

**A PHASE 1/2, DOSE ESCALATION, SAFETY AND  
TOLERABILITY STUDY OF BION-1301 IN ADULTS WITH  
REPLAPSED OR REFRACTORY MULTIPLE MYELOMA**

**Abbreviated Statistical Analysis Plan**

**VERSION 1.0**  
**DATE OF PLAN:**  
*18-Jul-2019*

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DATE OF PLAN:**

*18-Jul-2019*

**STUDY DRUG:**

*BION-1301*

**PREPARED FOR:**

*Aduro Biotech, Inc.  
740 Heinz Avenue  
Berkeley, CA 94710 USA  
Telephone: +1 510-848-4400*

Sponsor: Aduro Biotech, Inc.  
Protocol Number: ADU-CL-16  
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**Approval Signature Page:**



Document Author:   
Principal Biostatistician

Date

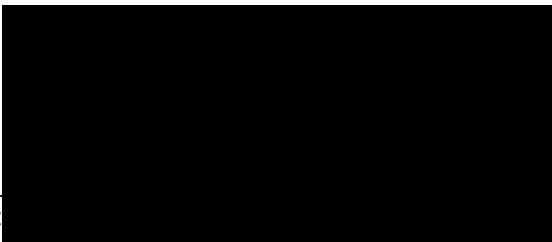
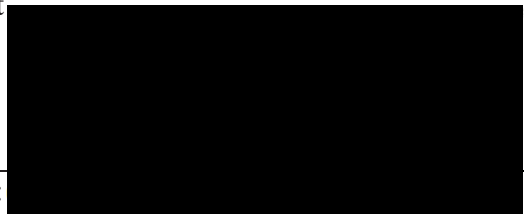
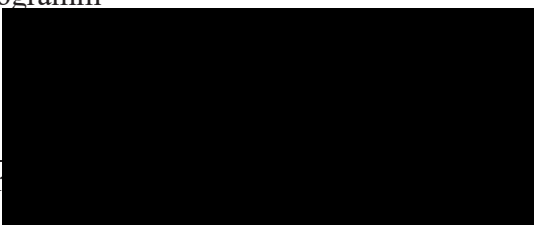


Document Reviewer:   
Associate Director of Biostatistics

Date

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## ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
APRIL	A proliferation-inducing ligand
ASAP	Abbreviated statistical analysis plan
ATC	Anatomical therapeutic chemical
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical study report
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EOT	End of treatment
IRR	Infusion related reaction
ISS	International staging system
IxRS	Interactive voice/web response system
LLN	Lower limit of normal
M-protein	Monoclonal Protein
MedDRA	Medical Dictionary for Medical Affairs
MM	Multiple myeloma
MRD	Minimal residual disease
MTD	Maximum tolerated dose
NA	Not applicable
NCI	National cancer institute
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
Q2W	Once every two weeks
QW	Once a week (weekly)
R-ISS	Revised international staging system
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse events
SAF	Safety analysis set
SD	Standard deviation
SOC	System Organ Class
SRT	Safety review team
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO-DDE B2	World Health Organization Drug Dictionary Enhanced B2

# 1. INTRODUCTION

This is an abbreviated statistical analysis plan (ASAP) designed to outline the planned analysis required to satisfy the Clinical Study Report (CSR) for study number ADU-CL-16: A Phase 1/2, Dose Escalation, Safety and Tolerability Study of BION-1301 in Adults with Relapsed or Refractory Multiple Myeloma. The derivation and analysis of pharmacokinetic, biomarker, and pharmacodynamic endpoints, will be discussed in another standalone document. The statistical analyses and summary tabulations described in this ASAP will provide the basis for the CSR synopsis reporting of the final analysis results from this trial and will be limited to the Phase 1 portion of the study.

Analysis populations, data handling rules, statistical methods, changes from the study protocol, and formats for data presentation are provided. The content of this ASAP is based on the protocol Amendment 2 dated 13Nov2018.

ASAP Revision Chronology:  
 V1.0                                 18JUL2019                                 Original

# 2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary</b>	
<ul style="list-style-type: none"> <li>• Evaluate safety and tolerability of BION-1301 when administered as a single-agent</li> </ul>	<ul style="list-style-type: none"> <li>• Incidence of dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), and changes in safety parameters</li> </ul>
<b>Secondary</b>	
<ul style="list-style-type: none"> <li>• Characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profile of BION-1301</li> <li>• Evaluate clinical activity of BION-1301</li> </ul>	<ul style="list-style-type: none"> <li>• PK parameters based on BION-1301 serum levels following a single dose and after repeated dosing *</li> <li>• Change from baseline in soluble anti-proliferation-inducing ligand (APRIL)*</li> <li>• Relative reduction in serum and urine monoclonal protein (M-protein) levels defined as the maximum percent reduction from baseline</li> </ul>

\* pharmacokinetic, biomarker, and pharmacodynamic endpoints will be addressed in a separate standalone PK/PD analysis plan



### 3. STUDY DESIGN

#### 3.1. Study Design and Population

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 consists of adults with relapsed or refractory Multiple Myeloma (MM) whose disease has progressed after at least 3 prior systemic therapies. BION-1301 will be administered in 28-day cycles.

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

The dosing interval was once every 2 weeks (Q2W) during initial dose escalation. Additional cohorts were 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 were evaluated for each cohort to inform the dosing schedule to be evaluated in subsequent cohorts. Subjects continued dosing until disease progression or unacceptable toxicity.

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

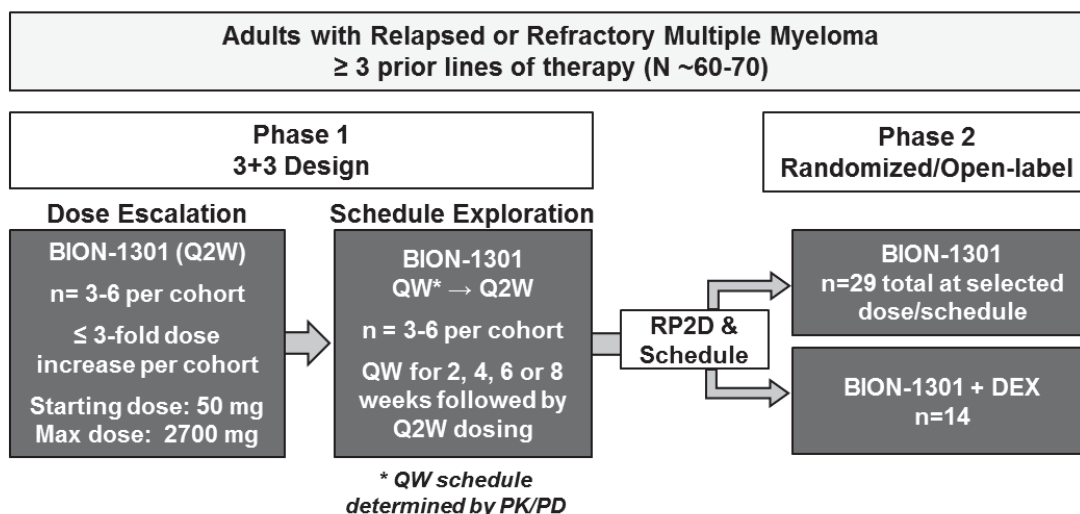
Additional guidelines specific to Phases 1 and 2 of the study as well as a schedule of visits and procedures are provided in the study protocol.

The study was prematurely terminated by the Sponsor on 07 May 2019 after enrollment of 21 subjects into 6 cohorts in Phase 1 of the study. Only the objectives and endpoints specified in the protocol for Phase 1 and identified in section 2 above will be described in this ASAP.

Figure 1: Study Design

<b>Screening Period</b> <i>Confirm eligibility</i> Up to 28 days	<b>Treatment Period (28-day Dosing Cycles)</b> <i>Until disease progression or unacceptable toxicity</i> BION-1301 (IV infusion) +/- Dexamethasone (40 mg QW PO; Phase 2 only)	<b>Follow-Up Period (Q12W)</b> Safety reporting Subsequent cancer treatment Survival
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**Study Population & Enrollment Plan:**



### 3.2. Randomization and Blinding

All subjects were sequentially assigned a unique identification number during Screening.

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

- In Phase 1 of the study, subjects were sequentially assigned to dose cohorts as specified in the study design
- The Cycle 1 Day 1 dose was staggered by at least 24 hours for the first 2 subjects dosed in each cohort

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

### 3.3. Sample Size Considerations

During Phase 1, dose escalation was 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.

### 3.4. Data Monitoring Committee/Safety Review Team

There was no formal Data Monitoring Committee for this study. Safety data and all unacceptable toxicities were reviewed by the Safety Review Team (SRT) comprised of participating Investigators in the study, the Medical Monitor, and representatives of the Sponsor. Dose escalation and reduction decisions, additional enrollment specifications, and recommendation of the RP2D(s) and dosing schedule for expansion were planned to be made by the SRT. TEAEs, DLTs and safety data will continue to be reviewed by the SRT throughout the study.

### 3.5. Interim Analysis

A Safety Review Team monitored data during the study, as described in Section 3.4. Otherwise, no other formal interim analysis activities were planned per the protocol.

### 3.6. Timing of Analyses

All available phase 1 data were reviewed to enable dose-escalation and dose selection decisions and will be part of the final analysis as of the final database lock. As of 07 May 2019, Aduro decided to cease development activities for BION-1301 after the last subject in cohort 6 completed treatment. The Phase 2 portion of the study was not enrolled.

## 4. DATA ANALYSIS CONSIDERATIONS

All analyses will be conducted based on SAS 9.4 or higher.

All clinical data in the database, with the exception of laboratory accession numbers, central lab collection dates, and study drug supply administrative data, will be presented in by-subject data listings.

Unless otherwise stated, all listings will be sorted by cohort, site ID, subject number, and assessment date (and time, if available).

Unless stated otherwise, continuous data will be summarized based on n, mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3), minimum value, and maximum value. For continuous variables, if n=1, the SD cannot be calculated and will be displayed as Not applicable (NA).

Unless stated otherwise, categorical data will be summarized using n and percentage based on the number of non-missing values.

- The number of missing values will be presented as a separate category with no percentage, but only if one or more subjects are missing data.

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- Counts of zero will be presented without percentages.

#### Precision

- Mean, Median, Q1, and Q3: one additional decimal place to that reported for Minimum and Maximum
- SD: two additional decimal places than the Minimum and Maximum
- Percentages: reported to one decimal place

Descriptive summaries will be presented by cohort and overall. No statistical significance test will be performed.

All data up to the time of study completion/withdrawal from the study will be included in the analysis, regardless of duration of treatment.

With exception to missing data handling noted in section 5.10, data will not be imputed for analysis purposes.

Summaries by visit will be produced for sample sizes  $\geq 2$ .

Numbering for data displays will be based on ICH E3.

#### 4.1. Stratification and Covariates

There are no formal plans for analysis stratification.

#### 4.2. Evaluation of Subgroups

Subgroup analyses are not planned to be performed for the final analysis.

#### 4.3. Multiple Comparisons and Multiplicity

Not Applicable.

### 5. GENERAL DATA HANDLING CONVENTIONS

#### 5.1. Assigned and Actual Treatment

Subjects were assigned to a study treatment based on study design as seen in Figure 1 and detailed in Table 1 and Table 2. The Phase 1 portion of the study evaluated single-agent BION-

1301, open-label, where subjects received infusion(s) at the study site. Subjects will be displayed based on assigned study dosing schedule.

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

<b>BION-1301 Dose Cohort (proposed dose <sup>1</sup>)</b>	<b>0/3 subjects have DLT<sup>2,3</sup></b>	<b>1/3 subjects have DLT<sup>2,3</sup></b>	<b>≤1/6 subjects have DLT<sup>2</sup></b>	<b>≥2 in a cohort have DLT<sup>2</sup></b>
<b>1 (50 mg) Q2W</b>	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 <sup>4</sup>
<b>2 (150 mg) Q2W</b>	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
<b>3 (450 mg) Q2W</b>	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
<b>4 (1350 mg) Q2W</b>	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
<b>5 (2700 mg) <sup>5</sup> Q2W</b>	Expand to 6 evaluable subjects	Expand to 6 evaluable subjects	Maximum dose reached	MTD exceeded; no further enrollment at dose level
<b>6 (1350 mg) <sup>6</sup> QW (x8) -&gt; Q2W</b>	Expand to 6 evaluable subjects	Expand to 6 evaluable subjects	Maximum dose reached	MTD exceeded; no further enrollment at dose level
<ol style="list-style-type: none"> <li>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.</li> <li>DLT evaluation period is 28 days after first dose of BION-1301 (Cycle 1).</li> <li>If a 4<sup>th</sup> subject is enrolled, all 4 subjects must complete DLT evaluation period. If 1/4 subjects has DLT, expand to 6 evaluable subjects.</li> <li>SRT will evaluate all available data and decide whether to initiate Dose Cohort -1 at a dose of 5 mg.</li> <li>Evaluation of additional intermediate dose cohorts will follow the same 3+3 rules for dose cohort expansion. Dose level will not exceed 2700 mg.</li> <li>Dosed every week for 8 weeks, followed by every 2 week dosing (see Table 2)</li> </ol> DLT = dose-limiting toxicity; MTD = maximum tolerated dose; SRT = safety review team; Q2W = dosed every 2 weeks; QW = dosed every week				

Table 2: Phase 1 - BION-1301 Dosing Schedule Exploration Options (21-day cycles)

<b>BION-1301 Dose Schedule</b>	<b>QW Dosing (Assigned QW dose level)<sup>1</sup></b>	<b>Q2W Dosing (Assigned dose level)<sup>1,2</sup></b>
Q2W	N/A	All Cycles: 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

<sup>1</sup> 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.

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

## 5.2. Reference Dates

- Informed Consent date is defined as the eCRF provided date on which a subject signed the informed consent.
- Treatment start date is defined as the date of first dose of study drug.
- Treatment end date is defined as the date of last dose of study drug.
- Age will not be calculated and will come directly from the eCRF. The eCRF uses the informed consent date as its reference date for age calculation.
- Safety data, such as AEs and laboratory assessments will use the treatment start date as a reference date.
- Study day will be based on treatment start date as a reference date.

## 5.3. Study Day and Duration Variables

Reference date calculations will generally be defined as the following, assuming non-missing dates:

- date of interest – reference date + 1 when the date of interest >= reference date;
- otherwise, date of interest – reference date.

If either date is missing, reference date calculations will not be performed. Date imputation will be performed as identified in Section 5.6.

For instance, study day will be based on the treatment start date as the reference date and would either have a negative value if collected before dosing or a positive value if collected on or after the day of drug dosing; there will be no study day zero.

Duration of time is dependent on reference dates and will be calculated in a manner similar to that of the reference date calculation, assuming that dates of interest will strictly follow reference dates (e.g. no negative values). For example, duration on study is defined as the end of study date – treatment start date + 1. Duration of treatment is defined as treatment end date – treatment start date + 1, where treatment end date is the date of last dose of study drug. Subjects still receiving ongoing treatment or participating in study follow up at the time of analysis will use imputed treatment end and end of study dates as described in Section 5.7.

When reporting duration outcomes, the results (in days) above will be converted to an appropriate unit. When reporting in months it will be divided by 30.4375; for reporting in weeks it will be divided by 7; and for reporting in years it will be divided by 365.25.

#### 5.4. Study Time Periods

Safety reporting in general will be classified by the following study periods for analysis:

- Pre-therapy is defined as the period prior to a subject’s treatment start date.
- On-therapy is defined as the period between a subject’s treatment start date and treatment end date +28 days.
- Post-therapy is defined as the period of time following the on-therapy period.

##### 5.4.1. Adverse Events

Adverse event study periods will be classified as follows:

<b>Event Type</b>	<b>Reporting Period</b>	<b>Additional Requirements</b>
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 of the study protocol
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## 5.5. Baseline, Post-Baseline Changes, and Last Observed Value (LOV)

Unless stated otherwise, baseline and post-baseline change values will be based on the following:

Baseline will be based on the last non-missing value collected prior to or on the treatment start date [and time, if applicable]. Post-baseline values will be those collected after the treatment start date.

Change from baseline is defined as: value at visit – baseline value.

Percentage change from baseline is defined as: (value at visit – baseline value)/baseline value X 100%.

Most extreme change: The maximum most extreme change will be based on be the maximum grade change. This calculation will consider assessments collected during the on-therapy period and assessed with CTCAE grading, scheduled or unscheduled.

Maximum percent reduction is defined as the largest percent reduction in the change from baseline at any visit.

## 5.6. Imputation of Partial Dates

### Adverse Events and Concomitant Medications

- If the AE start date is completely missing, or if the subject was not treated, no imputation will be conducted.
- If the AE start date is missing day and month, do the following:
  - If the treatment start date is missing or the AE start year does not fall in the same year as that of the treatment start date or if the AE record contains information to indicate that the event ended before the treatment start date (e.g. the AE end date month and year are earlier than the treatment start date or the full AE end date is known and occurs earlier than the treatment start date), then set the AE start month and day to January 1<sup>st</sup>.
  - Otherwise, set the AE start date to the treatment start date.
- If only the AE start day is missing, do the following:
  - If the study treatment start date is missing or the AE start month and year does not fall in the same month and year as that of the treatment start date or if the AE



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- contains information to indicate that the event ended before the treatment start date, then set the AE start day to the 1<sup>st</sup> day of the month of the AE start date.
- Otherwise, set the AE start date to the treatment start date.
- AE end dates will not be imputed.

These imputation rules will also be applied to concomitant medication dates.

### **Treatment and Study End Date**

Missing treatment and study end dates will not be imputed at the end of the study.

### **Date of Initial Multiple Myeloma Diagnosis**

- If the date is completely missing, no imputation will be conducted.
- If the date is missing month and day, they will be set to 01 January.
- If the date is missing only day, it will be set to 01 of the month.

## **5.7. Multiple Assessments and Visit Windows**

Nominal visits (e.g. those identified by the study CRF) will be the basis of summarization and statistical analysis; no visit date windowing will be conducted. Unscheduled data may be included in summaries of most extreme and baseline; summaries of specific abnormalities any time post-baseline; and subject data listings.

## **5.8. Missing Data**

Missing data imputation for AE, concomitant medication, and date of diagnosis date imputations are described in Section 5.6. Otherwise, missing data will not be imputed.

# **6. STUDY SUBJECT DATA**

## **6.1. Analysis Populations/Sets**

The Safety population (SAF) is defined as all subjects who receive any amount of study drug. All reporting of study data will be based on this population.

Additional analysis populations are described in the study protocol; however, the SAF is the only analysis set used for reporting study data in this ASAP, unless otherwise specified.

## **6.2. Subject Disposition**

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Summaries of analysis population membership; final study status (ongoing, completed or discontinued), including reasons for study discontinuation; treatment status (ongoing, completed or discontinued), including reasons for treatment discontinuation will be produced based on all subjects enrolled in the study. Time on study and duration of treatment will also be summarized.

Screen failures and final subject disposition status will be listed.

### 6.3. Protocol Deviations

Protocol deviations will be identified and classified as major or minor (violations) before the database is locked. Major protocol deviations may include but are not limited to:

- Violation of Inclusion/Exclusion Criteria
- Dose not properly administered
- Use of prohibited therapies

Protocol deviations will be summarized by cohort.

A listing of protocol deviations will be provided.

### 6.4. Demographic and Baseline Characteristics

Subject demographics will be summarized and listed for the SAF. These will include age in years, sex, ethnicity, race, baseline height (cm), baseline weight (kg), and baseline BMI (kg/m<sup>2</sup>). Age will also be categorized as a categorical variable (< 65, ≥ 65) for reporting.

The following conversions and equations will be used as applicable:

- Height (in cm) = height (in inches) \* 2.54
- Weight (in kg) = weight (in lbs) \* 0.4536
- BMI (kg/m<sup>2</sup>) = weight(kg)/[height(m)<sup>2</sup>]

Baseline disease characteristics will also be summarized by cohort. Subject's Eastern cooperative oncology group (ECOG) performance status, duration of time from initial diagnosis to informed consent (in months); International staging system (ISS) stage at diagnosis and study entry; Revised ISS (R-ISS) stage at diagnosis and study entry; MM heavy chain subtype at diagnosis; MM light chain subtype at diagnosis and study entry; cytogenetics abnormalities at diagnosis; evidence of lytic bone disease at study entry; evidence of extramedullary disease at diagnosis and study entry; and any prior cancer treatments categories (Yes/No) collected on the eCRF will be displayed.

Subject demographics and baseline characteristics will be listed.

## 6.5. Medical History

General medical history data will be listed.

## 6.6. Prior and Concomitant Medication

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred name based on the WHO Drug Dictionary (WHO-DDE B2, September 2017). Prior medications are those which have been identified to have been discontinued prior to first study treatment (e.g. taken exclusively during the pre-therapy period). Concomitant medications are those which have been identified to have been taken at any point during the on-therapy period.

Prior and concomitant medications will be presented in data listings; medications which do not occur during the on-therapy period will be identified.

## 6.7. Prior Anticancer Therapies

Prior anticancer therapies are collected in the eCRF and data will be presented in data listings:

- Prior radiotherapy including the site of radiotherapy and reason for therapy
- Prior cancer related surgery including type of surgery and reason for surgery
- Prior cancer systemic therapy including line of therapy, transplant information (if applicable), number of cycles and best overall response. Also, minimal residual disease (MRD) status, relapse or progression, reason for therapy and reason medication was stopped. Each therapy will be coded to ATC class and preferred name based on the WHODD (September 2017)
- Transfusions including type, number of units and indication for transfusion

## 6.8. Study Drug Exposure and Compliance

Data will be summarized for BION-1301 study treatment and will be displayed by each Phase 1 cohort.

Duration of treatment (in months, as described in Section 5.3) will be summarized as a continuous variable for BION-1301.

The number of infusions of BION-1301 will be reported as both a continuous and categorical outcome; categories for reporting will be < 5 infusions; 5 to 10 infusions; > 10 to 15 infusions; and > 15 infusions.

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The number of cycles of administration of BION-1301 will be reported as a continuous and categorical outcome; categories for reporting will include: < 5 Cycles; 5 to 15 Cycles; > 15 to 25 Cycles; and > 25 Cycles.

The average volume administered for each infusion within a cycle will be summarized. Total infusion volume administered at each infusion is collected on the eCRF. The average for each subject will be calculated as:

$$\frac{\sum(\text{total volume administered at each infusion})}{\text{number of infusions within the cycle}}$$

The average dose for each BION-1301 cycle will be summarized. Total expected dose of BION-1301 is reported at each infusion and is collected on the eCRF. As interruptions can occur, the total of dose given will be calculated as:

$$\frac{\text{Volume administered}}{\text{Volume Prepared}} \times \text{Total Dose}$$

The average dose within a cycle for each subject will be calculated as:

$$\frac{\sum(\text{total dose received at each infusion})}{\text{number of infusions within the cycle}}$$

The incidence of infusion interruptions as well as the total number of interruptions will be displayed. Reasons for infusion interruptions will be summarized. Also, subjects who discontinued BION-1301 infusion prior to completion along with the reason will be summarized.

BION-1301 administration, infusion interruption, as well as any derived drug exposure metrics, will be listed.

## 7. EFFICACY

Efficacy assessments evaluated in Phase 1 will be included in subject listings and will be presented on the SAF.

### 7.1. Tumor Response Assessments

Tumor assessment were performed throughout the study and evaluated according to the International Myeloma Working Group (IMWG) criteria. Response data as assessed by the investigator will be listed.

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## 7.2. Urine and Serum M-Protein

Efficacy laboratory assessments were collected throughout the study. Change from baseline and percent change from baseline will be derived as applicable and displayed in subject listings. The maximum percent reduction from baseline will be summarized by cohort.

## 8. PHARMACOKINETICS/PHARMACODYNAMICS

PK parameters will be assessed by non-compartmental analysis by a separate vendor, and will be discussed in a separate PK/PD/biomarker Analysis Plan.

## 9. SAFETY

All safety analysis reporting (tables and listings) will be based on the SAF. Summary tables will be presented by cohort and overall. Safety data will be listed by cohort, subject, cycle and infusion as applicable.

### 9.1. 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.

AEs will be assessed for severity using the NCI-CTCAE v. 4.03, relationship to BION-1301 (Definitely Related, Probably Related, Possibly Related, Unlikely Related, Unrelated), and seriousness (Yes, No). AEs will be considered treatment-emergent if the event occurs within the on-therapy period, the event was pre-existing and worsened in severity or became serious after the initiation of study drug.

An overview of treatment-emergent AEs (TEAEs) will be produced displaying counts and percentages of subjects with any incidences of: TEAEs, TEAEs with CTCAE Grade 3 or higher, TEAEs related to study treatment, TEAEs with CTCAE Grade 3 or higher related to study treatment, SAEs, TEAEs leading to study drug discontinuation, infusion-related reactions (IRRs), TEAEs leading to BION-1301 dose reduction/interruption; dose-limiting toxicities (DLTs), TEAEs of special interest (AESIs), and fatal TEAEs.

A separate overview of AEs identified as IRRs related to BION-1301 will be provided. This display will include the number of infusions received by subjects, the number of subjects having an IRR, total number of IRRs per subject, maximum IRR grade, and dose modifications resulting from IRRs.

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Adverse events will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA, Version 20.1) for reporting by system organ class (SOC) and preferred term (PT) in descending order of overall incidence. Events will be summarized. For these summaries, subjects with multiple AEs with the same SOC and/or PT will only be counted once at each level of summarization.

Summaries of adverse events by SOC and PT will include the following types:

- TEAEs;
- TEAEs related to study treatment (Definitely Related, Probably Related, or Possibly Related);
- TEAEs with CTCAE Grade 3 or higher;
- TEAEs with CTCAE Grade 3 or higher related to study treatment;
- BION-1301 IRR;
- TEAEs leading to dose reduction/interruption;
- SAEs;
- TEAEs leading to study drug discontinuation.

To account for potential differences in the extent of exposure between the treatment categories, a subject-year adjusted rate will also be presented. The rate is calculated as the number of subjects with an event divided by the total subject-years of safety observation, where subject-years of safety observation for each subject is defined as duration of safety observation in days divided by 365.25.

A comprehensive listing of all AEs reported will be provided in a by-subject data listing. Furthermore, a separate listing of SAEs will be provided.

Events occurring during the pre-therapy study period will be listed.

## **Deaths**

The number and percent of subjects who died along with primary cause of death will be summarized overall. All death data will be listed.

## **9.2. Clinical Laboratory Evaluations**

Clinical chemistry and hematology parameters will be reported based on the International System of Units (SI). The following laboratory evaluations will be reported in data summaries, with asterisks (\*) indicating those that will be graded using NCI-CTCAE:

Hematology: Hematocrit, white blood cell\*, absolute neutrophil count\*, lymphocytes\*, hemoglobin\*, monocytes, eosinophils, basophils, red blood cell, and platelet count\*

Clinical chemistry: sodium\*, potassium\*, chloride, bicarbonate, glucose\*, blood urea nitrogen, creatinine\*, lactate dehydrogenase, alanine aminotransferase\*, aspartate aminotransferase\*,

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alkaline phosphatase\*, bilirubin (total\*, direct, indirect), total protein, albumin\*, calcium, magnesium\*, phosphate\*, and uric acid.

Safety laboratory assessments will be summarized by absolute value and change from baseline at each visit will be displayed by cohort and cycle.

Shift tables displaying the shift from baseline to the worst value of NCI-CTCAE grade will be presented based on the most extreme change as it relates to the relevant NCI-CTCAE definition.

All laboratory parameters will be provided in subject data listings.

### 9.3. Other Safety Evaluations

The SAF population will be used for reporting the following other safety evaluations.

#### 9.3.1. Vital Signs

Vital signs include: respiratory rate (breaths/min); temperature (°C); systolic and diastolic blood pressure (mmHg); pulse (bpm); height (cm) and weight (kg).

Vital sign data will be provided in data listings.

#### 9.3.2. ECOG Performance Status

ECOG performance status is assessed from baseline to end of treatment (EOT) will be provided in data listings.

#### 9.3.3. Electrocardiogram

Electrocardiogram (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. Observed values for ECG parameters will be listed.

#### 9.3.4. Physical Examinations

Physical examinations including plasmacytoma evaluations will be presented in subject data listings.

## 10. CHANGES TO THE PLANNED ANALYSIS

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The ADU-CL-16 trial was ended after Phase 1 and before Phase 2. As such, all protocol-specified analyses related to the RP2D and the Phase 2 objectives and endpoints, including all efficacy analyses, are omitted and will not be summarized.



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## 12. APPENDICES

A full list of tables and listings will be provided in a separate document.