within 1 day prior to administration of study drug. The results from all relevant clinical laboratory assessments must be reviewed prior to dosing in order to determine whether to proceed with dosing or whether dose modification is required.

Tumor biopsies performed during the study should be made available to the sponsor or designee if feasible (see Section 7.5.7).

The schedules of events are provided in Appendix A. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

6.2. Part A (Monotherapy Dose-escalation and Expansion)

6.2.1. Screening Visit (Days –28 to 1)

- Informed consent (Section 10.1)
- Study eligibility per inclusion/exclusion criteria (Section 4)
- Medical history (Section 7.1)
- Serology (hepatitis B, C); if hepatitis C serology is positive, hepatitis C-virus (HCV) ribonucleic acid (RNA) test by polymerase chain reaction (PCR) is required to confirm
- Plasmacytoma evaluation per institutional standard imaging modality in cases of suspected or known plasmacytoma (Section 7.1)

6.2.2. Baseline Visit (Days –7 to 1)

- Weight and height
- Electrocardiogram (ECG) in triplicate (Section 7.7.14)
- Physical examination (Section 7.1)
- ECOG performance status (Section 7.7.15 and Appendix D)
- Blood and urine samples for local laboratory assessment (Section 7.7.11)
    - Serum chemistry panel
    - CBC with differential
    - Pregnancy test for subjects of childbearing potential

    - Prothrombin time (PT)/partial thromboplastin time (PTT)/international normalized ratio (INR)
    - Urinalysis (microscopy required if urinalysis results are abnormal)
    - Urine protein to creatinine ratio (UPCR) calculation; 24-hour urine collection required if UPCR >2 mg/mg
- Disease assessments by local laboratory (Section 7.2)
    - BM aspirate, including BM aspirate clot, and biopsy (to also be submitted for central assessment) (Window Day –10 to 1)
    - Serum protein electrophoresis (SPEP)/immunofixation
    - Urine protein electrophoresis (UPEP)/immunofixation (24-hour urine sample)
    - Serum free light chain (SFLC)
    - Quantitative immunoglobulins
    - Beta-2 microglobulin
    - Skeletal survey (via whole body plain film radiography, or via whole body computed tomography [CT] scan, to assess presence and size of lytic bony lesions)
- Blood sample for Modified SPEP for subjects with IgG myeloma only
- Blood samples for biomarkers assessments by central laboratory (Appendix B)

6.2.3. Treatment Period

The treatment period is Day 1 to 28 of each cycle.

6.2.3.1. Day 1 (–1 day)

If Baseline visit activities occur the day prior to Cycle 1, Day 1, the following assessments do not need to be repeated at Cycle 1, Day 1:

- Physical examination
- Weight and height
- ECOG performance status
- Serum chemistry panel
- CBC with differential
- Urinalysis (microscopy required if urinalysis results are abnormal)
- UPCR calculation via spot urine test; 24-hour urine collection required if UPCR >2 mg/mg

Results from clinical laboratory assessments must be reviewed prior to study drug dosing. Subjects must continue to meet eligibility prior to study drug administration on Cycle 1 Day 1. At subsequent cycles, dose modifications should be made in accordance with Section 5.2.3 and 5.7.1.

- Physical examination including weight

- Vital signs (Section 7.7.10):
  - Predose
  - During the infusion:
    - 15 minutes after start of infusion
    - 30 minutes after start of infusion
    - 30 minute intervals during infusion and after any change in rate of infusion
  - After completion of study treatment administration:
    - Within 5 minutes
    - 15 minutes after completion of infusion (Cycle 1 only)
    - 30 minutes after completion of infusion (Cycle 1 only)
    - 60 minutes after completion of infusion (Cycle 1 only)
    - 90 minutes after completion of infusion (Cycle 1 only)
    - 120 minutes after completion of infusion (Cycle 1 only)
    - 240 minutes after completion of infusion (Cycle 1 for dose-escalation)
    - 360 minutes after completion of infusion (Cycle 1 for dose-escalation)
- ECOG performance status
- Blood and urine samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
  - Urinalysis (microscopy required if urinalysis results are abnormal)
  - UPCR calculation; 24-hour urine collection required if UPC >2 mg/mg
- SEA-BCMA administration (Section 5.2.2)
- ECG in triplicate (Cycle 1 only)
- Predose
  - 30 minutes after completion of infusion
  - 2 hours after completion of infusion
  - For infusions ≤2 hours, 6 hours after completion of infusion
- Blood samples for PK/ATA/biomarkers assessments by central laboratory (Appendix B)

6.2.3.2. Day 2

- ECG in triplicate (Cycle 1 only)
- Blood samples for PK/biomarkers assessments by central laboratory (Cycles 1, 2 and 3; Appendix B)

6.2.3.3. Day 4 (±1 day)

- ECG in triplicate (Cycle 1 only)
- Blood samples for PK/biomarkers assessments by central laboratory (Cycles 1, 2 and 3; Appendix B)

6.2.3.4. Day 8 (±1 day)

- ECG in triplicate (Cycle 1 only)
- Blood samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
- Blood samples for PK/biomarkers assessments by central laboratory (Cycles 1, 2 and 3; Appendix B)

6.2.3.5. Day 15 (±1 day)

- Blood samples for local laboratory assessment
- CBC with differential
- Serum chemistry panel
- Blood samples for PK/biomarkers assessments by central laboratory (Appendix B)

Laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.

- Physical examination including weight
- ECOG performance status
- Vital signs:
  - Predose
  - During the infusion:
    - 15 minutes after start of infusion
    - 30 minutes after start of infusion
    - 30 minute intervals during infusion and after any change in rate of infusion
  - After completion of study treatment administration:
    - Within 5 minutes
- ECG in triplicate (Cycle 1 only)
  - Predose
  - 30 minutes after completion of infusion
  - 2 hours after completion of infusion
- Urine samples for local laboratory assessment

- Urinalysis (microscopy required if urinalysis results are abnormal)
- UPCR calculation via spot urine test

- SEA-BCMA administration

6.2.3.6. Days 16 and 18

- Blood samples for PK assessments by central laboratory (Cycle 1 only, for subjects who received SEA-BCMA administration at Day 15; Appendix B)

6.2.3.7. Day 22 (±1 day)

- Response assessments by local laboratory (Day 22 to 28)
  - BM aspirate, including BM aspirate clot, and biopsy (to be also submitted for central assessment) (Window Day 22 to Day 28) (Cycle 2 and at time of suspected CR)
  - SPEP/immunofixation
  - UPEP/immunofixation if screening UPEP ≥200 mg/24 hours or for assessment of very good partial response (VGPR) or better
  - In cases of suspected or known plasmacytoma, plasmacytoma evaluation per institutional standard imaging modality should be performed every 4 cycles or to confirm a response of PR or better, or as clinically indicated to confirm PD.
  - SFLC
  - Quantitative immunoglobulins
- Blood samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
- Blood sample for Modified SPEP for subjects with IgG myeloma only
- Blood samples for PK/biomarkers assessments by central laboratory (Cycles 1, 2, 3, and at time of suspected CR; Appendix B). When applicable, blood and BM samples must be collected on the same day.

6.2.3.8. Day 29

- Blood samples for PK assessments by central laboratory only for subjects not starting the next cycle on Day 29 and not at the EOT visit (Appendix B)

6.3. Part B (Monotherapy Intensive Dosing)

6.3.1. Screening Visit (Days –28 to 1)

- Informed consent (Section 10.1)
- Study eligibility per inclusion/exclusion criteria (Section 4)
- Medical history (Section 7.1)

- Serology (hepatitis B, C); if hepatitis C serology is positive, HCV RNA test by PCR is required to confirm
- Plasmacytoma evaluation per institutional standard imaging modality in cases of suspected or known plasmacytoma (Section 7.1)

6.3.2. Baseline Visit (Days –7 to Day 1)

- Weight and height
- ECG in triplicate (Section 7.7.14)
- Physical examination (Section 7.1)
- ECOG performance status (Section 7.7.15 and Appendix D)
- Blood and urine samples for local laboratory assessment (Section 7.7.11)
  - Serum chemistry panel
  - CBC with differential
  - Pregnancy test for subjects of childbearing potential
  - PT/PTT/INR
  - Urinalysis (microscopy required if urinalysis results are abnormal)
  - UPCR calculation via spot urine test
- Disease assessments by local laboratory (Section 7.2)
  - BM aspirate, including BM aspirate clot, and biopsy (to also be submitted for central assessment) (Window Day –10 to 1)
  - SPEP/immunofixation
  - UPEP/immunofixation (24-hour urine sample required on all subjects regardless of presence of measurable disease)
  - SFLC
  - Quantitative immunoglobulins
  - Beta-2 microglobulin
  - Skeletal survey (via whole body plain film radiography, or via whole body CT scan, to assess presence and size of lytic bony lesions)
- Blood sample for Modified SPEP for subjects with IgG myeloma only
- Blood samples for biomarkers assessments by central laboratory (Appendix B).

6.3.3. Treatment Period

The treatment period is Day 1 to 28 of each cycle.

6.3.3.1. Day 1 (–1 day)

If Baseline visit activities occur the day prior to Cycle 1, Day 1, the following assessments do not need to be repeated at Cycle 1, Day 1:

- Physical examination
- Weight and height
- ECOG performance status
- Serum chemistry panel
- CBC with differential
- Urinalysis (microscopy required if urinalysis results are abnormal)
- UPCR calculation via spot urine test

Results from clinical laboratory assessments must be reviewed prior to study drug dosing. Subjects must continue to meet eligibility prior to study drug administration on Cycle 1 Day 1. At subsequent cycles, dose modifications should be made in accordance with Sections 5.2.3 and 5.7.1.

- Physical examination including weight
- Vital signs (Section 7.7.10):
  - Predose
  - During the infusion:
    - 15 minutes after start of infusion
    - 30 minutes after start of infusion
    - 30 minute intervals during infusion and after any change in rate of infusion
  - After completion of study treatment administration:
    - Within 5 minutes
    - 15 minutes after completion of infusion (Cycle 1 only)
    - 30 minutes after completion of infusion (Cycle 1 only)
    - 60 minutes after completion of infusion (Cycle 1 only)
    - 90 minutes after completion of infusion (Cycle 1 only)
    - 120 minutes after completion of infusion (Cycle 1 only)
- ECOG performance status
- Blood and urine samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
  - Urinalysis (microscopy required if urinalysis results are abnormal)
- UPCR calculation via spot urine test
- Administer premedication approximately 45 to 90 minutes prior to the infusion of SEA-BCMA (Section 5.5)
- SEA-BCMA administration (Section 5.2.2)

- ECG in triplicate (Cycles 1, 2, and 3 only)
  - Predose
  - 30 minutes after completion of infusion
- Blood samples for PK/ATA/biomarkers assessments by central laboratory (Appendix B)

6.3.3.2. Day 2

- Blood samples for PK/biomarkers assessments by central laboratory (Cycle 1 only; Appendix B)

6.3.3.3. Day 4

- Blood samples for PK assessments by central laboratory (Cycle 1 only; Appendix B)

6.3.3.4. Day 8 (±1 day)

- Blood samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
- Blood samples for PK/biomarkers assessments by central laboratory (Cycle 1 and 2 only; Appendix B)

Cycles 1 and 2 only:

Laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.

- Physical examination including weight
- ECOG performance status
- Vital signs:
  - Predose
  - During the infusion:
    - 15 minutes after start of infusion
    - 30 minutes after start of infusion
    - 30 minute intervals during infusion and after any change in rate of infusion
  - After completion of study treatment administration:
    - Within 5 minutes
- ECG in triplicate
  - Predose
  - 30 minutes after completion of infusion
- Urine samples for local laboratory assessment

- Urinalysis (microscopy required if urinalysis results are abnormal)
- UPCR calculation via spot urine test

- Administer premedication approximately 45 to 90 minutes prior to the infusion of SEA-BCMA (Section 5.5)
- SEA-BCMA administration (Section 5.2.2)

6.3.3.5. Day 15 (±1 day)

- Blood samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
- Blood samples for PK/biomarkers assessments by central laboratory (Cycles 1, 2, and 3; Appendix B)

Laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.

- Physical examination including weight
- ECOG performance status
- Vital signs:
  - Predose
  - During the infusion:
    - 15 minutes after start of infusion
    - 30 minutes after start of infusion
    - 30 minute intervals during infusion and after any change in rate of infusion
  - After completion of study treatment administration:
    - Within 5 minutes
- ECG in triplicate (Cycles 1 and 2 only)
  - Predose
  - 30 minutes after completion of infusion
- Urine samples for local laboratory assessment
  - Urinalysis (microscopy required if urinalysis results are abnormal)
  - UPCR calculation via spot urine test
- Administer premedication approximately 45 to 90 minutes prior to the infusion of SEA-BCMA (Section 5.5).
- SEA-BCMA administration (Section 5.2.2)

6.3.3.6. Day 22 (±1 day)

- Response assessments by local laboratory (Day 22 to 28)
  - BM aspirate, including BM aspirate clot, and biopsy (to be also submitted for central assessment) (Window Day 22 to Day 28) (Cycle 2, Cycle 6, every 6 cycles thereafter, and at time of suspected CR)
  - SPEP/immunofixation
  - UPEP/immunofixation if screening UPEP ≥200 mg/24 hours or for assessment of VGPR or better
  - In cases of suspected or known plasmacytoma, plasmacytoma evaluation per institutional standard imaging modality should be performed every 4 cycles or to confirm a response of PR or better, or as clinically indicated to confirm PD.
  - SFLC
  - Quantitative immunoglobulins
- Blood samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
- Blood sample for Modified SPEP for subjects with IgG myeloma only
- Blood samples for PK/biomarkers assessments by central laboratory (Cycles 1, 2, 6 and every 6 cycles thereafter, and at time of suspected CR; Appendix B). When applicable, blood and BM samples must be collected on the same day.

Cycles 1 and 2 only:

Laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.

- Physical examination including weight
- ECOG performance status
- Vital signs:
  - Predose
  - During the infusion:
    - 15 minutes after start of infusion
    - 30 minutes after start of infusion
    - 30 minute intervals during infusion and after any change in rate of infusion
  - After completion of study treatment administration:
    - Within 5 minutes
- ECG in triplicate
  - Predose

- 30 minutes after completion of infusion

- Urine samples for local laboratory assessment
  - Urinalysis (microscopy required if urinalysis results are abnormal)
  - UPCR calculation via spot urine test
- Administer premedication approximately 45 to 90 minutes prior to the infusion of SEA-BCMA (Section 5.5).
- SEA-BCMA administration

6.4. Part C (SEA-BCMA plus Dexamethasone)

6.4.1. Screening Visit (Days –28 to 1)

- Informed consent (Section 10.1)
- Study eligibility per inclusion/exclusion criteria (Section 4)
- Medical history (Section 7.1)
- Serology (hepatitis B, C); if hepatitis C serology is positive, HCV RNA test by PCR is required to confirm
- Plasmacytoma evaluation per institutional standard imaging modality in cases of suspected or known plasmacytoma (Section 7.1)

6.4.2. Baseline Visit (Days –7 to Day 1)

- Weight and height
- ECG in triplicate (Section 7.7.14)
- Physical examination (Section 7.1)
- ECOG performance status (Section 7.7.15 and Appendix D)
- Blood and urine samples for local laboratory assessment (Section 7.7.11)
  - Serum chemistry panel
  - CBC with differential
  - HbA1c
    - If HbA1c is elevated (≥6.5%), refer subject to appropriate provider prior to or within 1 week of starting study treatment in Cycle 1 for glucose management).
  - Pregnancy test for subjects of childbearing potential
  - PT/PTT/INR
  - Urinalysis (microscopy required if urinalysis results are abnormal)
  - UPCR calculation via spot urine test
- Disease assessments by local laboratory (Section 7.2)
  - BM aspirate, including BM aspirate clot, and biopsy (to also be submitted for central assessment) (Window Day –10 to 1)

- SPEP/immunofixation
- UPEP/immunofixation (24-hour urine sample)
- SFLC
- Quantitative immunoglobulins
- Beta-2 microglobulin
- Skeletal survey (via whole body plain film radiography, or via whole body CT scan, to assess presence and size of lytic bony lesions)

- Blood sample for Modified SPEP for subjects with IgG myeloma only
- Blood samples for biomarkers assessments by central laboratory (Appendix B)

6.4.3. Treatment Period

The treatment period is Day 1 to 28 of each cycle.

6.4.3.1. Day 1 (–1 day)

If Baseline visit activities occur the day prior to Cycle 1, Day 1, the following assessments do not need to be repeated at Cycle 1, Day 1:

- Physical examination
- Weight and height
- ECOG performance status
- Serum chemistry panel
- CBC with differential
- Urinalysis (microscopy required if urinalysis results are abnormal)
- UPCR calculation via spot urine test

Results from clinical laboratory assessments must be reviewed prior to study drug dosing. Subjects must continue to meet eligibility prior to study drug administration on Cycle 1 Day 1. At subsequent cycles, dose modifications should be made in accordance with Sections 5.2.3 and 5.7.1.

- Physical examination including weight
- Vital signs (Section 7.7.10):
  - Predose
  - During the infusion:
    - 15 minutes after start of infusion
    - 30 minutes after start of infusion
    - 30 minute intervals during infusion and after any change in rate of infusion
  - After completion of study treatment administration:
    - Within 5 minutes

- 15 minutes after completion of infusion (Cycle 1 only)
- 30 minutes after completion of infusion (Cycle 1 only)
- 60 minutes after completion of infusion (Cycle 1 only)
- 90 minutes after completion of infusion (Cycle 1 only)
- 120 minutes after completion of infusion (Cycle 1 only)

- ECOG performance status
- Blood and urine samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
  - Urinalysis (microscopy required if urinalysis results are abnormal)
  - UPCR calculation via spot urine test
- Dexamethasone administration (1 to 3 hours prior to SEA-BCMA infusion)
- Administer premedication approximately 45 to 90 minutes prior to the infusion of SEA-BCMA (Section 5.5).
- SEA-BCMA administration (Section 5.2.2)
- Blood samples for PK/ATA/biomarkers assessments by central laboratory (Appendix B)

6.4.3.2. Day 2

- Blood samples for PK/biomarkers assessments by central laboratory (Cycle 1; Appendix B)

6.4.3.3. Day 4

- Blood samples for PK/biomarkers assessments by central laboratory (Cycle 1; Appendix B)

6.4.3.4. Day 8 (±1 day)

- Blood samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
- Blood samples for PK/biomarkers assessments by central laboratory (Cohort 1, Cycle 1 only; Cohort 2, Cycles 1 and 2 only; Appendix B)
- Dexamethasone administration (1 to 3 hours prior to SEA-BCMA infusion, if applicable)

Part C Cohort 2, Cycles 1 and 2 only:

Laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.

- Physical examination

- ECOG performance status
- Vital signs:
  - Predose
  - During the infusion:
    - 15 minutes after start of infusion
    - 30 minutes after start of infusion
    - 30 minute intervals during infusion and after any change in rate of infusion
  - After completion of study treatment administration:
    - Within 5 minutes
- Urine samples for local laboratory assessment
  - Urinalysis (microscopy required if urinalysis results are abnormal)
  - UPCR calculation via spot urine test
- Administer premedication approximately 45 to 90 minutes prior to the infusion of SEA-BCMA (Section 5.5).
- SEA-BCMA administration (Section 5.2.2)

6.4.3.5. Day 15 (±1 day)

- Blood samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
- Blood samples for PK/biomarkers assessments by central laboratory (Cycles 1, 2, and 3 only; Appendix B)

Laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.

- Physical examination including weight
- ECOG performance status
- Vital signs:
  - Predose
  - During the infusion:
    - 15 minutes after start of infusion
    - 30 minutes after start of infusion
    - 30 minute intervals during infusion and after any change in rate of infusion
  - After completion of study treatment administration:
    - Within 5 minutes

- Urine samples for local laboratory assessment
  - Urinalysis (microscopy required if urinalysis results are abnormal)
  - UPCR calculation via spot urine test
- Dexamethasone administration (1 to 3 hours prior to SEA-BCMA infusion)
- Administer premedication approximately 45 to 90 minutes prior to the infusion of SEA-BCMA (Section 5.5).
- SEA-BCMA administration (Section 5.2.2)

6.4.3.6. Day 22 (±1 day)

- Response assessments by local laboratory (Day 22 to 28)
  - BM aspirate, including BM aspirate clot, and biopsy (to be also submitted for central assessment) (Cycle 2, Cycle 6, every 6 cycles thereafter, and at time of suspected CR)
  - SPEP/immunofixation
  - UPEP/immunofixation if screening UPEP ≥200 mg/24 hours or for assessment of VGPR or better
  - In cases of suspected or known plasmacytoma, plasmacytoma evaluation should be performed per institutional standard imaging modality every 4 cycles or to confirm a response of PR or better, or as clinically indicated to confirm PD.
  - SFLC
  - Quantitative immunoglobulins
- Blood samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
- Blood sample for Modified SPEP for subjects with IgG myeloma only
- Blood samples for PK/biomarkers assessments by central laboratory (Cycles 1, 2, 3, 6, and every 6 cycles thereafter, and at time of suspected CR; (Appendix B). When applicable, blood and BM samples must be collected on the same day.
- Dexamethasone administration (1 to 3 hours prior to SEA-BCMA infusion, if applicable)

Part C Cohort 2 Cycles 1 and 2 only:

Laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.

- Physical examination
- ECOG performance status
- Vital signs:
  - Predose
  - During the infusion:

        - 15 minutes after start of infusion
        - 30 minutes after start of infusion
        - 30 minute intervals during infusion and after any change in rate of infusion
    - After completion of study treatment administration:
        - Within 5 minutes
- Urine samples for local laboratory assessment
    - Urinalysis (microscopy required if urinalysis results are abnormal)
    - UPCR calculation via spot urine test
- Administer premedication approximately 45 to 90 minutes prior to the infusion of SEA-BCMA (Section 5.5).
- SEA-BCMA administration (Section 5.2.2)

6.4.4. Qualitative Interview

Qualitative interview to be conducted within 1 cycle of the time of first OR (PR or better) or within 1 cycle of documentation of ongoing SD at the end of Cycle 4, whichever occurs first. See the Interview Guide for additional details. Qualitative interviews will be conducted in up to a total of 10 subjects from Part C and Part D.

6.5. Part D (SEA-BCMA plus Pomalidomide and Dexamethasone)

6.5.1. Screening Visit (Days -28 to 1)

- Informed consent (Section 10.1)
- Study eligibility per inclusion/exclusion criteria (Section 4)
- Medical history (Section 7.1)
- Serology (hepatitis B, C); if hepatitis C serology is positive, HCV RNA test by PCR is required to confirm
- Plasmacytoma evaluation per institutional standard imaging modality in cases of suspected or known plasmacytoma (Section 7.1)
- Pregnancy test for subjects of childbearing potential (10 to 14 days prior to planned Cycle 1 Day 1)

6.5.2. Baseline Visit (Days -10 to Day 1)

- Weight and height
- ECG in triplicate (Section 7.7.14)
- Physical examination (Section 7.1)
- ECOG performance status (Section 7.7.15 and Appendix D)
- Blood and urine samples for local laboratory assessment (Section 7.7.11)
    - Serum chemistry panel

- CBC with differential
- HbA1c
  - If HbA1c is elevated (≥6.5%), refer subject to appropriate provider prior to or within 1 week of starting study treatment in Cycle 1 for glucose management)
- Pregnancy test for subjects of childbearing potential (within 24 hours prior to planned Cycle 1 Day 1)
- PT/PTT/INR
- Urinalysis (microscopy required if urinalysis results are abnormal)
- UPCR calculation via spot urine test

- Disease assessments by local laboratory (Section 7.2)
  - BM aspirate, including BM aspirate clot, and biopsy (to also be submitted for central assessment) (Window Day –10 to 1)
  - SPEP/immunofixation
  - UPEP/immunofixation (24-hour urine sample)
  - SFLC
  - Quantitative immunoglobulins
  - Beta-2 microglobulin
  - Skeletal survey (via whole body plain film radiography, or via whole body CT scan, to assess presence and size of lytic bony lesions)
- Blood sample for Modified SPEP for subjects with IgG myeloma only
- Blood samples for biomarkers assessments by central laboratory (Appendix B)

6.5.3. Treatment Period

The treatment period is Day 1 to 28 of each cycle.

6.5.3.1. Day 1 (–1 day)

If Baseline visit activities occur the day prior to Cycle 1, Day 1, the following assessments do not need to be repeated at Cycle 1, Day 1:

- Physical examination
- Weight and height
- ECOG performance status
- Serum chemistry panel
- CBC with differential
- Urinalysis (microscopy required if urinalysis results are abnormal)
- UPCR calculation via spot urine test

Results from clinical laboratory assessments must be reviewed prior to study drug dosing. Subjects must continue to meet eligibility prior to study drug administration on Cycle 1 Day 1. At subsequent cycles, dose modifications should be made in accordance with Sections 5.2.3 and 5.7.1.

- Pregnancy test for subjects of childbearing potential
- Physical examination including weight
- Vital signs (Section 7.7.10):
  - Predose
  - During the infusion:
    - 15 minutes after start of infusion
    - 30 minutes after start of infusion
    - 30 minute intervals during infusion and after any change in rate of infusion
  - After completion of study treatment administration:
    - Within 5 minutes
    - 15 minutes after completion of infusion (Cycle 1 only)
    - 30 minutes after completion of infusion (Cycle 1 only)
    - 60 minutes after completion of infusion (Cycle 1 only)
    - 90 minutes after completion of infusion (Cycle 1 only)
    - 120 minutes after completion of infusion (Cycle 1 only)
- ECOG performance status
- Blood and urine samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
  - Urinalysis (microscopy required if urinalysis results are abnormal)
  - UPCR calculation via spot urine test
- Dexamethasone administration (1 to 3 hours prior to SEA-BCMA infusion)
- Pomalidomide administration (1 to 3 hours prior to SEA-BCMA infusion on Cycle 1 Day 1), and then daily self-administration thereafter on Days 2 to 21
- Administer premedication approximately 45 to 90 minutes prior to the infusion of SEA-BCMA (Section 5.5)
- SEA-BCMA administration (Section 5.2.2)
- Blood samples for PK/ATA/biomarkers assessments by central laboratory (Appendix B)

6.5.3.2. Day 2

- Blood samples for PK/biomarkers assessments by central laboratory (Cycle 1; Appendix B)

6.5.3.3. Day 4

- Blood samples for PK/biomarkers assessments by central laboratory (Cycle 1; Appendix B)

6.5.3.4. Day 8 (±1 day)

- Blood samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
- Blood samples for PK/biomarkers assessments by central laboratory (Cycle 1; Appendix B)
- Dexamethasone administration (1 to 3 hours prior to SEA-BCMA administration)

6.5.3.5. Day 15 (±1 day)

- Blood samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
- Blood samples for PK/biomarkers assessments by central laboratory (Cycles 1, 2, and 3 only; Appendix B)

Laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.

- Pregnancy test for subjects of childbearing potential
- Physical examination including weight
- ECOG performance status
- Vital signs:
  - Predose
  - During the infusion:
    - 15 minutes after start of infusion
    - 30 minutes after start of infusion
    - 30 minute intervals during infusion and after any change in rate of infusion
  - After completion of study treatment administration:
    - Within 5 minutes
- Urine samples for local laboratory assessment

- Urinalysis (microscopy required if urinalysis results are abnormal)
- UPCR calculation via spot urine test

- Dexamethasone administration (1 to 3 hours prior to SEA-BCMA infusion)
- Administer premedication approximately 45 to 90 minutes prior to the infusion of SEA-BCMA (Section 5.5).
- SEA-BCMA administration (Section 5.2.2)

6.5.3.6. Day 22 (±1 day)

- Response assessments by local laboratory (Day 22 to 28)
  - BM aspirate, including BM aspirate clot, and biopsy (to be also submitted for central assessment) (Cycle 2, Cycle 6, every 6 cycles thereafter, and at time of suspected CR)
  - SPEP/immunofixation
  - UPEP/immunofixation if screening UPEP ≥200 mg/24 hours or for assessment of VGPR or better
  - In cases of suspected or known plasmacytoma, plasmacytoma evaluation should be performed per institutional standard imaging modality every 4 cycles or to confirm a response of PR or better, or as clinically indicated to confirm PD.
  - SFLC
  - Quantitative immunoglobulins
- Blood samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
- Blood sample for Modified SPEP for subjects with IgG myeloma only
- Blood samples for PK/biomarkers assessments by central laboratory (Cycles 1, 2, 3, 6, and every 6 cycles thereafter, and at time of suspected CR; Appendix B). When applicable, blood and BM samples must be collected on the same day.
- Dexamethasone administration (1 to 3 hours prior to SEA-BCMA administration)

6.5.4. Qualitative Interview

Qualitative interview to be conducted within 1 cycle of the time of first OR (PR or better). See the Interview Guide for additional details. Qualitative interviews will be conducted in up to a total of 10 subjects from Part C and Part D.

6.6. Complete Response Assessment

- BM aspirate (and BM biopsy, if available) in subjects with a negative blood and urine M-protein (to be submitted for central assessment of markers of drug activity and resistance to SEA-BCMA)
- Blood samples for biomarkers assessments by central laboratory (Appendix B)

- 24-hour urine sample for UPEP/immunofixation
- Plasmacytoma evaluation, per institutional standard imaging modality, for subjects with plasmacytomas at baseline

6.7. Evaluation of Infusion/Hypersensitivity Reactions (Part A only)

Subjects in Part A experiencing a ≥ Grade 3 infusion reaction or delayed hypersensitivity reaction must have an IHR visit and an IHR Follow-up visit.

6.8. Infusion/Hypersensitivity Reaction Visit (Part A only)

For subjects in Part A, if the IHR occurs on the day of infusion, perform the IHR visit that day. If a delayed hypersensitivity reaction occurs, the IHR visit should be performed as soon as possible, preferably within 24 hours, but not more than 72 hours after occurrence.

The following assessments will be performed:

- Physical exam
- Vital signs
- Blood and urine samples by local laboratory
  - CBC with differential
  - Serum chemistry panel
  - Urinalysis (microscopy required if urinalysis results are abnormal)
- Blood sample collection for PK/biomarkers assessments by central laboratory (Appendix B)

Timing of the IHR visit blood draw may overlap with another protocol-defined blood draw (ie, 2 or 6 hours postdose, or other PK/biomarkers sampling time points). If this occurs, collect blood samples for the IHR visit; lab tests for the protocol-defined blood draw do not need to be duplicated if they are collected as part of the IHR visit. For example, if the IHR visit takes place 2 hours postdose, a separate blood draw for the protocol-defined 2-hour postdose PK/biomarkers blood draw is not required, because samples for Biomarker analyses will be collected as part of the IHR visit.

Similarly, a subject may experience a delayed hypersensitivity reaction so that the IHR visit takes place on Day 8. If this occurs, collect blood samples for the IHR visit. The protocol-defined Day 8 local labs (CBC and chemistry panel) do not need to be duplicated because they are collected as part of the IHR visit. The central lab Biomarkers blood tests (PK, immunophenotyping, cytokine, soluble target and ligands, PBMCs) do not need to be duplicated provided they are collected within the protocol-defined PK/biomarkers blood draw window.

6.9. Infusion/Hypersensitivity Reaction Follow-up Visit (24 to 72 hours; Part A only)

For subjects in Part A, the IHR Follow-up visit is scheduled 24-72 hours after the initial IHR visit, and the following assessments are performed:

- Physical exam

- Vital signs
- Blood and urine samples by local laboratory
  - CBC with differential
  - Serum chemistry panel
  - Urinalysis (microscopy required if urinalysis results are abnormal)
- Blood sample collection for PK/biomarkers assessment by central laboratory (Appendix B)

Timing of the IHR Follow-up visit blood draw may overlap with another protocol-defined blood draw. If this occurs, collect blood samples for the IHR Follow-up visit local and central labs as required; lab tests for the protocol-defined blood draw do not need to be duplicated if they are collected as part of the IHR Follow-up visit.

6.10. End of Treatment Visit (30 to 37 days after last dose of study drug)

EOT visits should occur 30 to 37 days after the last dose of study drug unless delayed due to an AE. Note: EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days after the last study treatment, the subject will be contacted 30 to 37 days following the last treatment to assess for AEs.

- ECG in triplicate
- Physical examination
- ECOG performance status
- Vital signs
- Weight
- Pregnancy test for subjects of childbearing potential
- Blood and urine samples for local laboratory assessment
  - CBC with differential
  - Serum chemistry panel
  - Urinalysis (microscopy required if urinalysis results are abnormal)
  - UPCR calculation via spot urine test (only required if not conducted within 4 weeks prior to EOT)
- Response assessments by local laboratory
  - SFLC
  - BM aspirate and biopsy, if collected per SOC, or to confirm CR, to be submitted for central assessment of markers of drug activity and resistance to SEA-BCMA
  - SPEP/immunofixation
  - UPEP/immunofixation

- In cases of suspected or known plasmacytoma, plasmacytoma evaluation, per institutional standard imaging modality, should be performed every 4 cycles or to confirm a response of PR or better, or as clinically indicated to confirm PD.
- Quantitative immunoglobulins

- Blood sample for Modified SPEP for subjects with IgG myeloma only
- Blood samples for PK/ATA/biomarkers assessments by central laboratory (Appendix B)

6.11. Follow-up (every 12 weeks ±2 weeks)

Subjects who discontinue from treatment with SEA-BCMA will remain on the study for follow-up until withdrawal of consent, death, or study closure, whichever occurs first.

The first follow-up visit will occur 12 weeks (±2 weeks) from the most recent prior response evaluation. Subsequent follow-up visits will be scheduled for 12 weeks (±2 weeks) from the previous follow-up visit.

Subjects who discontinue treatment due to PD or who have initiated subsequent therapy will not be assessed for response but will be followed for survival. Subjects who discontinue treatment will continue to be assessed for response after EOT until PD or initiation of a new therapy. These subjects will be followed at this schedule until withdrawal of consent, death, or study closure, whichever occurs first.

The following assessments will be performed until disease progression or initiation of subsequent therapy; subjects will be followed for survival thereafter.

- Blood samples for local laboratory assessment (obtain until disease progression or until initiation of subsequent anticancer therapy)
  - CBC with differential
  - Serum chemistry panel
- Response assessments by local laboratory
  - SFLC
  - SPEP/immunofixation
  - UPEP/immunofixation if measurable disease in urine
  - BM aspirate and biopsy (for confirmation of CR) (to be submitted for central assessment of markers of response)
  - In cases of suspected or known plasmacytoma, plasmacytoma evaluation, per institutional standard imaging modality, should be performed every 4 cycles or to confirm a response of PR or better, or as clinically indicated to confirm PD.
- Blood sample for Modified SPEP for subjects with IgG myeloma only (to be collected only until subsequent therapy is initiated)
- Survival status and collection of first subsequent anticancer treatment information until death or study closure

6.12. End of Study/End of Follow-up

The date the subject met criteria for study discontinuation and the reason for study discontinuation will be recorded.

7. STUDY ASSESSMENTS

7.1. Screening/Baseline Assessments

Only subjects who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study. Assessments will begin after obtaining a signed informed consent from the subject.

Subject medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications. The number of prior lines of therapy will be determined using the criteria established by Rajkumar et al. (Rajkumar 2015). In brief:

- If a treatment regimen is discontinued for any reason and a different treatment regimen is started, it is considered a new line of therapy
- A new line of therapy is also considered to start when an unplanned substitution or addition of 1 or more drugs is made to an existing course of therapy for any reason
- In subjects undergoing >1 ASCT (except in the case of a planned tandem ASCT), each transplant that follows the first one should be considered a new line of therapy
- A planned course of therapy that has multiple phases, such as induction therapy followed by the first ASCT and maintenance therapy, is considered to be a single line of therapy.

A baseline plasmacytoma scan, per institutional standard imaging modality, is conducted during screening only in cases of suspected or known plasmacytoma. During treatment, plasmacytoma evaluations can be performed at any time to confirm a response of PR or better, or as clinically indicated to confirm PD.

BM aspirate (including a BM aspirate clot) and biopsy are required as part of the baseline visit (Appendix A and Section 7.2).

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Weight and height will also be measured; measurements of height obtained within the prior 12 months may be utilized (Section 7.7.12).

Blood and urine tests will include CBC with differential, serum chemistry panel, serology (hepatitis B and C), PT/PTT/INR, HbA1c (for subjects in Part C) and urinalysis. A pregnancy test will be conducted for subjects of childbearing potential (Section 4.3). Urinalysis with microscopy is required if urinalysis results are abnormal; UPCR calculation is also required. Further details of these tests are provided in Section 7.7.11.

Blood samples will be collected for pharmacodynamic biomarker assessments by the central laboratory.

7.2. Response/Efficacy Assessments

Response assessment includes SPEP/immunofixation, UPEP/immunofixation (in subjects with a baseline urine M-protein ≥200 mg/24 hour or for assessment of VGPR or better), SFLC, quantitative immunoglobulins, and plasmacytoma evaluation, per institutional standard imaging

modality (at baseline, every 4 cycles, and at additional timepoints if clinically indicated). These samples will be collected for local assessment at the times provided in Appendix A. In addition, blood will be analyzed in the central laboratory using a modified SPEP for subjects with IgG myeloma.

BM aspirate, including a BM aspirate clot, and biopsy are required as part of the baseline visit, Day 22 to 28 of Cycle 2, and to confirm CR in subjects negative for blood and urine M-protein. In Part B, Part C, and Part D, BM aspirate and biopsy are also required in Cycle 6 and every 6 cycles thereafter. Both BM aspirate and biopsy samples will be assessed locally at the site for clinical evaluation. In addition, biomarker analyses will be performed centrally on these samples (see Section 7.5). Any additional BM aspirates and biopsies collected at any other time while on the trial may also be submitted for central assessment.

The BM specimens will be tested centrally for assessment of response/resistance to SEA-BCMA and may include but are not limited to: evaluation of BCMA expression, immune activation, disease risk profiling, gene expression profiling, and MRD assessment.

The determination of antitumor activity will be based on response assessments made according to the 2016 IMWG Criteria (Kumar 2016) (see Appendix J). Treatment decisions by the investigator will be based on these assessments. Clinical response of stringent complete response (sCR), CR, VGPR, PR, SD, and PD will be determined at each assessment based on local laboratory (and the modified SPEP run by the central laboratory for subjects with IgG MM), radiological, and clinical evaluations. PD is based on IMWG 2016 criteria and/or clinical disease progression per investigator. All IMWG responses must be confirmed responses. When applicable, determination of immunophenotypic CR, MRD status, and minimal response will be made per the IMWG 2016 criteria.

Subjects' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor (or its designee), upon request.

7.3. Qualitative Interviews

Up to a total of 10 subjects in Parts C and D will be interviewed within 1 cycle of the time of first OR (PR or better) or ongoing SD at the end of Cycle 4 (Part C only). See the Interview Guide for additional details.

7.4. Pharmacokinetic and Immunogenicity Assessments

Blood and BM samples for PK and ATA assessment will be collected at time points outlined in Appendix B. In Parts C and D, additional PK samples will be collected and archived for possible analysis of concentrations of combination drugs.

Qualified assays will be used to measure concentrations of SEA-BCMA in serum and BM and ATA in serum. Remaining PK samples will be archived for possible analysis of SEA-BCMA related species. The assays will include enzyme-linked immunosorbent assays (ELISA) assay, as well as other assays if further characterization is required.

A qualified electrochemiluminescence assay will be used to assess ATA.

7.5. Biomarker Studies

Peripheral blood and BM samples for biomarker analyses will be collected at time points outlined in Appendix B. In addition to protocol-mandated collections of tumor specimens, BM specimens collected at the discretion of the investigator may be submitted for central biomarkers analysis. For all BM collections, sites will supply BM aspirates as well as BM biopsy specimens and BM aspirate clot specimens as formalin-fixed, paraffin-embedded (FFPE) blocks. For samples acquired for SOC, unstained slides may be submitted if an FFPE block for the BM biopsy or clot are not available. Samples will be sent to the central lab for analysis as described in the laboratory manual.

Samples will be evaluated for expression of BCMA and relevant biomarkers that may be associated with the activity of SEA-BCMA and/or change in response to treatment. Analysis of tumor tissue and peripheral blood may also include markers associated with prognosis, response, or resistance. Changes in peripheral blood immune cell subsets will be measured as potential pharmacodynamic and safety markers.

7.5.1. Genetic profiling of effector cells

Single nucleotide polymorphisms of FcγRIIA and FcγRIIIA, which may influence the response to SEA-BCMA, may be determined, including, but not limited to, testing of the following polymorphisms:

- FcγRIIIA – 158V/F
- FcγRIIA – 131H/R

7.5.2. Serum Free Light Chain and modified SPEP

Kappa and Lambda FLCs will be quantified in serum of subjects as surrogate markers of antitumor activity.

For subjects with IgG myeloma who have low levels of serum M-protein SPEP, a reflex modified SPEP assay will be used to assess for residual serum M-protein in the absence of interference from SEA-BCMA.

7.5.3. Peripheral blood immunophenotyping

Peripheral blood samples will be collected for evaluation of circulating immune cells by flow cytometry. Changes in circulating immune cell subsets will be measured as potential pharmacodynamic markers of SEA-BCMA activity. Flow cytometry measurements will include, but not be limited to, characterizing NK cells, monocytes, T-cells, and B-cells.

7.5.4. Plasma cytokines/chemokines

The levels of circulating cytokines/chemokines may be assessed by ELISA and/or multiplex cytokine/chemokines assays.

7.5.5. Soluble target and ligands

The levels of circulating sBCMA, APRIL and BAFF may be assessed by ELISA or other methods (eg, LC-MS or flow cytometry).

7.5.6. Plasma Biomarkers and PBMCs

Plasma and PBMCs will be collected for retrospective analyses of cellular and circulating biomarkers associated with response and/or resistance to SEA-BCMA.

7.5.7. Characterization of Tumor Tissue

Baseline and on-treatment BM aspirates and biopsies will be collected to assess disease relevant immune subsets, characterize tumor burden, investigate depth of response and determine prognostic signatures and response to treatment. Additional protein, gene expression profiling, as well as further molecular characterization of the tumor for myeloma disease relevant risk markers, may also be evaluated to identify biomarkers predictive of response or resistance to SEA-BCMA.

7.5.7.1. Bone marrow immunophenotyping

Expression of BCMA on tumor plasma cells, as well as presence and changes of immune components in the BM, may be evaluated by flow cytometry and/or immunohistochemistry.

7.5.7.2. Gene Expression Profiling/NGS/FISH

Baseline and treatment-related changes in gene expression profiles in tumor and tumor microenvironment may be assessed by RNA sequencing of tumor (CD138-positive) and nontumor (CD138-negative) cells purified from BM aspirates, to determine prognostic disease-risk signatures as well as baseline characteristics and on-treatment changes that may correlate with response or resistance. Cytogenetic analyses or DNA sequencing of CD138-positive plasma cells enriched from BM aspirate collected at Baseline may also be carried out to further determine genetic changes that may predict or be associated with response to SEA-BCMA.

7.5.7.3. MRD

MRD evaluation using the Adaptive next generation sequencing (NGS) for MRD assay (Martinez-Lopez 2014) may be carried out on relevant specimens to understand the activity of SEA-BCMA.

7.5.7.4. Bone marrow plasma

BM plasma will be collected and may be tested for levels of soluble target, ligands, and/or cytokines/chemokines that may influence or correlate with response to SEA-BCMA.

7.6. Biospecimen Repository

In the US only, for subjects who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seagen and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of sensitivity and

resistance mechanisms to SEA-BCMA, and the identification of biomarkers of MM disease and response/resistance to therapy. Blood, BM, and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

7.7. Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication, and measurements of protocol-specified physical examination findings and laboratory tests.

Safety will be monitored as described in Section 9.3.9 over the course of the study by the SMC.

7.7.1. Adverse Events

7.7.1.1. Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a subject or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events CRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol-mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 predose through the end of the safety reporting period (see Section 7.7.7). Complications that occur in association with any procedure (eg, biopsy) should be recorded as AEs whether or not the procedure was protocol-mandated.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, record “anemia” rather than “low hemoglobin”).

7.7.2. Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing insubject hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.7.3.2 for the definition of potential DILI)

AE = adverse event, DILI = drug-induced liver injury, SAE = serious adverse event

7.7.3. Adverse Event Severity

AE severity should be graded using the NCI-CTCAE, v. 4.03. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs above).

7.7.3.1. Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (SEA-BCMA, and/or dexamethasone, and/or pomalidomide) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture)
Unrelated:	Another cause of the AE is more plausible (eg, due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

7.7.3.2. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or nondirected method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

Adverse reactions associated with the infusion of study drug may occur in this study. For IHRs, record the NCI-CTCAE terms of ‘infusion-related reaction,’ ‘allergic or hypersensitivity reaction,’ ‘cytokine release syndrome,’ or ‘anaphylaxis’ with an overall level of severity (per

NCI-CTCAE v. 4.03). In addition, record each sign or symptom of the reaction as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and an SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

7.7.4. Progression of the Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms “Disease Progression”, “Progression of Disease” or “Malignant disease progression” and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.

7.7.5. Pregnancy

7.7.5.1. Notification to Drug Safety

Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 6 months after the last dose of study drug(s) including any pregnancies that occur in the partner of a study subject who is able to father a child. Only report pregnancies that occur in a subject’s partner if the estimated date of conception is after the subject’s first study drug dose. Email or fax to the sponsor’s Drug Safety Department within 24 hours of becoming aware of a pregnancy. As part of the study, all pregnancies will be monitored for the full duration and all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

7.7.5.2. Collection of data on the CRF

All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded on the Adverse Events CRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.7.1.1) should be reported as SAEs.

7.7.6. Potential Drug-Induced Liver Injury

The observation of the critical importance of altered liver function has been referred to informally as Hy's Law (Reuben 2004). Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential hepatotoxicity in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

7.7.6.1. Definition

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (ALT and/or AST) elevation >3 x ULN

   AND

2. Total bilirubin >2 x ULN, without initial findings of cholestasis (ie, elevated serum alkaline phosphatase),

   AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

7.7.6.2. Reporting Requirements

Any potential Hy's Law case should be handled as an SAE associated with the use of the drug and reported promptly to the Sponsor.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

7.7.6.3. Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3 x ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, study drug should be withheld.

Regional guidelines should be followed. Additional information is provided in FDA Guidance for Industry, DILI: Premarketing Clinical Evaluation, 2009 and Health Canada Guidance Document; Pre-market Evaluation of Hepatotoxicity in Health Products, 2012.

7.7.7. Reporting Periods for Adverse Events, and Serious Adverse Events

The safety reporting period for all AEs, and SAEs is from study Day 1 (predose) through the EOT visit or 30 days after the last study treatment, whichever is later. However, all study protocol-related AEs are to be recorded from the time of informed consent. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the subject dies or withdraws consent. All nonserious AEs will be followed through the safety reporting period. Certain nonserious AEs of interest may be followed until resolution, return to baseline, or study closure.

7.7.8. Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, investigators are to report the event to the sponsor, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Subject number
- Date of event onset
- Description of the event
- Study treatment, if known
- Investigator causality assessment

The completed SAE form and SAE Fax Cover Sheet are to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email or fax number specified on the SAE report form) unless otherwise instructed on the sponsor's SAE form.

Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

7.7.9. Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the sponsor (see Section 7.7.8).

The sponsor will report all SAEs, including suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities as required per local regulatory reporting requirements.

7.7.10. Vital Signs

Vital signs measures are to include heart rate, blood pressure, and temperature. There is a 5-minute window to perform vital sign collection at the timepoints identified in Section 6.

7.7.11. Clinical Laboratory Tests

Samples will be drawn for central and local labs. Local laboratory testing will include institutional standard tests for evaluating safety and making clinical decisions. The following

laboratory assessments will be performed by the local lab to evaluate safety at scheduled time points (see Appendix A) during the course of the study:

- The chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, lactate dehydrogenase, phosphorus, potassium, sodium, glucose, total bilirubin, and uric acid.
- The CBC with differential is to include the following tests: white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, hemoglobin, and hematocrit.
- The eGFR should be calculated using the MDRD equation as applicable, with serum creatinine (Scr) reported in mg/dL.

  $$GFR\ (mL/min/1.73\ m^2) = 175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

- Urinalysis
  - Standard urinalysis (Note: specify ± reflexive microscopy)
  - Urine protein and urine creatinine for UPCR via spot urine test
- A serum or urine β-hCG pregnancy test for subjects of childbearing potential
- PT, PTT, INR
- Serology will include assessments of Hepatitis B and C status. If hepatitis C serology is positive, HCV RNA test by PCR is required to confirm.

7.7.12. Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Measurements of height obtained within the prior 12 months may be utilized.

7.7.13. Pregnancy Testing

For subjects of childbearing potential, a serum or urine β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline, within 7 days prior to Day 1 of each treatment cycle, and at the EOT visit in Parts A, B, and C. In Part D (containing pomalidomide), a pregnancy test will be performed 10 to 14 days prior to planned Cycle 1 Day 1, within 24 hours prior to planned Cycle 1 Day 1, q2wk during study treatment (prior to Day 1 and Day 15 dosing), and at the EOT visit. A negative pregnancy result is required before the subject may receive study drug. Pregnancy tests may also be repeated as requested per institutional review board/independent ethics committee (IRB/IEC) or if required by local regulations.

7.7.14. Electrocardiograms

Subjects will be monitored for changes in cardiac repolarization through assessment of ECGs conducted in triplicate at times outlined in Appendix A and Section 6. There is a 30-minute window to perform ECGs. Waiting periods between replicate ECGs are not required.

7.7.15. ECOG Performance Status

ECOG performance status (Appendix D) will be evaluated at protocol-specific time points defined in Appendix A and Section 6.

7.8. Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

Response will be assessed according to 2016 IMWG, which are standardized criteria for evaluating response in MM (Kumar 2016). The intervals of evaluation in this protocol are considered appropriate for disease management.

Immunogenicity is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to SEA-BCMA. PK assessments are also common in clinical studies to help characterize dose-exposure-response relationships.

8. DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1. Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of subjects at the site, Seagen or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current IB/package insert
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- IRB/IEC review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing and record keeping
- Subject coding and randomization (if applicable)
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Seagen representative will typically review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study subjects and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by Seagen or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2. Data Management Procedures

Seagen will provide CRF Completion Guidelines for eCRF data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3. Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are

satisfactory. Appropriate measures to protect subject confidentiality are to be employed during monitoring. The CRFs and related source documents will typically be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the CRFs, such as disease assessments, AEs, and concomitant medications, is complete and correct. Other study records, such as correspondence with the sponsor or its designee and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities and the IRB/IEC.

8.4. Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5. Quality Assurance Procedures

The Research and Development Quality group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Research and Development Quality group of Seagen as part of the written record.

8.6. Data Handling and Record Keeping

8.6.1. Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2. Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by Seagen, whichever is longer. The investigator must contact Seagen prior to

destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Seagen.

9. DATA ANALYSIS METHODS

9.1. Determination of Sample Size

Up to approximately 131 subjects are expected to be enrolled in this study. This number is based on the following assumptions:

- Up to approximately 45 subjects will be evaluated in Part A (monotherapy dose-escalation and expansion; q2wk dosing).

  With the mTPI study design, the exact number of subjects needed to complete the dose-escalation portion of the phase 1 study is unknown because it depends on the number of cohorts required to reach MTD and the number of subjects enrolled in each cohort. This number is based on the assumption that approximately 25 subjects will be evaluated in dose-escalation and that approximately 20 subjects will be evaluated in an expansion cohort at the MTD or optimal dose to further define the safety and antitumor activity of SEA-BCMA.

  Operating characteristics of the dose-escalation part of the study, including the average number of subjects allocated to each dose across a variety of toxicity scenarios are presented in the simulation report (Appendix C).

- Up to approximately 20 subjects will be evaluated in Part B, up to 60 subjects will be evaluated in Part C (up to 20 subjects in Cohort 1; up to 20 subjects in each dose level in Cohort 2) and up to 6 subjects will be evaluated in Part D.

No formal hypothesis is planned. The sample size is selected by providing a reasonable estimation precision. Assuming the observed ORR is between 30 to 70%, the 95% binomial exact CIs are summarized below.

ORR	95% CI (N=20)
30%	12%, 54%
40%	19%, 64%
50%	27%, 73%
60%	36%, 81%
70%	46%, 88%

9.2. Study Endpoint Definitions

Study endpoints are presented in Section 2. Endpoint definitions are presented in this section.

9.2.1. Objective Response Rate

A subject is determined to have an OR if, based on the 2016 IMWG uniform response criteria, they achieve a sCR, CR, VGPR, or a PR. The ORR is defined as the proportion of subjects with an OR per investigator. Subjects whose disease response cannot be evaluated per the 2016 IMWG uniform response criteria will be scored as Not Evaluable for calculating the ORR. Subjects who do not have postbaseline response assessment, or the response is Not Evaluable per IMWG criteria will be counted as non-responders in calculation of ORR.

9.2.2. Complete Response Rate

A subject is determined to have a CR if, based on the 2016 IMWG uniform response criteria they achieve a sCR or CR. The CR rate is defined as the proportion of subjects with a CR per investigator. Subjects whose disease response cannot be evaluated per the IMWG uniform response criteria will be scored as Not Evaluable for calculating the CR rate.

9.2.3. Duration of Objective Response

Duration of OR is defined as the time from first documentation of OR (sCR, CR, VGPR, or PR) to the first documentation of disease progression or to death due to any cause, whichever comes first. Disease progression includes objective evidence of tumor progression (based on serum, urine, or BM assessments) and/or clinical progression per investigator. Duration of response will be censored on the date of the last disease assessment documenting absence of PD for subjects who do not have disease progression and are still on study at the time of an analysis, or are removed from study prior to documentation of tumor progression. Subjects who have started a new antitumor treatment prior to documentation of PD will be censored at the last disease assessment prior to start of new treatment.

Duration of response will only be calculated for the subgroup of subjects achieving a sCR, or CR.

9.2.4. Duration of Complete Response

Duration of CR is defined as the time from first documentation of complete response (sCR, CR) to the first documentation of disease progression or to death due to any cause, whichever comes first. Disease progression includes objective evidence of tumor progression (based on serum, urine or BM assessments) and/or clinical progression per investigator. Duration of CR will be censored on the date of the last disease assessment documenting absence of PD for subjects who do not have disease progression and are still on study at the time of an analysis, or are removed from study prior to documentation of tumor progression. Subjects who have started a new antitumor treatment prior to documentation of PD will be censored at the last disease assessment prior to start of new treatment.

Duration of CR will only be calculated for the subgroup of subjects achieving a sCR or CR.

9.2.5. Progression-free Survival

PFS is defined as the time from the start of any study treatment to first documentation of disease progression or to death due to any cause, whichever comes first. Disease progression includes objective evidence of tumor progression (based on serum, urine or BM assessments) and/or clinical progression per investigator. PFS will be censored on the date of the last disease assessment documenting absence of PD for subjects who do not have disease progression and are still on study at the time of an analysis, or discontinuation of study prior to documentation of tumor progression. Subjects who have started a new antitumor treatment prior to documentation of PD will be censored at the last disease assessment prior to start of new treatment. Subjects lacking an evaluation of tumor response after their first dose will have their event time censored

at 1 day. A detailed censoring scheme will be described in the statistical analysis plan (SAP) for the study.

9.2.6. Overall Survival

OS is defined as the time from the start of any study treatment to the date of death due to any cause. Specifically,

OS = date of death - date of first dose of any study treatment + 1.

OS for subjects who are alive at their date of last contact, including those lost to follow-up, will be censored at the date of last contact. If the last recorded date where a subject is known to be alive is the date of first dose of any study treatment, survival time will be censored on the date of first dose of any study treatment (ie, OS duration of 1 day).

9.2.7. MRD-negativity rate

The rate of MRD negativity will be reported among subjects who achieved VGPR or better.

9.3. Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the SAP. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (eg, adding baseline assessments to define a subgroup). The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1. General Considerations

This is a phase 1 dose-escalation study with subsequent expansion cohort and combination cohort. All analyses will be descriptive.

Descriptive statistics (mean, median, standard deviation, minimum, maximum) will be used to describe continuous variables. Frequencies and percentages will be used to describe categorical variables.

9.3.1.1. Randomization and Blinding

This is a phase 1 dose-escalation and expansion, nonrandomized study. Blinding will not be performed.

9.3.1.2. Adjustments for Covariates

Adjustments for covariates are not planned.

9.3.1.3. Handling of Dropouts and Missing Data

Missing data will not be imputed, with the exception of AE dates while calculating duration of events and treatment-emergent status; details will be provided in the SAP. For time-related endpoints, eg, PFS, subjects who have no specified event will be censored at the time of the last valid assessment of the endpoint(s).

9.3.1.4. Multicenter Studies

There are multiple centers in this study; however, it is not anticipated that any center will accrue enough subjects to warrant an analysis by center.

9.3.1.5. Multiple Comparisons and Multiplicity

No multiple comparisons are planned, and no alpha adjustment is needed in this phase 1 study.

9.3.1.6. Data Transformations and Derivations

Time variables based on 2 dates (eg, start date and end date) will be calculated as (end date - start date +1 [in days]) unless otherwise specified in the planned analysis section.

Baseline values used in all statistical analyses will be the most recent non-missing measurement prior to the first dose of SEA-BCMA unless otherwise specified in the analysis plan.

9.3.1.7. Analysis Sets

9.3.1.7.1. All Treated Subjects Analysis Set

The All Treated Subjects set includes all subjects who receive any amount of SEA-BCMA. The All Treated Subjects set will be used for presentation of safety data and efficacy endpoints.

9.3.1.7.2. Efficacy-Evaluable Analysis Set

The efficacy-evaluable analysis set includes all treated subjects who had both a baseline and at least 1 postbaseline disease assessment per IMWG uniform response criteria, or per investigator claim of clinical progression.

9.3.1.7.3. DLT-Evaluable Analysis Set

The DE Analysis Set includes All Treated Subjects who either experienced a DLT, or were followed for the full DLT evaluation period and received a minimum 75% of the intended total Cycle 1 SEA-BCMA dose, and did not receive prohibited treatment (see Section 5.6.2 and Section 5.6.3). The DE analysis set will be used for determination of the MTD.

Additional details of analyses and analysis sets of subjects may be defined in the SAP.

9.3.1.8. Examination of Subgroups

All analyses will be presented by dose level and total. Details will be defined in the SAP.

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Subgroups may include but are not limited to the following:

- Age (<65 vs ≥65 years old)
- Cytogenetic risk group (high, intermediate, normal)
- Refractory to prior therapies (refractory to IMiDs and PIs vs not)
- Number of prior therapies (<5 vs ≥5)
- Baseline beta-2 microglobulin (<3.5 vs ≥3.5)

- BCMA expression levels

Detailed methodology will be provided in the SAP.

9.3.1.9. Timing of Analyses

The final analysis for this study will occur after all subjects have completed their treatment and the follow-up period or following study termination by the sponsor.

For timing of interim analysis, see Section 9.3.10.

9.3.2. Subject Disposition

An accounting of study subjects by disposition will be tabulated and the number of subjects in each analysis set will be summarized. Subjects who discontinue study treatment and subjects who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.3.3. Subject Characteristics

Demographics and other baseline characteristics will be summarized. Details will be provided in the SAP.

9.3.4. Treatment Compliance

The dose administered at each cycle, dose intensity, and dose modifications will be summarized. Details will be provided in the SAP.

9.3.5. Efficacy Analyses

All efficacy analyses will be presented using the All Treated Subjects set. Selected efficacy endpoints will also be presented using the efficacy-evaluable analysis set. The observed ORR and CR rate and corresponding 95% CIs will be presented. Subjects whose disease response cannot be assessed will be counted as non-responders. Subjects with intrasubject dose-escalation prior to achieving a response will be counted as non-responders at their initial dose.

Duration of response, PFS and OS will be estimated using Kaplan-Meier methodology, and Kaplan-Meier plots will be provided. Medians will be calculated, where possible. The 95% CIs may also be calculated, as appropriate.

Detailed methodology will be provided in the SAP.

9.3.6. Pharmacokinetic and Immunogenicity Analyses

The PK of SEA-BCMA will be evaluated by noncompartmental analysis. The following PK parameters will be determined where data allow:

- Area under the curve
- Concentration at the end of infusion (C_{eoi}) or C_{max}
- Trough concentration (C_{trough})
- Terminal or apparent terminal half-life ($t_{1/2}$)
- Systemic clearance and volume of distribution at steady state

- Accumulation ratio

The incidence of ATA will be summarized by descriptive statistics.

9.3.7. Qualitative Interview Analyses

No formal statistical analysis will be performed on the qualitative interviews.

9.3.8. Biomarker Analyses

Peripheral blood and BM aspirates and biopsies will be collected for biomarker assessments. Assessments performed with these samples may include, but are not limited to, myeloma cell monitoring and profiling, including expression of BCMA and assessments of immune cell populations. Additionally, BM samples may be analyzed to identify gene expression profiles, cytogenetic abnormalities, genetic mutations, and other tumor and tumor microenvironment-related biomarkers that may define disease risk profiles, predict response to SEA-BCMA, and clarify SEA-BCMA mechanisms of action. MRD will be analyzed in selected BM specimens using NGS. Plasma and serum will also be collected for quantification of biomarkers of drug activity, which may include SFLC, cytokines/chemokines, soluble BCMA, and other soluble biomarkers.

Relationships of biomarker and pharmacodynamic parameters (eg, baseline values, absolute and relative changes from baseline) to efficacy, safety and PK parameters will be explored. Relationships and associated data that are determined to be of interest will be summarized. These exploratory analyses will be described in a separate analysis plan (eg, the SAP or Biomarker Analysis Plan); clinically relevant findings may be described in the clinical study report or reported separately (eg, in an Exploratory Studies Report).

9.3.9. Safety Analyses

9.3.9.1. Extent of Exposure

Duration of treatment will be summarized and listed.

Duration of treatment, number of cycles, total dose and dose intensity will be summarized. Dose modifications will also be summarized. Details will be provided in the SAP.

9.3.9.2. Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, AEs leading to study treatment discontinuation, treatment-related TEAEs leading to study treatment discontinuation, TEAEs and treatment-related TEAEs leading to dose reduction and interruption. AEs will be defined as treatment-emergent if they are newly occurring or worsen following study treatment.

AEs will be listed and summarized by Medical Dictionary for Regulatory Activities (MedDRA), preferred term, SOC, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in 1 subject, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and treatment

group. AEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

9.3.9.3. Dose-Limiting Toxicity

The observed number and proportion of subjects experiencing a DLT will be reported for the dose-escalation part.

9.3.9.4. Deaths and Serious Adverse Events

All SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.9.5. Clinical Laboratory Results

Laboratory values (eg, chemistry, hematology, urinalysis, and pulmonary function tests) may be presented graphically by visit. Summary statistics may be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI-CTCAE v. 4.03 and flagged when values are outside the normal reference range.

9.3.9.6. Other Safety Analyses

Vital Signs

Vital signs will be listed for each vital sign by scheduled visit. Summary statistics may be tabulated where appropriate.

ECOG Status

ECOG status will be summarized for each visit. Shifts from baseline to the best and worst postbaseline score may be tabulated.

ECG

ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) may be summarized for each scheduled ECG and shifts from baseline may be tabulated.

Infusion-Related Reactions and Hypersensitivity Reactions

Subject incidence of IRRs and hypersensitivity reactions and associated signs and symptoms will be presented. Additional analyses may be done, including incidence of serious IRRs and hypersensitivity reactions as well as IRRs and hypersensitivity reactions that lead to treatment discontinuation.

9.3.10. Interim Analyses

Data will be evaluated after each dose cohort to determine DLTs and inform dose-escalation decisions. The SMC will monitor the trial for safety and DLTs on an ongoing basis. The process for SMC decisions and the roles and responsibilities of the SMC will be detailed in a separate document.

Interim data from the study may be presented at scientific meetings such as annual meetings of the American Society of Hematology or the American Society of Clinical Oncology.

10. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 (R2); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements.

10.1. Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for ensuring subjects are reconsented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each subject, or legally acceptable representative, if applicable to this study, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

For phase 1 studies, it is preferable for a subject to provide consent themselves. If informed consent is obtained from a legally acceptable representative for a subject who is unable to provide informed consent at study entry (if applicable), but the subject is later able to provide informed consent, the investigator must obtain written informed consent from the subject.

10.2. Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical IB and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (eg, quarterly, annual) reapproval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3. Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.3.1. Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators and name and address of the research facilities are included in the investigator file.

10.3.2. Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study subject) must be approved by the sponsor or its designee prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor or its designee and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.4. Study Documentation, Privacy and Records Retention

To protect the safety of subjects in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing subject medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the subject authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of subject identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

10.5. Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

11. REFERENCES

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APPENDIX A. SCHEDULE OF EVENTS

Schedule of Events: Part A (SEA-BCMA Monotherapy Dose-escalation and Expansion)

Assessment Type	Day	Screening/ Baseline		Enrollment	Treatment Cycles						IHR Visit[W]	IHR Follow-up Visit[W]	EOT	Long-Term F/U
		D -28 to 1	D -7 to 1	D -7 to 1	D1	D2	D4	D8	D15	D22		24 to 72 hr post IHR Visit	30 to 37 days post last dose[X]	Every 12 weeks
	Visit window				**–1**		**±1**	**±1**	**±1**	**±1**				**±2 weeks**
Baseline and Safety Assessments	Informed consent	X		Eligibility documentation submitted to sponsor or designee prior to study start										
	Inclusion/exclusion criteria	X			X									
	Medical history	X												
	Physical examination		X		X[C]				X		X	X	X	
	Vital signs				X[S]				X[S]		X	X	X	
	Weight and height[M]		X		X[C]				X				X	
	ECG in triplicate		X		X[A,B]	X[B]	X[B]	X[B]	X[A,B]				X	
	ECOG performance status		X		X[C]				X				X	
	Serum chemistry[D]		X		X[C]			X	X	X	X	X	X	X[F]
	CBC with differential[D]		X		X[C]			X	X	X	X	X	X	X[F]
	Pregnancy test[E]		X										X	
	Serology (hepatitis B, C)[P]	X												
	PT/PTT/INR		X											
	Urinalysis[Q]		X		X[C]				X		X	X	X	
	UPCR calculation[R]		X[Z]		X[C,Z]				X				X[G]	
	Concomitant medications and AEs	Collect any related to study protocol procedures			Collect from Day 1 (predose) through 30 days post last dose or through EOT visit, whichever is later									
Treatment	SEA-BCMA administration				X				X[Y]					
PK/ATA	Blood samples for PK		See PK/ATA/Biomarkers table – **Note visits at D16 and D18 in Cycle 1 with study drug administration at Day 15. Perform Day 29 visit for sample collection if subject is not starting a cycle on Day 29.**											
	Blood samples for ATA													
Biomarkers	BM for biomarkers[I]													
	Blood sample for biomarkers													
Response Assessments	BM aspirate[I]		X[T]							X[K,L]			X[U,V]	X[F,U,V]
	BM biopsy[I]		X[T]							X[K,L]			X[U,V]	X[F,U,V]
	Plasmacytoma evaluation[N]	X								X[L]			X	X[F]
	SPEP/Immunofixation		X							X[L]			X	X[F]
	UPEP/Immunofixation[J]		X							X[L]			X	X[F]
	Serum free light chain		X							X[L]			X	X[F]

Assessment Type	Day	Screening/ Baseline		Enrollment	Treatment Cycles						IHR Visit[W]	IHR Follow-up Visit[W]	EOT	Long-Term F/U
		D -28 to 1	D -7 to 1	D -7 to 1	D1	D2	D4	D8	D15	D22		24 to 72 hr post IHR Visit	30 to 37 days post last dose[X]	Every 12 weeks
	Visit window				**–1**		**±1**	**±1**	**±1**	**±1**				**±2 weeks**
	Quantitative immunoglobulins		X							X[L]			X	
	Beta-2 microglobulin		X											
	Skeletal survey[O]		X											
	Survival status													X[H]

AE = adverse event; ATA = antitherapeutic antibody; BCMA = B-cell maturation antigen; BM = bone marrow; CBC = complete blood count; CR = complete response; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; F/U = follow-up; HCV = hepatitis C-virus; IHR = infusion/hypersensitivity reaction; PCR = polymerase chain reaction; PD = progressive disease; PK = pharmacokinetic; PR = partial response; PT/PTT/INR = prothrombin time/partial thromboplastin time/ international normalized ratio; RNA = ribonucleic acid; SPEP = serum protein electrophoresis; UPCR = urine protein to creatinine ratio; UPEP = urine protein electrophoresis; VGPR = very good partial response

A Multiple ECG timepoints. See requirements detailed in Section 6.2.3.1 (Day 1), 6.2.3.5 (Day 15), and 7.7.14 (global).
B Cycle 1 only
C Not required in Cycle 1 if baseline is within 1 day of Day 1
D Serum chemistry and CBC with differential must be performed at least weekly during dose delays
E For subjects of childbearing potential
F Obtain until disease progression or until initiation of subsequent anticancer therapy, whichever occurs first.
G Only required if not conducted within 4 weeks prior to EOT
H Contact subject for survival status and collection of first subsequent anticancer treatment information until death or study closure
I Bone marrow aspirate and biopsy required at baseline, Cycle 2 Day 22 to 28, and to confirm CR in subjects with negative blood and urine M-protein. If a nonprotocol-mandated BM examination is conducted at any time, submit BM sample (aspirate and/or biopsy) for central assessment
J Obtain urine for UPEP (24-hour urine sample) and urine immunofixation at screening (all subjects) and Day 22 to 28 of every cycle only if screening UPEP ≥200 mg/24 hours; 24-hour urine sample for UPEP/immunofixation is also required for any subject with unconfirmed or confirmed response of VGPR or better
K Bone marrow aspirate and biopsy required at end of Cycle 2 and at time of suspected CR
L Window Day 22 to 28
M Height only required at baseline
N Baseline and EOT scans are only needed in cases of suspected or known plasmacytoma. During treatment, plasmacytoma evaluations should be performed per institutional standard imaging modality every 4 cycles or to confirm a response of PR or better, or as clinically indicated to confirm PD.
O Follow-up skeletal survey should be performed to look for evidence of disease progression, if clinically indicated
P If hepatitis C serology is positive, HCV RNA test by PCR is required to confirm
Q Microscopy required if urinalysis result is abnormal
R UPCR via spot urine test
S Multiple timepoints required for collection. See Section 6.2.3 for details.
T Day –10 to 1.
U Bone marrow aspirate and biopsy collected per standard of care at EOT and/or follow-up, should be submitted for central assessment
V Obtain only for confirmation of CR for subjects who have not started another anticancer treatment
W In the event of a ≥ Grade 3 infusion reaction or delayed hypersensitivity reaction
X If subject is starting a new treatment post last SEA-BCMA dose, collect appropriate samples prior to start of new therapy. A phone call at 30 to 37 days is still required for AE check.
Y If a subject has a clinically significant, unresolved AE on Day 15 that prevents dosing, the Day 15 visit may be delayed for ≤7 days. On the seventh day, if a subject cannot receive the dose, the Day 15 visit is skipped and Day 22 performed.
Z 24-hour urine collection required if UPCR >2 mg/mg

Schedule of Events: Part B (SEA-BCMA Intensive Dosing)

Assessment Type	Day	Screening/ Baseline		Enrollment	Treatment Cycles				EOT	Long-Term F/U
		D -28 to 1	D -7 to 1	D -7 to 1	D1	D8	D15	D22	30 to 37 days post last dose[W]	Every 12 weeks
	Visit window				**–1**	**±1**	**±1**	**±1**		**±2 weeks**
Baseline and Safety Assessments	Informed consent	X		Eligibility documentation submitted to sponsor or designee prior to study start						
	Inclusion/exclusion criteria	X			X					
	Medical history	X								
	Physical examination		X		X[C]	X[D]	X	X[D]	X	
	Vital signs[S]				X	X[D]	X	X[D]	X	
	Weight and height [M]		X		X[C]	X[D]	X[D]	X[D]	X	
	ECG in triplicate		X		X[A, B]	X[A,D]	X[A,D]	X[A,D]	X	
	ECOG performance status		X		X[C]	X[D]	X	X[D]	X	
	Serum chemistry[Y]		X		X[C]	X	X	X	X	X[F]
	CBC with differential[Y]		X		X[C]	X	X	X	X	X[F]
	Pregnancy test[E]		X						X	
	Serology (hepatitis B, C)[P]	X								
	PT/PTT/INR		X							
	Urinalysis[Q]		X		X[C]	X[D]	X	X[D]	X	
	UPCR calculation[R]		X[W]		X[C,W]	X[D]	X	X[D]	X[G]	
	Concomitant medications and AEs	Collect any related to study protocol procedures			Collect from Day 1 (predose) through 30 days post last dose or through EOT visit, whichever is later					
Treatment	Premedication[Z]				X	X	X	X		
	SEA-BCMA administration				X	X[D, X]	X[X]	X[D, X]		
PK/ATA	Blood samples for PK		See PK/ATA/Biomarkers table – **Note visits at D2 and D4 in Cycle 1**							
	Blood samples for ATA									
Biomarkers	BM for biomarkers[I]									
	Blood sample for biomarkers									
Response Assessments	BM aspirate[I]		X[T]					X[K,L]	X[U,V]	X[F,U,V]
	BM biopsy[I]		X[T]					X[K,L]	X[U,V]	X[F,U,V]
	Plasmacytoma evaluation[N]	X						X[L]	X	X[F]
	SPEP/Immunofixation		X					X[L]	X	X[F]
	UPEP/Immunofixation [J]		X					X[L]	X	X[F]
	Serum free light chain		X					X[L]	X	X[F]
	Quantitative immunoglobulins		X					X[L]	X	
	Beta-2 microglobulin		X							
	Skeletal survey[O]		X							

Assessment Type	Day	Screening/ Baseline		Enrollment	Treatment Cycles				EOT	Long-Term F/U
		D -28 to 1	D -7 to 1	D -7 to 1	D1	D8	D15	D22	30 to 37 days post last dose[W]	Every 12 weeks
	Visit window				**–1**	**±1**	**±1**	**±1**		**±2 weeks**
	Survival status									X[H]

AE = adverse event; ATA = antitherapeutic antibody; BCMA = B-cell maturation antigen; BM = bone marrow; CBC = complete blood count; CR = complete response; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; F/U = follow-up; HCV = hepatitis C-virus; PCR = polymerase chain reaction; PD = progressive disease; PK = pharmacokinetic; PR = partial response; PT/PTT/INR = prothrombin time/ partial thromboplastin time/international normalized ratio; RNA = ribonucleic acid; SPEP = serum protein electrophoresis; UPCR = urine protein to creatinine ratio; UPEP = urine protein electrophoresis; VGPR = very good partial response

A Multiple ECG timepoints. See requirements detailed in Section 6.3.3.1 (Day 1), Section 6.3.3.4 (Day 8), 6.3.3.5 (Day 15), 6.3.3.6 (Day 22) and 7.7.14 (global).
B Cycle 1, 2, and 3 only
C Not required in Cycle 1 if baseline is within 1 day of Day 1
D Cycles 1 and 2 only
E For subjects of childbearing potential
F Obtain until disease progression or until initiation of subsequent anticancer therapy, whichever occurs first.
G Only required if not conducted within 4 weeks prior to EOT
H Contact subject for survival status and collection of first subsequent anticancer treatment information until death or study closure
I Bone marrow aspirate and biopsy required at baseline, Cycle 2 Day 22 to 28, Cycle 6 and every 6 cycles thereafter, and to confirm CR in subjects with negative blood and urine M-protein. If a nonprotocol-mandated BM examination is conducted at any time, submit BM sample (aspirate and/or biopsy) for central assessment
J Obtain urine for UPEP (24-hour urine sample) and urine immunofixation at screening (all subjects) and Day 22 to 28 of every cycle only if screening UPEP ≥200 mg/24 hours; 24-hour urine sample for UPEP/immunofixation is also required for any subject with unconfirmed or confirmed response of VGPR or better
K Bone marrow aspirate and biopsy required at end of Cycle 2, Cycle 6, every 6 cycles thereafter, and at time of suspected CR
L Window Day 22 to 28
M Height only required at baseline
N Baseline and EOT scans are only needed in cases of suspected or known plasmacytoma. During treatment, plasmacytoma evaluations should be performed per institutional standard imaging modality every 4 cycles or to confirm a response of PR or better, or as clinically indicated to confirm PD.
O Follow-up skeletal survey should be performed to look for evidence of disease progression, if clinically indicated
P If hepatitis C serology is positive, HCV RNA test by PCR is required to confirm
Q Microscopy required if urinalysis result is abnormal
R UPCR via spot urine test
S Multiple timepoints required for collection. See Section 6.3.3 for details.
T Day –10 to 1.
U Bone marrow aspirate and biopsy collected per standard of care at EOT and/or follow-up, should be submitted for central assessment
V Obtain only for confirmation of CR for subjects who have not started another anticancer treatment
W If subject is starting a new treatment post last SEA-BCMA dose, collect appropriate samples prior to start of new therapy. A phone call at 30 to 37 days is still required for AE check.
X In Cycles 1 and 2, if a subject has a clinically significant, unresolved AE that prevents dosing, the dose may be delayed for ≤3 days. On the third day, if a subject cannot receive the dose, the dose of SEA-BCMA will be eliminated and the corresponding visit will be skipped. In Cycle 3 and beyond, if a subject has a clinically significant, unresolved AE on Day 15 that prevents dosing, the Day 15 visit may be delayed for ≤7 days. On the seventh day, if a subject cannot receive the dose, the Day 15 visit is skipped and Day 22 performed (see Section 5.2.3).
Y Serum chemistry and CBC with differential must be performed at least weekly during dose delays
Z Premedication for infusion reactions must be administered prior to SEA-BCMA infusion

Schedule of Events: Part C (SEA-BCMA Plus Dexamethasone)

Assessment Type	Day	Screening/ Baseline		Enrollment	Treatment Cycles				EOT	Long-Term F/U
		D -28 to 1	D -7 to 1	D -7 to 1	D1	D8	D15	D22	30 to 37 days post last dose[X]	Every 12 weeks
	Visit window				**–1**	**±1**	**±1**	**±1**		**±2 weeks**
Baseline and Safety Assessments	Informed consent	X		Eligibility documentation submitted to sponsor or designee prior to study start						
	Inclusion/exclusion criteria	X			X					
	Medical history	X								
	Physical examination		X		X[C]	X[D]	X	X[D]	X	
	Vital signs[S]				X	X[D]	X	X[D]	X	
	Weight and height[M]		X		X[C]		X		X	
	ECG in triplicate[A]		X						X	
	ECOG performance status		X		X[C]	X[D]	X	X[D]	X	
	Serum chemistry[Z]		X		X[C]	X	X	X	X	X[F]
	CBC with differential[Z]		X		X[C]	X	X	X	X	X[F]
	HbA1c		X[AA]							
	Pregnancy test[E]		X						X	
	Serology (hepatitis B, C)[P]	X								
	PT/PTT/INR		X							
	Urinalysis[Q]		X		X[C]	X[D]	X	X[D]	X	
	UPCR calculation[R]		X		X[C]	X[D]	X	X[D]	X[G]	
	Concomitant medications and AEs	Collect any related to study protocol procedures			Collect from Day 1 (predose) through 30 days post last dose or through EOT visit, whichever is later					
Treatment	Dexamethasone administration[CC]				X	X	X	X		
	Premedication[B]				X	X	X	X		
	SEA-BCMA administration				X	X[D,W]	X[Y,W]	X[D,W]		
PK/ATA	Blood samples for PK		See PK/ATA/Biomarkers table – **Note visits at D2 and D4 in Cycle 1**							
	Blood samples for ATA									
Biomarkers	BM for biomarkers[I]									
	Blood sample for biomarkers									
Response Assessments	BM aspirate[I]		X[T]					X[K,L]	X[U,V]	X[F,U,V]
	BM biopsy[I]		X[T]					X[K,L]	X[U,V]	X[F,U,V]
	Plasmacytoma evaluation[N]	X						X[L]	X	X[F]
	SPEP/Immunofixation		X					X[L]	X	X[F]
	UPEP/Immunofixation[J]		X					X[L]	X	X[F]
	Serum free light chain		X					X[L]	X	X[F]
	Quantitative immunoglobulins		X					X[L]	X	

Assessment Type	Day	Screening/ Baseline		Enrollment	Treatment Cycles				EOT	Long-Term F/U
		D -28 to 1	D -7 to 1	D -7 to 1	D1	D8	D15	D22	30 to 37 days post last dose[X]	Every 12 weeks
	Visit window				**–1**	**±1**	**±1**	**±1**		**±2 weeks**
	Beta-2 microglobulin		X							
	Skeletal survey[O]		X							
	Qualitative Interview[BB]									
	Survival status									X[H]

AE = adverse event; ATA = antitherapeutic antibody; BCMA = B-cell maturation antigen; BM = bone marrow; CBC = complete blood count;
CR = complete response; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; F/U = follow-up;
HbA1c = Hemoglobin A1c; HCV = hepatitis C-virus; PCR = polymerase chain reaction; PD = progressive disease; PK = pharmacokinetic; PR = partial response;
PT/PTT/INR = prothrombin time/partial thromboplastin time/international normalized ratio;
RNA = ribonucleic acid; SD = stable disease; SPEP = serum protein electrophoresis; UPCR = urine protein to creatinine ratio; UPEP = urine protein electrophoresis;
VGPR = very good partial response

A See requirements detailed in Section 7.7.14.
B Premedication for infusion reactions must be administered prior to SEA-BCMA infusion.
C Not required in Cycle 1 if baseline is within 1 day of Day 1
D Cohort 2 Cycles 1 and 2 only
E For subjects of childbearing potential
F Obtain until disease progression or until initiation of subsequent anticancer therapy, whichever occurs first.
G Only required if not conducted within 4 weeks prior to EOT
H Contact subject for survival status and collection of first subsequent anticancer treatment information until death or study closure
I Bone marrow aspirate and biopsy required at baseline, Cycle 2 Day 22 to 28, Cycle 6, and every 6 cycles thereafter, and to confirm CR in subjects with negative blood and urine M-protein. If a nonprotocol-mandated BM examination is conducted at any time, submit BM sample (aspirate and/or biopsy) for central assessment
J Obtain urine for UPEP (24-hour urine sample) and urine immunofixation at screening (all subjects) and Day 22 to 28 of every cycle only if screening UPEP ≥200 mg/24 hours; 24-hour urine sample for UPEP/immunofixation is also required for any subject with unconfirmed or confirmed response of VGPR or better
K Bone marrow aspirate and biopsy only required at end of Cycle 2, Cycle 6, every 6 cycles thereafter, and at time of suspected CR
L Window Day 22 to 28
M Height only required at baseline
N Baseline and EOT scans are only needed in cases of suspected or known plasmacytoma. During treatment, plasmacytoma evaluations should be performed per institutional standard imaging modality every 4 cycles or to confirm a response of PR or better, or as clinically indicated to confirm PD.
O Follow-up skeletal survey should be performed to look for evidence of disease progression, if clinically indicated
P If hepatitis C serology is positive, HCV RNA test by PCR is required to confirm
Q Microscopy required if urinalysis result is abnormal
R UPCR via spot urine test
S Multiple timepoints required for collection. See Section 6.4.3 for details.
T Day –10 to 1.
U Bone marrow aspirate and biopsy collected per standard of care at EOT and/or follow-up, should be submitted for central assessment
V Obtain only for confirmation of CR for subjects who have not started another anticancer treatment
W In Cohort 2 Cycles 1 and 2, if a subject has a clinically significant, unresolved AE that prevents dosing, the dose may be delayed for ≤3 days. On the third day, if a subject cannot receive the dose, the dose of SEA-BCMA will be eliminated and the corresponding visit will be skipped (see Section 5.2.3)
X If subject is starting a new treatment post last SEA-BCMA dose, collect appropriate samples prior to start of new therapy. A phone call at 30 to 37 days is still required for AE check.
Y In Cohort 1, if a subject has a clinically significant, unresolved AE on Day 15 that prevents dosing, the Day 15 visit may be delayed for ≤7 days. On the seventh day, if a subject cannot receive the dose, the Day 15 visit is skipped and Day 22 performed (see Section 5.2.3)
Z Serum chemistry and CBC with differential must be performed at least weekly during dose delays
AA If HbA1c is elevated (≥6.5%), refer subject to appropriate provider prior to or within 1 week of starting study treatment in Cycle 1 for glucose management.
BB Schedule qualitative interview at first PR or better or at the end of Cycle 4 for subjects with SD (see Section 6.4.4).
CC Administer 1 to 3 hours prior to SEA-BCMA administration

Schedule of Events: Part D (SEA-BCMA plus Pomalidomide and Dexamethasone)

Assessment Type	Day	Screening/ Baseline		Enrollment	Treatment Cycles				EOT	Long-Term F/U
		D -28 to 1	D -10 to 1	D -7 to 1	D1	D8	D15	D22	30 to 37 days post last dose[W]	Every 12 weeks
	Visit window				**–1**	**±1**	**±1**	**±1**		**±2 weeks**
Baseline and Safety Assessments	Informed consent	X		Eligibility documentation submitted to sponsor or designee prior to study start						
	Inclusion/exclusion criteria	X			X					
	Medical history	X								
	Physical examination		X		X[C]		X		X	
	Vital signs[S]				X		X		X	
	Weight and height[M]		X		X[C]		X		X	
	ECG in triplicate[A]		X						X	
	ECOG performance status		X		X[C]		X		X	
	Serum chemistry[X]		X		X[C]	X	X	X	X	X[F]
	CBC with differential[X]		X		X[C]	X	X	X	X	X[F]
	HbA1c		X[Y]							
	Pregnancy test[E]	X[CC]	X[DD]		X		X		X	
	Serology (hepatitis B, C)[P]	X								
	PT/PTT/INR		X							
	Urinalysis[Q]		X		X[C]		X		X	
	UPCR calculation[R]		X		X[C]		X		X[G]	
	Concomitant medications and AEs	Collect any related to study protocol procedures			Collect from Day 1 (predose) through 30 days post last dose or through EOT visit, whichever is later					
Treatment	Dexamethasone administration[AA]				X	X	X	X		
	Pomalidomide administration[BB]				X	Daily on Days 1 to 21				
	Premedication[D]				X		X			
	SEA-BCMA administration				X		X[B]			
PK/ATA	Blood samples for PK		See PK/ATA/Biomarkers table – **Note visits at D2 and D4 in Cycle 1**							
	Blood samples for ATA									
Biomarkers	BM for biomarkers[I]									
	Blood sample for biomarkers									
Response Assessments	BM aspirate[I]		X[T]					X[K,L]	X[U,V]	X[F,U,V]
	BM biopsy[I]		X[T]					X[K,L]	X[U,V]	X[F,U,V]
	Plasmacytoma evaluation[N]	X						X[L]	X	X[F]
	SPEP/Immunofixation		X					X[L]	X	X[F]
	UPEP/Immunofixation[J]		X					X[L]	X	X[F]
	Serum free light chain		X					X[L]	X	X[F]

Assessment Type	Day	Screening/ Baseline		Enrollment	Treatment Cycles				EOT	Long-Term F/U
		D -28 to 1	D -10 to 1	D -7 to 1	D1	D8	D15	D22	30 to 37 days post last dose[W]	Every 12 weeks
	Visit window				**–1**	**±1**	**±1**	**±1**		**±2 weeks**
	Quantitative immunoglobulins		X					X[L]	X	
	Beta-2 microglobulin		X							
	Skeletal survey[O]		X							
	Qualitative Interview[Z]									
	Survival status									X[H]

AE = adverse event; ATA = antitherapeutic antibody; BCMA = B-cell maturation antigen; BM = bone marrow; CBC = complete blood count; CR = complete response; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; F/U = follow-up; HbA1c = Hemoglobin A1c; HCV = hepatitis C-virus; PCR = polymerase chain reaction; PD = progressive disease; PK = pharmacokinetic; PR = partial response; PT/PTT/INR = prothrombin time/partial thromboplastin time/international normalized ratio; RNA = ribonucleic acid; SPEP = serum protein electrophoresis; UPCR = urine protein to creatinine ratio; UPEP = urine protein electrophoresis; VGPR = very good partial response

A See requirements detailed in Sections 7.7.14.
B If a subject has a clinically significant, unresolved AE on Day 15 that prevents dosing, the Day 15 visit may be delayed for <7 days. On the seventh day, if a subject cannot receive the dose, the Day 15 visit is skipped and Day 22 performed (see Section 5.2.3).
C Not required in Cycle 1 if baseline is within 1 day of Day 1
D Premedication for infusion reactions must be administered prior to SEA-BCMA infusion (see Section 5.5 for exceptions).
E For subjects of childbearing potential
F Obtain until disease progression or until initiation of subsequent anticancer therapy, whichever occurs first.
G Only required if not conducted within 4 weeks prior to EOT
H Contact subject for survival status and collection of first subsequent anticancer treatment information until death or study closure
I Bone marrow aspirate and biopsy required at baseline, Cycle 2 Day 22 to 28, Cycle 6, and every 6 cycles thereafter, and to confirm CR in subjects with negative blood and urine M-protein. If a nonprotocol-mandated BM examination is conducted at any time, submit BM sample (aspirate and/or biopsy) for central assessment
J Obtain urine for UPEP (24-hour urine sample) and urine immunofixation at screening (all subjects) and Day 22 to 28 of every cycle only if screening UPEP ≥200 mg/24 hours; 24-hour urine sample for UPEP/immunofixation is also required for any subject with unconfirmed or confirmed response of VGPR or better
K Bone marrow aspirate and biopsy only required at end of Cycle 2, Cycle 6, every 6 cycles thereafter, and at time of suspected CR
L Window Day 22 to 28
M Height only required at baseline
N Baseline and EOT scans are only needed in cases of suspected or known plasmacytoma. During treatment, plasmacytoma evaluations should be performed per institutional standard imaging modality every 4 cycles or to confirm a response of PR or better, or as clinically indicated to confirm PD.
O Follow-up skeletal survey should be performed to look for evidence of disease progression, if clinically indicated
P If hepatitis C serology is positive, HCV RNA test by PCR is required to confirm
Q Microscopy required if urinalysis result is abnormal
R UPCR via spot urine test
S Multiple timepoints required for collection. See Section 6.5.3 for details.
T Day –10 to 1.
U Bone marrow aspirate and biopsy collected per standard of care at EOT and/or follow-up, should be submitted for central assessment
V Obtain only for confirmation of CR for subjects who have not started another anticancer treatment
W If subject is starting a new treatment post last SEA-BCMA dose, collect appropriate samples prior to start of new therapy. A phone call at 30 to 37 days is still required for AE check.
X Serum chemistry and CBC with differential must be performed at least weekly during dose delays
Y If HbA1c is elevated (≥6.5%), refer subject to appropriate provider prior to or within 1 week of starting study treatment in Cycle 1 for glucose management.
Z Schedule qualitative interview at first PR or better (see Section 6.5.4).
AA Administer 1 to 3 hours prior to SEA-BCMA administration
BB Administer 1 to 3 hours prior to SEA-BCMA administration on Cycle 1, Day 1; daily self-administration thereafter
CC 10 to 14 days prior to planned Cycle 1 Day 1
DD Within 24 hours prior to Cycle 1 Day pomalidomide dose

APPENDIX B. PK, ATA, AND BIOMARKER SAMPLING TIME POINTS

Pharmacokinetic, immunogenicity, and biomarker sample collection time points – Part A

					Peripheral Blood[A]										Bone Marrow[A]			
Cycle	Study day	Time	Window	Relative Time	SEA-BCMA PK	SEA-BCMA ATA	Genotyping	Immunophenotyping	Plasma cytokines/ chemokines	Soluble target and ligands	Plasma Biomarkers	PBMCs	SFLC	Modified SPEP[L]	Immunophenotyping (including BCMA characterization)	Gene expression/NGS/FISH	MRD	BM plasma
NA	Baseline/ screening	Non-dosing	D –10 to 1	NA			X	X[J,P]		X[J]	X[J]	X[J]	X	X	X[J]	X	X	X[J]
Cycles 1, 2, and 3	1	Predose	Within 4 h prior to dose	START of infusion, 1st dose	X	X[C]		X	X	X	X	X	X					
		1 hr intradose	±15 min	START of infusion, 1st dose	X[N]													
		2 hr intradose	±15 min	START of infusion, 1st dose	X[O]													
		End of study drug administration	Within 15 min post IV infusion	END of infusion, 1st dose	X													
		2 hr	±15 min	END of infusion, 1st dose	X			X[D,P]	X[D]									
		6 hr[M]	±15 min	END of infusion, 1st dose	X				X[D]									
	2[H]	24 hr	±4 hr	START of infusion, 1st dose	X			X[D,P]	X[D]									
	4[H]	72 hr	±4 hr	START of infusion, 1st dose	X			X[D,J,P]	X[D,J]	X[D,J,P]		X[D,J,P]						
	8	168 hr	±24 hr	START of infusion, 1st dose	X			X[D,P]	X[D]	X[D]		X[D,P]	X[D]					
	15	336 hr	±72 hr	START of infusion, 1st dose	X[B]													
		Predose	Within 4 hr prior to dose[G]	START of infusion, 2nd dose	X			X[E]	X[E]	X[E]		X[E]	X[E]					

Cycle	Study day	Time	Window	Relative Time	Peripheral Blood[A]										Bone Marrow[A]			
					SEA-BCMA PK	SEA-BCMA ATA	Genotyping	Immunophenotyping	Plasma cytokines/ chemokines	Soluble target and ligands	Plasma Biomarkers	PBMCs	SFLC	Modified SPEP [L]	Immunophenotyping (including BCMA characterization)	Gene expression/NGS/FISH	MRD	BM plasma
		1 hr intradose	±15 min	START of infusion, 2nd dose	X[N,D]													
		2 hr intradose	±15 min	START of infusion, 2nd dose	X[O,D]													
		End of study drug administration	Within 15 min post IV infusion	END of infusion, 2nd dose	X													
		2 hr	±15 min	END of infusion, 2nd dose	X[D]													
		6 hr[M]	±15 min	END of infusion, 2nd dose	X[D]													
	16	24 hr	±4 hr	START of infusion, 2nd dose	X[D,R]													
	18	72 hr	±4 hr	START of infusion, 2nd dose	X[D,R]													
	22	168 hr	±24 hr	START of infusion, 2nd dose	X[D]			X[F,J,P]	X[F,J]	X[F,J]		X[F,J]	X[D]	X	X[F,J]	X[F]	X[F]	X[F,J]
	29	336 hr	±72 hr	START of infusion, 2nd dose	X[B]													
Cycle 4 and subsequent cycles	1	Predose	Within 4 hr prior to dose	START of infusion, 1st dose	X	X[C]			X	X	X[K]	X	X					
		End of study drug administration	Within 15 min post IV infusion	END of infusion, 1st dose	X													
	15	Predose	Within 4 hr prior to dose	START of infusion, 2nd dose	X													
		End of study drug administration	Within 15 min post IV infusion	END of infusion, 2nd dose	X													

Cycle	Study day	Time	Window	Relative Time	Peripheral Blood[A]										Bone Marrow[A]			
					SEA-BCMA PK	SEA-BCMA ATA	Genotyping	Immunophenotyping	Plasma cytokines/ chemokines	Soluble target and ligands	Plasma Biomarkers	PBMCs	SFLC	Modified SPEP [L]	Immunophenotyping (including BCMA characterization)	Gene expression/NGS/FISH	MRD	BM plasma
	22	168 hr	±24 hr	START of infusion, 2nd dose										X				
IHR visit				NA	X	X			X			X						
IHR follow-up visit				NA	X	X			X			X						
At time of CR assessment				NA					X[J]	X[J]	X	X[J]			X[J]	X	X	X[J]
EOT				NA	X	X		X[J]	X	X	X	X	X	X	X[I,J]	X[I]	X[I]	X[I,J]
Follow-up				NA										X[Q]	X[I,Q]	X[I,Q]	X[I,Q]	X[I,Q]

ATA = antitherapeutic antibody; BCMA = B-cell maturation antigen; BM = bone marrow; CR = complete response; EOT = end of treatment; FISH = fluorescent in situ hybridization; IHR = infusion/hypersensitivity reaction; IV = intravenous; MRD = minimal residual disease; NA = not applicable; NGS = next generation sequencing; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; SFLC = serum free light chain; SPEP = serum protein electrophoresis

A Blood and bone marrow aspirate and biopsy to be collected for central analysis. Analysis may include BCMA characterization (flow cytometry, gene expression, and immunohistochemistry), risk stratification (gene expression profiling, phenotypic profiling), and NGS analysis (including MRD determination).
B Sample obtained only for subjects not starting the next dose on Day 15 or 29 [±72 h] and not in EOT visit
C Required in first 5 cycles and every fifth cycle thereafter
D Cycle 1 only
E Cycle 1 and 2 only
F End of Cycle 2 only (Day 22 to 28)
G Cycle 1 Day 1 predose window is within 1 day of Day 1
H Labs may be drawn at the site or, except for Cycle 1, may be drawn by a home healthcare provider
I Bone marrow aspirate and bone marrow biopsy, if available, to be submitted for central assessment of response and resistance to SEA-BCMA. To be collected to confirm CR in subjects who have not started another anticancer treatment.
J Blood and bone marrow samples must be collected on the same day, if applicable. A window of ±1 day in Cycle 1 is permitted to accommodate same-day sampling.
K Every 3 cycles after Cycle 3: Cycle 6, 9, 12, etc.
L For subjects with IgG myeloma only. Collect specimen at the same time as local disease assessment sample collection.
M Collect only if SEA–BCMA infusion time is ≤2 hr
N Collect only if infusion duration >1 hr, blood samples collected during SEA–BCMA infusion should be obtained from the contralateral arm, or different vascular access site relative to infusion site
O Collect only if infusion duration >2 hr, blood samples collected during SEA–BCMA infusion should be obtained from the contralateral arm, or different vascular access site relative to infusion site
P Collect only in expansion cohort.
Q Collect until initiation of subsequent therapy
R Specimens collections on Days 16 and 18 to be performed only for subjects who received SEA–BCMA administration at Day 15

Pharmacokinetic, immunogenicity, and biomarker sample collection time points – Part B

Cycle	Study day	Time	Window	Relative Time	Peripheral Blood[A]									Bone Marrow[A]			
					SEA-BCMA PK	SEA-BCMA ATA	Genotyping	Plasma cytokines/ chemokines	Soluble target and ligands	Plasma Biomarkers	PBMCs	SFLC	Modified SPEP[K]	Immunophenotyping (including BCMA characterization)	Gene expression/ NGS/FISH	MRD	BM plasma
NA	Baseline/ screening	Non-dosing	D –10 to 1	NA			X	X[I]	X[I]	X[I]	X[I]	X	X	X[I]	X	X	X[I]
Cycles 1, 2 and 3	1	Predose	Within 4 h prior to dose[F]	START of infusion, 1st dose	X	X[B]		X	X	X	X	X	X				
		1 hr intradose	±15 min	START of infusion, 1st dose	X[M,C]												
		2 hr intradose	±15 min	START of infusion, 1st dose	X[N,C]												
		End of study drug administration	Within 15 min post IV infusion	END of infusion, 1st dose	X[C]				X[D]								
		2 hr	±15 min	END of infusion, 1st dose	X[C]			X[D]									
		6 hr[L]	±15 min	END of infusion, 1st dose	X[C]												
	2[G]	24 hr	±4 hr	START of infusion, 1st dose	X[C]			X[C]			X[C]						
	4[G]	72 hr	±4 hr	START of infusion, 1st dose	X[C]												
	8	Predose	Within 4 hr prior to dose	START of infusion, 2nd dose	X[D]			X[C]	X[C]			X[C]					

Cycle	Study day	Time	Window	Relative Time	Peripheral Blood[A]									Bone Marrow[A]			
					SEA-BCMA PK	SEA-BCMA ATA	Genotyping	Plasma cytokines/ chemokines	Soluble target and ligands	Plasma Biomarkers	PBMCs	SFLC	Modified SPEP[K]	Immunophenotyping (including BCMA characterization)	Gene expression/ NGS/FISH	MRD	BM plasma
	15	Predose	Within 4 hr prior to dose	START of infusion, 3rd dose	X			X[D]	X[D]		X[D]	X[D]					
	22	Predose	Within 4 hr prior to dose	START of infusion, 4th dose	X[D]			X[E,I]	X[E,I]		X[E,I]	X[C]	X	X[E,I]	X[E]	X[E]	X[E,I]
Cycle 4 and subsequent cycles	1	Predose	Within 4 hr prior to dose	START of infusion, 1st dose	X	X[B]						X					
	22	168 hr	±24 hr	START of infusion, 2nd dose				X[O]	X[O]	X[O]	X[O]		X	X[O]	X[O]	X[O]	X[O]
At time of CR assessment				NA				X[I]	X[I]	X[I]	X[I]			X[I]	X[I]	X[I]	X[I]
EOT				NA	X	X		X[I]	X[I]	X[I]	X[I]	X	X	X[H,I]	X[H,I]	X[H,I]	X[H,I]
Follow-up				NA									X[J]	X[H,J]	X[H,J]	X[H,J]	X[H,J]

ATA = antitherapeutic antibody; BCMA = B-cell maturation antigen; BM = bone marrow; CR = complete response; EOT = end of treatment; FISH = fluorescent in situ hybridization; IHR = infusion/hypersensitivity reaction; IV = intravenous; MRD = minimal residual disease; NA = not applicable; NGS = next generation sequencing; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; SFLC = serum free light chain; SPEP = serum protein electrophoresis

A Blood and bone marrow aspirate and biopsy to be collected for central analysis. Analysis may include BCMA characterization (flow cytometry, gene expression, and immunohistochemistry), risk stratification (gene expression profiling, phenotypic profiling), and NGS analysis (including MRD determination).
B Required in first 5 cycles and every fifth cycle thereafter
C Cycle 1 only
D Cycle 1 and 2 only
E End of Cycle 2 (Day 22 to 28) and at time of suspected CR
F Cycle 1 Day 1 predose window is within 1 day of Day 1
G Labs may be drawn at the site or may be drawn by a home healthcare provider
H Bone marrow aspirate and bone marrow biopsy, if available, to be submitted for central assessment of response and resistance to SEA–BCMA. To be collected to confirm CR in subjects who have not started another anticancer treatment.
I Blood and bone marrow samples must be collected on the same day, if applicable. A window of ±1 day in Cycle 1 is permitted to accommodate same-day sampling.
J Collect until initiation of subsequent therapy.
K For subjects with IgG myeloma only. Collect specimen at the same time as local disease assessment sample collection.
L Collect only if SEA–BCMA infusion time is ≤2 hr
M Collect only if infusion duration >1 hr, blood samples collected during SEA–BCMA infusion should be obtained from the contralateral arm, or different vascular access site relative to infusion site
N Collect only if infusion duration > 2 hr, blood samples collected during SEA–BCMA infusion should be obtained from the contralateral arm, or different vascular access site relative to infusion site
O To be collected on Day 22 to 28 of Cycle 6 and every 6 cycles thereafter, and at time of suspected CR

Pharmacokinetic, immunogenicity, and biomarker sample collection time points – Part C

					Peripheral Blood[A]										Bone Marrow[A]			
Cycle	**Study day**	**Time**	**Window**	**Relative Time**	**SEA-BCMA PK**	**Dexamethasone PK**	**SEA-BCMA ATA**	**Genotyping**	**Plasma cytokines/ chemokines**	**Soluble target and ligands**	**Plasma Biomarkers**	**PBMCs**	**SFLC**	**Modified SPEP [L]**	**Immunophenotyping (including BCMA characterization)**	**Gene expression/ NGS/FISH**	**MRD**	**BM plasma**
NA	Baseline/ screening	Non-dosing	D –10 to 1	NA				X	X[J]	X[J]	X[J]	X[J]	X	X	X[J]	X	X	X[J]
Cycles 1, 2 and 3	1	Predose	Within 4 h prior to dose[G]	START of infusion, 1st dose	X	X[D]	X[C]		X	X	X	X	X	X				
		1 hr intradose	±15 min	START of infusion, 1st dose	X[N,D]	X[D]												
		2 hr intradose	±15 min	START of infusion, 1st dose	X[O,D]	X[D]												
		End of study drug administration	Within 15 min post IV infusion	END of infusion, 1st dose	X[D]	X[D]				X[E]								
		2 hr	±15 min	END of infusion, 1st dose	X[D]	X[D]			X[E]									
		6 hr[M]	±15 min	END of infusion, 1st dose	X[D]	X[D]												
	2[H]	24 hr	±4 hr	START of infusion, 1st dose	X[D]	X[D]			X[D]			X[D]						
	4[H]	72 hr	±4 hr	START of infusion, 1st dose	X[D]	X[D]												
	8	Predose	Within 4 hr prior to dose	START of infusion, 2nd dose	X[P]	X[D]			X[D]	X[D]			X[D]					
	15	Predose	Within 4 hr prior to dose	START of infusion, 3rd dose	X	X[D]			X[E]	X[E]		X[E]	X[E]					
	22	Predose	Within 4 hr prior to dose	START of infusion, 4th dose	X[B,E]				X[F,J]	X[E,J]		X[F,J]	X[D]	X	X[F,J]	X[F]	X[F]	X[F,J]
Cycle 4 and	1	Predose	Within 4 hr prior to dose	START of infusion, 1st dose	X		X[C]						X					

Cycle	Study day	Time	Window	Relative Time	Peripheral Blood[A]										Bone Marrow[A]			
					SEA-BCMA PK	Dexamethasone PK	SEA-BCMA ATA	Genotyping	Plasma cytokines/ chemokines	Soluble target and ligands	Plasma Biomarkers	PBMCs	SFLC	Modified SPEP [L]	Immunophenotyping (including BCMA characterization)	Gene expression/ NGS/FISH	MRD	BM plasma
subsequent cycles	22	168 hr	±24 hr	START of infusion, 2nd dose					X[K]	X[K]	X[K]	X[K]		X	X[K]	X[K]	X[K]	X[K]
At time of CR assessment				NA					X[J]	X[J]	X[J]	X[J]			X[J]	X[J]	X[J]	X[J]
EOT				NA		X	X		X[J]	X[J]	X[J]	X[J]	X	X	X[I,J]	X[I]	X[I]	X[I,J]
Follow-up				NA										X[Q]	X[I,Q]	X[I,Q]	X[I,Q]	X[I,Q]

ATA = antitherapeutic antibody; BCMA = B-cell maturation antigen; BM = bone marrow; CR = complete response; EOT = end of treatment; FISH = fluorescent in situ hybridization; IHR = infusion/hypersensitivity reaction; IV = intravenous; MRD = minimal residual disease; NA = not applicable; NGS = next generation sequencing; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; SFLC = serum free light chain; SPEP = serum protein electrophoresis

A Blood and bone marrow aspirate and biopsy to be collected for central analysis. Analysis may include BCMA characterization (flow cytometry, gene expression, and immunohistochemistry), risk stratification (gene expression profiling, phenotypic profiling), and NGS analysis (including MRD determination).
B Cohort 2 only
C Required in first 5 cycles and every fifth cycle thereafter
D Cycle 1 only
E Cycle 1 and 2 only
F End of Cycle 2 only (Day 22 to 28) and at time of suspected CR
G Cycle 1 Day 1 predose window is within 1 day of Day 1; Collect predose samples before dexamethasone administration.
H Labs may be drawn at the site or, may be drawn by a home healthcare provider
I Bone marrow aspirate and bone marrow biopsy, if available, to be submitted for central assessment of response and resistance to SEA–BCMA. To be collected to confirm CR in subjects who have not started another anticancer treatment.
J Blood and bone marrow samples must be collected on the same day, if applicable. A window of ±1 day in Cycle 1 is permitted to accommodate same-day sampling.
K To be collected on Day 22 to 28 of Cycle 6, every 6 cycles thereafter, and at time of suspected CR.
L For subjects with IgG myeloma only. Collect specimen at the same time as local disease assessment sample collection.
M Collect only if SEA–BCMA infusion time is ≤2 hr
N Collect only if infusion duration >1 hr, blood samples collected during SEA–BCMA infusion should be obtained from the contralateral arm, or different vascular access site relative to infusion site
O Collect only if infusion duration >2 hr, blood samples collected during SEA–BCMA infusion should be obtained from the contralateral arm, or different vascular access site relative to infusion site
P For cohort 1: Cycle 1 only; for cohort 2: Cycle 1 and 2 only
Q Collect until initiation of subsequent therapy

Pharmacokinetic, immunogenicity, and biomarker sample collection time points – Part D

					Peripheral Blood[A]											Bone Marrow[A]			
Cycle	**Study day**	**Time**	**Window**	**Relative Time**	**SEA-BCMA PK**	**Dexamethasone PK**	**Pomalidomide PK**	**SEA-BCMA ATA**	**Genotyping**	**Plasma cytokines/ chemokines**	**Soluble target and ligands**	**Plasma Biomarkers**	**PBMCs**	**SFLC**	**Modified SPEP [K]**	**Immunophenotyping (including BCMA characterization)**	**Gene expression/ NGS/FISH**	**MRD**	**BM plasma**
NA	Baseline/ screening	Non-dosing	D –10 to 1	NA					X	X[I]	X[I]	X[I]	X[I]	X	X	X[I]	X	X	X[I]
Cycles 1, 2 and 3	1	Predose	Within 4 h prior to dose[F]	START of infusion, 1st dose	X	X[C]	X[C]	X[B]		X	X	X	X	X	X				
		1 hr intradose	±15 min	START of infusion, 1st dose	X[M,C]	X[C]	X[C]												
		2 hr intradose	±15 min	START of infusion, 1st dose	X[N,C]	X[C]	X[C]												
		End of study drug administration	Within 15 min post IV infusion	END of infusion, 1st dose	X[C]	X[C]	X[C]				X[D]								
		2 hr	±15 min	END of infusion, 1st dose	X[C]	X[C]	X[C]			X[D]									
		6 hr[L]	±15 min	END of infusion, 1st dose	X[C]	X[C]	X[C]												
	2[G]	24 hr	±4 hr	START of infusion, 1st dose	X[C]	X[C]				X[C]			X[C]						
	4[G]	72 hr	±4 hr	START of infusion, 1st dose	X[C]	X[C]													
	8	168 hr	±24 hr	START of infusion, 1st dose	X[C]	X[C]				X[C]	X[C]			X[C]					
	15	Predose	Within 4 hr prior to dose	START of infusion, 2nd dose	X	X[C]				X[D]	X[D]		X[D]	X[D]					
	22	168 hr	±24 hr	START of infusion, 2nd dose	X[D]					X[E,I]	X[D,I]		X[EI]	X[C]	X	X[E,I]	X[E]	X[E]	X[E,I]
Cycle 4 and	1	Predose	Within 4 hr prior to dose	START of infusion, 1st dose	X			X[B]						X					

Cycle	Study day	Time	Window	Relative Time	Peripheral Blood[A]											Bone Marrow[A]			
					SEA-BCMA PK	Dexamethasone PK	Pomalidomide PK	SEA-BCMA ATA	Genotyping	Plasma cytokines/ chemokines	Soluble target and ligands	Plasma Biomarkers	PBMCs	SFLC	Modified SPEP [K]	Immunophenotyping (including BCMA characterization)	Gene expression/ NGS/FISH	MRD	BM plasma
subsequent cycles	22	168 hr	±24 hr	START of infusion, 2nd dose						X[J]	X[J]	X[J]	X[J]		X	X[J]	X[J]	X[J]	X[J]
At time of CR assessment				NA						X[I]	X[I]	X[I]	X[I]			X[I]	X[I]	X[I]	X[I]
EOT				NA	X			X		X[I]	X[I]	X[I]	X[I]	X	X	X[H,I]	X[H]	X[H]	X[H,I]
Follow-up				NA											X[O]	X[H,O]	X[H,O]	X[H,O]	X[H,O]

ATA = antitherapeutic antibody; BCMA = B-cell maturation antigen; BM = bone marrow; CR = complete response; EOT = end of treatment; FISH = fluorescent in situ hybridization; IHR = infusion/hypersensitivity reaction; IV = intravenous; MRD = minimal residual disease; NA = not applicable; NGS = next generation sequencing; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; SFLC = serum free light chain; SPEP = serum protein electrophoresis

A Blood and bone marrow aspirate and biopsy to be collected for central analysis. Analysis may include BCMA characterization (flow cytometry, gene expression, and immunohistochemistry), risk stratification (gene expression profiling, phenotypic profiling), and NGS analysis (including MRD determination).
B Required in first 5 cycles and every fifth cycle thereafter
C Cycle 1 only
D Cycle 1 and 2 only
E End of Cycle 2 only (Day 22 to 28) and at time of suspected CR
F Cycle 1 Day 1 predose window is within 1 day of Day 1; Collect predose samples before dexamethasone and pomalidomide administration.
G Labs may be drawn at the site or, may be drawn by a home healthcare provider
H Bone marrow aspirate and bone marrow biopsy, if available, to be submitted for central assessment of response and resistance to SEA–BCMA. To be collected to confirm CR in subjects who have not started another anticancer treatment.
I Blood and bone marrow samples must be collected on the same day, if applicable. A window of ±1 day in Cycle 1 is permitted to accommodate same-day sampling.
J To be collected on Day 22 to 28 of Cycle 6, every 6 cycles thereafter, and at time of suspected CR.
K For subjects with IgG myeloma only. Collect specimen at the same time as local disease assessment sample collection.
L Collect only if SEA–BCMA infusion time is ≤2 hr
M Collect only if infusion duration >1 hr, blood samples collected during SEA–BCMA infusion should be obtained from the contralateral arm, or different vascular access site relative to infusion site
N Collect only if infusion duration >2 hr, blood samples collected during SEA–BCMA infusion should be obtained from the contralateral arm, or different vascular access site relative to infusion site
O Collect until initiation of subsequent therapy

APPENDIX C. MODIFIED TOXICITY PROBABILITY INTERVAL DESIGN SIMULATION REPORT

Introduction

This is a phase 1 study with dose-escalation of SEA-BCMA in subjects with RRMM. The primary objective of this study is to evaluate the safety, tolerability, and identify the MTD and/or optimal dose of SEA-BCMA. Toxicity will be measured by DLTs observed within the first cycle of therapy. Dose-escalation will be conducted according to a modified toxicity probability interval (mTPI) method.

Dose-escalation

Overview

The primary objective of the dose-escalation portion of the study is to estimate an MTD and/or optimal dose for SEA-BCMA. There will be 5 selected dose levels. Intermediate dose levels of SEA-BCMA may be included during the execution phase at the discretion of the sponsor upon recommendation by the SMC.

The starting dose of SEA-BCMA will be dose level 1. Dose-escalation will be conducted according to the mTPI method and also according to a set of rules governing entry into the study and assignment of dose level. Decision rules are described in Section 3.1.1 of the study protocol and detailed in this appendix. Decision rules will be based on the posterior distribution of DLT-rate and derived independently for each dose level. The trial is continuously monitored for safety and for successfully identifying the MTD. In the event that the SMC recommends exploration of an intermediate level, (eg, a dose level between dose level 4 and dose level 5), an additional dose level may be added. In the event that SMC recommends a different schedule on the existing dose levels, the same dose-escalation algorithm will be applied separately.

Modified Toxicity Probability Interval Method

Dose-escalation is conducted using the mTPI method. The implementation programs are available at: http://health.bsd.uchicago.edu/yji/software2.htm.

For each dose level i = 1, 2, …, 5, the probability of a DLT on dose i is denoted by p_i. The target toxicity probability in this study is defined as 25%, with a 5% margin. The equivalence interval is [20%, 30%], which contains the doses close to the target DLT rate that physicians would deem acceptable for treating future subjects. The equivalence interval partitions the unit interval (0, 1) into 3 subintervals: (0%, 20%), (20%, 30%) and (30%, 100%). Doses in these 3 intervals correspond to:

1. Under dosing: p_i <20%
2. Proper dosing: 20% ≤ p_i ≤30%
3. Over dosing: p_i >30%

In each dose level, we assume the prior distribution of DLT probability p_i is noninformative *Beta(1, 1).* After each subject is treated and assessed for DLT, the posterior distribution of p_i is

updated to *Beta(1 + x_i, 1 + n_i - x_i),* where x_i, n_i denote the number of DLTs and number of DE subjects at dose level *i* respectively. The dose-escalation decision is based on the unit probability mass (UPM) on the posterior distribution of p_i. For a given interval [*a, b*], the UPM is defined as the ratio of the probability of the interval to the length of the interval, where for any DLT probability p_i and $0 \leq a < b \leq 1$:

$UPM(a, b) = Pr(a < p_i < b) / (b - a)$

After the toxicity outcomes are observed, the UPM on (0%, 20%), [20%, 30%] and (30%, 100%) at current dose will be calculated and the dosing decision rules would be:

1. Escalate (E) if (0, 20%) has the largest UPM
2. Stay at the current dose (S) if [20%, 30%] has the largest UPM
3. De-escalate (D) if (30%, 100%) has the largest UPM

Additionally, we define the toxicity of a dose being unacceptable if there is more than 95% probability that the DLT rate is higher than 25%:

Toxicity at dose *i* is unacceptable: $Pr(p_i > 25\%) > 95\%$

If dose level *i* is determined to be unacceptable, the next cohort of subjects is treated at dose level *i – 1* and dose *i* and higher are excluded from the trial. If *i = 1*, terminate the trial and, if no lower dose levels are of interest to explore, conclude that no dose level is safe. The decision rules for each dose level are provided in Table 9.

Table 9: Dose-finding spreadsheet for mTPI design

Number of DLTs	Number of DLT-evaluable subjects treated at current dose														
	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	E	E	E	E	E	E	E	E	E	E
2	DU	D	D	S	S	S	S	S	S	S	S	S	E	E
3		DU	DU	DU	D	S	S	S	S	S	S	S	S	S
4			DU	DU	DU	DU	DU	D	S	S	S	S	S	S
5				DU	DU	DU	DU	DU	DU	D	S	S	S	S
6					DU	DU	DU	DU	DU	DU	DU	DU	D	S
7						DU	DU	DU	DU	DU	DU	DU	DU	DU
8							DU	DU	DU	DU	DU	DU	DU	DU
9								DU	DU	DU	DU	DU	DU	DU
10									DU	DU	DU	DU	DU	DU
11										DU	DU	DU	DU	DU
12											DU	DU	DU	DU
13												DU	DU	DU
14													DU	DU
15														DU

D = de-escalate to the next lower dose, DLT = dose-limiting toxicity, DU = current dose is unacceptably toxic, E = escalate to the next higher dose, mTPI = modified toxicity probability interval, S = stay at the current dose,

At the end of the trial when the toxicity outcomes of all the enrolled subjects are observed, a dose will be selected as the estimated MTD. The estimation is separated from the design for dose finding. The MTD is selected by performing an isotonic regression that borrows strength cross doses. Let $\hat{p}_i$ be the posterior mean of DLT rate, the pooled adjacent violators algorithm is applied on $\hat{p}_i$ so that the resulting transformed values $\hat{p}_i^*$ increase with the dose levels. That is $\hat{p}_i^* \leq \hat{p}_{i+1}^*$ for all i. The recommended MTD is the dose with a toxicity probability $\hat{p}_i^*$ closest to the target DLT rate 25%, ie:

Estimated MTD = argmin $|\hat{p}_i^* - 25\%|$

Dose-escalation Rules

Dose-escalation begins with enrollment subjects to dose level 1. In each cohort, up to 4 subjects are enrolled. Once all subjects in previous cohorts have completed DLT evaluation, the next cohort of subjects can be enrolled. Subsequent enrollment and dose selection occurs via the following rules:

4. No untried dose levels may be skipped. At least 2 evaluable subjects per dose level is required to escalate until 1 DLT is observed at any dose level, then 3 evaluable subjects are required for further dose-escalation.
5. If a dose level i is unacceptable, de-escalate to the lower dose level and never treat future subjects at level i. If i = 1, stop the trial and conclude no dose is safe.

Interim Monitoring

The dose-escalation will be closely monitored for safety and for identifying the MTD. If no doses are safe, dose-escalation for that population will stop and no MTD will be declared.

Safety Monitoring

If no doses are safe, dose-escalation will stop and no MTD will be declared. Formally if:

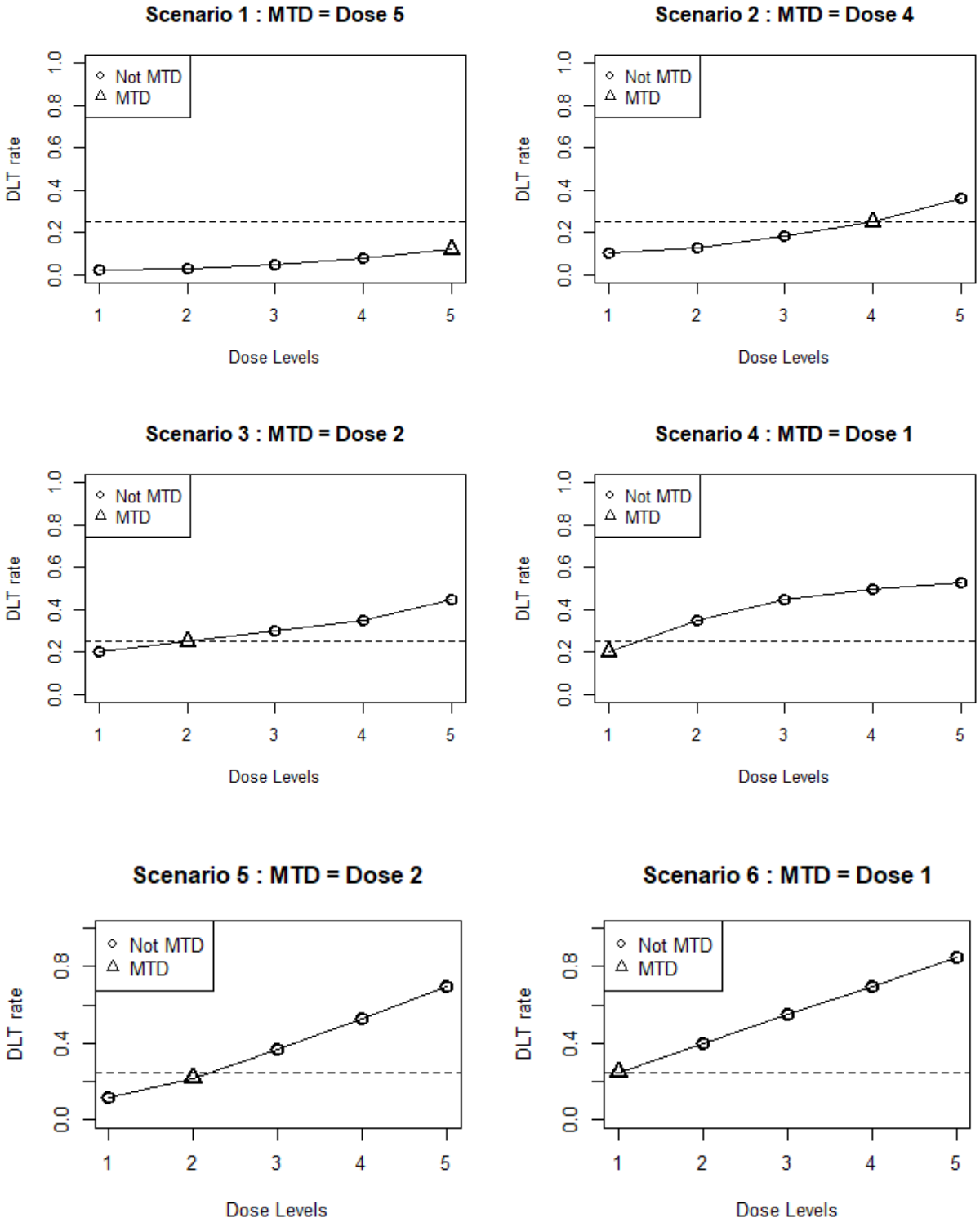
Pr(pi >25%) >95% for all *i*

Identification of MTD

After each dose level cohort, the estimation of MTD will be performed. If at least 6 DE subjects have been treated at the estimated MTD level and the model's next recommended dose is the same or below the MTD, the dose-escalation may be stopped and MTD can be declared. Alternatively, if the model's next recommended dose is above the estimated MTD level, and at least 6 DE subjects have already been treated at the higher dose level, and the observed DLT rate at the recommended higher dose level exceeds the target DLT rate of 25%, the dose-escalation may also be stopped and MTD can be declared.

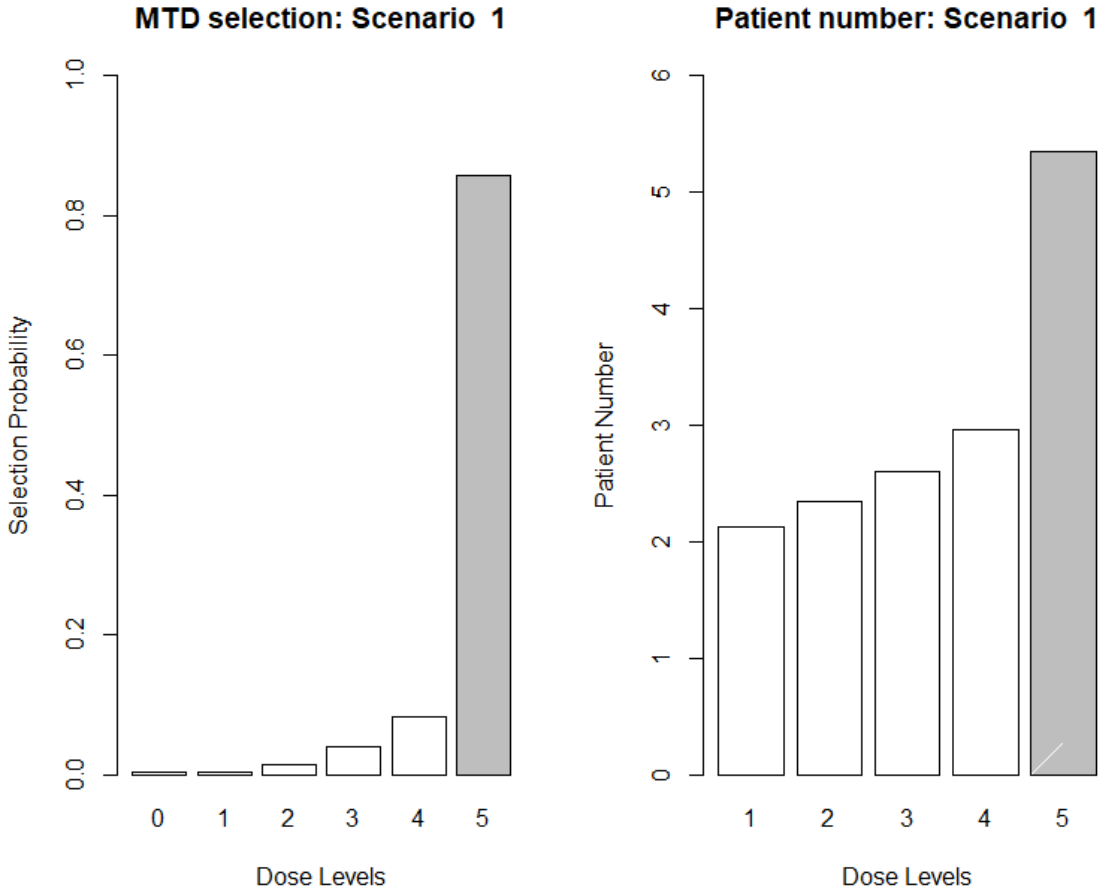
Simulation Studies

To evaluate the operating characteristics of the dose-escalation design, simulation studies were performed considering the following different scenarios.



The plots illustrate the true DLT rate at each dose level.

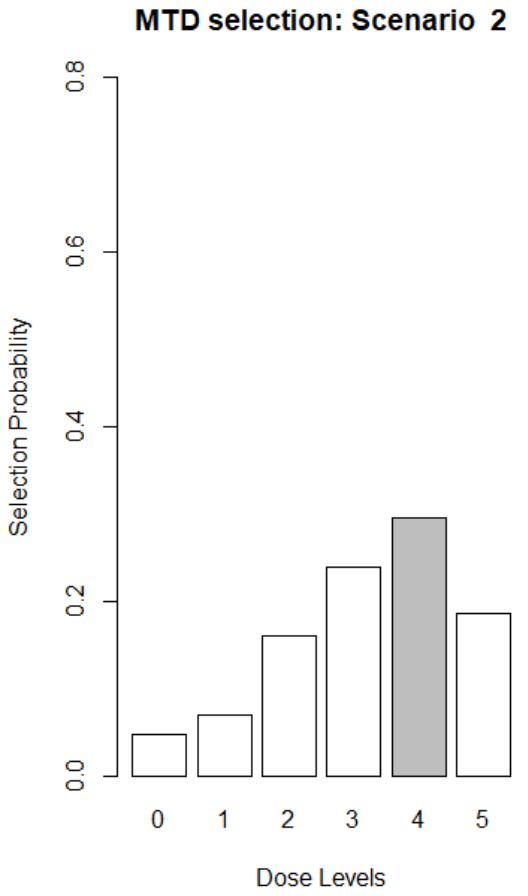
In each scenario, the dose-escalation and MTD-estimation process is replicated with 1000 replications. The probability of being selected as MTD, average number of DLT and the average number of subjects treated for each dose level is provided.

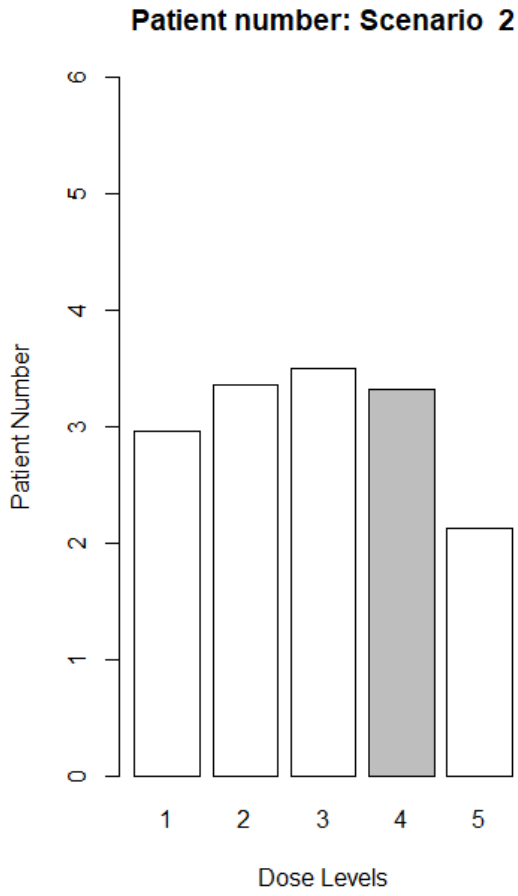


Scenario 1: Dose 5 is MTD	No dose is safe	1	2	3	4	**5**
True DLT rate		0.02	0.03	0.05	0.08	**0.12**
Mean # of subjects		2.129	2.350	2.607	2.963	**5.352**
Mean # of DLTs		0.031	0.087	0.150	0.264	**0.633**
Pr(Chosen MTD)	0.003	0.003	0.015	0.039	0.082	**0.858**

DLT = dose-limiting toxicity; MTD = maximum tolerated dose; Pr = probability

Under Scenario 1, the probability of selecting the true MTD is 0.858 according to simulation study. The observed average DLT rate is 0.075.

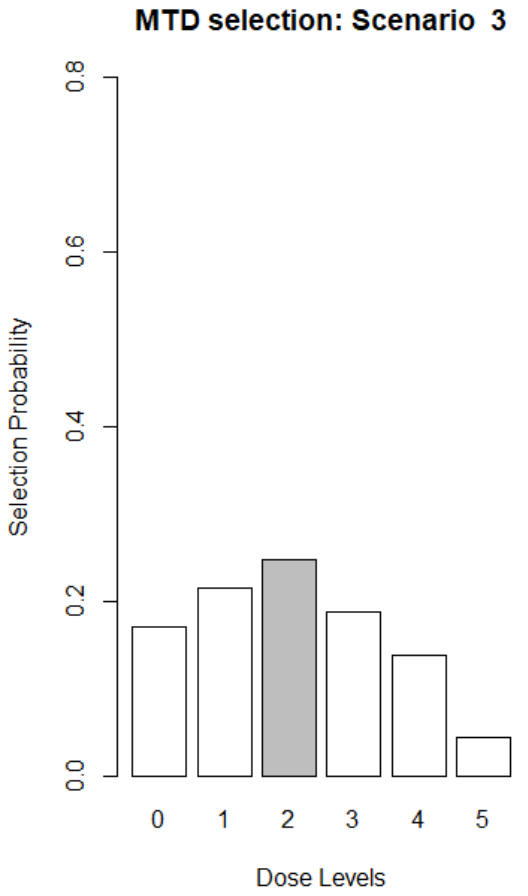


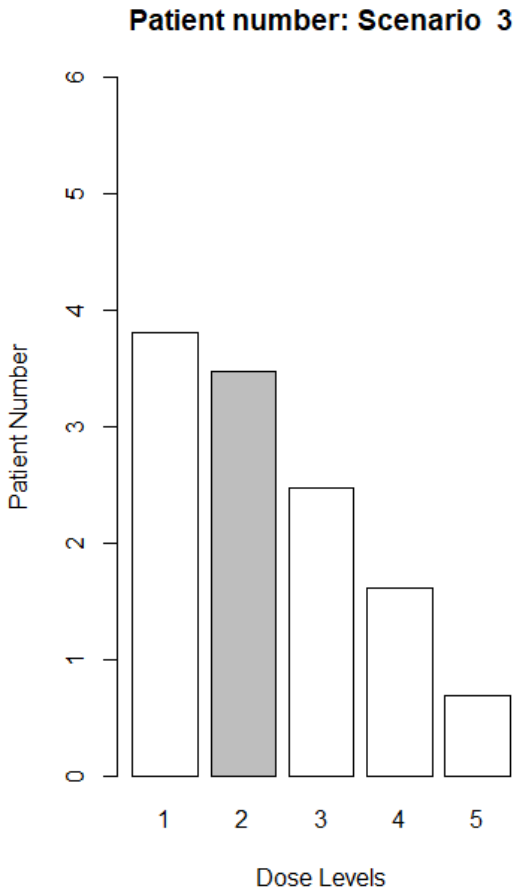


Scenario 2: Dose 4 is MTD	No dose is safe	1	2	3	**4**	5
True DLT rate		0.1	0.13	0.18	**0.25**	0.36
Mean # of subjects		2.957	3.359	3.499	**3.325**	2.126
Mean # of DLTs		0.290	0.445	0.641	**0.875**	0.804
Pr(Chosen MTD)	0.048	0.070	0.161	0.239	**0.296**	0.186

DLT = dose-limiting toxicity; MTD = maximum tolerated dose; Pr = probability

Under Scenario 2, the probability of selecting the true MTD is 0.296 according to simulation study. The observed average DLT rate is 0.219 and the number of subjects treated above MTD is 2.126.

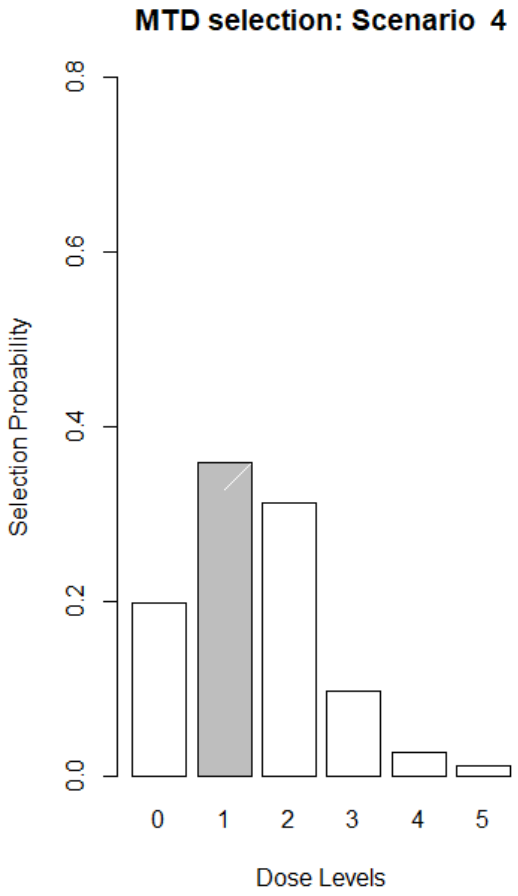


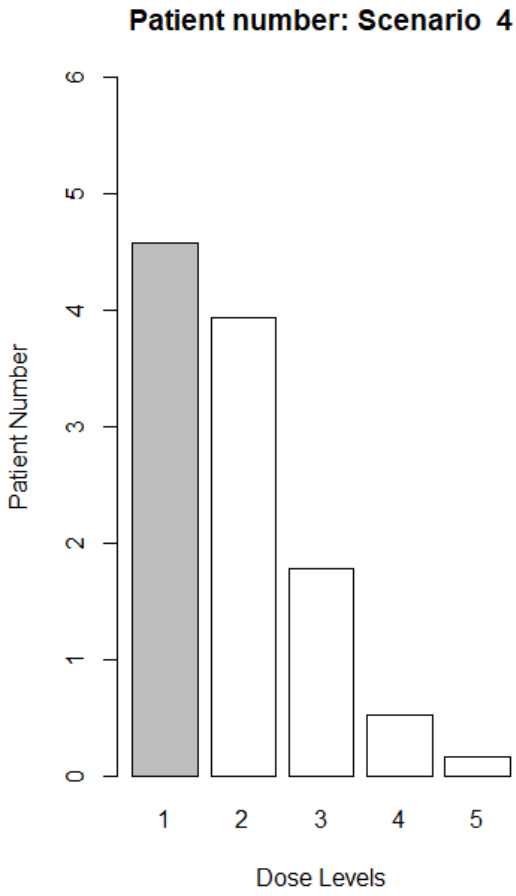


Scenario 3: Dose 2 is MTD	No dose is safe	1	**2**	3	4	5
True DLT rate		0.2	**0.25**	0.3	0.35	0.45
Mean # of subjects		3.810	**3.471**	2.476	1.615	0.690
Mean # of DLTs		0.762	**0.836**	0.712	0.521	0.316
Pr(Chosen MTD)	0.170	0.215	**0.247**	0.187	0.138	0.043

DLT = dose-limiting toxicity; MTD = maximum tolerated dose; Pr = probability

Under Scenario 3, the probability of selecting the true MTD is 0.247 according to simulation study. The observed average DLT rate is 0.318 and the number of subjects treated above MTD is 4.781.

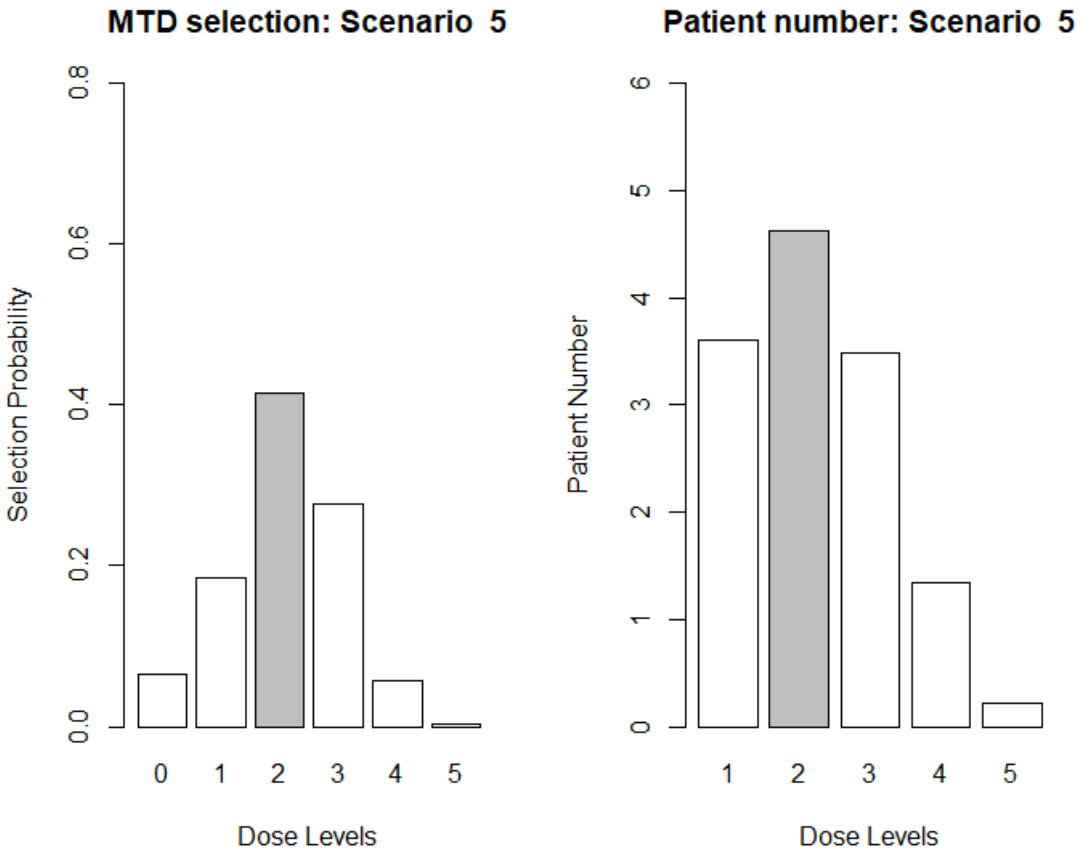




Scenario 4: Dose 1 is MTD	No dose is safe	1	**2**	3	4	5
True DLT rate		**0.2**	0.35	0.45	0.5	0.53
Mean # of subjects		**4.579**	3.931	1.777	0.522	0.163
Mean # of DLTs		**0.949**	1.352	0.793	0.246	0.077
Pr(Chosen MTD)	0.197	**0.358**	0.312	0.096	0.026	0.011

DLT = dose-limiting toxicity; MTD = maximum tolerated dose; Pr = probability

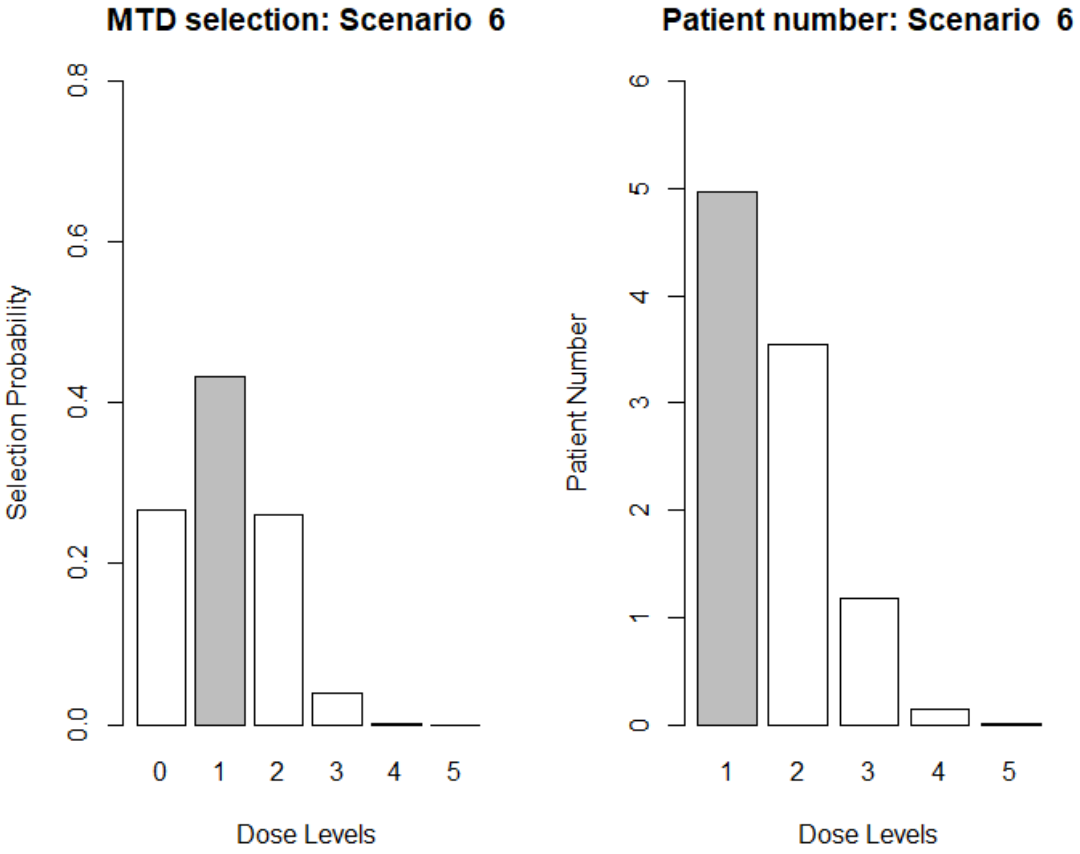
Under Scenario 4, the probability of selecting the true MTD is 0.358 according to simulation study. The observed average DLT rate is 0.358 and the number of subjects treated above MTD is 6.393.



Scenario 5: Dose 2 is MTD	No dose is safe	1	**2**	3	4	5
True DLT rate		0.12	**0.22**	0.37	0.53	0.7
Mean # of subjects		3.601	**4.630**	3.486	1.337	0.217
Mean # of DLTs		0.421	**1.069**	1.309	0.703	0.154
Pr(Chosen MTD)	0.065	0.184	**0.414**	0.277	0.057	0.003

DLT = dose-limiting toxicity; MTD = maximum tolerated dose; Pr = probability

Under Scenario 5, the probability of selecting the true MTD is 0.414 according to simulation study. The observed average DLT rate is 0.291 and the number of subjects treated above MTD is 5.04.



Scenario 6: Dose 1 is MTD	No dose is safe	**1**	2	3	4	5
True DLT rate		**0.25**	0.4	0.55	0.7	0.85
Mean # of subjects		**4.976**	3.545	1.174	0.150	0.002
Mean # of DLTs		**1.267**	1.429	0.675	0.115	0.002
Pr(Chosen MTD)	0.266	**0.432**	0.260	0.040	0.002	0.000

DLT = dose-limiting toxicity; MTD = maximum tolerated dose; Pr = probability

Under Scenario 6, the probability of selecting the true MTD is 0.432 according to simulation study. The observed average DLT rate is 0.408 and the number of subjects treated above MTD is 4.871.

Overall, mTPI has high probability to identify the true MTD and avoid treating subjects at unsafe doses. Based on the simulation results, the mTPI method is both reliable and safe in dose-escalation.

APPENDIX D. PERFORMANCE STATUS SCALES CONVERSION

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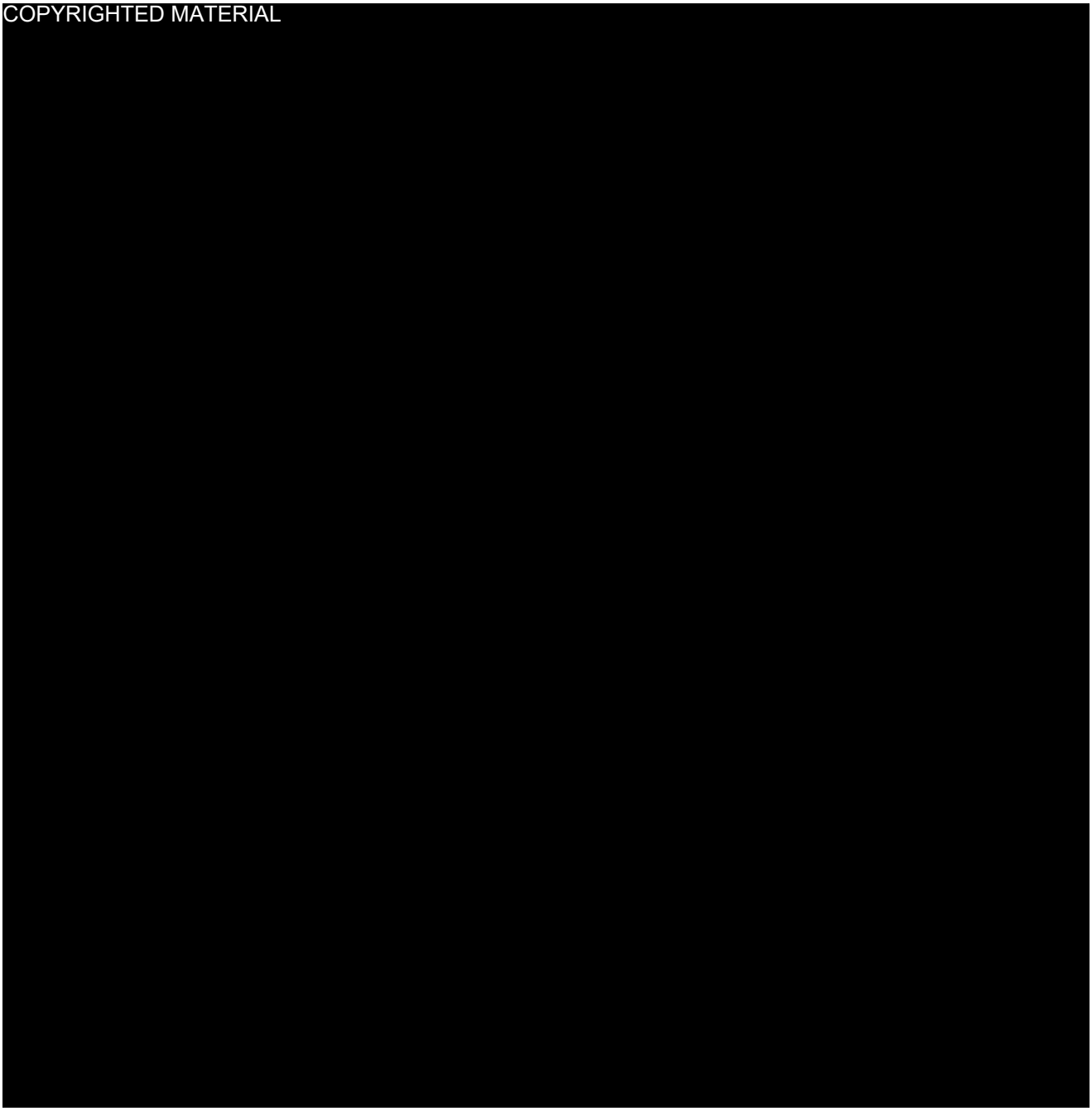

APPENDIX E. GUIDANCE ON CONTRACEPTION: PARTS A, B, AND C

Acceptable methods for highly effective birth control

Subjects who can father children[a] and who are sexually active with a pregnant or breastfeeding person must use the contraceptives in Option 1 or 2:

- Option 1: Male condom with spermicide and cervical cap
- Option 2: Male condom with spermicide and diaphragm

Subjects who are of childbearing potential[b] or whose partners are of childbearing potential who are sexually active in a way that could lead to pregnancy may choose to use any TWO of the following methods:

- Hormonal methods of contraception (excluding progestin-only pills).
- Intrauterine device with failure rate <1%
- Tubal ligation
- Partner's vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- A barrier method (male or female condom with spermicide, cervical cap with spermicide, diaphragm with spermicide)[c]

[a] A subject who can father children is anyone born male who has testes and who has not undergone surgical sterilization (eg, vasectomy followed by a clinical test proving that the procedure was effective).

[b] A subject of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

[c] A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double-barrier method, are not considered highly effective contraceptive measures (see unacceptable methods of contraception)

Unacceptable methods of contraception

- Abstinence (including periodic abstinence)
- No method
- Withdrawal
- Rhythm
- Any barrier method without spermicide
- Spermicide only
- Progesterone-only pills
- Barrier methods alone; including double-barrier methods

Tables adapted from "Recommendations related to contraception and pregnancy testing in clinical trials" advisory non-binding guidance represented at the Clinical Trials Facilitation Group meeting, Rome 2014.

APPENDIX F. GUIDANCE ON CONTRACEPTION: PART D

Acceptable methods for highly effective birth control

Subjects who can father children[a] and who are sexually active with a pregnant or breastfeeding person must use a condom even if the subject is vasectomized (must be confirmed by two negative semen analyses).

Subjects who are of childbearing potential[b] are sexually active in a way that could lead to pregnancy may choose to use any TWO of the following methods:

- Intrauterine devices (IUD) excluding progesterone T
- Hormonal methods of contraception (hormonal patches, injections, vaginal rings, implants, or birth control pills excluding progestin-only "mini pills").
- Tubal ligation
- Partner's vasectomy (must be confirmed by two negative semen analyses)
- Barrier methods (male condoms and female diaphragm or cervical cap)[c]

Subjects who can father children[a] and are sexually active with a person of childbearing potential[b] in a way that could lead to pregnancy must consistently use 2 methods of birth control, one of which must be a latex or synthetic condom even if the subject is vasectomized (must be confirmed by two negative semen analyses) along with any one of the following methods:

- Intrauterine devices (IUD) excluding progesterone T
- Hormonal methods of contraception (hormonal patches, injections, vaginal rings, implants, or birth control pills excluding progestin-only "mini pills)
- Tubal ligation

[a] A subject who can father children is anyone born male who has testes and who has not undergone surgical sterilization (eg, vasectomy followed by a clinical test proving that the procedure was effective).

[b] A subject of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined per the pomalidomide REMS program as 24 months of amenorrhea in a person born female over age 50 in the absence of other biological, physiological, or pharmacological causes.

[c] A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double-barrier method, are not considered highly effective contraceptive measures (see unacceptable methods of contraception)

Unacceptable methods of contraception

- Abstinence (including periodic abstinence)
- No method
- Withdrawal
- Intrauterine device Progesterone T
- Rhythm
- Female condom
- Cervical shield
- Spermicide only
- Progesterone-only pills
- Barrier methods alone; including double-barrier methods

Tables adapted from "Recommendations related to contraception and pregnancy testing in clinical trials" advisory non-binding guidance represented at the Clinical Trials Facilitation Group meeting, Rome 2014.

APPENDIX G. NEW YORK HEART ASSOCIATION CLASSIFICATION

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Online source: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

APPENDIX H. PROHIBITED CONCOMINANT MEDICATIONS

CYP3A4	Strong Inhibitors[1]	boceprevir, clarithromycin, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole
	Moderate Inhibitors[2]	aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
	Strong Inducers[1]	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
	Moderate Inducers[2]	bosentan, efavirenz, etravirine, phenobarbital, primidone
P-gp	Inhibitors[1]	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
	Inducers[2]	rifampin

1 Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers [online]. Available from: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed Jan 07, 2021.

2 This information is based on or an extract from UW Drug Interaction Database (DIDB) Copyright University of Washington. Accessed: Jan 05, 2021.

APPENDIX I. MODIFICATION OF DIET IN RENAL DISEASE EQUATION

- The estimated GFR should be calculated using the MDRD equation as applicable, with serum creatinine (Scr) reported in mg/dL (Levey 2006).
- GFR (mL/min/1.73 m^2) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)

APPENDIX J. DEFINITION OF RESPONSE AND PROGRESSION CRITERIA (MODIFIED FROM IMWG)

Response Subcategory	Response Criteria[a]
Stringent Complete Response (sCR)	CR, as defined below, plus the following: Normal FLC ratio[b] and absence of clonal cells[c] in bone marrow by immunohistochemistry or immunofluorescence
Complete Response (CR)[b]	Negative immunofixation of serum and urine and disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow.
Very Good Partial Response (VGPR)[b]	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein level plus urine M-protein level <100 mg per 24 hour.
Partial Response (PR)	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg per 24 hour. If serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Minor (Minimal) Response (MR)	25 to 49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50 to 89%, which still exceeds 200 mg per 24 hours. In addition, if present at baseline, 25 to 49% reduction in the size of soft tissue plasmacytomas is also required. No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or progression.
Progressive disease	Any of the following: • Increase of 25% from lowest response value in any one or more of the following: 1. Serum M-component (absolute increase must be ≥0.5 g/dL)[d] and/or 2. Urine M-component (absolute increase must be ≥200 mg per 24 hr) and/or 3. Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL 4. Bone marrow plasma cell percentage (absolute % must be ≥10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/100 mL) that can be attributed solely to the plasma cell proliferative disorder

a All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

b Note clarification to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects is defined as a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects is defined as a >90% decrease in the difference between involved and uninvolved FLC levels.

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

d For progressive disease, serum M-component increase of ≥ 1 g/dL is sufficient to define progression if starting M-component is ≥5 g/dL

Note: for IgA and IgD myelomas, quantitative immunoglobulin measurements are preferred for disease assessments; the same percentage change applies as for serum M-spike

APPENDIX K. INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled A phase 1 study of SEA-BCMA in subjects with relapsed or refractory multiple myeloma.

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature	Date

Investigator Name, Printed

APPENDIX L. DOCUMENT HISTORY

Version	Date
Original	26-Mar-2018
Amendment 1	17-May-2018
Amendment 2	14-Feb-2019
Amendment 3	27-Feb-2020
Amendment 4	13-May-2020
Amendment 5	04-Mar-2021
Amendment 6	22-Mar-2021
Amendment 7	06-Aug-2021
Amendment 8	31-Mar-2022
Amendment 9	03-Jun-2022

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
3.1.1 Table 2	Revised the mTPI methodology to stipulate the following: Using a target DLT rate of 25% with a 5% margin, the 3 intervals will be (0, 20%), (20%, 30%), and (30%, 100%), and the corresponding dosing decision rules would be: Escalate if current DLT rate is most likely <20% Continue if current DLT rate is most likely between 20% and 30% De-escalate if current DLT rate is likely >30% The dose-finding spreadsheet was revised based to reflect the target DLT rate of 25% with a 5% margin	To reflect that a target DLT rate 25% with a 5% margin will be used during dose-escalation
3.1.3 5.2.3	Revised the DLT criteria to clarify that any treatment-related deaths will be considered DLTs. In addition, AEs considered DLTs were revised to reflect the following: ○ Grade 4 neutropenia lasting more than 5 days ○ Thrombocytopenia ≥ Grade 4, or Grade 3 thrombocytopenia with clinically significant bleeding ○ Any ≥ Grade 4 infusion-related reactions (IRRs) or Grade 3 IRRs that do not resolve to ≤ Grade 2 within 24 hours with infusion interruption, infusion rate reduction, and/or standard supportive measures. In the event of a Grade 3 IRR in ≥20% of subjects (ie, 2 or more in the first 10 subjects), all subsequent subjects will require premedication and/or modification of infusion approach per the recommendation of the SMC. For subjects receiving premedication, any ≥ Grade 3 IRR will be considered a DLT. ○ Any Grade ≥3 electrolyte abnormality that does not resolve, with or without intervention, to ≤ Grade 1 or the baseline grade within 72 hours Section 5.2.3was revised to include additional follow-up for subjects with Grade 4 neutropenia or Grade 3 electrolyte abnormalities as follows: During dose-escalation, subjects with Grade 4 neutropenia must have a follow-up CBC with differential obtained 5 days from the time of assessment for evaluation of DLT. In addition, subjects with Grade 3 electrolyte abnormalities must have a follow-up chemistry panel obtained 72 hours from the time of assessment for evaluation of DLT.	To provide more conservative DLT criteria during dose-escalation
3.1.4	Revised the stopping criteria to indicate that the study will be halted if the rate of on-study toxic deaths unrelated to underlying disease occurring within 30 days of dose exceeds 10% (initially, 2 or more of the first 20 subjects)	To provide more conservative stopping criteria for on-study toxic deaths

Section(s)	Change	Rationale
5.2.2 6.4.1	Revised the observation period for Cycle 1, Day 1 as follows: On Cycle 1, Day 1, subjects will be closely observed in the clinic for at least 6 hours after completion of study treatment administration during dose-escalation. Vital signs will be collected as described in Section 6.4. Additional monitoring for subsequent cycles will be considered upon review of safety data with the SMC. The observation period after completion of study treatment administration on Cycle 1, Day 1 may be reduced to 2 hours during dose expansion if the SMC determines that safety is adequate after review of data from the dose-escalation cohort. In addition, vital sign monitoring time points of 240 minutes and 360 minutes were added to Schedule of Events for the Cycle 1, Day 1 visit for subjects in dose-escalation	Extended observation after the Cycle 1, Day 1 infusion will be utilized during dose-escalation, and may be discontinued during dose expansion if supported by safety data
Table 4	Revised the dose modifications for nonhematologic AEs and laboratory abnormalities as follows: Grade 3: Withhold dose until toxicity is ≤ Grade 1 or baseline[a], and then resume treatment at a lower dose level[b] Grade 4: Discontinue study treatment	To revise the recommended dose modifications for SEA-BCMA-associated toxicity
Appendix C	Revised the mTPI simulation report to reflect a target DLT rate of 25% with a 5% margin Added Scenarios 5 and 6 to the simulation report	To reflect the 25% target DLT rate and to expand the evaluation of the operating characteristics of the mTPI model

AE = adverse event; DLT = dose-limiting toxicity; IRR = infusion-related reaction; mTPI = modified toxicity probability interval; SMC = Safety Monitoring Committee

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Multiple	Revised to reflect that PK assessments are performed using serum samples only	Correction
3.1.1	Revised the required observation period between dosing of the first 2 subjects above Dose Level 1 from 72 hours to 24 hours	To reduce the time to dosing of the second subject at each dose level above Dose Level 1
7.6.1.2	Revised the AE reporting requirements as follows: Progression of the Underlying Malignancy ~~Cancer~~ Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression", "Progression of Disease" or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs. ~~Do not use the term "disease progression" alone when reporting AEs, including SAEs, because it is too nonspecific. Symptoms of disease progression that meet the criteria for an SAE must be reported. When possible, report the specific disease (clinical) manifestation of the progression (eg, "malignant pleural effusion", "spinal bone metastases", "lymphadenopathy", "brain metastases"). Otherwise, it is acceptable to report the specific disease (eg, non-Hodgkin lymphoma) as an SAE.~~	To clarify that disease progression should not be captured as an AE or SAE
7.6.1.2	Revised pregnancy monitoring requirements as follows: As part of the study, all pregnancies will be monitored for the full duration and all perinatal and neonatal outcomes should be reported.	To clarify that pregnancy monitoring is to be performed as part of the study
7.6.6	Revised the requirement for electrocardiograms (ECGs) as follows: Subjects will be monitored for changes in cardiac repolarization through assessment of ECGs conducted in triplicate at times outlined in Appendix A and Section 6 There is a 30-minute window to perform ECGs. Waiting periods between replicate ECGs are not required.	To clarify that all ECG measurements are to be collected in triplicate
Appendix A	Revised table to indicate that Day 15 ECG measurements are required during Cycle 1 only Revised footnote A to clarify ECG collection requirements	Clarification
Appendix B	Revised the time point associated with the Baseline/Screening visit from "predose" to "non-dosing"	Clarification

AE = adverse event; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Title page	Updated phase of study from 1 to 1b	To reflect the amended study design
Synopsis, Sections 1.6.1, 2, 3.1.2, 3.1.8, 3.1.8.2, 3.3, 4.1, 6.3, 7.2, 9.1, 9.3.10, Appendix A, Appendix B	Added Part B: Monotherapy Intensive Dosing Affected sections include • Rationale for intensive dosing schedule • Objectives • Study design • Safety monitoring • Method of assigning subjects to treatment groups • Inclusion criteria o added criterion 4b. Part B and Part C: Subjects must have received at least 3 prior lines of antimyeloma therapy and must be refractory to at least 1 agent in each of the following classes: PI, IMiD, and an anti-CD38 antibody • Study activities • Response/Efficacy assessments • Determination of sample size • Interim analyses • Schedule of events • PK, biomarker, and biomarker sampling time points	To evaluate an alternative SEA-BCMA monotherapy dosing schedule
Synopsis, Sections 1.6.2, 2, 3.1.3, 3.1.6, 3.1.8, 3.1.8.2, 3.3, 3.3.1.2, 4.1, 4.2, 4.4.1, 5.2.3, 5.3, 5.4, 6.4, 7.2, 7.3, 7.4, 9.1, 9.3.7, 9.3.10, Appendix A, Appendix B	Added Part C: SEA-BCMA in combination with dexamethasone Affected sections include • Rationale for dexamethasone combination therapy • Objectives • Study design • Retreatment • Safety monitoring • Method of assigning subjects to treatment groups • Rationale for selection of combination therapy • Inclusion criteria o added criterion 4b. Part B and Part C: Subjects must have received at least 3 prior lines of antimyeloma therapy and must be refractory to at least 1 agent in each of the following classes: PI, IMiD, and an anti-CD38 antibody • Exclusion criteria o Added exclusion criterion 17. Part C only: Known intolerance to corticosteroids	To evaluate the safety, tolerability, and efficacy of SEA-BCMA in combination with dexamethasone

Section(s)	Change	Rationale
	○ Added exclusion criterion 18. Part C only: Any uncontrolled psychoses • Discontinuation of study treatment • Dose modifications • Dexamethasone treatment ○ Description, method of procurement, dose and administration, dose modifications, storage and handling, packaging and labeling, and preparation • Required premedication and postmedication • Study activities • Response/Efficacy assessments • Qualitative interviews • Pharmacokinetic and immunogenicity assessments • Determination of sample size • Interim analyses • Schedule of events • PK, biomarker, and biomarker sampling time points	
Section 1.1	Updated with newly approved regimens for subjects with MM. Removed the following sentence: SEA-BCMA in combination with an autologous T-cell product expressing an antibody-coupled T-cell receptor that recognizes antibodies, is currently being evaluated in a phase I study with MM subjects.	Update with current information
Section 2, 9.2.6	Added exploratory endpoint to assess MRD in subjects with VGPR or better	To improve efficacy monitoring
Section 3.1.4	Edited the following DLT: • Any Grade ≥3 ~~electrolyte~~ asymptomatic laboratory abnormality that does not resolve, with or without intervention, to ≤ Grade 1 or the baseline grade within 72 hours	To improve safety monitoring
Section 3.1.7	Added section to allow treatment beyond progression under specified conditions.	To allow subjects receiving clinical benefit to be retreated
Section 3.3.1.1	Added rationale for selection of monotherapy expansion dose	Update with current information
Sections 5.2.3, 5.6.1	Updated dose modifications recommendations for SEA-BCMA monotherapy	To refine dose modification guidance; as IRRs have not yet been correlated with dose, and all IRRs that occurred during Cycle 1 Day 1 were successfully prevented by premedication at the next dose, dose reduction at the next dose can be considered but is not required

Section(s)	Change	Rationale
Section 7.7.3	Removed amylase and lipase from clinical laboratory tests	Streamline safety monitoring; no signal of pancreatic toxicity has been detected thus far on the phase 1 trial
Section 6.2, Appendix A, Appendix B	Removed q4wk SEA-BCMA dosing schedule	To remove unused dosing schedule
Sections 6.2, 6.3, 6.4, 6.9, 7.1, 7.7.3, Appendix A	Clarified that UPC calculation is urine protein to creatinine ratio and added units of mg/mg. For example, • Urine protein to creatinine ratio (UPCR) calculation; 24-hour urine collection required if UPCR >2 mg/mg	Clarification
Sections 6.6, 6.7, 6.8	Only subjects in Part A will have IHR and IHR follow-up visits	To specify that IHR visits are conducted for subjects in Part A only
Appendix H	Added definition of response and progression criteria modified from IMWG guidance	Clarification
Throughout protocol	Minor corrections and clarifications	Corrections and clarifications

BCMA = B-cell maturation antigen; CD38 = cluster of differentiation 38; DLT = dose-limiting toxicity; IHR = infusion/hypersensitivity reaction; IMiD = immunomodulatory drug; IMWG = International Myeloma Working Group; IRR = infusion-related reaction MM = multiple myeloma; MRD = minimal residual disease; PI = proteasome inhibitor; PK = pharmacokinetic; UPC = urine protein to creatinine; UPCR = urine protein to creatinine ratio; VGPR = very good partial response

Summary of Changes in Amendment 4

Section(s)	Change	Rationale
Section 6.2.3.1, Appendix A	Added text to specify that in Part A, ECGs will be conducted on Day 1 of Cycle 1, but not conducted on Day 1 of subsequent cycles.	To specify that in Part A, ECGs should not be conducted on Day 1 of Cycle 2 and subsequent cycles.

ECG = electrocardiogram

Summary of Changes in Amendment 5

Section(s)	Change	Rationale
Throughout	"Seattle Genetics" replaced with "Seagen" throughout	To reflect change in the company name
Synopsis, Sections 3.1.1, 3.2, and 5.2.3	Added criteria for intrasubject dose escalation.	To provide objective criteria for decisions about intrasubject dose escalation
Sections 3.1.2 and 3.1.3	If 2 or more DLTs occur in the first 6 subjects in any Part B or C cohort, the MTD will be considered exceeded.	To improve subject safety and enable a more accurate estimation of the MTD
Sections 3.1.3 and 3.3.1.2	Specified that in Part C Optional Cohort 2, SEA-BCMA will be administered at a dose of 800 mg during Cyles 1 and 2	To clearly specify the starting dose of SEA-BCMA dose in Part C Optional Cohort 2
Section 3.1.5	Study stopping criteria apply throughout the entire study	Clarification
Section 3.1.7	Removed section allowing treatment beyond progression	To require treatment discontinuation at the time of IMWG confirmed progressive disease
Section 5.2.3 and 5.6.1	Specified that recommended dose modifications are for toxicities regardless of relatedness to SEA-BCMA. Specified that after Grade 3 non-hematologic toxicities have recovered to baseline or ≤ Grade 1, SEA-BCMA may be resumed at 50% of the previous dose.	To improve subject safety

Summary of Changes in Amendment 6

Section(s)	Change	Rationale
Protocol Synopsis	Added criterion for Part D to Study Population. Added Number of Planned Subjects for Part D. Added Part D Study Design. Added pomalidomide to Combination Products. Changes Statistical Methods to include 30 to 70% ORR (previously 30 to 50%).	To delineate the differences between Part D criterion, patient population, response benchmarks, and treatment from those for Parts A, B, and C.
1.1	Added information on the use of pomalidomide/dexamethasone in combination with monoclonal antibodies to treat multiple myeloma.	Justification of this combination with SEA-BCMA.
1.6	Added information on the favorable safety profile and preliminary evidence of clinical activity based on data from Part A.	Justification for the investigation of SEA-BCMA in combination with approved SOC agents.
1.3.2.2	Added rationale for pomalidomide and dexamethasone combination therapy.	To describe the enhancement of natural killer cell expansion and its potentiation of ADCC.
3.1	Added Study Design Schema image.	To visually clarify and summarize the 4 parts of the study design.
3.1.3	Added Part D to Combination Therapy Cohorts.	NA
3.3.6	Changed Retreatment criterion from a partial PR or better to clinical benefit (defined as stabilization or improvement of disease-related symptoms as assessed by the investigator).	To allow for consideration of retreatment in subjects receiving clinical benefit.
4.1	Added Part D to Inclusion Criteria. Added more stringent guidance for subjects of childbearing potential.	To delineate between criterion for Part D and those for Parts A, and B/C.
4.2	Added exclusion criterion specific to Part D.	To capture risks specific to pomalidomide treatment.
4.3	Added washout period guidance for females treated with FSH.	Improve subject safety
4.3.1	Added information specific to Part D for women of childbearing potential.	To delineate between criterion for Part D and those for Parts A, and B/C.
4.4.1	Added Discontinuation of Study Treatment information specific to Part D.	Information related to new Part D cohort.
5.4	Added pomalidomide section to Treatments.	Information related to new part D cohort.
5.6	Added required premedication regimen	Improve subject safety
5.7.1	Changes to Required Concomitant Therapy.	Emerging safety data as well as the requirement of thromboembolic prophylaxis with pomalidomide.
5.7.3	Added Part D to Prohibited Concomitant Therapy.	Information related to new Part D cohort.
6.2.3, 6.4.3	Added requirement that premedication be delivered approximately 45 to 90 minutes prior to the infusion of SEA-BCMA.	Improve subject safety

Section(s)	Change	Rationale
6.4.3.1	Changed UPCR calculation to spot urine test.	Clarification
6.5	Added Part D Study Activities.	Information related to new Part D cohort.
9.1	Assumption for Determination of Sample Size changed from ORR between 30 and 50% to between 30 and 70%.	Upper range of response increased due to addition of Part D combination therapy in an earlier line.
Appendix A	Premedication added to Schedule of Event tables for Parts B and C. Schedule of events table added for Part D.	Improve subject safety and information related to new Part D cohort.
Appendix B	PK, ATA, and Biomarker Sampling Timepoints added for Part D.	Information related to new Part D cohort.
Appendix F	Contraceptive guidance specific to Part D added.	Align with guidance required for pomalidomide.

Summary of Changes in Amendment 7

Section(s)	Change	Rationale
Global	Changed the term “patient” to “subject” when referring to a person who is involved in a clinical study	Modification to style guide
Global	Changed the phrase “approval of the SMC” to “recommendation of the SMC”	Accuracy of terminology
Synopsis	Clarified patient run-in language for Part C Optional Cohort 2	Clarification
Synopsis, 1.6.2.4, 3.1, 3.3.1.2, 4, 5.5, 5.7, 6.1, 9.1, 9.3 1.2, 1.6.2.3	Added new cohort: SEA-BCMA in combination with nirogacestat and dexamethasone (Part E)	New cohort
Synopsis, 3.1.3, 3.3.1.2, 6.5.3	Added new cohort: intensive dosing of SEA-BCMA in combination with pomalidomide and dexamethasone (Part D)	New cohort
7.7	Added adverse events of special interest to Reporting Periods Added investigator causality assessment to Serious Adverse Events Require Immediate Reporting New section on Adverse Events of Special Interest	To improve subject safety
Appendix A Appendix B	Schedule of Events and PK/ATA/Biomarker Sampling Tables added for Part D Cohort 2 and Part E	Information related to new cohorts
Appendix E Appendix F	Unacceptable methods of contraception language around barrier methods modified	Clarification
Appendix H	New appendix with information on P-gp and CYP3A4 inducers/inhibitors	Background on exclusion criteria surrounding the use strong inducers or moderate to strong inhibitors of CYP3A4 or strong inhibitors or inducers of P-glycoprotein for Parts D and E

Summary of Changes in Amendment 8

Section(s)	Change	Rationale
Synopsis, Section 2	Modified the following primary objective: • Identify the maximum tolerated dose (MTD) and/or optimal dose and schedule of SEA-BCMA monotherapy, and in combination with dexamethasone, in subjects with RRMM Removed the following primary objective: • Evaluate the safety and tolerability of SEA-BCMA in combination with nirogacestat and dexamethasone in subjects with RRMM Removed the following exploratory objective: • Assess the PK of nirogacestat in combination with SEA-BCMA and dexamethasone. Modified the following exploratory objective: • Assess impact of SEA-BCMA in combination with standard of care therapies ~~and SEA-BCMA in combination with nirogacestat and dexamethasone~~ on health-related quality of life (HRQoL) from the subject's perspective.	Reflects modified study design
Synopsis	Study population for Parts B and C modified as follows: In Parts B~~,~~ and C, ~~and E,~~ subjects must not have other therapeutic options known to provide clinical benefit in multiple myeloma available, must have received at least 3 prior lines of antimyeloma therapy, and must be refractory to ~~a~~at least 1 agent in each of the following classes: PI, IMiD, and an anti-CD38 antibody.	Aligned with wording in Section 4 for clarity
Synopsis, Sections 3, 9.1, 9.3.10, Figure 1	Study design and statistical methods updated to reflect the following changes to expected sample sizes: Up to approximately ~~305~~131 subjects are expected to be enrolled in this study. This number is based on the following assumptions: • Up to approximately ~~65~~45 subjects will be evaluated in Part A (monotherapy dose- escalation and expansion; every 2 weeks [q2wk] dosing). • Up to approximately ~~40~~20 subjects will be evaluated in Part B (monotherapy intensive dosing; once weekly [q1wk] for 8 weeks, followed by q2wk dosing). • Up to approximately ~~80~~60 subjects total will be evaluated in the Part C dexamethasone combination therapy cohorts ~~(up to 40~~20 ~~in each of 2 optional cohorts)~~. Up to 20 subjects will be enrolled in cohort 1 (standard dosing SEA-BCMA). Up to 40 subjects will be enrolled in cohort 2 (intensive dosing	To reflect change in sample size for Parts A, B, C, and D; and removal of Part E.

Section(s)	Change	Rationale
	SEA-BCMA): 20 subjects in each of up to 2 parallel dose levels. • Up to approximately ~~80~~6 DLT-evaluable subjects ~~total~~ will be evaluated in the Part D pomalidomide and dexamethasone combination ~~cohorts (up to 40 in each of 2 optional cohorts~~safety run-in cohort.	
Synopsis, Section 4.1	Part D inclusion criterion 2c and corresponding text in synopsis revised require that subjects have received 3 or more prior lines of therapy, and remove prohibition of prior pomalidomide therapy: In Part D, subjects ~~must have not received prior pomalidomide,~~ must have received at least ~~2~~3 prior lines of antimyeloma therapy, including ~~at least 2 consecutive cycles of both lenalidomide and a PI (given separately or in combination)~~a PI, IMiD, and an anti-CD38 antibody, and must have documented International Myeloma Working Group (IMWG) disease progression on or within 60 days of completion of their last treatment.	Reflects modified study design
Synopsis, Figure 1, Sections 3.1, 3.3.1.2, 4, 6.5.3, 9.1	Removed Part D Cohort 2; modified Part D cohort 1 to a 6-subject safety run-in.	Reflects modified study design
Synopsis, Figure 1, Sections 1.6.2, 3.1, 3.3.1.2, 4, 5.3.3, 5.5, 5.6.2, 5.6.3, 5.7, 6, 7.3, 7.7.9, 9.1, 9.3.1.7.3, Appendix E	Removed Part E (SEA-BCMA in combination with nirogacestat and dexamethasone)	Reflects removal of Part E
Section 3.1.2	Removed the following text: Initially, up to 20 subjects may be enrolled in Part B; an interim futility analysis will be performed after 20 subjects are efficacy-evaluable at optimal dose to determine whether the cohort may be expanded up to 40 subjects	To reflect Part B sample size of 20 subjects
Appendix A, B	Removed schedule of events and sample collection schedule for Part E. Removed assessments specific to Part D Optional Cohort 2.	Reflects modified study design
Appendix H	Removed list of p-gp and CYP3A inhibitors and inducers. List was applicable only to nirogacestat (Part E).	Does not apply; Part E/nirogacestat removed from study design.

Summary of Changes in Amendment 9

Section(s)	Change	Rationale
Section 1.1	Updated the description of current treatment landscape	To reflect current treatment landscape in the US and Europe
Section 1.6.1	Discussion and Rationale for Study Design was moved from Section 3.2 to Section 1.6.1.	Consolidate related information
Section 1.6.3.3	Added section for Patient Input Into Design	Further details on study
Section 1.7	Added section for Benefit/Risk Assessment	Improve subject safety
Section 3.1.1	Removed the following text from Section 3.1.1.1: Subjects may continue on treatment until progressive disease (PD) or unacceptable toxicity, whichever occurs first.	Moved to Section 3.1.4
Synopsis and Section 3.1.3.3 Section 4.1 Section 4.3.1	Clarified that Part D will enroll subjects in the US only.	Clarification
Sections 3.1.4	Added Section 3.1.4 to capture duration of treatment information for all cohorts in one location.	Clarity of treatment duration
Section 3.1.6.1	Added Section 3.1.6.1 to detail when enrollment will be paused at the cohort level.	Improve subject safety
Section 3.1.6.2	Added the following bolded text and removed text in strikethrough in Section 3.1.6.2 Enrollment Halt for the Entire Study: **Enrollment in the entire study will be halted by the sponsor if the overall benefit-risk balance is considered unfavorable**. Stopping criteria will be continuously monitored throughout the study by the sponsor **in consultation with the SMC, considering enrollment halt if the incidence and/or the severity of toxicity leads to a risk-benefit assessment that is unacceptable to the study population.** The sponsor will consult the SMC to **consider whether to allow subjects already receiving treatment to continue,** to consider modifying the protocol to continue the trial, or to terminate the study. **If enrollment is halted due to safety concerns, enrollment can only be restarted after appropriate amendments and notifications to Regulatory Authorities, with approval to resume, if required by local regulations**~~In the event there is a recommendation to amend the protocol to continue, regulatory authorities will be consulted~~**.**	Improve subject safety
Section 3.1.8	Section added to describe study close	Clarify study duration
Section 4.1	Inclusion Criterion 2b for Parts B and C was revised to add: Prior BCMA-directed myeloma therapy, excluding prior treatment with SEA-BCMA, is permitted (eg, ADC, CAR-T cell therapy, or bispecific antibody targeting BCMA) provided that at least 3 months will have elapsed from the last dose of prior BCMA targeting therapy and	Change in treatment landscape of RRMM

Section(s)	Change	Rationale
	Cycle 1 Day 1 of this study, and that the subject has recovered from any clinically significant toxicity of the prior BCMA-targeting therapy.	
Section 4.2	Exclusion Criterion 1 modified, with deletions shown in strikethrough text: Parts A ~~, B, C,~~ and D: Prior exposure to any other BCMA-directed therapy	Change in treatment landscape of RRMM
Section 5.1	Added the following bolded text to Treatments Administered: SEA-BCMA is a non-fucosylated monoclonal antibody directed against BCMA**. Subjects will receive the investigational medicinal product SEA-BCMA as monotherapy or combination therapy (Section 3.1). Subjects in combination therapy cohorts will also receive dexamethasone or dexamethasone plus pomalidomide.** Guidance for intrasubject dose-escalation for subjects who have the potential to achieve greater benefit at a dose higher than the dose level assigned during dose-escalation is described in Section 5.2.3.	Clarify treatment regimens
Section 5.2.7	Section added regarding access to study drug after the end of the study.	Clarify duration of access to study drug
Section 5.3.2	Dexamethasone method of procurement modified with new text in bold and deleted text in strikethrough: **In the US, dexamethasone will be sourced by study sites from commercial supply. In other countries, oral dexamethasone will be provided to the study sites by the sponsor or dexamethasone (oral or IV) will be sourced by study sites from commercial supply.** ~~Dexamethasone is commercially available and approved by the US FDA. Dexamethasone will be supplied by the study site and billed to subjects and/or their third-party payer (insurance, a healthcare provider, or applicable government program).~~	Reflect regional variability
Section 5.4.2	Pomalidomide method of procurement modified with new text in bold and deleted text in strikethrough: **In the US, pomalidomide will be sourced by study sites from commercial supply.** ~~Pomalidomide is commercially available and approved by the US FDA. Pomalidomide will be supplied by the study site and billed to subjects and/or their third-party payer (insurance, a healthcare provider, or applicable government program).~~	Reflect regional variability
Section 6	Skeletal survey defined as: via whole body plain film radiography, or via whole body computed tomography [CT] scan, to assess presence and size of lytic bony lesions	To add definition of study assessment
Sections 6, 7.1, 7.2, Appendix A	Added detail in bold to indicate plasmacytoma scans will be conducted: **per institutional standard imaging modality**	To add definition of study assessment
Synopsis, Sections 6.4.4, 6.5.4, 7.3	Indicated that qualitative interviews will be conducted in 10 subjects total from Part C and Part D.	Clarification

Section(s)	Change	Rationale
Appendix A	Part C Schedule of Events: removed footnote DD “24-hour urine collection required if UPCR >2 mg/mg”	Correction
Appendix B	Part D Schedule of Events footnotes C and P were redundant, so footnote P was replaced with footnote C.	Correction
Appendix B	Pharmacokinetic, immunogenicity, and biomarkers sample collection tables for Parts B, C and D modified to remove peripheral blood immunophenotyping sample collection.	To reflect updated sample collection requirement
Throughout	Minor corrections and clarifications	Corrections and clarifications