5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before randomization.

The inclusion and exclusion criteria for enrolling participants in this study are described below. Investigators should ensure that all study enrollment criteria have been met at screening. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

A participant is considered eligible if the last observation before administration of the study treatment satisfies the inclusion and exclusion criteria. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before administration of the study treatment such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

Age

1. Be ≥18 years of age (or the legal age of majority in the jurisdiction in which the study is taking place, whichever is greater) at the time of informed consent.

Type of Participant and Disease Characteristic(s)

2. Documented multiple myeloma as defined by the criteria below:
   a. Multiple myeloma diagnosis according to the IMWG diagnostic criteria (Appendix 9).
   b. Measurable disease at screening as assessed by central laboratory, defined by any of the following:
      i. Serum M-protein level ≥0.5 g/dL (central laboratory); or
      ii. Urine M-protein level ≥200 mg/24 hours (central laboratory); or
      iii. Light chain multiple myeloma without measurable M-protein in the serum or the urine: serum Ig FLC ≥10 mg/dL (central laboratory) and abnormal serum Ig kappa lambda FLC ratio (central laboratory) (see Appendix 9).

   NOTE: All attempts should be made to determine eligibility of the participant based on the central laboratory results of screening blood and urine M-protein measurements. In exceptional circumstances and after discussion with and written approval by the sponsor, the local laboratory results of blood and urine M-protein measurements may be used to determine initial eligibility, but only if the results are clearly (ie, ≥25% or more) above the

thresholds for measurability. In such cases, central laboratory results should still be obtained prior to the start of administration of study treatment in order to establish baseline values and confirm the results from the local laboratory.

3. Relapsed or refractory disease as defined below:
   a. Relapsed disease is defined as an initial response to prior treatment, followed by confirmed PD by IMWG criteria >60 days after cessation of treatment.
   b. Refractory disease is defined as <25% reduction in M-protein or confirmed PD by IMWG criteria during previous treatment or ≤60 days after cessation of treatment.
4. Documented evidence of PD or failure to achieve a minimal response to the last line of therapy based on investigator's determination of response by IMWG criteria on or after their last regimen.
5. Have an ECOG performance status score of 0, 1, or 2 at screening and immediately prior to the start of administration of study treatment.

Sex and Contraceptive/Barrier Requirements

6. A POCBP must have a negative highly sensitive serum pregnancy test within 10 to 14 days prior to C1D1 and a further negative serum or urine pregnancy test within 24 hours prior to the start of study treatment, and must agree to further urine or serum pregnancy tests during the study and within 6 months after receiving the last dose of study treatment.
7. A participant must be (as defined in Appendix 4):
   a. Not of childbearing potential, or
   b. Of childbearing potential and
      i. Practicing true abstinence; or
      ii. Practicing at least 2 reliable methods of contraception simultaneously, including one highly effective method of contraception and one other effective method of contraception (details in Appendix 4). Contraception must begin 4 weeks prior to dosing, continue during study treatment, including during dose interruptions, and through 6 months after the last dose of study treatment.

   Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy (Appendix 4).

   NOTE: If a participant becomes of childbearing potential after start of the study they must comply with point (b) as described above. If a participant's reproductive status is questionable, additional evaluation should be considered.

   NOTE: An interaction between hormonal contraception and talquetamab or teclistamab has not been formally studied. Therefore, it is unknown whether talquetamab or teclistamab may reduce the efficacy of the contraception method. If a participant is receiving talquetamab or teclistamab and is using hormonal contraceptives, an additional barrier method must be used.

   NOTE: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in

relation to the duration of the study and the preferred and usual lifestyle of the participant.

8. A participant using PO contraceptives must use an additional contraceptive method (details in Appendix 4).
9. A participant must agree not to be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study treatment.
10. A participant must agree not to donate gametes (ova, oocytes, sperm) or freeze for future use for the purposes of assisted reproduction during the study and for 6 months after receiving the last dose of study treatment. Participants should consider preservation of gametes prior to study treatment as anticancer treatments may impair fertility.
11. A participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for a minimum of 6 months after receiving the last dose of study treatment.
    NOTE: If the participant's partner is a person of childbearing potential, the participant must use condoms (with or without spermicide) and the partner of the participant must also be practicing a highly effective method of contraception (see Appendix 4). A participant who is vasectomized must still use a condom (with or without spermicidal), but the partner is not required to use contraception.
12. A participant must agree not to plan to father a child while enrolled in this study or within 6 months after the last dose of study treatment.

Informed Consent

13. Criterion modified per Amendment 2:
    13.1. Must sign an ICF indicating that participant understands the purpose of, and procedures required for, the study and is willing to participate in the study. In certain circumstances, when it is determined that a potential research participant is cognitively impaired, has fluctuating or limited decision-making capacity or prospective incapacity, consent may be obtained from a legally designated representative, if permitted by local regulations.
14. Must be willing and able to adhere to the lifestyle restrictions specified in this protocol (Section 5.3; including to not donate blood or blood components), including adherence to the global PPP or local PPP/REMS program for pomalidomide.

Prior Therapy Restrictions or Requirements

15. Criterion modified per Amendment 2:
    15.1. Received 1 to 4 prior lines of antimyeloma therapy (Appendix 10) including a minimum of 2 consecutive cycles of an anti-CD38 mAb at the dosing schedule (or minimum of 6 doses if anti-CD38 mAb was only part of a maintenance regimen) in any prior line and 2 consecutive cycles of lenalidomide in any prior line.
    NOTE: Participants who have received only one prior line of myeloma therapy must be considered lenalidomide refractory or intolerant to treatment (ie, have demonstrated PD by IMWG criteria on or within 60 days of completion of lenalidomide containing regimen). Participants who received ≥2 prior lines of antimyeloma therapy must be considered lenalidomide exposed.

NOTE: A single line of therapy may consist of 1 or more agents and may include induction, hematopoietic stem cell transplantation, and maintenance therapy. Radiotherapy, bisphosphonate, or a single short course of corticosteroids (no more than the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy.

Clinical Laboratory Values

16. Have clinical laboratory values meeting the following criteria during the Screening Phase and within 72 hours of the first dose of study treatment. If 1 or more criteria are not met 72 hours prior to dosing, one repeat of laboratory testing is permitted.

Table 15: Adequate Organ Function

Hematology	
Hemoglobin	≥8 g/dL (≥5 mmol/L; without transfusion support or erythropoietin use within 7 days before the laboratory test)
Platelets	≥75×10^9/L in participants in whom <50% of bone marrow nucleated cells are PCs and ≥50×10^9/L in participants in whom ≥50% of bone marrow nucleated cells are PCs (without transfusion support or thrombopoietin receptor agonist within 7 days before the laboratory test)
ANC	≥1×10^9/L (prior growth factor support is permitted but must be without support for 7 days for G-CSF or GM-CSF and for 14 days for pegylated G-CSF before the laboratory test)
Chemistry	
AST and ALT	≤2.5×ULN
eGFR	≥30 mL/min based on Modified Diet in Renal Disease 4-variable formula calculation (see Appendix 11) or creatinine clearance measured by a 24-hour urine collection
Total bilirubin	≤2×ULN; except in participants with congenital bilirubinemia, such as congenital nonhemolytic hyperbilirubinemia (in which case direct bilirubin ≤1.5×ULN is required)
Serum calcium corrected for albumin	≤14 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L; see Appendix 12)

17. HIV-positive participants are eligible if they meet all of the following:
    a. No detectable viral load (ie, <50 copies/mL) at screening
    b. CD4+ count >300 cells/mm^3 at screening
    c. No AIDS-defining opportunistic infection within 6 months of screening
    d. Receiving HAART. Any changes in HAART due to resistance/progression should occur at least 3 months prior to screening. A change in HAART due to toxicity is allowed up to 4 weeks prior to screening.
    NOTE: HAART that could interfere with study treatment is excluded (consult the sponsor for a review of medications prior to enrollment).

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Medical Conditions

1. Criterion modified per Amendment 2:
   1.1. Contraindications or life-threatening allergies, hypersensitivity, or intolerance to any study drug or its excipients (refer to the talquetamab IB, teclistamab IB, and appropriate prescribing information). Additional exclusion criteria pertaining to specific study drugs include:
   a. GPRCD5-directed therapy or pomalidomide.
   b. A participant is not eligible to receive PVd in Arm C if any of the following are applicable:
      i. Does not meet criteria for bortezomib retreatment (failure to achieve at least PR to prior bortezomib treatment, or progression by IMWG criteria on therapy or within 6 months after cessation of prior bortezomib treatment)
      ii. Intolerance, defined as prior therapy discontinued due to any AE related to bortezomib
      iii. Grade 1 peripheral neuropathy with pain or Grade ≥2 peripheral neuropathy as defined by NCI-CTCAE Version 5.0
      iv. Received a strong CYP3A4 inducer (see Section 6.9.3.3) within 5 half-lives prior to randomization.
   c. A participant is not eligible to receive EPd (Arm C)
      i. if they have received prior elotuzumab therapy.
      ii. If they have NOT received prior proteosome inhibitor AND lenalidomide.
   d. Received prior teclistamab therapy.
   e. Participants with history of multiple myeloma that is refractory to any T-cell-redirected therapy per IMWG diagnostic criteria (Appendix 9).
2. Stroke, transient ischemic attack, or seizure within 6 months prior to signing ICF.
3. Criterion modified per Amendment 2:
   3.1. Presence of the following cardiac conditions:
   a. NYHA Class III or IV congestive heart failure (see Appendix 19)
   b. Myocardial infarction, unstable angina, or coronary artery bypass graft ≤6 months prior to randomization
   c. History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
   d. History of severe non-ischemic cardiomyopathy.
4. Major surgery or had significant traumatic injury within 2 weeks prior to the start of administration of study treatment, or will not have fully recovered from surgery, or has major surgery planned during the time the participant is expected to be treated in the study or within 2 weeks after administration of the last dose of study treatment. **NOTE**: Participants with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery. If there is a question whether a procedure is considered a major surgery, the

investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study.

5. Concurrent medical or psychiatric condition or disease that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study, such as:
    a. Acute diffuse infiltrative pulmonary disease.
    b. Evidence of active systemic viral, fungal, or bacterial infection, requiring systemic antimicrobial therapy.
    c. Active autoimmune disease requiring systemic immunosuppressive therapy within 6 months before start of study treatment. **EXCEPTION**: Participants with vitiligo, controlled type I diabetes, and prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing are eligible regardless of when these conditions were diagnosed.
    d. Disabling psychiatric conditions (eg, alcohol or drug abuse), severe dementia, or altered mental status.
    e. Any other issue that would impair the ability of the participant to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
    f. History of noncompliance with recommended medical treatments.

Prior/Concomitant Therapy

6. Prior or concurrent exposure to any of the following, in the specified time frame prior to randomization:
    a. T-cell redirection therapy (eg, antibody therapy or BiTEs) within 3 months.
    b. Gene-modified adoptive cell therapy (eg, CAR-T cells, NK cells) within 3 months.
    c. Targeted therapy, epigenetic therapy, mAb therapy, cytotoxic therapy, or treatment with an investigational drug or an invasive investigational medical device within 21 days or ≥5 half-lives, whichever is less.
    d. Investigational vaccine other than SARS-CoV-2 vaccine approved or authorized for emergency use within 4 weeks.
    e. Live, attenuated vaccine within 4 weeks. Non-live and non-replicating vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed.
    f. PI therapy within 14 days.
    g. IMiD agent therapy within 14 days.
    h. Focal radiation within 7 days.
7. Received either of the following:
    a. An allogeneic stem cell transplantation within 6 months before the first dose of study treatment. Participants who received an allogeneic transplant must be off all immunosuppressive medications during the 6 weeks before the start of study treatment administration without signs of graft-versus-host disease.
    b. An autologous stem cell transplantation within 12 weeks before the start of study treatment administration.

8. A maximum cumulative dose of corticosteroids of ≥140 mg of prednisone or equivalent within 14-day period before the first dose of study drug (does not include pretreatment medications; Appendix 13).

Diagnostic Assessments

9. Any of the following:
   a. Hepatitis B infection (ie, HbsAg or HBV-DNA positive): In the event the infection status is unclear, quantitative viral levels are necessary to determine the infection status. See Section 8.3.5 for further required assessments.
   b. Active hepatitis C infection as measured by positive HCV-RNA testing. Participants with a history of HCV antibody positivity must undergo HCV-RNA testing. If a participant with history of chronic hepatitis C infection (defined as both HCV antibody and HCV-RNA positive) completed antiviral therapy and has undetectable HCV-RNA for at least 12 weeks following the completion of therapy, the participant is eligible for the study.

Other Exclusions

Not applicable.

Disease Characteristics

10. Known active CNS involvement or exhibits clinical signs of meningeal involvement of multiple myeloma. If either is suspected, negative whole brain MRI and lumbar cytology are required.
11. PC leukemia at the time of screening, Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes), or primary amyloid light chain amyloidosis.
12. Any of the following:
   a. Ongoing myelodysplastic syndrome or B cell malignancy (other than multiple myeloma).
   b. Any history of malignancy, other than multiple myeloma, which is considered at high risk of recurrence requiring systemic therapy.
   c. Any active malignancy (ie, progressing or requiring treatment change in the last 24 months) other than multiple myeloma. The only allowed exceptions are malignancies treated within the last 24 months that are considered cured:
      i. Non-muscle invasive bladder cancer (solitary Ta-PUN-LMP or low grade, <3 cm, no CIS)
      ii. Non-melanoma skin cancers treated with curative therapy or localized melanoma treated with curative surgical resection alone
      iii. Non-invasive cervical cancer
      iv. Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ or history of localized breast cancer (antihormonal therapy is permitted)
      v. Localized prostate cancer (M0, N0) with a Gleason Score ≤7a, treated locally only (RP/RT/focal treatment)
      vi. Other malignancy that is considered cured with minimal risk of recurrence in consultation with the sponsor's medical monitor.

NOTE: In the event of any questions, consult with the sponsor's medical monitor prior to enrolling a participant.