CLINICAL STUDY PROTOCOL

A Phase 1/2, Dose Escalation, Safety and Tolerability Study of BION-1301 in Adults with Relapsed or Refractory Multiple Myeloma

Protocol Number:	ADU-CL-16
Original Protocol:	04 August 2017
Amendment 1:	28 September 2017
Amendment 2:	13 November 2018
Investigational Product:	BION-1301 (humanized IgG4 anti-a proliferation-inducing ligand [APRIL] monoclonal antibody)
IND Number:	132,892
ClinicalTrials.gov:	NCT03340883
Sponsor:	Aduro Biotech, Inc. 740 Heinz Avenue Berkeley, CA 94710 USA Telephone: +1 510-848-4400
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2 SYNOPSIS

TITLE: A Phase 1/2, Dose Escalation, Safety and Tolerability Study of BION-1301 in Adults with Relapsed or Refractory Multiple Myeloma

PROTOCOL NUMBER: ADU-CL-16

INVESTIGATIONAL PRODUCT:

BION-1301 (humanized IgG4 anti-a proliferation-inducing ligand [APRIL] monoclonal antibody)

PHASE: 1/2

SITES: Multicenter study conducted at approximately 15 sites in the United States

INDICATION: Treatment of adults with relapsed or refractory multiple myeloma (MM)

OBJECTIVES:

- Evaluate safety and tolerability of BION-1301 when administered as a single-agent or with low-dose dexamethasone (BION-1301+DEX)
- Identify the recommended Phase 2 dose (RP2D) and schedule of BION-1301 when administered as a single-agent
- Characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profile of BION-1301
- Evaluate clinical activity of BION-1301 and BION-1301+DEX

ENDPOINTS:

Phase 1

- Incidence of dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), and changes in safety parameters
- PK parameters based on BION-1301 serum levels following a single dose and after repeated dosing
- Change from baseline in soluble APRIL
- Relative reduction in serum and urine M-protein levels defined as the maximum percent reduction from baseline

Phase 2

- Objective response rate (ORR) based on International Myeloma Working Group (IMWG) uniform response criteria of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR)
- Relative reduction in serum and urine M-protein levels defined as the maximum percent reduction from baseline

- Progression-free survival (PFS) defined as time from first dose of study drug to date of first tumor progression or death due to any cause
- Overall survival (OS) defined as the time from first dose of study drug to date of death due to any cause
- Incidence of TEAEs, changes in safety parameters, and unacceptable toxicities
- PK parameters based on BION-1301 serum levels following a single dose and after repeated dosing

Exploratory Endpoints evaluated throughout the study as appropriate include:

- Duration of response (DOR) defined as the time from the first tumor assessment that supports the subject's ORR to the time of disease progression or death due to any cause
- Disease control rate (DCR) defined as the percentage of subjects with sCR, CR, VGPR, PR, or stable disease (SD) per IMWG criteria; or minimal response (MR) per European Group for Blood and Marrow Transplantation (EBMT) criteria
- Change from baseline in soluble B cell maturation antigen (sBCMA; TNFRSF17) levels
- Changes in additional biomarkers and immune monitoring

STUDY DESIGN:

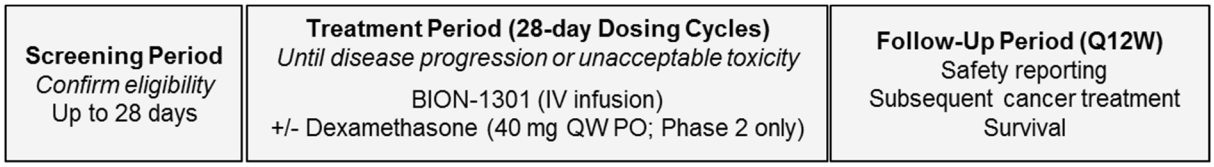
ADU-CL-16 is an open-label, multicenter, first in human, dose escalation study to evaluate the safety, tolerability, and PK-PD of BION-1301, a first-in-class monoclonal antibody targeting APRIL. The population for this study will consist of adults with relapsed or refractory MM whose disease has progressed after at least 3 prior systemic therapies. BION-1301 will be administered in 28-day cycles.

The study will be conducted in 2 parts as depicted in the study design diagram below. Phase 1 will be conducted using a 3+3 dose escalation design and seeks to determine the RP2D by evaluating safety and tolerability and characterizing the PK-PD of BION-1301. Dose escalation decisions will be based on available safety, PK-PD, and efficacy data from all evaluable subjects in each cohort.

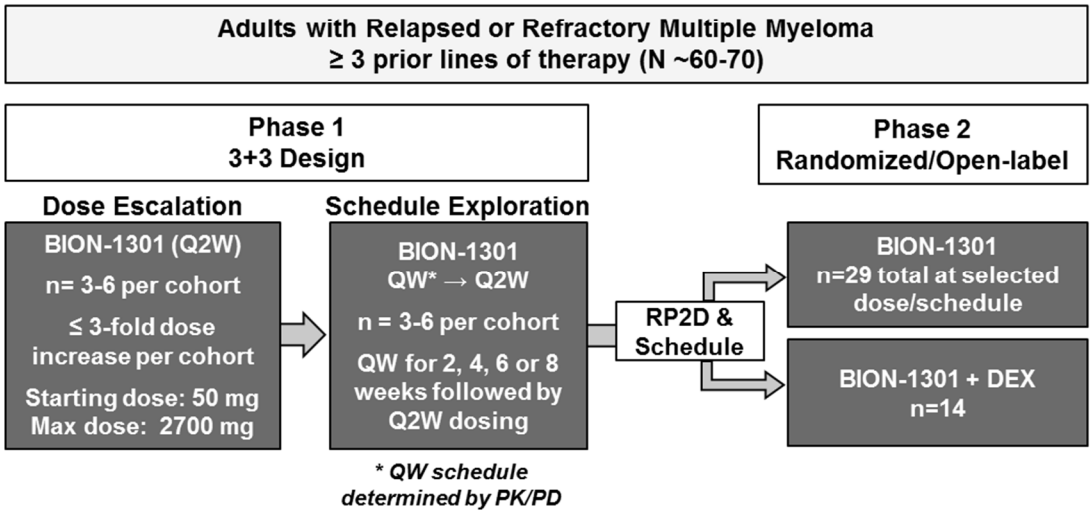
The dosing interval will be once every two weeks (Q2W) during initial dose escalation. Additional cohorts will be enrolled to evaluate weekly (QW) dosing for up to 8 weeks, followed by Q2W dosing with the same or a lower dose. PK-PD data will be evaluated for each cohort to inform the dosing schedule to be evaluated in subsequent cohorts.

Once an RP2D and schedule are identified, Phase 2 of the study will open and continue to evaluate the safety and preliminary efficacy of BION-1301 administered as a single agent or with low-dose dexamethasone. Subjects enrolled in Phase 2 will be randomized to receive either BION-1301 or BION-1301+DEX open-label.

ADU-CL-16 Study Schema



Study Population & Enrollment Plan:



A schedule of visits and procedures is provided in Table 2-1.

DURATION OF SUBJECT PARTICIPATION:

The Screening Period may last up to 28 days. Eligible subjects will receive BION-1301 or BION-1301+DEX at the assigned dose and schedule until disease progression or unacceptable toxicity. Following disease progression and/or discontinuation of study drug, subjects will be followed for survival until death, withdrawal of consent, lost to follow up, or end of study. The end of the study is defined as the date when all subjects have completed the final protocol-specified safety assessment and/or discontinued study participation (withdrawal of consent or lost to follow-up), whichever occurs first. Following the in-clinic portion of study additional biomarker analyses may take place prior to Clinical Study Report submission. At end of the study, all remaining subjects will be offered enrollment in a long-term extension study.

STUDY POPULATION:

Key Inclusion Criteria

Individuals eligible to participate in this study must meet the following key criteria and additional criteria as specified in the protocol:

1. Male or female, aged ≥ 18 years
2. Confirmed diagnosis of MM per IMWG criteria
3. Measurable disease as defined by one or more of the following:

- Serum M-protein ≥ 0.5 g/dL
- Urine M-protein ≥ 200 mg/24 hours
- Serum Free Light Chain (FLC) assay: involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal
- In cases where SPEP is unreliable, serum quantitative immunoglobulin (qIgA) ≥ 750 mg/dL (0.75 g/dL) is acceptable

4. Relapsed or refractory (Rajkumar et al. 2011) to 3 or more different prior lines of therapy for MM, including immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), chemotherapies, or monoclonal antibodies, and not a candidate for, or intolerant to established therapy known to provide clinical benefit
    - Relapse defined as progression of disease after an initial response (minimal response [MR] or better) to previous treatment, more than 60 days after cessation of treatment
    - Refractory disease defined as < 25% reduction in M-protein or progression of disease during treatment or within 60 days after cessation of treatment
5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 – 1

Key Exclusion Criteria

Individuals who meet any of the following key exclusion criteria (and/or other protocol-specified exclusion criteria) will not be eligible to participate in the study:

1. Monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, Waldenstrom's macroglobulinemia, or IgM myeloma
2. Active plasma cell leukemia (> 2.0×10^9/L circulating plasma cells by standard differential)
3. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
4. Prior treatment directed to B-cell Activating Factor (BAFF; BLyS), B-cell Maturation Antigen (BCMA;TNFSF17) or Transmembrane Activator and CAML interactor (TACI; TNFSF13B), including antibodies or BCMA- or TACI-directed Chimeric Antigen Receptor (CAR)-T cell therapy

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

BION-1301 is supplied as a solution intended for intravenous (IV) administration. BION-1301 will be diluted and administered at the assigned dose level by IV infusion over approximately 2 hours for the initial dose (3 hours for doses ≥2000 mg), and may be reduced to 1 hour for subsequent doses (2 hours for doses ≥2000 mg) following SRT review of infusion-related tolerability data.

Dexamethasone is supplied as tablets intended for oral (PO) administration; a dose of 40 mg will be taken PO by the subject QW, in the morning and prior to BION-1301 administration (as applicable).

STATISTICAL ANALYSES:

The procedures for handling missing, unused, or spurious data, along with the detailed method for analysis of each variable, transformations, and exploratory analyses will be presented in the Statistical Analysis Plan.

Efficacy Analyses

Clinical response will be based on Investigator assessment and interpretation, and used for analysis of efficacy. During the course of the study, the Sponsor may conduct central review of assessments for secondary supportive analyses. All efficacy variables will be defined and analyzed according to IMWG criteria (Rajkumar et al. 2011), unless otherwise indicated.

Safety Analyses

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and assessed for severity using the NCI-CTCAE v. 4.03. Shifts from baseline in ECOG and changes in vital signs, physical examination findings, electrocardiogram parameters, and hematology, serum chemistry, and urinalysis parameters from baseline to the end of treatment will be examined.

Pharmacokinetic/Pharmacodynamic Analyses

PK parameters will be assessed by non-compartmental analysis. PK-PD modeling and simulation will be performed and may be used in support of dose escalation decisions and determination of the RP2D and dosing schedule.

SAMPLE SIZE DETERMINATION:

Phase 1

During Phase 1, dose escalation will be based on 3+3 guidelines to determine the RP2D and evaluate safety data (including DLTs and TEAEs) and PK-PD of each dose level/schedule. The sample size in Phase 1 is predicated on the number of dosing cohorts examined and the number of observed DLTs.

Phase 2

For the BION-1301 monotherapy arm, a sample size of 29 evaluable subjects achieves 80% power to detect a difference of 9% in ORR using a one-sided exact test with a target significance level of 0.05. The actual significance level achieved by this test is 0.034. The calculation assumes that the population ORR under the null hypothesis is 1% and under the alternative hypothesis is 10%. The sample size includes subjects treated at the corresponding RP2D/schedule during Phase 1 (Dose Escalation). If more than one dose/schedule is studied in Phase 2, this design will be applied to each RP2D independently.

For the BION-1301+DEX arm, a sample size of 14 evaluable subjects achieves 80% power to detect a difference of 19% in ORR using a one-sided exact test with a target significance level of 0.05. The actual significance level achieved by this test is 0.008. The calculation assumes that the population ORR under the null hypothesis is 1% and under the alternative hypothesis is 20%.

Table 2-1. Schedule of Events

Study Visit	**Screen**	**Cycle 1[1]**						**Cycle 2**					**Cycle 3 and Beyond**		**EOT [3]**	**Follow-up (call) [4]**
Cycle Day	**-28 to 0**	**1**	**2**	**3[2]**	**8**	**15**	**22[20]**	**1**	**2**	**8**	**15**	**22[20]**	**1**	**15**	**28 d post last dose**	**Q12W**
Visit Window (days)	**-**	**-**	**-**	-	±1	±3	±3	±3	-	±1	±3	±3	±3	±3	+7	±7
Informed Consent	X															
Inclusion/Exclusion Criteria	X	X														
Medical History, Height [5]	X															
Skeletal Survey (X-ray) [6]	X							Additional imaging as needed per Investigator's discretion								
Safety and Efficacy Evaluations																
SPEP/UPEP (serum, 24-hr urine)[7]	X	X[7]						X					X		X	
ECOG Performance Status	X	X						X					X		X	
Vital status/current cancer therapy																X
Vital Signs [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination, Weight [9]	X	X[9]				X[9]		X[9]			X[9]		X[9]	X[9]	X	
Electrocardiogram [10]	X	X						X							X	
Adverse Events	X[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Specimens (obtain prior to dosing, unless otherwise specified)																
Virology Screen, β-2M, CRP [12]	X															
Hematology, Chemistry [12]	X	X[12]	X		X	X	X	X	X	X	X	X	X	X	X	
Coagulation [12]		X[12]				X										
Urinalysis [12]	X	X[12]						X					X		X	
Pregnancy Test (WOCBP) [12]	X	X						X					X		X	
Immunogenicity (serum) [13, 14]		X				X		X			X		X [14]		X	
BION-1301 PK (serum) [13,15, 16]		X[15]	X	X	X	X[15]	X[15]	X[15]		X	X[15]	**X[15]**	X[16]		X	
PD Biomarkers (blood,serum)[13,15,16]	X [13]	X[15]	X	X	X	X[15]	X [15]	X[15]		X	X[15]	**X[15]**	X [16]		X	
Bone Marrow Sample [13, 17]	X										X		As indicated [17]		X	
PBMC (select sites) [18]	X	X												Odd-cycles[18]	X	
Study Drug Administration (assigned; see Table 2-2)																
BION-1301 Q2W Schedule [19]		X				X		X			X		X	X		
BION-1301 QW Schedule [20]		QW doses as assigned (Table 2-2) Q2W thereafter [20]											X	X		
Dexamethasone (Phase 2 only) [21]		Self-administered in morning on Days 1, 8, 15, 22 of each cycle (prior to BION-1301 dose)														

FOOTNOTES FOR Table 2-1 (See Section 7.5 for additional information)

[1] Cycle length is 28 days.

[2] Cycle 1 Day 3 Visit: Subjects will complete Day 3 visit during Cycle 1; based on available PK-PD data, visit may be moved out to Day 5 if needed for complete assessment of PK-PD profile. Sponsor will notify sites of any change in visit schedule.

[3] EOT Visit occurs within 28 days (+7 days) after the last dose of study drug or prior to commencing new therapy. If EOT occurs earlier, schedule a telephone contact at least 28 days post-last dose of study drug to satisfy reporting requirements for AEs. If an AE requires monitoring beyond the EOT Visit, follow until resolution or confirmed stability of the event.

[4] Follow-up: Subjects may be contacted via phone for survival and any subsequent cancer-related therapies. A telephone contact should also be scheduled for 90 days post-last dose of study drug to satisfy reporting requirements for SAEs.

[5] Medical History, Height: includes demographic data (date of birth, age, gender, ethnicity, and race). Medical history includes all active conditions and any condition considered to be clinically significant by the Investigator. Record details of MM date of diagnosis, primary tumor histology, prior surgery(ies), radiation therapy, chemo- and biological therapies, and stage of cancer. Obtain standing height.

[6] Skeletal Survey: Radiographic imaging (includes standard radiography of cervical, thoracic and lumbar spine, skull, chest, pelvis, humeri and femora) conducted within 30 days prior to Screening may be used, otherwise collect prior to Cycle 1 Day 1; perform Screening MRI as follow-up only if X-ray survey appears normal in the setting of bone pain or neurologic deficits, or if the subject has a history of plasmacytoma of the bone. Additional imaging during the study may be performed at the Investigator's discretion, e.g. in case of bone pain.

[7] SPEP/UPEP/IFE/FLC: Serum and urine monoclonal protein profiles including total protein and immunoglobulin (IgA, IgG and IgM) levels. Fasting is preferred for blood samples, but not required. Obtain 24-hour urine and blood samples on the same day if feasible, but not more than 7 days apart; 24-hour urine collection must be completed prior to dosing. Not required on Cycle 1 Day 1 if Screening assessment completed within 72 hours of dose administration. UPEP (24-hour urine sample): urine protein IFE and total protein measured at screening and Cycle 1 Day 1 (all subjects) and Day 1 of every Cycle thereafter only if Cycle 1 Day 1 UPEP $\geq$200 mg/24 hours; UPEP will also be collected (all subjects) to confirm a response or progression. Analysis of urine and serum samples will be performed at the institution's local laboratory; additional serum samples will be collected and stored to be evaluated at a central laboratory at a later date.

[8] Vital Signs: Blood pressure, pulse, respiratory rate, and temperature. On dosing days, collect prior to dosing (-5 min) and at least every 30 minutes (± 5 min) during and after the infusion through the observation period until subject is considered clinically stable; perform additional monitoring as clinically indicated.

[9] Physical Examination: Complete physical examinations at Screening and EOT; all other indicated visits are symptom-directed physical examinations. Not required at Cycle 1 Day 1 if Screening exam completed within 72 hours prior to Cycle 1 Day 1 visit. Weight at each indicated visit. Assessment may be done up to 3 days prior to visit.

[10] Electrocardiogram: Perform routine 12-lead ECGs in triplicate with subject in recumbent or semi-recumbent position after 5 minutes rest at Screening, then pre-dose on Day 1 of Cycles 1 and 2, and EOT. On dosing days, perform ECG after all pre-medications are administered and prior to BION-1301 dosing. Frequency may be increased if clinically indicated.

[11] Adverse events: Collect from the time of informed consent according to safety-reporting periods specified in Table 7-4 and reporting procedures in Section 8.

[12] Virology, Hematology, Chemistry, Coagulation, Urinalysis, Pregnancy Tests (WOCBP only): See Sections 7.5.4.1 and 7.5.4.2 for specific analytes; testing performed at local laboratory unless otherwise indicated. Samples indicated on dosing days must be pre-dose and may be obtained up to 5 days before Day 1 of each dosing cycle. Cycle 1 Day 1 hematology, chemistry, coagulation, or urinalysis assessments are not required if the corresponding Screening assessment was performed within 24 hours prior to dosing.

[13] Immunogenicity, PK, PD, PGx Samples: Collect samples as outlined in the Laboratory Manual; process and ship to central laboratory(ies) for analysis. At Screening, collect one whole blood sample for PGx analysis. Additional immunogenicity, PK-PD samples may be collected as clinically indicated (e.g. in cases of infusion-related or other immune-mediated reaction).

[14] Immunogenicity: blood for ADA, specificity and neutralizing antibodies (as applicable) will be collected pre-dose. For Cycle 3 and beyond, sampling will be collected on Day 1 of Cycle 4 and Cycle 7 only.

[15] BION-1301 PK and PD Samples: For planned time points up to 48 hours post infusion, blood samples for PK and PD assessment must be taken from a peripheral vein contralateral to the arm/location into which BION-1301 is administered. Record start time of infusion, completion time, and sample collection time.

[16] BION-1301 PK and PD Time points: Collect blood samples as specified in Table 7-5; requirements vary based on dosing schedule and study phase.

[17] Bone Marrow Samples: Baseline samples should be collected near the end of screening assessments to avoid unnecessary procedures to individuals who may not meet eligibility. Samples will be used for cytogenetic analysis. Obtain prior to administration of study drug on indicated days. If M-protein levels indicate CR, a bone marrow aspirate or biopsy should be taken for confirmation. Additional bone marrow samples may be taken to investigate new symptoms or at the Investigator's discretion during the course of study; a sample should be retained if possible for Sponsor research evaluation. Bone marrow samples may also be used for biomarker analysis to monitor immune cell populations, MM cells, and/or soluble biomarkers. Bone marrow samples collected at required time points will be analyzed locally; a second research sample will be sent to the central laboratory for Sponsor research evaluation. Detailed instructions for bone marrow collection, processing, and shipment are provided in the Laboratory Manual.

[18] PBMC (collected at select sites only): Baseline samples should be collected near the end of screening assessments to avoid unnecessary procedures on individuals who may not meet eligibility Cycle 1 Day 1 sample may be obtained up to 7 days prior to dosing; required on Day 15 of every odd-numbered cycle prior to dosing beginning with Cycle 3.

[19] BION-1301: Administer premedication as indicated. Administer BION-1301 by IV infusion over approximately 2 hours for the initial dose (3 hours if BION-1301 dose ≥2000 mg), reduce to 1 hour (2 hours if BION-1301 dose ≥2000 mg) for subsequent doses following SRT review of infusion-related tolerability data. Observe for at least 4 hours after the first infusion (or following any infusion where there is a dose modification from the previous infusion) and release once considered clinically stable. For subsequent dosing, monitor at least 1 hour after infusion and release only when considered clinically stable.

[20] QW Dosing: Follow assigned dosing schedule in Table 2-2; Day 22 visit ONLY required if QW BION-1301 dosing indicated. No fewer than 5 days and no greater than 8 days may elapse between QW BION-1301 doses.

[21] Dexamethasone (if assigned to BION-1301+DEX in Phase 2): Instruct the subject to take 40 mg PO QW at home in the morning on Days 1, 8, 15, and 22 of each cycle.

ABBREVIATIONS FOR Table 2-1

ADA = antidrug antibodies; AE = adverse event; β2M = beta 2 microglobulin; CRP = C-reactive protein; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; IFE = immunofixation electrophoresis; MM = multiple myeloma; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamic(s); PGx = pharmacogenetics; PK = pharmacokinetic(s); Q12W = once every 12 weeks; FLC = serum free light chain; SPEP = serum protein electrophoresis, UPEP = urine protein electrophoresis; WOCBP = woman of childbearing potential.

Table 2-2. BION-1301 Potential Dosing Schedule Options [1]

Dosing Cycle	Cycle 1				Cycle 2				Cycle 3 and Beyond	
Cycle Day	**1**	**8**	**15**	**22[2]**	**1**	**8**	**15**	**22[2]**	**1**	**15**
BION-1301 Q2W	X		X		X		X		X	X
BION-1301 QW × 2 → Q2W	X	X	X		X		X		X	X
BION-1301 QW × 4 → Q2W	X	X	X	X	X		X		X	X
BION-1301 QW × 6 → Q2W	X	X	X	X	X	X	X		X	X
BION-1301 QW × 8 → Q2W	X	X	X	X	X	X	X	X	X	X

[1] BION-1301 dose and schedule options summarized in table are intended as a guide; not all dosing schedules listed above may be explored during the study (Section 5.2.5). BION-1301 dose and schedule will be assigned during subject enrollment. Administer BION-1301 at assigned dose level, which may differ between QW and Q2W (i.e. QW schedule may utilize a higher dose, which is reduced for Q2W dosing). No fewer than 5 days and no greater than 8 days may elapse between QW BION-1301 doses. Doses given on Q2W dosing schedule are always on Days 1 and 15 of each cycle; and begin one week following the last QW dose.

[2] Cycle 1 Day 22 visit required ONLY if assigned to QW × 4, QW × 6, or QW × 8 dosing schedule. Cycle 2 Day 22 visit required ONLY if assigned to QW × 8 dosing schedule. All Day 22 visits are intended for BION-1301 dosing only and are NEVER REQUIRED for subjects assigned to QW × 2 or Q2W dosing schedules.

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3.2 LIST OF FIGURES

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APRIL	A proliferation-inducing ligand (TNFSF13)
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BAFF	B-cell Activating Factor (BLyS)
BCMA	B cell maturation antigen (TNFRSF17)
BION-1301	humanized IgG4 anti-APRIL monoclonal antibody
C_{max}	maximum concentration observed
CAR	chimeric antigen receptor
CFR	Code of Federal Regulations
CR	complete response
CRA	clinical research associate
CT	computed tomography
CTCAE	Common Terminology Criteria For Adverse Events
DCR	disease control rate
DEX	Dexamethasone
DLT	dose-limiting toxicity
DOR	duration of response
EBMT	European Group for Blood and Marrow Transplantation
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	End of Treatment
FDA	United States Food and Drug Administration
FISH	fluorescence in situ hybridization
FLC	free light chain
GCP	Good Clinical Practice
HIV	human immunodeficiency virus

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IFE	immunofixation electrophoresis
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IV	Intravenous
MABEL	minimum anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
nAb	neutralizing antibody
NCI	National Cancer Institute
NOAEL	no-observed adverse effect level
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PD-L1	programmed cell death ligand-1
PFS	progression-free survival
PGx	Pharmacogenetic
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PO	orally, by mouth (*per os*)
PR	partial response
qIg	quantitative immunoglobulin
QW	once per week
Q*x*W	once every *x* weeks
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SMPP	serum monoclonal protein profile
SPEP	serum protein electrophoresis
SRT	Safety Review Team
$t_{1/2}$	terminal half-life
TACI	transmembrane activator and CAML interactor (TNFSF13B)

TE	target engagement
TEAE	treatment-emergent adverse event
TGF-β	transforming growth factor beta
TNFSF	tumor necrosis family superfamily
ULN	upper limit of normal
UPEP	urine protein electrophoresis
VEGF	vascular endothelial growth factor
VGPR	very good partial response
WOCBP	woman of child bearing potential

The terms “investigational product” and “study drug” refer to BION-1301 in this study and may be used interchangeably.

5 INTRODUCTION

Treatment of active (symptomatic) multiple myeloma (MM) generally consists of anti-myeloma therapy with supportive care to alleviate symptoms of the disease and side effects of treatment (About Multiple Myeloma 2016). In addition to autologous stem cell transplant (ASCT), six drug classes are used in treatment: immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), chemotherapy, histone deacetylase inhibitors, steroids, and most recently, monoclonal antibodies. Recent treatment advances for the treatment of patients with relapsed or refractory MM have demonstrated significant improvements in response rates, duration of response, and long-term survival compared to traditional chemotherapy or other standards of care.

Despite these advances, MM remains incurable; more than 90% of patients relapse after treatment and succumb to the disease (Hoyos and Borrello 2016). This highlights the need for new, additional therapies or combinations with novel mechanisms to fill these treatment gaps.

BION-1301 is a first-in-class humanized monoclonal antibody directed against a proliferation-inducing ligand (APRIL) currently in development for the treatment of relapsed or refractory MM. This clinical study is a first-in-human dose-finding study to evaluate the safety, tolerability, and initial clinical activity of BION-1301 administered as a single agent or with low-dose dexamethasone. The incidence of dose-limiting toxicities (DLTs), pharmacokinetic/pharmacodynamic (PK-PD) profile, and observed clinical activity will guide dose selection and further elucidate the mechanism of action of BION-1301.

5.1 Rationale for Targeting APRIL in Multiple Myeloma

The rationale to target APRIL in the treatment of advanced MM is supported by the following:

- APRIL is produced by cells in the bone marrow niche and triggers BCMA to drive proliferation and survival of human MM cells (Tai et al. 2016).
- APRIL has been shown to drive expression of the immune checkpoint inhibitor programmed cell death ligand-1 (PD-L1), interleukin-10 (IL-10), vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-β), forcing an immunosuppressive phenotype on BCMA positive cells (Tai et al. 2016).
- APRIL induces resistance to lenalidomide, bortezomib, and other standard-of-care drugs (Tai et al. 2016).
- Patients with MM have elevated APRIL serum levels which have been correlated with poor prognosis (Lascano et al. 2015).
- BION-1301 has been shown to target MM cells in a tumor-protective bone marrow microenvironment providing preclinical proof of concept (Tai et al. 2016).

Therefore, the mechanism-of-action and evidence of *in vitro* and *in vivo* antitumor activity strongly support APRIL as a rational target for the treatment of relapsed or refractory MM.

5.2 BION-1301

BION-1301 is a humanized IgG4 monoclonal antibody directed against APRIL in development for the treatment of relapsed or refractory MM.

Proof-of-concept studies in murine models supported by *in vitro* and *ex vivo* data suggest BION-1301 initiates a productive antitumor response with no/ limited toxicity observed in non-human primate studies.

5.2.1 Summary of Nonclinical Studies

BION-1301 does not bind to mouse APRIL; as such the murine parental antibody, hAPRIL.01A, served as the surrogate for murine models. hAPRIL.01A was characterized *in vitro* and *in vivo* and shown to bind to APRIL, fully block APRIL binding to BCMA and TACI, and block tumor development in a multiple myeloma humanized severe combined immunodeficiency (SCID) mouse model.

BION-1301, derived from hAPRIL.01A by CDR-grafting, exhibited similar binding and blocking characteristics in biochemical assays and cellular assays. To further establish PD activity, BION-1301 was shown to suppress T cell-independent (TI) B cell responses in mice and cynomolgus monkeys.

A series of nonclinical studies in nonhuman primates evaluated the pharmacology, PK, and toxicology of BION-1301. The cynomolgus monkey was selected as the relevant toxicity species for the GLP safety evaluation of BION-1301 based on sequence homology between cynomolgus APRIL and human APRIL. No toxicity was observed in the toxicology studies. A drop in production of immunoglobulins (IgA, IgG and IgM) was observed following dosing with BION-1301 to cynomolgus monkeys; this was not considered an adverse effect and confirmed APRIL blockade is relevant for plasma cells.

Safety pharmacology studies indicated no effects on the cardiovascular or central nervous systems; there were no effects on vital organs noted with BION-1301. Human and cynomolgus monkey tissue cross-reactivity showed no staining with BION-1301 in any tissue panel examined.

The anticipated PK of BION-1301 in humans has been predicted by modeling of the available nonclinical data. The predicted human systemic plasma C_{max} and AUC_t for an intravenous (IV) dose of 50 mg are [redacted], respectively.

[redacted] Overall, nonclinical studies support use of BION-1301 in humans at the proposed dose levels. A complete summary of nonclinical information on BION-1301 is provided in the Investigator's Brochure (IB).

5.2.2 Summary of Clinical Studies

ADU-CL-16 is the first study to investigate the safety and tolerability of BION-1301 in humans. Preliminary safety data (as of 15AUG2018) are available for 11 subjects administered BION-1301 at dose levels between 50 and 450 mg. Treatment-related treatment-emergent adverse events (TEAEs) were reported for 3 of the 11 subjects, which included arthralgia (reported for 2 subjects) and wheezing. The treatment-related TEAE of wheezing was assessed as Grade 3 in severity and was considered the principal symptom of a possible infusion-related reaction; the subject was discontinued from study drug.

The most current information related to anticipated safety risks based on nonclinical information and/or predicted by mechanism of action is provided in the IB.

5.2.3 Risk-benefit Assessment

Since essentially all patients with MM eventually relapse, there is an unmet medical need to provide new therapies with novel mechanisms of action, such as BION-1301. Blocking APRIL provides a novel approach to inhibit MM cell proliferation and survival, overcome drug resistance, and prevent immune suppression. BION-1301 induces antitumor activity *in vitro* and *in vivo*, and may confer therapeutic benefit in the treatment of MM.

Nonclinical toxicology studies with BION-1301 showed no signs of toxicity after single or repeat dosing of BION-1301 in cynomolgus monkeys. Decreases in IgA, IgM and IgG were observed following BION-1301 administration; however no adverse effects were associated with the pharmacologic activity of BION-1301. However, as observed with other treatments for MM, it is not known whether BION-1301 could further compromise the immune system, thereby leading to an increased risk of infection. Based on evidence from nonclinical studies, the risk/benefit assessment of BION-1301 is expected to be favorable in adults with relapsed or refractory MM.

Since this is the first study to investigate administration of BION-1301, there may be unexpected toxicities. The risk to subjects in this trial may be mitigated by compliance with the eligibility criteria and study procedures, close clinical monitoring, and applying dose modification/dose delay criteria. To mitigate tolerability issues and the potential for infusion-related reactions, the use of supportive care by Investigators should be used as needed.

Available data indicate BION-1301 has the potential to exhibit clinical activity in the treatment of MM; nonclinical data identified no undue safety issues that would preclude use in adults with relapsed or refractory MM. To date, BION-1301 has generally been well-tolerated in the current clinical study. The hypothesized mechanism of action reinforced by nonclinical data therefore supports clinical investigation with BION-1301 in adults with relapsed or refractory MM.

5.2.4 Dose Selection Rationale

The recommended BION-1301 starting dose and dosing schedule for this first-in-human study are based on nonclinical safety, tolerability, and PK-PD data obtained from the non-GLP PK-PD

and GLP toxicology studies in cynomolgus monkeys. The dose was selected using a minimum anticipated biological effect level (MABEL) approach.

The maximum recommended starting dose takes into consideration the novel mechanism of action of BION-1301 and the study population of advanced cancer patients with relapsed/refractory MM. Since APRIL is a soluble ligand driving proliferation and survival of MM cells (Tai et al. 2016), the extent and duration of APRIL blockade by BION-1301 needed to impact MM cells in patients is not defined with the same approach utilized with therapeutic antibodies which function via direct cytotoxicity.The pharmacology of APRIL antagonism suggests that the vast majority of APRIL should be bound in order to achieve a clinical effect. The duration of Full Target Engagement (TE; reduction of free APRIL in blood, Section 7.1.1.1) at the initial dose should be long enough to provide a potential for clinical benefit but short enough to ensure subject safety. A Full TE duration of one day or less is unlikely to represent a potential clinical benefit, therefore the Full TE duration is conservatively set to be 2 days. This will allow for a potential clinical benefit without unnecessary risk. Using PK-PD modeling, a fixed dose of 50 mg is predicted to reach Full TE for approximately 48 hours. Serial serum measurements of free APRIL to determine TE are included in this study. These sampling occasions allow monitoring of maximum TE.

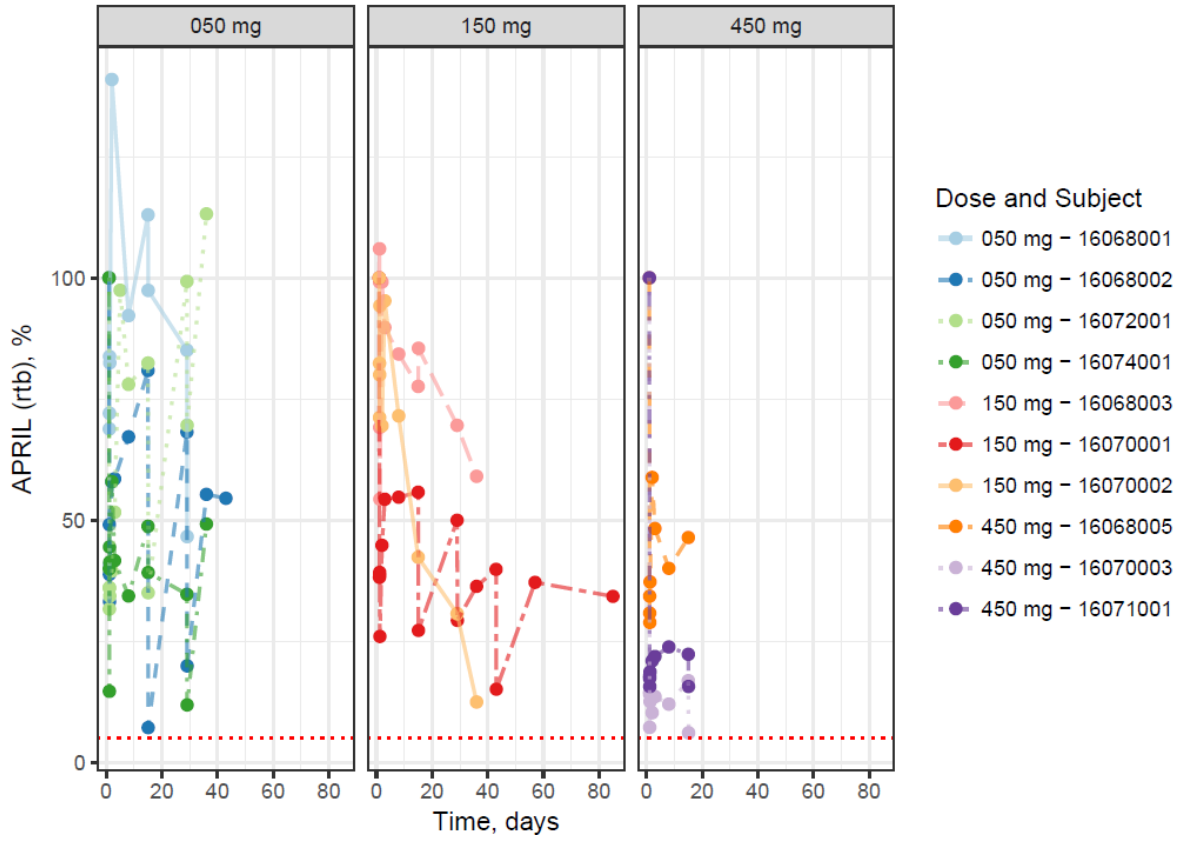
Nonclinical data indicate weekly IV administration of BION-1301 to cynomolgus monkeys was well tolerated at doses ≤ 100 mg/kg. The starting dose of 50 mg proposed for the Phase 1 clinical trial has at least [redacted] in cynomolgus monkeys. Thus, adequate safety factors exist to support the proposed human IV doses of BION-1301 to adults with relapsed or refractory MM. The maximum dose administered will not exceed 2700 mg. The maximum dose level was selected based on available tolerability and PK-PD data from the ongoing ADU-CL-16 clinical study. Predicted exposure (based on AUC and C_{max}) at the 2700 mg dose level is [redacted] to the AUC and C_{max} observed at the NOAEL in cynomolgus monkeys.

5.2.5 Dose Schedule Exploration

A preliminary PK-PD model has been built based on data available from subjects dosed at the 50 mg, 150 mg, and 450 mg dose levels. The current PK-PD model incorporates an APRIL sink, which could represent APRIL binding to targets such as TACI or BCMA. Extrapolating from this preliminary model, Full TE would be achieved after approximately 3 months at a BION-1301 dose of 1350 mg dosed once every two weeks (Q2W), or after approximately 2 months when dosed once per week (QW). Dose levels higher than 1350 mg are anticipated to achieve Full TE earlier. Since longer-term QW dosing may pose a burden on patients, an extrapolation of the initial regime was performed. Results suggest that 3 to 8 weeks of QW dosing at 2700 mg followed by Q2W dosing at 1350 mg might achieve Full TE more quickly and maintain it over prolonged periods of time.

While data are not mature and modeling is still at an early stage, the overall trend of increasing target engagement with increasing dose and over time is confirmed in individual data plots (Figure 5-1), and is consistent with the conclusions derived from model extrapolations. Additional data will be used to further inform the PK-PD models, and will be used to support further dose escalation and schedule decisions.

Figure 5-1. Serum Free APRIL Levels Relative to Baseline over Time after BION-1301 Dosing



Source: ADU-CL-16 data (August 2018)

5.2.6 Rationale for BION-1301 + Dexamethasone in Multiple Myeloma

Dexamethasone is a synthetic glucocorticoid with anti-inflammatory, immunosuppressive, and analgesic properties. Dexamethasone is used in treatment regimens for various hematologic malignancies and as an antiemetic in conjunction with chemotherapy. Glucocorticoids used as part of combination regimens are a backbone of MM treatment in the first-line and relapsed/refractory settings (Burwick and Sharma 2018).

Monoclonal antibodies approved for the treatment of MM are often administered with dexamethasone or with dexamethasone-containing regimens. Daratumumab is approved for use in various dexamethasone-containing regimens (e.g. dexamethasone with lenalidomide, bortezomib or pomalidomide) for patients with varying degrees of previously-treated MM

(DARZALEX 2018). Elotuzumab is approved for use in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received one to three prior therapies (EMPLICITI 2017). *In vitro,* APRIL blockade sensitizes MM cell lines to dexamethasone-induced apoptosis (Tai et al. 2016). Dexamethasone is thereby hypothesized to potentially add clinical benefit to BION-1301 therapy.

The low-dose dexamethasone regimen (40 mg QW) employed in Phase 2 of this study follows current management practices in MM (Rajkumar and Kumar 2016). The regimen is recommended based on results of a randomized trial where low-dose dexamethasone was associated with superior overall survival (OS) and significantly lower toxicity than a high-dose regimen (Rajkumar et al. 2010).

6 STUDY OBJECTIVES AND ENDPOINTS

The objectives of the study are to:

- Evaluate safety and tolerability of BION-1301 when administered as a single-agent or with low-dose dexamethasone (BION-1301+DEX)
- Identify the recommended Phase 2 dose (RP2D) and schedule of BION-1301 when administered as a single-agent
- Characterize the PK and PD profile of BION-1301
- Evaluate clinical activity of BION-1301 and BION-1301+DEX

The study has been designed with an appropriate study population, sufficient size, and duration to enable a preliminary assessment of safety and efficacy as related to the following specific endpoints:

ENDPOINTS:

Phase 1

- Incidence of DLTs, TEAEs, and changes in safety parameters
- PK parameters based on BION-1301 serum levels following a single dose and after repeated dosing
- Changes from baseline in soluble APRIL
- Relative reduction in serum and urine M-protein levels defined as the maximum percent reduction from baseline

Phase 2

- Objective response rate (ORR) based on International Myeloma Working Group (IMWG) uniform response criteria of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR)
- Relative reduction in serum and urine M-protein levels defined as the maximum percent reduction from baseline
- PFS defined as time from first dose of study drug to date of first tumor progression or death due to any cause
- OS defined as the time from first dose of study drug to date of death due to any cause
- Incidence of TEAEs, changes in safety parameters, and unacceptable toxicities
- PK parameters based on BION-1301 serum levels following a single dose and after repeated dosing

Exploratory Endpoints evaluated throughout the study as appropriate include:

- Duration of response (DOR) defined as the time from the first tumor assessment that supports the subject's ORR to the time of disease progression or death due to any cause
- Disease control rate (DCR) defined as the percentage of subjects with sCR, CR, VGPR, PR, or stable disease (SD) per IMWG criteria; or minimal response (MR) per European Group for Blood and Marrow Transplantation (EBMT) criteria.
- Change from baseline in soluble B cell maturation antigen (sBCMA; TNFRSF17) levels
- Changes in additional biomarkers and immune monitoring

7 INVESTIGATIONAL PLAN

7.1 Study Design

ADU-CL-16 is an open-label, multicenter, first in human, dose escalation study to evaluate the safety, tolerability, and PK-PD of BION-1301, a first-in-class monoclonal antibody targeting APRIL. The population for this study will consist of adults with relapsed or refractory MM whose disease has progressed after at least 3 prior systemic therapies. BION-1301 will be administered in 28-day cycles.

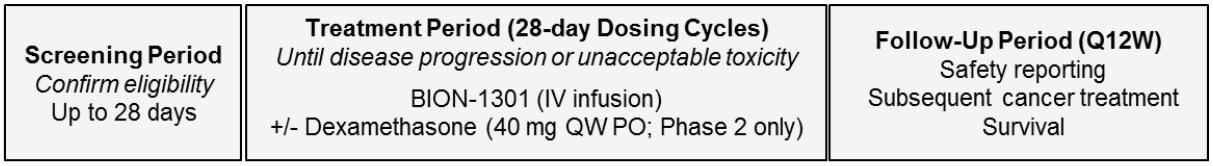
The study will be conducted in 2 parts as depicted in Figure 7-1. Phase 1 will be conducted using a 3+3 dose escalation design and seeks to determine the RP2D by evaluating safety and tolerability and characterizing the PK-PD of BION-1301. Dose escalation decisions will be based on available safety, PK-PD, and efficacy data from all evaluable subjects in each cohort.

The dosing interval will be Q2W during initial dose escalation. Additional cohorts will be enrolled to evaluate QW dosing for up to 8 weeks, followed by Q2W dosing with the same or a lower dose. PK-PD data will be evaluated for each cohort to inform the dosing schedule to be evaluated in subsequent cohorts.

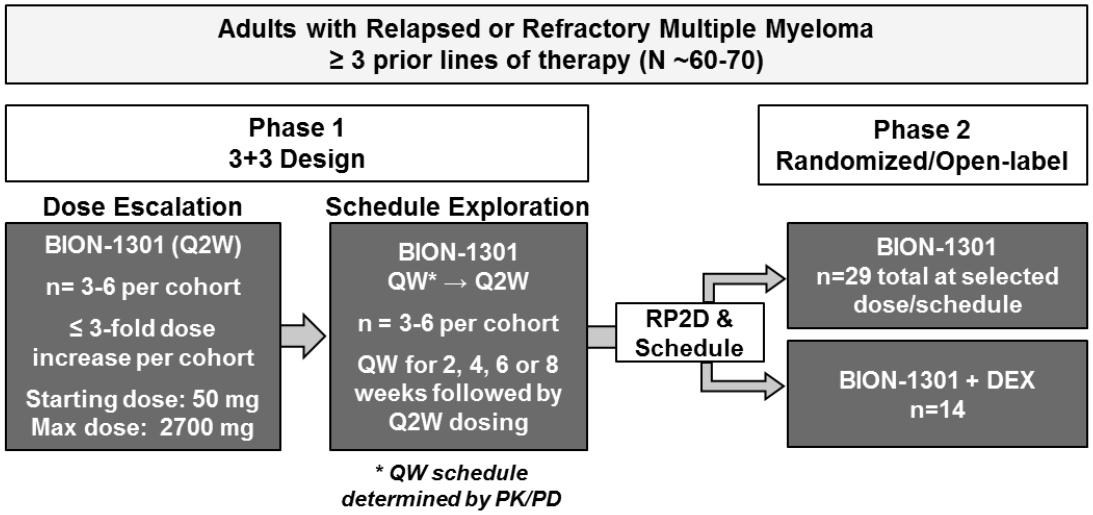
Once an RP2D and dosing schedule are identified, Phase 2 of the study will open and continue to evaluate the safety and preliminary efficacy of BION-1301 administered as a single agent or with low-dose dexamethasone.

Additional guidelines specific to Phases 1 and 2 of the study are provided in Sections 7.1.1 and 7.1.2, respectively. A schedule of visits and procedures is provided in Table 2-1.

Figure 7-1. ADU-CL-16 Study Schema



Study Population & Enrollment Plan:



7.1.1 Phase 1: Dose Escalation

Phase 1 of the study seeks to evaluate the safety and tolerability of BION-1301 when administered as a single agent. Initially, BION-1301 will be administered at the 50 mg dose level; subsequent dose escalations will follow both safety and pre-specified dose escalation rules (Section 7.1.1.1).

Subjects within a dose cohort will be evaluated through Cycle 1 for DLTs (28-day evaluation period) and PK-PD parameters (14-day evaluation period). Dose escalation decisions will be based on available safety, PK-PD, and efficacy data from all evaluable subjects in each cohort.

The Safety Review Team (SRT) convened for the study, will consist of the Investigators who enrolled subjects in the study, Medical Monitor, and Sponsor representatives. Dose escalation and reduction decisions, additional enrollment specifications, and recommendation of the RP2D(s) and dosing schedule for expansion will be made by the SRT. TEAEs, DLTs and safety data will continue to be reviewed by the SRT throughout the study.

7.1.1.1 Enrollment Plan and Dose Escalation Rules

During the dose escalation part of the study, cohorts will be enrolled and treated with BION-1301 following a 3+3 dose escalation plan (Table 7-1) until the RP2D (or MTD) is achieved. The Cycle 1 Day 1 dose must be staggered by at least 24 hours for the first 2 subjects dosed in each cohort.

Subjects will be considered evaluable for dose-escalation assessment if all scheduled doses were administered during Cycle 1, adequate PK-PD samples were collected at Cycle 1 Day 1 through Cycle 1 Day 15, and the DLT evaluation period (Cycle 1 Days 1-28) was completed; or the subject experienced a DLT-defining event. Evaluation of a cohort of at least 3 evaluable subjects is required prior to determining the dose for the next cohort. To proactively ensure at least 3 subjects are considered evaluable, a 4th subject may be enrolled and treated. No dose escalation decisions will be made until all subjects enrolled at a given dose level have completed the DLT evaluation period. If one subject experiences a DLT, the cohort will expand to 6 evaluable subjects.

Table 7-1. Phase 1: BION-1301 Enrollment and Dose Escalation Plan

BION-1301 Dose Cohort (proposed dose [1])	**0/3 subjects have DLT[2, 3]**	**1/3 subjects have DLT[2, 3]**	**≤1/6 subjects have DLT[2]**	**≥2 in a cohort have DLT[2]**
1 (50 mg)	Escalate to Dose Cohort 2 per Dose Escalation rules	Expand to 6 evaluable subjects	Escalate to Dose Cohort 2 per Dose Escalation rules	MTD exceeded; de-escalate to Dose Cohort -1[4]
2 (150 mg)	Escalate to Dose Cohort 3 per Dose Escalation rules	Expand to 6 evaluable subjects	Escalate to Dose Cohort 3 per Dose Escalation rules	MTD exceeded; no further enrollment at dose level
3 (450 mg)	Escalate to Dose Cohort 4 per Dose Escalation rules	Expand to 6 evaluable subjects	Escalate to Dose Cohort 4 per Dose Escalation rules	MTD exceeded; no further enrollment at dose level
4 (1350 mg)	Escalate to Dose Cohort 5 per Dose Escalation rules	Expand to 6 evaluable subjects	Escalate to Dose Cohort 5 per Dose Escalation rules	MTD exceeded; no further enrollment at dose level
5 (2700 mg) [5]	Expand to 6 evaluable subjects	Expand to 6 evaluable subjects	Maximum dose reached	MTD exceeded; no further enrollment at dose level

1. Dose levels may be escalated up to maximum 3-fold increases; actual dose determined empirically by SRT based on available safety, PK-PD, and efficacy data. Additional incremental dose levels (either increased or decreased) may be investigated.
2. DLT evaluation period is 28 days after first dose of BION-1301 (Cycle 1).
3. If a 4th subject is enrolled, all 4 subjects must complete DLT evaluation period. If 1/4 subjects has DLT, expand to 6 evaluable subjects.
4. SRT will evaluate all available data and decide whether to initiate Dose Cohort -1 at a dose of 5 mg.
5. Evaluation of additional intermediate dose cohorts will follow the same 3+3 rules for dose cohort expansion. Dose level will not exceed 2700 mg.

DLT = dose-limiting toxicity; MTD = maximum tolerated dose; SRT = safety review team

To better understand the safety, tolerability, PK, and PD of BION-1301 administered as a single agent, additional subjects may be enrolled in previously cleared cohorts (for up to a total of 6 subjects per cohort), or additional cohorts of up to 6 subjects may be enrolled at intermediate dose levels before or while proceeding with further dose escalation, or to confirm the RP2D before proceeding to Phase 2.

7.1.1.1.1 Dose-limiting Toxicity Criteria

During Phase 1, the DLT evaluation period is defined as the first 28 days of treatment (Cycle 1). The occurrence of any of the toxicities presented in Table 7-2 will be considered a DLT unless clearly and incontrovertibly due to disease progression or extraneous causes. DLTs should be assessed and reported as directed in Section 8.

Table 7-2. Criteria for Defining Dose-limiting Toxicities

Grade 5 event not clearly due to disease progression or extraneous causes
Hematologic toxicity defined as: • Febrile neutropenia of any duration • Grade 4 neutropenia or thrombocytopenia that persists for >7 days, or Grade 3 thrombocytopenia associated with bleeding
Serum chemistry values consistent with Hy's Law criteria (all 3 of the following must co-exist): • Alanine aminotransferase or aspartate aminotransferase ≥3× institutional upper limit of normal (ULN) • Total bilirubin ≥2× ULN • Alkaline phosphatase <2× ULN
Grade 3 or higher infusion-related reaction per NCI CTCAE v 4.03
Any other Grade 3 or higher non-hematologic toxicity except: • Grade 3 nausea, vomiting, or diarrhea that persists <72 hours with adequate antiemetic and other supportive care • Grade 3 fatigue <7 days

Emergent safety data will continue to be evaluated on an ongoing basis by the SRT.

7.1.1.1.2 Definitions for Dose Escalation and Identification of Recommended Phase 2 Dose

Target Engagement (TE) is defined as the reduction of free APRIL in blood relative to baseline. In this study, TE will be measured by the levels of free APRIL in the serum at trough, relative to study baseline. TE will be typically quantified on the basis of PK-PD modeling and simulation.

Full TE is defined as complete APRIL antagonism (i.e. >95%) in the blood at trough, as measured by the level of remaining free APRIL in serum. Full TE corresponds to levels of free APRIL of ≤5% relative to baseline for the duration of the dosing cycle at steady state.

Mark TE is defined as complete APRIL antagonism (i.e. >95%) in bone marrow, as measured by the level of remaining free APRIL in bone marrow. Mark TE corresponds to levels of free APRIL of ≤5%. TE in bone marrow will be calculated using PK-PD modeling of available clinical data.

Maximum-tolerated Dose (MTD) is defined as the maximum dose at which an acceptable level of toxicity is observed, as evidenced by a DLT rate of < 33% (i.e. 0 DLT in 3 evaluable subjects or ≤ 1 DLT in 6 evaluable subjects). The MTD is one dose level lower than a dose level where a DLT rate ≥33% was observed.

Recommended Phase 2 Dose is defined as the dose level at or below the MTD (or up to the highest dose tested if MTD is not reached) selected on the basis of a cumulative review of safety, tolerability, and clinical activity; may include PK, PD, and other available efficacy data.

7.1.1.1.3 Dose Escalation Rules

Dose escalation decisions will be based on the totality of available safety, efficacy, PK and PD data, complemented with PK-PD modeling if data allow. Dose escalation decisions and identification of the MTD will be made by the SRT. The following dose escalation rules will be followed:

- If DLTs are observed a traditional step-up step-down ruleset (3+3) will be triggered; escalation will be stopped if the MTD has been reached. Subjects who were enrolled into the MTD Dose Cohort and are tolerating treatment may continue with dosing at that dose level.
- If two or more subjects in Dose Cohort 1 have a DLT, new subjects will be enrolled into Dose Cohort -1, at a dose of 5 mg. Subjects who were enrolled into Dose Cohort 1 and are tolerating treatment may continue with dosing at the Dose Cohort 1 dose. Following completion of Dose Cohort -1, additional cohorts may be evaluated using the 3+3 dose escalation plan as outlined above, at dose levels not to exceed 3-fold increases and below 50 mg.
- Dose escalations will be selected such that the next dose level will target an increase of full TE duration by a maximum 3-fold, which is expected to generally translate to a 3-fold increase in dose (no higher increases in dose will be used). Dose escalations will account for observed safety in the preceding cohort and will not exceed safety factors based on the NOAEL established in non-human primates, but would allow for appropriate dose escalation to potentially therapeutically effective dose levels.
- Escalation may be stopped if BION-1301 exposure or the level of TE has not increased and/or is not expected to increase to a clinically relevant extent.

7.1.1.2 Dosing Schedule Exploration

Additional cohorts may be enrolled during Dose Escalation to assess whether initial weekly administration of BION-1301 improves levels of target engagement (Section 5.2.5). One or more of the dose schedule options presented in Table 7-3 will be evaluated; no additional dosing schedules will be explored. BION-1301 may be administered QW initially for up to 8 weeks, followed by Q2W dosing maintained at the same dose level, or reduced to a lower dose level. Cohorts of 3-6 subjects will be enrolled following a similar 3+3 design (Table 7-1).

The selected QW dose and duration of QW dosing will be based on safety and on PK-PD results from previous cohorts. All dose levels explored during QW dosing will have first been cleared at

a Q2W dosing schedule during Dose Escalation; the QW dose level will not exceed 2700 mg. For example, if 2700 mg Q2W is well tolerated, such that no more than 0/3 or 1/6 subjects in the cohort experiences a DLT, then a later cohort may be enrolled to evaluate 2700 mg QW for up to 8 weeks, followed by Q2W dosing at 2700 mg or at a lower dose level.

Depending on the assigned QW dosing duration, subjects may be required to return to the clinic on Cycle 1 Day 22 and Cycle 2 Day 22 for weekly BION-1301 infusions and assessments as indicated (Table 2-2).

Table 7-3. Phase 1: BION-1301 Potential Dosing Schedule Exploration Options (21-day cycles)

BION-1301 Dose Schedule	**QW Dosing (Assigned QW dose level)[1]**	**Q2W Dosing (Assigned dose level)[1,2]**
Q2W	N/A	All Cycles: Days 1, 15
QW × 2→Q2W	Cycle 1: Days 1, 8	Cycle 1: Day 15 Cycle 2 and beyond: Days 1, 15
QW × 4→Q2W	Cycle 1: Days 1, 8, 15, 22	Cycle 2 and beyond: Days 1, 15
QW × 6→Q2W	Cycle 1: Days 1, 8, 15, 22 Cycle 2: Days 1, 8	Cycle 2: Day 15 Cycle 3 and beyond: Days 1, 15
QW × 8→Q2W	Cycle 1: Days 1, 8, 15, 22 Cycle 2: Days 1, 8, 15, 22	Cycle 3 and beyond: Days 1, 15

[1] QW and Q2W assigned dose level may vary within a given schedule; the BION-1301 dose administered during Q2W dosing may be at the same dose level used for QW dosing, or at a lower dose level.

[2] Doses given on Q2W dosing schedule are always on Days 1 and 15 of each cycle; one week following the last QW dose

7.1.1.3 Intra-subject Dose Adjustments

Once the RP2D has been selected, individual subjects enrolled in Dose Escalation may have the option to subsequently receive BION-1301 at the RP2D level following completion of at least 3 treatment cycles; provided the individual subject has not experienced unacceptable drug-related toxicity, and the Investigator deems a dose adjustment appropriate for an individual subject. All intra-subject dose adjustments must be approved by the Medical Monitor.

7.1.2 Phase 2: Dose Expansion

Phase 2 of the study seeks to further evaluate the safety and tolerability and preliminary clinical efficacy of BION-1301 when administered as a single agent or with low-dose dexamethasone. Once the RP2D and schedule of BION-1301 have been identified, Phase 2 may open for enrollment. Subjects enrolled in Phase 2 will be randomized to receive either BION-1301 or

BION-1301+DEX open-label. Additional dose expansion cohorts may be evaluated in Phase 2 based on available safety, PK-PD and efficacy data.

7.1.3 Discussion of Study Design

The study was designed as an open-label, multicenter Phase 1/2 study. The study is a first-in-human study intended to provide information regarding appropriate BION-1301 dose levels, safety and tolerability, along with indicators of clinical efficacy and OS. As such, the initial stage of the study will be dose-finding in nature using available safety and PK-PD data to drive dose escalation decisions.

BION-1301 is a first in class monoclonal antibody targeting APRIL. Given the novel mechanism of action, the study design incorporates PK-PD modeling to assess levels of TE and potentially guide selection of the RP2D. This approach is hypothesized to maximize clinical activity and minimize safety risks traditionally associated with dosing at or near the MTD. Once the RP2D and schedule have been identified, additional subjects will be enrolled to further characterize safety and to provide information on potential efficacy. In Phase 2, subjects will be randomized to provide a more robust dataset for BION-1301 dose confirmation and explore clinical activity and tolerability of BION-1301 administered with low-dose dexamethasone.

Given the life-threatening nature of the disease in this study population (i.e. patients without further established treatment options), a placebo-controlled trial is not appropriate in this setting, nor at this stage of clinical development. Since all subjects will receive the same investigational product (BION-1301) blinding is unnecessary; study drug will be provided open-label.

The study is being conducted to evaluate initial safety and efficacy signals of BION-1301 as a single-agent or with low-dose dexamethasone. This initial study will also serve to characterize the PK-PD profile of BION-1301 following a single dose and repeat dosing. The data obtained in this study will drive further clinical development decisions and provide necessary data before initiating a larger randomized trial and/or evaluating BION-1301 in one or more drug combinations.

7.2 End of Study

The end of the study is defined as the date when all subjects have completed the final protocol-specified safety assessment and/or discontinued study participation (withdrawal of consent or lost to follow-up), whichever occurs first (estimated to be approximately 18 months from the last subject commencing treatment). Following the in-clinic portion of study additional biomarker analyses may take place prior to Clinical Study Report submission. At end of the study, all remaining subjects will be offered enrollment in a long-term follow-up study for survival.

The Sponsor may terminate the study at any time for any reason. Should the study be terminated, subjects will be contacted to complete the End of Treatment (EOT) visit and protocol-defined safety follow-up procedures.

7.2.1 Study Stopping Rules

Subjects will be monitored throughout the study for DLTs and unacceptable toxicities (Table 7-2); provisions are in place for dose escalation, dose modification, and oversight by the SRT. The following additional safety rules will apply outside the 28-day DLT monitoring period to further mitigate potential risk to subjects:

- Grade 5 toxicity (death) in any subject within 28 days of receipt of study drug(s) unless clearly related to an alternative cause other than study drug
- Unacceptable toxicity occurring in >33% of subjects (at the same dose level)

Should these events occur the SRT will evaluate available data within 72 hours of notification of the event(s) and recommend whether to stop the study, suspend dosing and/or enrollment, or determine whether additional dose adjustments are warranted.

7.3 Study Population

The population for this study will consist of adults with a confirmed diagnosis of MM (per IMWG criteria) whose disease is considered relapsed or refractory. Subjects must have received (or were intolerant to) at least 3 prior treatment regimens for advanced disease with no further established treatment options available. Prior treatment includes multiple modalities recognized as standard of care in clinical practice; there is no maximum number of prior treatment regimens which would preclude an individual from participating in this study.

7.3.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

1. Male or female, aged ≥ 18 years
2. Confirmed diagnosis of MM per IMWG criteria
3. Measurable disease as defined by one or more of the following:
   - Serum M-protein ≥ 0.5 g/dL
   - Urine M-protein ≥ 200 mg/24 hours
   - Serum Free Light Chain (FLC) assay: involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal
   - In cases where SPEP is unreliable, serum quantitative immunoglobulin (qIgA) ≥ 750 mg/dL (0.75 g/dL) is acceptable
4. Relapsed or refractory (Rajkumar et al. 2011) to 3 or more different prior lines of therapy for MM, including IMiDs, PIs, chemotherapies, or monoclonal antibodies, and not a candidate for, or intolerant to established therapy known to provide clinical benefit:
   - Relapse defined as progression of disease after an initial response (MR or better) to previous treatment, more than 60 days after cessation of treatment
   - Refractory disease defined as < 25% reduction in M-protein or progression of disease during treatment or within 60 days after cessation of treatment
5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 – 1

6. Adequate organ and marrow function (i.e. without growth factors or transfusions) at Screening, as defined by the following laboratory parameters:

Hematologic	Renal	Hepatic
ANC ≥ 1000/µL Platelets ≥ 75,000/µL Hemoglobin ≥ 7.5 g/dL Albumin ≥ 3.0 g/dL	Creatinine clearance or eGFR >30 mL/min	AST/ALT ≤ 3 × ULN ALP ≤ 2 × ULN (ALP ≤ 5 × ULN for subjects with isozymes specific to bone) Bilirubin < 2 × ULN; or Bilirubin ≤ 3 × ULN if due to Gilbert's disease [1]
[1] If diagnosis of Gilbert's disease has not been previously established, the following will be required: (a) evidence of prior isolated rises in bilirubin; (b) evidence that hyperbilirubinemia is due to rise in unconjugated bilirubin (indirect bilirubin); (c) normal CBC in previous 12 months; (d) blood smear and reticulocyte count; (e) evidence of normal transaminases and ALP in previous 12 months. ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate (Cockcroft-Gault); ULN = institutional upper limit of normal		

7. Women of childbearing potential (WOCBP) and fertile males with WOCBP partners must use highly effective contraception (CTFG 2014) throughout the study (from first dose and through 28 days after final dose of study drug)
8. Provide written informed consent and is willing and able to comply with all study procedures.

7.3.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, Waldenstrom's macroglobulinemia, or IgM myeloma
2. Active plasma cell leukemia (> 2.0×10^9/L circulating plasma cells by standard differential)
3. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
4. Prior treatment directed to B-cell Activating Factor (BAFF; BLyS), B-cell Maturation Antigen (BCMA;TNFSF17) or transmembrane activator and CAML interactor (TACI; TNFSF13B), including antibodies or BCMA- or TACI-directed Chimeric Antigen Receptor (CAR)-T cell therapy
5. Prior biological agents, including monoclonal antibodies within 4 weeks prior to first dose of study drug
6. Prior chemotherapy, targeted anticancer small molecule therapy, or radiation therapy within 2 weeks prior to first dose of study drug
7. ASCT or bone marrow transplant within 12 weeks prior to first dose of study drug
8. Ongoing adverse effects (i.e. > Grade 1) due to a previously administered anticancer agent. Individuals with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion.

9. Participated in any other study in which receipt of an investigational new drug, or investigational device occurred within 28 days of first dose of study drug
10. Receiving systemic steroid therapy (> 10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug
11. Chronic or active infection requiring systemic therapy
12. Known or suspected allergy or hypersensitivity to any component of BION-1301; **[*Phase 2 only*:** dexamethasone or its excipients]; or history of severe hypersensitivity reaction to any monoclonal antibody
13. Received a diagnosis of, and/or tested positive at screening for human immunodeficiency virus (HIV)
14. Received a diagnosis, and/or tested positive at screening for hepatitis B or hepatitis C for which there is no clear evidence of natural immunity, immunity subsequent to vaccination, or successful eradication of the virus following antiviral therapy (individuals who are hepatitis C antibody positive may be enrolled if negative viral load confirmed at Screening)
15. Active other malignancy requiring treatment with the exception of any of the following:
    - Adequately treated basal cell carcinoma
    - Squamous cell carcinoma of the skin, or in situ cervical cancer
    - Low-risk prostate cancer (i.e. Gleason score < 7 and prostate specific antigen < 10 ng/mL); or
    - Any other cancer from which the individual has been disease-free for ≥ 3 years
16. Clinically significant heart disease (such as uncontrolled angina, myocardial infarction within 3 months of study initiation, congestive heart failure, or New York Heart Association Class III or IV heart failure)
17. Major surgery or significant traumatic injury occurring within 28 days prior to first dose of study drug. If major surgery occurred > 28 days prior to first dose of study drug, individual must have recovered adequately from the toxicity and/or complications from the intervention prior to the first dose of study drug.
18. If WOCBP, pregnant or breastfeeding; negative pregnancy status must be confirmed by serum pregnancy test at Screening
19. Intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements, or in the Investigator's assessment would place the subject at an unacceptable risk for study participation.
20. Active known central nervous system disease due to MM
21. Unwilling to discontinue use of biotin supplements higher than the recommended Daily Value (300 mcg; FDA) (1 day washout required prior to Screening laboratory assessments)
22. ***Phase 2 only:*** Presence of condition for which dexamethasone is contraindicated (e.g. active viral or fungal disease, uncontrolled psychoses, receipt of live viral vaccine in prior 30 days); or prior adverse reaction or intolerance to dexamethasone that resulted in treatment discontinuation.

7.3.3 Subject Discontinuation

Subjects will be encouraged to complete the study; however, a subject may voluntarily withdraw from treatment or the study at any time. The Investigator will provide a reason for discontinuation from treatment. Subjects who wish to discontinue treatment will be encouraged to complete EOT and Follow-up assessments.

A subject in this clinical study may be discontinued from treatment for any of the following reasons:

- The subject withdraws consent or requests discontinuation for any reason
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol
- Confirmed disease progression
- Any DLT, serious adverse event (SAE), clinically significant adverse events (AEs), severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject
- Pregnancy
- Subject failure to comply with protocol requirements or study-related procedures
- Termination of the study by the Sponsor or regulatory authority

7.4 Study Treatments

All subjects will receive BION-1301 as a single agent, administered by IV infusion. In Phase 2, subjects will be randomized to receive either BION-1301 as a single agent or BION-1301 and low-dose dexamethasone (BION-1301+DEX), administered orally (PO).

7.4.1 Method of Assigning Subjects to Treatment

All subjects will be sequentially assigned a unique identification number during Screening.

Subjects meeting all inclusion and exclusion criteria and completing all screening requirements will be assigned treatment depending on the study enrollment status:

- In Phase 1 of the study, subjects will be sequentially assigned to dose cohorts as specified in the study design (Section 7.1.1).
- In Phase 2 of the study, subjects will be randomized 1:1 ratio to either the BION-1301 or BION-1301+DEX treatment arm until the BION-1301+DEX arm is filled (n=14); thereafter, all remaining subjects will be assigned to BION-1301 until the arm is filled (n=29 total at selected dose/schedule). If more than one dose level/schedule of BION-1301 is selected for further evaluation in Phase 2, subjects will randomized in the same fashion.

7.4.2 Blinding

All study treatments will be administered open-label; no study participants or site personnel will be blinded to study treatment.

7.4.3 Investigational Product: BION-1301

BION-1301 is a sterile solution intended for IV administration. BION-1301 is supplied in a single-use stoppered glass vial, containing 20 mg/mL BION-1301 in a 6 mL vial with an extractable volume of at least 5 mL. BION-1301 should be stored at 2 °C to 8 °C prior to dilution and administration.

The investigational product was manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) regulations. Section 10.2.1 provides guidance for disposition and accountability of investigational products. Additional information on physical and chemical properties of BION-1301 may be found in the IB.

7.4.3.1 BION-1301 Administration

Details for storage, preparation, and administration of BION-1301 are provided in the Pharmacy Manual. Refer to Section 7.4.5 for additional details on BION-1301 administration, dosing modifications and interruptions.

7.4.3.1.1 Pre-Medication

The following pre-medications are required prior to the first infusion of study drug:

- Acetaminophen (975 mg or 1 gram per institutional standard) orally (PO) 30 minutes to 2 hours prior to infusion
- Antihistamine (clemastine 1 mg IV or cetirizine 10 mg PO, or equivalent) 30 minutes to 2 hours prior to study drug infusion

Use of pre-medications for subsequent infusions may be reduced or withheld based on Investigator discretion and the subject's tolerance of prior infusions.

7.4.3.1.2 BION-1301 Infusion

BION-1301 will be diluted as described in the Pharmacy Manual to achieve the assigned fixed dose level prior to administration. BION-1301 will be administered by IV infusion over approximately 2 hours for the initial dose (3 hours at dose levels ≥ 2000 mg), and may be reduced to 1 hour for subsequent doses (2 hours at dose levels ≥ 2000 mg) following SRT review of infusion-related tolerability data.

BION-1301 may be administered using central lines or other venous access devices. The start and stop times for each infusion will be recorded.

7.4.3.1.3 Supportive Care, Infusion-related Toxicities, and Post-infusion Monitoring

To minimize or mitigate infusion-related toxicity, the infusion rate may be decreased and supportive care may be used as needed. All medications must be recorded on the electronic case report form (eCRF).

Subjects will be observed in the clinic for at least 4 hours after the first infusion (or following any infusion where there is a dose modification from the previous infusion) and released once considered clinically stable. For subsequent dosing, subjects should be monitored at least 1 hour after infusion and released only when considered clinically stable.

In the event of a suspected systemic infusion-related and/or hypersensitivity reaction, immediately discontinue the infusion and administer appropriate supportive therapy per institutional guidelines, which may include, but is not limited to, epinephrine, IV fluids, corticosteroids, vasopressors, oxygen, bronchodilators, antihistamines, or acetaminophen. Subjects should be evaluated and carefully monitored until complete resolution (i.e. all hypersensitivity signs and symptoms have resolved).

For subjects with Grade 2 infusion reactions, if it is appropriate to restart the infusion, the infusion rate should be decreased by 50% (e.g. the total duration of the infusion should be doubled). If the subject is to receive additional infusions in subsequent weeks, the rate of these infusions should be discussed with and agreed upon prospectively by the Investigator and the Medical Monitor. In addition, for all subsequent infusions, maximal premedication must be administered according to institutional practice and should include an H1 blocker, an H2 blocker, an antipyretic such as acetaminophen and a steroid (e.g. 25-50 mg hydrocortisone IV).

In case of infusion reaction Grade ≥3 during the infusion or in the 4-hour observation period, glucocorticoid equivalent to 100 mg prednisolone can be given after the infusion has been stopped. The subject should be monitored for a minimum of at least six additional hours after the infusion reaction and released only when considered clinically stable.

7.4.4 Phase 2 Study Treatment: Dexamethasone

Dexamethasone is a synthetic glucocorticoid with low mineralocorticoid activity. Dexamethasone is supplied as tablets intended for oral administration.

Dexamethasone may increase the risk of infection or psychiatric disorders; information on special precautions and warnings may be found in the package insert. Additional information on the product presentation, formulation, storage, and administration of dexamethasone may also be found in the package insert.

7.4.4.1 Dexamethasone Administration

For subjects assigned to BION-1301+DEX, instruct the subject to take 40 mg PO QW at home in the morning on Days 1, 8, 15, and 22 of each cycle (prior to clinic visit, if scheduled). The dose

should preferably be taken in the morning to minimize insomnia, and prior to any scheduled BION-1301 dosing.

Subjects > 75 years of age or BMI < 18.5 may receive dexamethasone at 20 mg per Investigator discretion. Other dose modifications are allowed based on Investigator discretion and written approval from Medical Monitor (Section 7.4.5.2).

At the end of dexamethasone treatment, the dose may be tapered if required in a stepwise fashion per Institutional practice.

7.4.5 Dose Modifications and Dosing Interruptions

Dose modifications and/or interruptions are recommended for subjects who do not tolerate the protocol-specified dosing schedule.

Following the first 4 cycles of study treatment, dosing interruptions are also permitted in the case of medical / surgical events, palliative radiation, or logistical reasons not related to study therapy (e.g. elective surgery, unrelated medical events, vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

7.4.5.1 Dose Modifications for Suspected BION-1301-related Events

The following general dose modification guidelines will be applied for suspected BION-1301-related events:

- If a subject experiences a DLT at any point during the study, study drug should be withheld. Consult the Medical Monitor prior to resuming treatment following the occurrence of a DLT.
- Generally if a dose is interrupted or withheld for AE, treatment may be resumed at the same (or lower) dose level on the same dosing schedule following resolution of the AE to Grade 1 or baseline.
    - If the Investigator considers it in the subject's best interest to resume treatment before the AE has resolved to Grade 1, the Medical Monitor should first be consulted.
    - Reductions in study drug dose must be approved by the Medical Monitor.
    - If the subject is on a QW dosing schedule; frequency may be reduced to Q2W following consultation with the Medical Monitor.
- If dose interruptions persist > 6 weeks (from the expected day of dosing), the subject will be discontinued from the study unless there is evidence of clinical benefit and the Investigator deems it is in the subject's best interest to remain on study. In such cases, the Medical Monitor must be consulted.
- If a subject requires more than 2 dose reductions/modifications for the same toxicity, BION-1301 should be discontinued.

7.4.5.2 Dose Modifications for Suspected Dexamethasone-related Events

Dose modifications are allowed for suspected dexamethasone-related events or intolerance based on Investigator discretion.

Subjects who experience unacceptable toxicity directly attributable to dexamethasone may continue on study and receive BION-1301 as a single agent following Medical Monitor approval.

If dexamethasone is discontinued, the dose may be tapered (if required) in a stepwise fashion until a complete stop per Institutional practice.

7.4.6 Concomitant Medications and Procedures

Subjects may receive concomitant medications and procedures as required or deemed necessary for supportive care, unless specifically restricted or prohibited in this study (Section 7.4.7).

During the course of the study, subjects are anticipated to continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria.

Antihypertensive therapy is allowed as concomitant medication; however, because transient hypotension has occurred during infusions of monoclonal antibodies, consideration should be given to withholding antihypertensive medications for 12 hours prior to infusion of BION-1301.

7.4.7 Prohibited Medications and Procedures

A subject may be discontinued from study treatment for use of prohibited medications or procedures. Approval must be obtained from the Medical Monitor for a subject to continue dosing if a prohibited medication is administered within the specified timeframes. The following therapies are not permitted or are restricted during the study:

- Non-study chemotherapy, small molecule, anticancer-directed hormonal therapy, immunotherapy, or other therapeutic monoclonal antibodies (approved or investigational)
- ASCT or bone marrow transplant
- Radiation therapy (dosing interruption allowed for palliative radiation)
- Plasmapheresis
- Any other investigational product or device
- Systemic corticosteroids > 10 mg/day of prednisone or equivalent (except use of dexamethasone as study treatment, or corticosteroids used to treat infusion-related reaction [Section 7.4.3.1.3])
- Biotin supplements at doses higher than recommended Daily Value (300 mcg)
- Live viral vaccines (BION-1301+DEX arm in Phase 2 only)

There are no prohibited therapies or procedures once the subject has completed the EOT visit.

7.4.8 Treatment Compliance

BION-1301 will be administered by a qualified health care professional at an approved study site. The date, time, and volume of each dose of BION-1301 administered to each subject must be recorded in the source document. If assigned to BION-1301+DEX, treatment compliance (i.e. date and time of dose) for dexamethasone will be self-reported by the subject in a diary. The objective is 100% compliance, and Investigators and site personnel should evaluate compliance at each visit and take appropriate steps to optimize compliance.

7.5 Study Assessments and Procedures

Screening assessments will be conducted to confirm eligibility and to obtain baseline measurements. Screening must be completed within 28 days prior to first dose of study drug. An enrollment form will confirm subject eligibility after completion of all screening procedures. Subjects must initiate dosing of study drug within 2 weeks from the date of the approved enrollment form.

Subjects will be requested to complete multiple clinic visits during the initial two dosing cycles; visit frequency is reduced beginning at Cycle 3 and beyond. An EOT Visit will occur 28 days after the last dose of study drug. If the subject begins another anticancer therapy before the end of the 28-day period, all EOT Visit assessments should be completed prior to commencing the new therapy. Unresolved AEs will be monitored until resolution or confirmed stability of the event.

Subjects who discontinue study treatment for reasons other than progressive disease should continue tumor response assessments as per the standard of care frequency until disease progression is documented, withdrawal of consent, or study end.

Follow-up calls will occur every 12 weeks after the last dose of study drug. Data will be collected on survival and any subsequent cancer-related therapies. Telephone contact(s) should also be scheduled to satisfy safety reporting requirements as specified in Table 7-4.

All study visits (and visit windows), assessments, and procedures will be performed as indicated in the Schedule of Events (Table 2-1). On days when study drug is administered, assessments should be performed prior to dosing unless otherwise specified. Further details of study procedures and assessments can be found in the Study Reference and Laboratory Manuals.

7.5.1 General (Baseline) Assessments

7.5.1.1 Informed Consent

Before any screening or study-specific procedure is performed, an individual must be given a complete explanation of the purpose and requirements of the study, and an informed consent form (ICF) approved by the Institutional Review Board and/or Ethics Committee (IRB/EC) and an authorization for use and disclosure of protected health information must be signed. An

original signed consent form will be retained in the subject's source documentation at the site; a copy will be provided to the subject.

Assessments conducted as standard of care prior to informed consent may be considered for eligibility requirements if performed within the required Screening Period.

7.5.1.2 Eligibility

Potential subjects will be evaluated for entry into the study according to the stated inclusion and exclusion criteria (Section 7.3). Individuals deemed ineligible for study enrollment do not need to complete all screening procedures. The reason for ineligible status will be documented. Tests with results that fail eligibility requirements may be repeated once during the Screening Period if the Investigator believes the results to be in error. Additionally, a subject who fails Screening may repeat the process one time if the Investigator believes there has been a change in eligibility status (e.g. after recovery from an infection).

For subjects who meet all inclusion/exclusion criteria, an enrollment form will be completed and sent to Sponsor or designee for review and approval. The first dose of study drug will not be administered until the Investigator receives approval of the enrollment form.

7.5.1.3 Demographics, Medical History, and Height

Demographic data and a complete medical history will be collected at Screening by the Investigator or qualified designee. Demographic information (as allowed by local regulations) will include date of birth, age, gender, ethnicity, and race. Medical history should include all active conditions and any condition considered to be clinically significant by the Investigator.

Details regarding the disease for which the subject has enrolled in this study (e.g. date of diagnosis, primary tumor histology, prior surgery(ies), radiation therapy, chemo- and biological therapies, and stage of cancer) will be recorded.

Height will be obtained at Screening with a stadiometer. Body mass index will be derived using height and weight.

7.5.1.4 Skeletal Survey

A complete skeletal survey will be conducted during Screening prior to Cycle 1 Day 1. The skeletal survey includes standard radiography of cervical, thoracic and lumbar spine, skull, chest, pelvis, humeri and femora. Additional tumor imaging (i.e. MRI) will only be conducted at Screening if the skeletal survey is normal in the setting of bone pain or neurologic deficits, or if the subject has a history of plasmacytoma of the bone. Plasmacytoma, if present at screening, should be monitored throughout the study using the same technique and as clinically appropriate. A plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the cross diameter is at least 1 cm. Smaller plasmacytomas will be considered non-measurable. Skeletal survey conducted as standard of care within 30 days prior to Cycle 1 Day 1 may be used as baseline data.

Additional imaging (X-ray, CT or MRI) during the study may be performed at the Investigator's discretion, e.g. in case of bone pain. In this case the Investigator must choose the imaging technology based on the clinical indication. Reading of the skeletal surveys will be done by a radiologist.

7.5.2 Efficacy Measures

The assessments to derive efficacy variables are described below and will be conducted according to the Schedule of Events in Table 2-1. Efficacy endpoints and associated analyses are described in Section 6 and Section 7.6.5.

7.5.2.1 Urine and Serum Monoclonal Protein and Free Light Chain Profiles

A panel of assays routinely used in the assessment of MM will be conducted on serum and 24-hour urine samples as indicated. Urine and blood assessments should be obtained on the same day if feasible, but no more than 7 days apart. Testing will be performed at the institution's local laboratory.

BION-1301 may potentially interfere with assays used to monitor M-protein, analogous to interference observed with daratumumab and elotuzumab. Potential interference could be of relevance in distinguishing a VGPR from a CR (van de Donk et al. 2016). Additional serum samples will be collected and stored to retrospectively evaluate for potential interference at a central laboratory.

7.5.2.1.1 Serum Monoclonal Protein Profiles

The serum monoclonal protein profile (SMPP) includes:

- serum protein electrophoresis (SPEP)
- serum free light chain (FLC) assay
- serum immunofixation electrophoresis (IFE; IgG, IgA, IgM)
- total protein

Fasting is preferred but not required. Details of fasting status/duration will be recorded.

7.5.2.1.2 Urine Profiles

The subject will collect urine for a 24-hour period during Screening, and prior to dosing at Cycle 1 Day 1. The Cycle 1 Day 1 collection is not required if the Screening assessment was completed within 72 hours of Cycle 1 Day 1 dose administration. Additional 24-hour urine samples will only be collected on Day 1 of every Cycle thereafter if Cycle 1 Day 1 UPEP >200 mg/24 hours, or to confirm a response or disease progression. Urine will be tested at the institution's local laboratory.

Urine protein electrophoresis (UPEP) includes:

- urine IFE (IgG, IgA, IgM)
- total protein

7.5.2.2 Tumor Response Assessment

Assessment of response according to IMWG (Appendix A) and EBMT for MR (Appendix B) will be performed by the Investigator. During the course of the study, the Sponsor may conduct central review of assessments for secondary supportive analyses.

Subjects who discontinue study treatment for reasons other than progressive disease should continue tumor response assessments as per the standard of care frequency until disease progression is documented, withdrawal, or study end.

7.5.2.2.1 Disease Progression

Continued treatment decisions (i.e. study discontinuation due to progressive disease) will follow IMWG. In case of clinical deterioration or suspicion of disease progression, a follow-up SMPP assessment should be performed promptly rather than waiting for the next scheduled assessment. Subjects with confirmed disease progression or who are no longer deriving clinical benefit will be discontinued from treatment.

7.5.2.3 Survival Follow-Up

Following the last dose of study drug, subjects will be contacted at 12-week (3-month) intervals to assess vital status and subsequent cancer-related therapies. For subjects who withdraw from the study prior to completion of the Follow-up Period, reasonable efforts will be made to collect survival outcome. In the case of subjects lost to follow-up, attempts to contact the subject will be documented in the subject's study records. Sites will attempt to obtain vital status data from public records or other external sources where possible if a subject withdraws consent from study (i.e. refuse follow-up for vital status) or is documented as lost to follow up. All deaths must be reported on the eCRF. Requests for subject survival status may be conducted periodically between the EOT and the protocol-defined end of study (Section 7.2).

7.5.3 Safety Assessments

Safety will be assessed by collection of data on TEAEs, clinical laboratory assessments, ECOG performance status, vital signs, weight, physical examination, electrocardiogram (ECG) parameters, and concomitant medications. Clinically significant changes from pre-treatment values in safety assessments should be reported as AEs. Safety assessments described below will be conducted according to the Schedule of Events (Table 2-1).

7.5.3.1 Eastern Cooperative Oncology Group Scale of Performance Status

The ECOG Scale of Performance Status is recognized as a standard tool to measure disease impact on daily living activities (Oken et al. 1982). The ECOG scale will be used by site personnel to determine eligibility and characterize a subject's level of functioning (self-care, daily activity, and basic physical ability) as indicated throughout the study.

7.5.3.2 Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature will be performed at each indicated study visit prior to dosing. On BION-1301 dosing days, collect prior to dosing (- 5 min) and at least every 30 minutes (± 5 min) during and after the infusion, through the observation period and until the subject is considered clinically stable. Additional measurements should be obtained if clinically indicated.

Any clinically significant abnormal findings in vital signs should be recorded as an AE (or infusion-related DLT if applicable).

7.5.3.3 Physical Examination and Weight

7.5.3.3.1 Complete Physical Examination

Complete physical examinations will be conducted at Screening and EOT. Complete physical examinations must be performed by a medically qualified individual such as a licensed Physician, Physician's Assistant, or an advanced Registered Nurse Practitioner, as local law permits.

The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver and spleen); extremities; lymph nodes; and a brief neurological examination. Before the first dose of study drug, clinically significant abnormal findings should be recorded as medical history. After the first dose of study drug, new clinically significant abnormal findings should be recorded as AEs.

7.5.3.3.2 Symptom-directed Physical Examination

Symptom-directed physical examinations may be conducted at all other visits as indicated (up to 3 days prior to dosing). The Investigator or medically qualified designee will perform a symptom-directed evaluation as clinically indicated. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings. New clinically significant abnormal findings should be recorded as AEs.

7.5.3.3.3 Weight

Weight will be obtained at each indicated visit, and prior to receiving any study drug.

7.5.3.4 Electrocardiogram

Routine 12-lead ECGs will be performed. ECGs should be performed in triplicate after the subject has rested in a recumbent or semi-recumbent position for ≥5 minutes. On BION-1301 dosing days, perform ECG after all pre-medications are administered and prior to study drug dosing.

ECG parameters include heart rate, PR interval, QT interval, QRS duration, and QTcF (Fridericia's correction). The ECG will be interpreted by the Investigator as normal, not clinically

significant abnormal, or clinically significant abnormal. Clinically significant abnormal findings should be recorded as an AE.

Additional ECGs may be performed throughout the study if clinically indicated.

7.5.3.5 Adverse Events

After signing informed consent, and prior to the first study drug administration, any medical occurrence considered related to screening procedures (e.g. tumor biopsy, venipuncture) will be captured as an AE; all other medical events will be captured in the subject's medical history (Section 7.5.1.3).

Safety reporting periods for this study are defined in Table 7-4. The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 8.

Table 7-4. Safety Reporting Periods

Event Type	Reporting Period	Additional Requirements
Adverse Events/Serious Adverse Events (Screening)	Date of informed consent and prior to first dose of study drug	Report as AE/SAE only if related to study procedures during Screening
Adverse Events (treatment-emergent)	First dose of study drug through 28 days following last dose of study drug	
Serious Adverse Events (treatment-emergent)	First dose of study drug through 90 days following last dose of study drug, or 28 days following last dose of study drug if the subject initiates new anti-cancer therapy	Report new SAEs outside of window if assessed as possibly or probably related to study drug
Event of Special Interest (treatment-emergent)	First dose of study drug through EOT visit	
Pregnancy of subject or partner	Date of informed consent through 28 days following last dose of study drug	Follow pregnancy reporting and follow-up procedures in Section 8.4

If the EOT visit occurs less than 28 days from the last dose of study drug, the subject will be contacted by telephone at least 28 days after the date of last study drug administration to complete the AE reporting period. A telephone contact should also be scheduled for 90 days post-final dose of study drug to satisfy reporting requirements for SAEs.

7.5.3.6 Prior and Concomitant Medications

Medications used within 28 days prior to Cycle 1 Day 1 will be recorded as prior medications. Concomitant medications include pre-medications and all prescription, over-the-counter medications, herbal remedies and dietary supplements administered from Cycle 1 Day 1. The generic name, dosage, duration, and reason for the concomitant medication should be documented. Changes in the use of concomitant medications will be captured at each study visit.

7.5.3.7 Clinical Laboratory Evaluation for Safety

Routine hematology, serum chemistry, and urinalysis will be performed throughout the study as a safety measure (Section 7.5.4.2). The Medical Monitor may, depending on study criteria, be consulted before enrollment about a potential subject with abnormal laboratory values that are not considered clinically significant by the Investigator.

The clinical significance of laboratory parameter findings will be determined by the Investigator throughout the study. All abnormal laboratory values considered clinically significant by the Investigator must be recorded in the AE page of the eCRF. Any abnormal test that is determined to be an error does not require reporting as an AE. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

Additional safety laboratory assessments include immunogenicity (antidrug antibodies; ADA; neutralization assays (Section 7.5.4.2.1).

7.5.4 Laboratory Assessments

A panel of laboratory assessments on blood, urine, and bone marrow samples will be used to characterize the study population, assess safety and efficacy, and characterize PK-PD throughout the study per the Schedule of Events (Table 2-1).

7.5.4.1 Screening-specific Laboratory Assessments

Blood samples will be obtained at Screening to confirm eligibility for each subject and the study population. These initial laboratory assessments will be conducted at the institution's local laboratory and include:

- Virology screen for HIV antibody, hepatitis B surface antigen, hepatitis C antibody, and Epstein-Barr virus (EBV)
  - Hepatitis C viral load (if indicated)
- Beta-2 microglobulin
- C-reactive protein

7.5.4.2 Safety Laboratory Assessments

Routine hematology, serum chemistry, and urinalysis will be conducted to assess eligibility and as a measure of safety per protocol requirements. All clinical laboratory evaluations will be performed by the institution's local laboratory. Testing may be completed up to five days prior to each study drug administration. Fasting is not required.

The following routine laboratory parameters will be evaluated at Screening through EOT as indicated:

- Hematology: complete blood count (white blood cells, red blood cells, hematocrit, hemoglobin, platelet count, and differential)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, lactate dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin (total, direct, indirect), total protein, albumin, calcium, magnesium, uric acid, and phosphate
- Coagulation panel: D-dimer, fibrinogen, INR of PT, and aPTT
- Urinalysis (dipstick): bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity

7.5.4.2.1 Immunogenicity

Blood samples will be screened at a central laboratory for the development of anti-drug antibodies (ADA). Immunogenicity testing will utilize a 3-tiered approach; if ADA are detected, assays for specificity confirmation (i.e. titer) and neutralizing antibodies (nAb) will be performed. Additional samples may be collected in cases of infusion-related or other immune-mediated reaction.

7.5.4.2.2 Pregnancy Testing and Contraception Requirements

The effects of the study drugs on a fetus *in utero* or on the composition of sperm are unknown. Therefore WOCBP and fertile males must consent to use highly effective contraception (CTFG 2014) throughout the study (or for 28 days after final dose of study drug).

A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. For study eligibility, WOCBP must have negative serum pregnancy tests (HCG) at Screening. At all other indicated visits, only a urine pregnancy test is required. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test. Pregnancy of a subject or partner must be reported and followed (Section 8.4).

7.5.4.3 Drug Concentration Measurements

In Phase 1, blood samples for analysis of BION-1301 serum concentrations will be obtained to characterize the PK profile of BION-1301 following a single dose (Cycle 1 Day 1), and repeat-dosing (sparse sampling), as indicated in Table 7-5. In Phase 2, the full PK-PD profile of BION-1301 will be assessed in a subset of subsets (i.e. the first 6 subjects enrolled per arm) following the sampling schedule for Phase 1 Dose Escalation (Table 7-5); for all remaining subjects in Phase 2 a sparse sampling approach will be employed (Table 7-5).

For planned time points up to 48 hours post-infusion, blood samples must be taken from a peripheral vein contralateral to the arm/location into which BION-1301 is administered. If a peripheral line is used for study drug infusion, a central line may be used for PK-PD sample

collection per institutional guidelines for collecting a clean, undiluted sample using an appropriate method such as the push-pull or discard method. Samples will be collected and processed by sites as outlined in the Laboratory Manual. All analyses will be conducted by the Sponsor or designee.

Table 7-5. PK-PD Sampling Schedule

		PHASE 1: DOSE ESCALATION		PHASE 2[3]
		Q2W DOSING SCHEDULE	**QW DOSING SCHEDULE**	**SPARSE SAMPLING [3]**
CYCLE	**DAY**	**SCHEDULED TIME (Sampling Window) [1]**		
Screening	0	During visit	During visit	During visit
Cycle 1	1	Pre-dose Post-dose: 30 min (±5 min); 1 hr (±10 min), 2 hrs (±10 min), and one sample between 4-8 hrs	Pre-dose Post-dose: 30 min (±5 min); 1 hr (±10 min), 2 hrs (±10 min), and one sample between 4-8 hrs	Pre-dose Post-dose: 30 min (±5 min);
	2	During visit	During visit	NO SAMPLE
	3[2]	During visit	During visit	During visit
	8	During visit	Pre-dose	Pre-dose (QW only)
	15	Pre-dose Post-dose: 30 min (±5 min)	Pre-dose Post-dose: 30 min (±5 min)	Pre-dose Post-dose: 30 min (±5 min)
	22	N/A	Pre-dose (if visit required for QW dosing)	Pre-dose (if visit required for QW dosing)
Cycle 2	1	Pre-dose Post-dose: 30 min (±5 min)	Pre-dose Post-dose: 30 min (±5 min)	Pre-dose
	8	During visit	Pre-dose (if applicable) or During visit	Pre-dose (if applicable) or During visit
	15	Pre-dose Post-dose: 30 min (±5 min)	Pre-dose Post-dose: 30 min (±5 min)	Pre-dose
	22	N/A	Pre-dose (if visit required for QW dosing)	Pre-dose (if visit required for QW dosing)
Cycles 3-7	1	Pre-dose	Pre-dose	Pre-dose
Cycle 9 (and beyond)	1	Cycle 9 and all odd-numbered cycles thereafter: Pre-dose Post-dose: 30 min (±5 min)	Cycle 9 and all odd-numbered cycles thereafter: Pre-dose Post-dose: 30 min (±5 min)	Cycle 9 and every 3 cycles thereafter: Pre-dose Post-dose: 30 min (±5 min)

[1] Obtain pre-dose samples within 60 min prior to start of infusion. Post-dose is defined as time from completion of BION-1301 infusion.
[2] Subjects will complete a Day 3 visit during Cycle 1. Based on available PK-PD data and to confirm complete assessment of PK-PD profile the Day 3 visit may be moved to Day 5. If this change is required, written notification will be provided by the Sponsor or its designee.
[3] In Phase 2, assess the full PK-PD profile in the first 6 subjects enrolled per arm following the sampling schedule for Phase 1 Dose Escalation; all remaining subjects in Phase 2 follow the sparse sampling schedule.

7.5.4.4 Pharmacodynamic Markers and Indicators of Biological Activity

Research assessments will be conducted (where not prohibited by local regulations or policies) on blood (plasma/serum) and bone marrow samples; a subset of sites will also collect and process whole blood for analysis of peripheral blood mononuclear cells. The results may help to inform dose selection, monitor baseline and post-treatment immune responses; and possibly further characterize the mechanism of action and/or determine potential prognostic and/or predictive biomarkers.

The Sponsor may retain samples and their derivatives (e.g. DNA, RNA, and protein) for possible future research beyond the end of the study. Samples will be collected and stored according to applicable FDA guidance (FDA 2013, 2018) and will not carry personal health information. Samples will be destroyed 15 years after study completion (or term defined per local policies), or if the subject withdraws consent during the study and also requests sample destruction.

Samples required for laboratory evaluations will be collected at the visits indicated in Table 2-1 and processed by sites as outlined in the Laboratory Manual. Based on emerging data or for operational reasons, certain samples may not be collected and/or analyzed. All analyses will be conducted by the Sponsor or designee.

7.5.4.4.1 Pharmacogenetic Sample

One baseline blood sample for pharmacogenetic (PGx) analysis will be obtained during Screening. The sample will be used to correlate individual subject DNA sequence variation (e.g. SNPs) with safety, tolerability, and potential clinical benefit. Information obtained will be used solely to further characterize drug effects and will not have clinical diagnostic or therapeutic implications for the individual subject. The identity of the subject will not be disclosed to the Sponsor or its designee performing the analysis. Since the analysis is for research purposes only, individual results will not be shared with the Investigator, the subject, and/or the subject's relatives. Any information obtained is not intended for inclusion in the medical record.

7.5.4.4.2 Biomarkers

Biomarkers initially planned for this study include:

- Immunoglobulin levels (Total IgG, IgA and IgM; Section 7.5.2.1)
- Free APRIL
- Soluble BCMA, IL-6, CD138

Blood and bone marrow samples may also be used for biomarker analysis to monitor immune cell populations, MM cells, and/or soluble biomarkers. Additional analytical assessments, methodologies, and exploratory biomarkers, including but not limited to biomarkers identified in other clinical studies, may also be assessed at the Sponsor's discretion. .

7.5.4.4.3 Bone Marrow Samples

Bone marrow samples will be collected pre-treatment and on-treatment to evaluate cellular or genomic changes in markers of immune response or disease status. Standard techniques should be used. Pre-treatment samples will also be used for cytogenetic analysis using fluorescence in-situ hybridization (FISH) at the local laboratory.

The on-treatment sample must be obtained prior to administration of study drug on indicated days. If, while on treatment the Investigator deems the procedure is contraindicated for the subject, the site must discuss with the Medical Monitor to determine if an alternative acceptable method and/or timing may be allowed.

If M-protein levels indicate CR, a bone marrow aspirate or biopsy should be taken for confirmation. If additional bone marrow biopsies, aspirates or relevant samples are collected for routine care during the course of study, a sample should be retained if possible for Sponsor research evaluation.

Bone marrow samples collected at required time points will be analyzed locally; a second research sample will be sent to the central laboratory. Detailed instructions for bone marrow collection, processing, and shipment are provided in the Laboratory Manual.

7.5.5 Appropriateness of Measures

The safety parameters to be evaluated in this study include standard assessments such as recording of medical history, AEs and SAEs, physical examination, vital signs, ECGs, serum chemistry and hematology, urinalysis, concomitant medications, and other routine clinical and laboratory procedures. The DLT criteria for dose-escalation decisions are based on available nonclinical data combined with general practices in the development of immunotherapeutic agents.

Conventional radiography is recommended by the IMWG to determine the extent of bone disease in relapsed MM (Dimopoulos et al. 2009). Approximately 80% of patients with myeloma have radiological evidence of skeletal involvement on the skeletal survey. Therefore, a complete skeletal survey will be conducted at Screening; additional tumor imaging (i.e. MRI) will only be conducted as follow-up if the skeletal survey is normal in the setting of bone pain or neurologic deficits or plasmacytoma of the bone is present at study entry.

Tumor response will be evaluated using IMWG criteria (Durie et al. 2006), widely accepted as uniform response criteria for MM. Specific recommendations for uniform reporting of clinical trial results in myeloma have also been adapted (Rajkumar et al. 2011). ORR, is generally an accepted surrogate of efficacy appropriate for use studies with smaller sample sizes (FDA 2007). Additional efficacy variables will also be derived from tumor response assessments. OS is the universally accepted direct measure of benefit and is an objective measure, although interpretation may be confounded by subsequent anti-cancer therapies and non-cancer deaths.

Pre-treatment and on-treatment bone marrow and blood samples will provide an initial investigation into the mechanism of action of BION-1301. Characterization of a broad panel of biomarkers may be predictive of response to therapy and may also give insight into appropriate endpoints in additional clinical studies. PK sampling times are driven by typical profiles observed for monoclonal antibodies delivered by IV infusion and available nonclinical data. As may occur with any therapeutic monoclonal antibody, BION-1301 may elicit an immune response resulting in development of ADA. Subjects will therefore be monitored for the development of ADA in parallel with select PK time points to assess potential impacts on exposure, PD effects, and neutralization of activity.

7.6 Statistical Analysis

The completeness of the data affects the integrity and accuracy of the final study analysis. Therefore, efforts will be made to ensure complete, accurate and timely data collection, and to avoid missing data. The procedures for handling missing, unused, or spurious data, along with the detailed method for analysis of each variable, transformations, and exploratory analyses will be presented in the Statistical Analysis Plan (SAP); the information below is intended as a guide to planned analyses.

The study is designed in 2 parts: dose escalation (Phase 1) followed by dose-expansion (Phase 2). Phase 1 dose escalation is exploratory in nature and inferential statistics are not the primary focus. Data from the dose escalation and dose expansion components will be summarized separately. There is no intention to compare dose cohorts. In Phase 2, all comparisons will be conducted descriptively.

7.6.1 Sample Size Determination

During Phase 1, dose escalation will be based on 3+3 guidelines to determine the RP2D and evaluate safety data (including DLTs and TEAEs) and assess the PK-PD of each dose level. The sample size in Phase 1 is predicated on the number of dosing cohorts examined and the number of observed DLTs.

Two treatment arms will be evaluated in Phase 2: BION-1301 monotherapy and BION-1301+DEX.

In Phase 2, a sample size of 29 evaluable subjects in the BION-1301 monotherapy arm achieves 80% power to detect a difference of 9% in ORR using a one-sided exact test with a target significance level of 0.05. The actual significance level achieved by this test is 0.034. The calculation assumes that the population ORR under the null hypothesis is 1% and under the alternative hypothesis is 10%. The sample size includes subjects treated at the corresponding RP2D/schedule during Phase 1 (Dose Escalation).

If more than one dose/schedule is studied in Phase 2, this design will be applied to each RP2D independently.

In Phase 2, a sample size of 14 evaluable subjects in the BION-1301+DEX arm, achieves 80% power to detect a difference of 19% in ORR using a one-sided exact test with a target significance level of 0.05. The actual significance level achieved by this test is 0.008. The calculation assumes that the population ORR under the null hypothesis is 1% and under the alternative hypothesis is 20%.

7.6.2 General Considerations

Descriptive statistics will be provided for selected demographic, safety, and PK data by dose level. Descriptive summaries on continuous data will include number of subjects, means, medians, standard deviations, minimum and maximum values. Categorical data will be summarized using frequency counts and percentages. Descriptive summaries of time to event data from Kaplan Meier estimates will include the number of events, number censored, medians, quartiles and 95% confidence intervals (CIs). Graphical summaries of the data may be presented. All data will be listed for all treated subjects.

If more than 1 dose level or dosing schedule is evaluated in Phase 2, there are no formal comparisons planned between the RP2Ds. No inferential comparison between BION-1301 and BION-1301+DEX arms will be performed in Phase 2.

All statistical analyses will be performed using SAS.

7.6.3 Analysis Sets

The following analysis sets will be used for this study:

- ***Evaluable Analysis Set (EAS):*** All subjects who received any amount of study drug and have at least one evaluable post-baseline tumor response assessment or were discontinued due to toxicity. The EAS will be the primary population for analyses of ORR, PFS, DCR, DOR, and relative reduction in M-protein.
- ***Full analysis set (FAS):*** All subjects who receive any amount of study drug. The FAS will be used for analyses of OS, biomarkers, sensitivity analysis of select tumor response-related endpoints, and exploratory endpoints.
- ***Safety population,*** defined as all subjects who receive any amount of study drug. All safety analyses will be based on this population. The safety population and FAS are identical.

All analyses of safety, PK, PD, and efficacy data will be performed on all subjects who were enrolled and received at least one dose of study drug.

Additional analysis sets (e.g. evaluable per protocol analysis set) may be defined in the SAP.

7.6.4 Subject Information

Subject disposition summaries will include the number of enrolled subjects, the number of subjects receiving study drug, the number of subjects completing the study, the number of

subjects withdrawing prematurely, and the reasons for discontinuation. Terminations and premature withdrawals will be summarized by counts and percentages.

Demographics, baseline disease characteristics, prior disease related therapies, and concomitant medications will be summarized using descriptive statistics.

7.6.5 Efficacy Analyses

Clinical response will be based on Investigator assessment and interpretation and used for analysis of efficacy. During the course of the study, the Sponsor may conduct central review of assessments for secondary supportive analyses. All efficacy variables will be defined and analyzed according to IMWG criteria (Rajkumar et al. 2011), unless otherwise indicated.

7.6.5.1 Efficacy Variables and Analysis (Phase 2)

Objective Response Rate (ORR) defined as the proportion of subjects with a best overall response of sCR, CR, VGPR, or PR, according to IMWG criteria (Appendix A) as assessed by the Investigator, will be used as the primary analysis for efficacy. The ORR along with a 95% CI, based on the Clopper-Pearson interval will be reported. Secondary analyses of ORR may be repeated in FAS, counting a missing best overall response as a non-responder. ORR will be summarized by each response assessment and best overall response.

Relative reduction in M-protein is defined as the maximum percent reduction from baseline in serum and urine M-protein levels at any time point while on treatment.

Progression-free survival (PFS) is defined as the time from first dose of study drug to first documentation of disease progression or death due to any cause. Subjects who do not experience PD and are alive will be censored at the time of last evaluable tumor assessment. Subjects who do not experience PD and start new anti-cancer therapy will be censored at the last evaluable tumor assessment on or prior to the time of the new anti-cancer therapy. For analyses conducted in the FAS, subjects with no evaluable post-baseline tumor assessments will be censored at the time of receipt of first study drug. Subjects who are lost to follow-up for assessment of PD will be censored at their last evaluable tumor assessment.

Overall Survival (OS) defined as the time from first dose of study drug until date of death due to any cause. Subjects without documentation of death at the time of analysis will be censored as of the date the subject was last known to be alive, or the data cut-off date, whichever is earlier.

PFS and OS will be summarized using Kaplan-Meier estimates.

7.6.5.2 Exploratory Efficacy Variables and Analysis

Duration of response (DOR) is defined as the time from the first tumor assessment that supports the subject's objective disease response to the time of disease progression or death due to any cause. Subjects who do not experience disease progression or death at the time of analysis will be censored using the same rules as described for PFS. DOR will be summarized using Kaplan-

Meier estimates, including the number of events, number of censored subjects, median and 95% confidence intervals.

Disease control rate (DCR) is defined as the percentage of subjects with sCR, CR, VGPR, PR, or stable disease (SD) per IMWG criteria; or MR per EBMT criteria (Appendix B). The analysis of DCR will be conducted in the same manner as ORR.

7.6.6 Safety Analyses

AEs will be coded according to the current Medical Dictionary for Regulatory Activities (MedDRA) and assessed for severity by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v. 4.03. TEAEs will be summarized by system organ class and preferred term and presented in decreasing order of frequency. Incidences of TEAEs and SAEs will be summarized overall and with respect to CTCAE grade and relationship to study drug. TEAEs leading to study drug discontinuation, dose reduction/interruption, and with an outcome of death will also be summarized. Incidence SAEs will be summarized overall and with respect to study drug.

Shifts from baseline in ECOG and changes in vital signs, ECG parameters, hematology and serum chemistry parameters from baseline to the EOT will be examined. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified. Changes in NCI toxicity grading will be presented using shift tables and listings of clinically significant values.

7.6.7 Pharmacokinetic/Pharmacodynamic Analyses

PK parameters will be assessed by non-compartmental analysis, including maximum concentration observed (C_{max}), area under the concentration time curve (AUC) to the end of the dosing interval ($AUC_{0\text{-}tau}$), to infinite time ($AUC_{0\text{-}inf}$), clearance, elimination half-life ($t_{1/2}$) and volume of distribution will be calculated, if data allow.

PK-PD modeling and simulation will be performed and may be used in support of dose escalation decisions and determination of the RP2D and dosing schedule; it will however be reported separately.

An explorative analysis of the relationship between exposure and body weight, if data allow, will be conducted, either graphically or as part of the PK-PD modeling activities.

Further exploratory analysis of PK data may be performed, such as the potential relationship with other covariates. These analyses will be described in a separate document outside of the SAP.

Exploratory biomarker analyses will be performed using descriptive biostatistics.

7.6.8 Research Laboratory Analyses

Analyses of research laboratory samples, tumor biopsies, and immune response data will be described separately outside the context of this protocol and the SAP.

7.6.9 Timing of Analysis

In Phase 1, all available data will be reviewed to enable dose-escalation and dose selection decisions.

In Phase 2, the primary analysis will be conducted after all subjects have completed at least 6 cycles of treatment and completed the EOT Visit, or discontinued study treatment. A supplemental analysis may be completed at the end of study that includes the cumulative data collected after the final analysis (i.e. through the Follow-up Period).

7.6.10 Data Monitoring Committee

There will be no formal Data Monitoring Committee for this study. Safety data and all unacceptable toxicities will be reviewed by the SRT comprised of participating Investigators in the study, the Medical Monitor, and representatives of the Sponsor.

8 ADVERSE EVENT REPORTING

AEs, SAEs, events of special interest, and pregnancy occurring during the protocol-specified timeframes defined in Section 7.5.3.5 will be assessed and reported following guidelines provided in the following sections.

8.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Subjects should be instructed to report any AE that they experience to the Investigator. At each indicated visit, Investigators should make an assessment for AEs and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g. surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure.

Any medical condition already present prior to the first dose of study drug should be reported in medical history unless the medical condition or signs or symptoms present at baseline change in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g. ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

Examples of AEs include the following:

- Exacerbation of a chronic or intermittent preexisting condition, including an increase in frequency or intensity of the condition
- Signs, symptoms, or the clinical sequelae of a suspected interaction with another medical product

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational agent or a concurrent medication.

An overdose should not be reported as an AE or SAE; instead, the symptoms resulting from the overdose should be reported as the AE or SAE.

Examples of AEs do not include the following:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); instead, the medical condition that led to the procedure is an AE
- Situations that are unwanted but in which an untoward medical occurrence did not occur (e.g. admissions for respite care)
- Anticipated day-to-day fluctuations of a pre-existing disease or condition (present or detected before enrollment) that does not worsen overall

A follow-up is required for all subjects with AEs until the event has been resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal laboratory values at the EOT visit assessment, these events will be followed up until resolution or until they become clinically not relevant.

8.1.1 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE and the potential relationship between the AE and the study drug.

8.1.1.1 Assessment of Severity

The severity of all AEs should be graded according to the NCI-CTCAE v. 4.03 (http://ctep.cancer.gov/reporting/ctc.html). For AEs not listed in the CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject's daily activities
- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with subject's usual activities, but still acceptable
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject's daily activities, unacceptable
- Life-threatening (CTCAE Grade 4): Life-threatening consequences; urgent intervention indicated
- Death (CTCAE Grade 5): Death-related AE

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8.1.1.2 Attribution of Causality

The Investigator is obligated to estimate the relationship between the study drug(s) and the occurrence of each AE or SAE. The relationship (synonym: causality) is based on the Investigator's clinical judgment regarding the likelihood that study treatment caused the AE and may include consideration of some or all of the following factors:

- Alternative possible causes of the AE, including the subject's underlying disease or co-morbid conditions, other drugs, or other host and environmental factors
- The temporal sequence between the exposure to study treatment and the AE
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study treatment
- Whether the AE resolved or improved with decreasing the dose or stopping the study treatment (i.e. dechallenge); or recurred or worsened with re-exposure to the drug (i.e. rechallenge).

The Investigator should consult the IB in the determination of the assessment. The Investigator should consider all possible etiologies for the AE and render a causality assessment based on the most likely contributing factor to the AE.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report. However, the Investigator must assess causality for every event before the transmission of the SAE. The Investigator may change his or her opinion of the causality in light of follow-up information, amending the SAE report.

The assessment of the relationship between the AE and the study drug will be determined using one of the following attribution categories as outlined in the NCI Guidelines: Adverse Event Reporting Requirements (2013).

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely Related	The AE *is doubtfully related* to the intervention
Related to investigational agent/intervention	Possibly Related	The AE *may be related* to the intervention
	Probably Related	The AE *is likely related* to the intervention
	Definitely Related	The AE *is clearly related* to the intervention

AEs listed as possibly, probably, or definitely related are considered to have a suspected "reasonable causal relationship" to the investigational agent/intervention (ICH E2A). Per the ICH E2A and FDA guidelines, the expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

Additional guidelines in describing relationship:

- Related AEs follow a reasonable temporal sequence from the study drug administration and cannot be excluded as possibly or probably being caused by the study drug (e.g. existence of similar reports attributed to the suspected drug and/or its analogues; reactions attributable to the pharmacologic effect of the drug), and can be excluded as possibly being caused by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment. The AE can be fully explained by the administration of study treatment.
- Not Related: AE does not follow a reasonable temporal sequence from the study drug administration and can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment. Another factor is clearly the cause of the AE.
- For AEs occurring prior to initiation of study drug administration, the Investigator will assess relationship between the event and the protocol-required study procedures.

8.1.2 Disease-Related Events

Progression of the cancer under study is not considered an AE in this study unless it is considered treatment-related by the Investigator. The term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (e.g. resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s)..

8.1.3 Events of Special Interest

Drug induced liver injury is considered an event of special interest in this study and is defined as serum chemistry laboratory values consistent with Hy's Law criteria (i.e. all 3 of the following must coexist):

- ALT or AST $\geq 3 \times$ ULN
- Total bilirubin $\geq 2 \times$ ULN
- ALP $< 2 \times$ ULN

Laboratory values meeting all criteria for potential Hy's Law cases from the time of first study drug administration through the EOT visit should be reported following SAE reporting procedures Section 8.3.

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
    - NOTE: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalization;
    - NOTE: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e. no place to stay, live too far away to come for hospital visits) or for observation post-study drug administration will not be considered a SAE.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect; or
- An important medical event
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

8.3.1 Initial Reports

All SAE information whether initial or follow-up and any supporting documents (e.g. discharge summary, autopsy report) must be reported/forwarded to the Sponsor (or designee) within 24 hours of the knowledge of the information.

An SAE report will be completed for each observed or reported SAE as thoroughly as possible including all available details about the event and the signature of the Investigator. If the

Investigator does not have all information about an SAE, the Investigator will not wait to receive additional information before notifying the Sponsor of the event. The report will be updated when additional information is received.

8.3.2 Safety Reporting Contact Information

SAE and pregnancy reporting contact information may be found in the Study Reference Manual. Sites should contact the Medical Monitor for any safety concerns or questions.

8.3.3 Expedited Reporting Requirements

The Sponsor (or designee) will report all SAEs that are unexpected and considered related to the administration of the investigational agent to the appropriate health and regulatory authorities and Investigators in the form of an expedited safety report within 15 calendar days after receiving information on the SAE. The Investigators will notify their reviewing IRB/EC and other committee(s) as required by institutional policies.

The Sponsor will also report to the appropriate health and regulatory authorities by facsimile, email, or phone within 7 days of receiving the information, any unexpected life-threatening or fatal SAEs that are considered related to the investigational agent.

8.3.4 Follow-Up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit any supporting documentation (e.g. subject discharge summary or autopsy reports) via fax or email to the Sponsor or designee.

8.4 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 28 days of discontinuing study drug (or if the subject initiates new anticancer therapy, whichever is earlier) the Investigator should report the pregnancy and any follow-up information to the Sponsor or its designee within 24 hours of awareness of the information.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and Early Termination study procedures will be performed as appropriate. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Abortion, whether therapeutic, accidental, or spontaneous, should be reported as an SAE. Similarly, any congenital anomaly or birth defect in a child born to a subject exposed to the study drug should be reported as an SAE.

Monitoring of the subject or partner and pregnancy should occur until the conclusion of the pregnancy or final outcome. Report the outcome, including any premature termination. Follow live births for a minimum of 30 days or until the first well-baby visit. Any relevant information received by the Investigator after these time periods will be forwarded to the sponsor.

If the subject gives permission for her primary physician to be informed, the Investigator is to notify the subject's primary physician that she was participating in a clinical study at the time she became pregnant, and provide details of the treatment that the subject received.

The pregnancy reporting form along with the form completion instructions are provided in the Investigator study files.

9 DATA MANAGEMENT AND RECORD KEEPING

9.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRA will verify data recorded in the electronic data capture (EDC) system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for and electronically signed by the Investigator or assignee.

Data will be processed using a validated computer system conforming to regulatory requirements.

9.2 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

9.3 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator in order to be considered complete.

9.4 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study drugs, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

10.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

10.2 Investigator Requirements

Each Investigator must provide the Sponsor and/or its designee a completed and signed Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572 and Financial Disclosure Forms must be completed for all sub-Investigators listed on Form FDA 1572.

10.2.1 Disposition and Accountability of Investigational Products

The Investigator is responsible for the control of investigational products under study. An investigational product dispensing log must be kept current and should contain the following information:

- The identification number for each subject who is administered the investigational product
- The date(s) and quantity of the investigational product administered to the subject
- Documentation of proper disposal of used investigational product vials or unused vials subjected to temperature excursion
- Documentation of proper disposal (or return, at Sponsor's request) of unused investigational product vials.

The Investigator is responsible for investigational product accountability during on-site monitoring visits. All records and used/unused supplies of the investigational product must be available for inspection at every monitoring visit.

The study sites, per institutional guidelines, will destroy used investigational product vials after formulation for administration. The formulation of investigational product for administration and the destruction of each used vial will be documented in the investigational product accountability log. Unused investigational product will be destroyed at the study site after final investigational product accountability and notification by Sponsor, unless otherwise directed by Sponsor.

10.3 Institutional Review Board/Ethics Committee

The IRB/EC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB/EC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written

information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/EC by the Investigator.

Federal regulations and International Conference on Harmonisation (ICH) require that approval be obtained from an IRB/EC prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB/EC.

No study drug will be released to the site for dosing until written IRB/EC authorization has been received by the Sponsor.

10.4 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/EC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed and will document consent was obtained prior to enrollment in the study in the source documentation. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, auditors, the IRB/EC, and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

10.5 Study Monitoring Requirements

To ensure the study is conducted in accordance with the protocol, ICH GCP and applicable government regulations, the study monitor will aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, study drug management, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the monitor will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will

be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the site by signature and date on the study-specific monitoring log.

10.6 Disclosure of Data

Data generated by this study must be available for inspection by health and regulatory authorities (such as FDA, Health Canada, European Medicines Authority, and others), the Sponsor or designee, and the IRB/EC as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

10.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g. eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

10.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

10.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR §54. In addition, Investigators must commit to

promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

10.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

10.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (i.e. initiation of study centers) when the CTA and favorable ethics opinion have been received.

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SIGNATURE PAGE

STUDY TITLE:

I, the undersigned, have read Protocol ADU-CL-16 Amendment 2 and agree it contains all necessary information required to conduct the study.

Signature	Date
[redacted]	11/14/2018

INVESTIGATOR AGREEMENT

STUDY TITLE: A Phase 1/2, Dose Escalation, Safety and Tolerability Study of BION-1301 in Adults with Relapsed or Refractory Multiple Myeloma

By signing below I agree that:

I have read the amended protocol and agree it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provisions of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Aduro Biotech to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know this information is confidential and proprietary to Aduro Biotech and may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Aduro Biotech, with or without cause. I have the right to suspend enrollment of subjects at my study site if necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with United States Food and Drug Administration Regulations, Institutional Review Board/Ethics Committee Regulations, and International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

APPENDIX A: INTERNATIONAL MYELOMA WORKING GROUP CRITERIA FOR MEASURABLE DISEASE AND TUMOR RESPONSE

IMWG uniform response criteria by response subcategory for multiple myeloma (Rajkumar et al. 2011)

CR*	Stringent complete response (sCR)†	VGPR*	PR	SD	PD†
Negative immunofixation of serum and urine, *and*	CR as defined, *plus*	Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or*	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours	Not meeting criteria for CR, VGPR, PR, or PD	Increase of 25% from lowest response value in any of the following:
Disappearance of any soft tissue plasmacytomas, *and*	Normal FLC ratio *and*	≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 h	If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria		Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or*
< 5% PCs in bone marrow	Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry		If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥ 30%		Urine M-component (absolute increase must be ≥ 200 mg/24 h), *and/or*
			In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required		Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
					Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage 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/dL) that can be attributed solely to the PC proliferative disorder

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

PCs indicate plasma cells.

↵* Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

↵† Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels; “25% increase” refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the “lowest response value” does not need to be a confirmed value.

APPENDIX B: EUROPEAN GROUP FOR BLOOD AND MARROW TRANSPLANTATION CRITERIA FOR MINIMAL RESPONSE

Additional response criteria and updates (Rajkumar et al. 2011)

MR in patients with relapsed refractory myeloma adopted from the EBMT criteria	Immunophenotypic CR	Molecular CR
≥ 25% but ≤ 49% reduction of serum M protein *and* reduction in 24-hour urine M-protein by 50%-89%	Stringent CR *plus*	CR plus negative ASO-PCR, sensitivity 10^{-5}
In addition to the above criteria, if present at baseline, 25%-49% reduction in the size of soft tissue plasmacytomas is also required	Absence of phenotypically aberrant PCs (clonal) in BM with a minimum of 1 million total BM cells analyzed by multiparametric flow cytometry (with > 4 colors)	
No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)		

EBMT indicates European Group for Blood and Marrow Transplantation; PCs, plasma cells; and ASO-PCR, allele-specific oligonucleotide polymerase chain reaction.