MAGNETISMM-1

A PHASE I, OPEN LABEL STUDY TO EVALUATE THE SAFETY, PHARMACOKINETIC, PHARMACODYNAMIC AND CLINICAL ACTIVITY OF ELRANATAMAB (PF-06863135), A B-CELL MATURATION ANTIGEN (BCMA) - CD3 BISPECIFIC ANTIBODY, AS A SINGLE AGENT AND IN COMBINATION WITH IMMUNOMODULATORY AGENTS IN PATIENTS WITH RELAPSED/REFRACTORY ADVANCED MULTIPLE MYELOMA (MM)

Investigational Product Number:	PF-06863135
Investigational Product Name:	Elranatamab
United States (US) Investigational New Drug (IND) Number:	133,940
European Clinical Trials Database (EudraCT) Number:	2019-000822-24
ClinicalTrials.gov NCT:	NCT03269136
Protocol Number:	C1071001
Phase:	1

Document History

Document	Version Date	Summary of Changes
Original protocol	10 May 2017	N/A
Amendment 1	28 September 2017	1. Summary, Sections 3.1, 3.3, and 9.2.1: Revised DLT rate to 25% with an acceptable equivalence interval of (20%-30%) following feedback from the FDA. 2. Summary, Section 3.1: Removed Part 2B combination therapy section since details of combination portion will only be provided in a future amendment. 3. Schedule of activities: Clarified that results from the patient's last bone marrow assessments may be utilized for screening if the results were collected within 3 months from planned study drug treatment. 4. Schedule of activities and Section 3.1: Added 72 hr hospitalization on Cycle 1 Day 1 (C1D1) for patients in Part 1 and 72 hr hospitalization on Cycle 1 Day 8 (C1D8) for patients in Part 1A, per request from the FDA. 5. Section 3.1.4. and Appendix 8: Dose decision rules have been revised following a change in DLT target rate. 6. Section 3.2: Dose limiting toxicity (DLT) criteria have been revised following FDA's recommendations. 7. Section 3.5: A new stopping criteria section has been included to provide rules for stopping the study in Part 2 dose expansion. 8. Section 4.1: Administrative edits were made to clarify inclusion criteria #1 to ensure that only patients with measurable disease and either a biopsy proven plasmacytoma or bone marrow plasma cells >20% will be included. Criteria for prior therapy have been moved to criteria #2

Document	Version Date	Summary of Changes
		so that all patients are now required to meet these criteria. 9. Section 5.5.3 Table 3: Revised dose modification criteria for non-hematological toxicities grades 3 and 4 such that a grade 3 event would require dose -de-escalation and grade 4 events will require discontinuation, per guidance from the FDA. 10. Section 7.1.2: Added treatment guidance for patients who have received an allogeneic bone marrow transplant. 11. Section 7.1.3: Added option for sites to analyze cytokines locally should this be required for patient management. 12. Section 7.2.1: Provided information regarding potential daratumumab interference information and clarified that the FLC assay should be utilized if daratumumab treatment was given <114 days prior to planned treatment day (C1D1).
Amendment 2	25 April 2018	1. Protocol Summary and Section 3: Addition of subcutaneous (SC) cohorts in Part 1 and Part 1A to allow for evaluation of SC dosing. Evaluation of 1 hr infusion has been revised such that it will now occur in Part 2 as a lead-in cohort. 2. Protocol Summary and Section 2: Administrative changes have been made to the wording in exploratory biomarker endpoints. 3. Schedule of assessment A and B and Section 5.8.6: Addition of local site injection tolerability assessment to evaluate injection site reactions (ISR). 4. Schedule of assessment A and B: Revision of biochemical disease assessments from weekly

Document	Version Date	Summary of Changes
		to per cycle timeframe to account for half-life of M-proteins and to reduce burden on sites. 5. Schedule of assessment A and B and Section 7.1.5: Triplicate ECGs will only be taken on C1D1 until C2D15. All other assessments will be based on a single ECG. 6. Schedule of assessment A and B and Section 7.2.2: Administrative edits to bone marrow collection and assessment to ensure alignment between the schedule of assessments and Section 7.2.2. 7. Schedule of assessment A and B: Reduced number of urinalysis assessments such that it will only be performed when clinically indicated. 8. Schedule of assessment B: Removal of weekly weight assessment in Schedule of assessment B to align with Schedule of assessment A and Section 5.4.1 where weight is evaluated on Day 1 of each cycle. 9. Section 1.2.4: SC non-clinical safety information has been added to justify incorporation of SC dosing in this study. 10. Section 1.2.6.2: SC starting dose rationale has been added to support the addition of SC administration. 11. Section 4: Inclusion criteria has been revised such that biopsy proven plasmacytoma and ⩾20% plasma cells in bone marrow is no longer a requirement since this will expand the number of potential relapse/ refractory multiple myeloma patients that may be enrolled. 12. Section 4 and Section 5.8.14: Inclusion criteria have been revised such that transfusion support will be allowed during screening. Specifically, Section 5.8.14 has been added to

Document	Version Date	Summary of Changes
		clarify when transfusion support will be allowed. 11. Section 4: Clarification has been made to patients treated with elotuzumab or other anti-SLAMF7 receptor (also known as anti-CD319) therapy such that they will only be excluded if last dose of therapy is less than 30 days from enrollment into study. 12. Section 4: Exclusion criteria for prior BCMA therapies has been clarified for Part 1 and Part 1A such that known BCMA negative patients will not be eligible but patients with BCMA positive relapse may be allowed following discussion with the sponsor. For Part 2, the exclusion criteria have been clarified to all BCMA targeted therapy. 13. Section 7.1.3 and 7.5.4: Targeted panel for ad hoc central cytokine panel has been replaced with the full panel to align with the central assessments that will be completed. 14. Appendix 9: Added: to provide guidance on subcutaneous injections.
Amendment 3	07 February 2019	1. EudraCT number 2019-000822-24 was added to the cover page 2. Protocol Summary: For the purpose of clarity, reference to Section 3.1.1.3 (IV Priming and Maintenance Dose Escalation) is now listed with each summary describing dosing groups. 3. Protocol Summary: For the purpose of clarity, the Part 2 expansion paragraph had language removed which was repeated in Section 3.1.2. 4. Protocol Summary and Table 1 in Section 3.1.4: Addition of 90 and 270 µg/kg doses for the IV cohorts (Part 1) based on

Document	Version Date	Summary of Changes
		emerging data that TBD have been identified. 5. Section 1.2.6: Title was updated to Starting Dose Rationale to clarify the content of the section. 6. Protocol summary and Section 1.2.6.2: Clarified language for subcutaneous starting dose rationale explained in detail in Section 3.1.1.2. 7. Section 1.2.6.3: Updated title and modified language to clarify sentence that the priming and maintenance part may be evaluated prior to reaching MTD. 8. Section 3.1: Updated study schema to reflect study design and added footnote to specify that the no lead-in cohort will be conducted if the subcutaneous route is selected for Part 2. 9. Section 3.1.1.3: Added guidance for priming and maintenance dose for Part 1A IV cohorts. 10. Protocol Summary, Section 1.2.6.2 Section 1.2.6.3, Section 3.1.1.1, Section 3.1.1.2, Section 3.2 and Appendix 5: Clarified language to remove tocilizumab and/or vasopressors from the management of CRS and replaced (where appropriate) with language that would enable the treatment with standard of care per the institution's, investigator's or treating physician's guidelines. 11. Protocol Summary Schedule of Activities B: Footnote #21 was corrected from Cycle 1 Day 1 to Cycle 1 Day 8 for the maintenance dose. 12. Section 3.1.1.1: Changed language to clarify that doses above 270 µg/Kg will be

Document	Version Date	Summary of Changes
		explored and added language that Part 1 subcutaneous or IV maintenance may be initiated. 13. Section 3.1.1.2: Modified language to start the subcutaneous part independent of Grade 3 CRS and allow SC starting dose at higher dose level based on current IV preliminary safety, PK, and CRS data. 14. Section 3.1.1.3: Revised text to leave only Priming and Maintenance for Part 1A IV. 15. Section 3.1.1.4: Deleted section for Part 1A subcutaneous administration. 16. Section 3.1.1.5: Deleted section for Part 1A IV administration. 17. Section 3.1.4: Modified language so that higher doses in the IV administration cohorts can be evaluated. 18. Section 3.1.2: Added a statement that, based on emerging clinical data from the Part 1 dose escalation, either IV or SC administration, including priming and maintenance dose, will be selected for the Part 2 dose expansion. Additionally, a sentence was added that no lead-in cohort will be conducted if subcutaneous route is selected for Part 2 expansion. 19. Section 3.2: The Dose Limiting Toxicity Definition was updated for Grade 4 thrombocytopenia to account for subjects that have a platelet count between 25,000 and 50,000 and added for Grade 4 thrombocytopenia with $\geqslant$ Grade 2 bleeding. 20. Section 4.1: Reflect the following clarifications:

Document	Version Date	Summary of Changes
		21. Inclusion criterion #1a and Appendix 2: Lowered the M-protein to greater than or equal to 0.5 g/dL for Part 1 and greater than or equal to 1.0 g/dL for Part 2. 22. Inclusion criterion #1c: Updated to reflect measurable disease for FLC. 23. Inclusion criterion #2 and Section 3.1.1.1: Clarified that patients must have received prior therapies with proteasome inhibitors, IMiD drugs, and anti-CD38 monoclonal antibodies, where approved and available. 24. Inclusion criterion #2: Revised to specify that patients must have progressed on or are intolerant of established therapies known to provide clinical benefit in multiple myeloma. 25. Inclusion criterion #5: Lowered the platelet count to 25,000/mm3, clarified that hemoglobin may be greater than or equal to 8 g/dL, transfusion support is allowed for both situations if completed prior to planned C1D1. 26. Inclusion criterion #6: Modified the creatinine clearance to $\geqslant$30 mL/min and serum creatinine to $\leqslant$2.5 mg/dL. 27. Exclusion criterion #6: Modified to include additional $\geqslant$ Grade 3 immune-mediated adverse events and added exceptions for immune-related adverse events appropriately managed by checkpoint inhibitors. 28. Exclusion criterion #14: Clarified to reflect the language regarding patients with relapse following BCMA targeted therapy eligibility.

Document	Version Date	Summary of Changes
		29. Exclusion criterion #15: Eliminated the requirement for prior BCMA therapies in Part 2 only. 30. Section 5.3.1: Dosage Form(s) and Packaging: title was revised to reflect the Pharmaceutical form and refer to the Investigational Product Manual and Investigator's Brochure for additional details regarding PF-06863135. 31. Section 5.3.2: Removed the phrase "Investigational Product Manual" and abbreviated the name as it was previously spelled in the prior paragraph. 32. Section 5.5.2: Clarified situation in which patients require discontinuation of the study drug for more than 42 days, clarified that it would be from Day 1 of the current cycle. 33. Section 5.5.3: Added >42 days for patients experiencing a DLT of prolonged myelosuppression. 34. Appendix 2: (See inclusion criteria for modifications) was added in the IMWG response criteria for serum M-protein. 35. Additional administrative changes and clarifications were made throughout the protocol.
Amendment 4	31 October 2019	The purpose of this amendment is primarily to enable evaluation of combinations of PF-06863135 with anti-PD1 antibody PF-06801591 or with lenalidomide and allow the option of subcutaneous every 2 week dosing of PF-06863135. In addition, clarifications, administrative and typographical modifications were made. 1. Protocol Summary, background and rationale: Added language to indicate the combination of PF-06863135 with an

Document	Version Date	Summary of Changes
		anti-PD-1 antibody or an IMiD will be investigated. 2. Protocol Summary, study design, Study Objectives and Endpoints, Schedule of Activities B, Sections 2, 3.1.1, 3.1.1.2, 3.1.1.3, 3.1.1.4, 5.4.1, 9.6 and Figure 6: renamed Part 1A Priming and Maintenance Dose Escalation to Part 1.1 Priming and Maintenance Dose Escalation. 3. Protocol Summary, study design and Section 3 and Figure 6: Added language to specify what each Part of the study will each investigate and the number of patients that each Part will enroll. 4. Protocol Summary, study design and Figure 6: Clarified the dose escalating doses of PF-06863135 for Parts 1 IV and SC. 5. Protocol Summary, study design: Added a statement that clarifies the 72-hour hospitalization period on C1D1 for all monotherapy dose escalation cohorts and to further evaluate the hospitalization period in the expansion cohorts. 6. Protocol Summary, study design: Added language for Part 1 monotherapy to specify DLT period and specify period for intra-patient dose escalation and restrictions to enroll the same patient into different Parts of the study. 7. Protocol Summary, Study Design, Schedule of Activities B, sections 3.1.1.3: Modified the priming schedule to start on C0D1 and maintenance on C1D1. In addition, an alternative step-up regimen and prophylactic steroid options were added to the schedule. 8. Protocol Summary, study design, schedule of activities B, sections 3.1.1.3, 5.4.2: added

Document	Version Date	Summary of Changes
		subcutaneous route for priming and maintenance. Included lenalidomide and PF-06801591 in this Part. Added two week schedule option for monotherapy, lenalidomide and PF-06801591. Removed days 9 and 10 from cycle 1, changed schedule to a 4 week cycle. 9. Protocol Summary, study objectives and endpoints and Section 2: Added language that defines the objectives and endpoints for each combination dose finding and expansion Parts of the study. 10. Protocol Summary, Schedule of activities A: Renamed so that all weekly intravenous and subcutaneous monotherapy dose escalation schedules follow either SOA A or B, rearranged the procedures by section, clarified the visit window in the pharmacokinetic, soluble factor and cytokine activities. 11. Protocol Summary, Schedule of activities C: Was created to reflect new combination dose finding, expansion monotherapy and combination cohorts, clarified to check for MRD when a patient achieves complete response. 12. Protocol Summary, Schedule of activities A, B, C, Sections 5.9.3, 5.9.4, Appendix 5, Tables 12, 14: Added new ASTCT consensus criteria for CRS and ICANS management of cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS). 13. Study design, schedule of activities A, B and C: Clarified throughout the pharmacodynamic, pharmacokinetic, soluble factor and cytokine assessments tables when bone marrow should be collected for the intravenous route and

Document	Version Date	Summary of Changes
		added clarification on when these procedures should be taken relative to C1D1. 14. Sections 1 Introduction: Updated to add supporting background pre-clinical information and clinical data regarding combination of CD3 bispecifics and anti-PD1/L1 or lenalidomide. 15. Sections 1.2.8.1, 1.2.8.4, 3.1.1.4, 3.1.2 and 3.1.4, 5.4.3: Updated to indicate that a fixed dose approach will be used for PF-06863135 in combination dose finding in all expansion cohorts. 16. Section 1.2.8.3: Added to specify the starting doses for all combination Parts. 17. Section 1.2.8.5: Added to allow a Q2W dosing interval option for patients treated with weekly dosing at least 6 months. 18. Section 3: Study design scheme was created that reflects all new combination dose finding and expansion cohorts. 19. Section 3.1.1.2: Updated to reflect actual starting dose of Part 1 subcutaneous monotherapy. 20. Section 3.1.1.4 describes combination dose finding cohorts. 21. Section 3.1.2: Was updated to describe the combination expansion cohorts. 22. Section 3.1.4: Table 1 was updated to include doses used in the intravenous dose escalation. Table 2 was added to include subcutaneous planned doses and language was added to clarify weekly and every two week dosing intervals.

Document	Version Date	Summary of Changes
		23. Section 3.2: The DLT definition was updated to specify DLT periods for 3 and 4 week cycles. DLT definitions were revised to provide clarity for Grade 4 neutropenia, febrile neutropenia and isolated Grade 3 laboratory abnormalities. 24. Section 3.2.1: Late toxicity evaluation schedules were clarified for combination and monotherapy dose escalation cohorts. 25. Section 3.4: Revised to provide clarity regarding determination of the recommended phase 2 dose of PF-06863135 in combination cohorts. 26. Sections 4.1 was and 4.2 were revised as follows: • Inclusion Criteria #1a: Revised to have a serum M-protein of 0.5 g/dL for both, Part 1 and 2. • Inclusion Criteria #5: Revised to clarify the requirements for adequate hematological function for ANC and platelet count for Part 1C and 2C of the study. • Inclusion Criteria #6 : Revised to specify the creatine clearance for Part 1C and 2C of the study. • Inclusion Criteria #8: Revised to provide clarity for hepatitis B and C testing. • Inclusion Criteria #12: Language was updated to reflect new template protocol information regarding informed consent requirements.

Document	Version Date	Summary of Changes
		• Inclusion Criteria 14: Added TSH, T3 and T4 for patients enrolled in Part 1B and 2B. • Exclusion criteria #11: Provided clarity for antibody based therapies. • Exclusion Criteria #14: Clarified requirements for patients that have received prior BCMA therapy. • Exclusion Criteria #16: Added new template language for requirements on ECG results. • Exclusion Criteria #20: Revised to include requirements for PF-06801591. • Exclusion Criteria #23: Added disease restrictions for patients enrolled into Parts 1B and 2B. • Exclusion Criteria #24: Added restriction regarding the use of corticosteroids and immunosuppressants. • Exclusion Criteria #25: Added to exclude patients with Grade ⩾3 anaphylactic reactions to antibodies. • Exclusion Criteria #26: Added a restriction for Parts 1C and 2C for patients who had previous lenalidomide dose reductions. 27. Section 4.3: Added that 2 highly effective methods of contraception are required for Parts 1C and 2C. 28. Section 5.3.3: Revised language to reference the IP manual and IB for PF-06863135.

Document	Version Date	Summary of Changes
		29. Section 5.3.2: Clarified the preparation and dispensing for both, PF-06863135 and PF-06801591. 30. Section 5.3: Added lenalidomide as an investigational product. 31. Section 5.4.1: Added clarity to when and how the option of 2 week interval dosing can be done for PF-06863135 IV administration. 32. Section 5.4.2: Added clarity to when and how option of 2 week interval dosing can be done for PF-06863135 SC administration. 33. Section 5.4.3: Added instructions on the administration of PF-06801591. 34. Section 5.5: Added dose modifications that can occur for PF-06801591 and lenalidomide. 35. Section 5.7 and 5.7.1: Revised titles to include non-investigational products. 36. Section 5.9.10: Removed restriction on the use of hematopoietic growth factors only at cycle 2 and beyond. 37. Section 5.9.15: Removed restriction on transfusion support during cycle 1 and within 14 days prior to cycle 1. 38. Section 6.4: Added requirement for follow-up of late immune related adverse events in Parts 1B and 2B. 39. Section 7.1.3: Deleted duplicated information. Clarified hepatitis tests, added TSH, T4 requirements in table 8. 40. Section 7.1.5: Allowed discussion with sponsor for continuation of study treatment for patients that experience transient

Document	Version Date	Summary of Changes
		prolonged QTcF if the investigator believes it is in the best interest of the patient. 41. Section 7.1.7 and appendix 9: Provided information on the use of abdominal quadrants for the subcutaneous administration of PF-06863135 and PF-06801591. 42. Section 7.2.2: Clarified assays to be used for MRD testing. 43. Section 7.3: Added a blood pharmacokinetics sample collection for PF-06801591. 44. Section 7.4: Added anti-drug antibody analysis for PF-06801591. 45. Section 7.5: Added clarification for bone marrow samples at 6 and 9 month timepoints. 46. Section 7.5.2: Added that PD-1 receptor occupancy will be evaluated in Parts 1B and 2B. 47. Section 7.5.4: Revised language to provide clarity on collection of samples for CRS assessment. 48. Section 8.1.4: Added language to specify adverse event collection period for PF-06801591 in Parts 1B and 2B. 49. Section 9.1: Added definition for pharmacokinetic and immunogenicity tests in Parts 1B and 2B. 50. Section 9.3: Added clarification to support the calculation of sample sizes for combination dose escalation and expansion cohorts.

Document	Version Date	Summary of Changes
		51. Section 9.5.1 and 9.5.2: Added pharmacokinetic analysis for Parts 1B and 2B. 52. Appendix 10: Added management for immune-related adverse events in Parts 1B and 2B.
Amendment 5	13 July 2020	The primary purpose of this amendment is to add pomalidomide as a combination therapy with PF-06863135. In addition, clarifications, administrative, and typographical modifications were made. 1. Corrected item 30 in list of Summary of Changes for Amendment 4. The correct section number should be 5.3 and lenalidomide should have been listed as investigational product. 2. Global: Replaced PF-06801591 with sasanlimab. Where needed for clarity added the following "sasanlimab (formerly PF-06801591)". 3. Protocol Summary Schedules of Activities A, B, and C footnote # 37, Sections 3.1, 6.3, and 6.6: Increased treatment duration/follow up with PF-06863135 from 12 up to 24 months after the last patient first dose as other BCMA-targeting agents have seen reported response duration beyond 1 year. 4. Protocol Summary and Globally (where applicable, including study Objectives Section 2): Added pomalidomide to list of combination agents (Part 1D and Part 2D). 5. Protocol Summary and Globally (where indicated for clarity): Specified Parts 1B and 2B will be conducted ex-US only. 6. Protocol Summary and Global Sections (as applicable, including Schema): Added

Document	Version Date	Summary of Changes
		Parts 1D and 2D (pomalidomide combination cohorts). 7. Protocol Summary and Globally (where applicable), included "or maximum administered dose (MAD)" or "/MAD" after maximum tolerated dose (MTD). 8. Protocol Summary and Globally: Revised doses for Part 1 subcutaneous (SC) administration (changed 200 to 215 µg/kg, changed 300 to 360 µg/kg, and added doses of 600 and 1000 µg/kg). 9. Protocol Summary and Section 3.1: Added: Upon reaching MTD/MAD, up to approximately 6-12 patients total at selected level(s) below the MTD/MAD weekly and Q2W dosing up to the same dose intensity as the MTD/MAD weekly regimen may be evaluated further to support the RP2D decision. 10. Protocol Summary: Specified that the safety cohort for Part 1B will use a dose-escalation/de-escalation approach for PF-06863135 starting at least 1 dose level below the monotherapy MTD/MAD or the RP2D, whichever is lower and will be combined with a fixed SC dose of 300 mg sasanlimab. 11. Protocol Summary, Section 3.1, and 9.3: Updated patient numbers. Approximately 100 patients are expected to be enrolled into Parts 1/1.1/1B, 1C, and 1D. Parts 2A, 2B, 2C, and 2D will enroll approximately 20 patients each. Updated sample size calculation section. 12. Protocol Summary and Section 2: Added "and bone marrow by flow cytometry analysis" to the third Tertiary/Exploratory Endpoint bullet.

Document	Version Date	Summary of Changes
		13. Schedules of Activities: Added reference to Appendix 11 for alternative measure guidelines due to COVID-19. 14. Clarified dosing in Schedule of Activities C footnote #7 for Part 1 SC Q2W. 15. Clarified hospitalization as optional in Schedules of Activities B footnote #7 for Parts 2A, 2B, 2C, and 2D at C1D1. 16. Clarified timing of pregnancy testing for patients in Parts 1C, 1D, 2C, and 2D in Schedule of Activities B, and C footnote #20 and Section 7.1.1 per lenalidomide and pomalidomide requirements for pregnancy testing. 17. Schedules of Activities A, B, and C footnote #24, Section 7.2.2, and Appendix 3: Clarified patient status for assessment of MRD (minimal residual disease) and added clarifying language for central and local assessment for MRD. 18. Schedules of Activities A, B, and C footnote #25, revised text regarding timing of assessments for fluorodeoxyglucose (FDG) positron emission tomography (PET)/computerized tomography (CT). Deleted "as clinically indicated" in the Schedule of Activities Visit Identifier column. Aligned Section 7.2.3. 19. Added language to Schedules of Activities A, B, and C footnote #28 and Section 7.6.2 regarding genetic analysis; added bone marrow aspirates will be evaluated at the local lab, and instructions for when assessments cannot be done. Clarified timing. 20. Added clarifying language to footnote #35 in Schedule of Activities B to include Parts 1 and 2B as part of the one-month

Document	Version Date	Summary of Changes
		follow-up and late follow-up for late immune-related adverse events. Added "2B" to footnote #35 in Schedule of Activities C. 21. Schedule of Activities C: Added Parts 1D and 2D to the title and description, added row for pomalidomide administration (Parts 1D and 2D) and added a footnote with additional details (including dose). 22. Schedule of Pharmacokinetic, Soluble Factor and Cytokine Activities C: Added Parts 1D and 2D to title and description, added rows for sample collection for lenalidomide and pomalidomide PK (aligned Section 7.3). Aligned sBCMA sample collection for Part 2 with PK collection for Part 2. 23. To ensure consistency with timing of samples in Part 2, added Cycles 1 and 2 Day 22 0 hr timepoints for the collection of samples for PF-06863135 and soluble BCMA in the Schedule of Pharmacokinetics, Soluble factor, and Cytokine Assessments Activities B. 24. Correction to the links of the Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments so they correctly link to their respective Schedule of Activities B or C. 25. Sections 1.2.3.1. 1.2.3.1.1, 1.2.3.1.2, and 1.2.3.2: Added safety and efficacy data as of 15 April 2020 for patients in Part 1 treated with PF-06863135. 26. Section 1.2.7: Added ex-US sources for lenalidomide product information (and added to reference list). Added rationale for why dexamethasone will not be

Document	Version Date	Summary of Changes
		administered with lenalidomide in Parts 1C and 2C. 27. Section 1.2.8: Added description of pomalidomide and references for complete information. 28. Section 1.2.9.1: Added link to Section 1.2.9.4 for additional details of the fixed-dosing approach. 29. Section 1.2.9.3: Added Parts 1C and 1D provided details on pomalidomide dose. 30. Section 1.2.9.4: Added preliminary population PK data for PF-06863135 to support fixed dosing approach. 31. Section 3.1.1: Added language for the evaluation of up to 6-12 patients total at selected level(s) below the MTD/MAD weekly and Q2W dosing up to the same dose intensity as the MTD/MAD weekly regimen may be evaluated further to support the RP2D decision. 32. Section 3.1.1.3: Corrected error (see strikethrough text): The 48 hr observation period for the first patient in each dose level in Part 1.1 will begin on C1~~0~~D1 during the second hospitalization period. 33. Section 3.1.1.4: Revised Part 1 combination dose finding text regarding MAD and RP2D starting dose and de-escalation, clarified that the fixed dose of 300 mg would be administered SC, and added a paragraph for Part 1D. 34. Section 3.1.2: Added text regarding subcutaneous fixed dose of PF-06863135 for patients in Part 2A, added paragraph for Part 2D, and removed paragraph for intravenous administration since IV is no longer considered for dose expansion.

Document	Version Date	Summary of Changes
		Removed reference to "IV only" from SCHEDULE OF PHARMACOKINETIC, SOLUBLE FACTOR AND CYTOKINE ACTIVITIES C (including footnote *) to align. 35. Section 3.1.4: Deleted last row of Table 1 (dose level 8 and up, dose TBD), modified Table 2 doses for dose levels 3, 4, and 5 and added a 6th dose level, deleted nonapplicable paragraph. Clarified that in Part 1.1, the starting maintenance dose will be no more than 2-fold above the priming dose established from Part 1. 36. Section 3.2.1: Clarified start of late toxicities. 37. Section 3.3: Added Maximum Administered Dose to section title, added definition of MAD. 38. Section 4.1: Inclusion criterion #5, added platelet count for Parts 1D and 2D, correction made to inclusion criterion #8 to exclude patients with active hepatitis B or C. 39. Section 4.2: Exclusion criterion #4, added reference to Appendix 11 for additional clarification as it relates to SARS-CoV2 infection, #20, added requirement for contraception duration following the last dose of lenalidomide and pomalidomide. 40. Section 4.2: Added criteria #27, 28, and 29 describing exclusions for patients enrolling in pomalidomide combination cohorts Parts 1D and 2D (patients previously received pomalidomide, patients receiving strong CYP1A2 inhibitors, and patients with any level of hepatic impairment that would require dose reduction of pomalidomide, respectively).

Document	Version Date	Summary of Changes
		41. Section 4.3: Updated contraception for females of childbearing potential to include a list of highly effective methods and incorporated pomalidomide and lenalidomide where appropriate. Added that any risk and evaluation and mitigation strategy required by local regulations for lenalidomide and pomalidomide must be followed. 42. Section 4.1: The last Inclusion Criterion had been merged into the header for the Exclusion Criteria section. It now reads as Inclusion criteria #14. 43. Section 5.3.1: Revised lenalidomide paragraph, added paragraph for pomalidomide. 44. Section 5.4.2: Deleted paragraph describing duration of administration of sasanlimab. 45. Section 5.5.2: Added ANC and platelet values for pomalidomide, added reference to Appendix 11 for guidelines for dose delays of PF-06863135 for participants with active or presumed SARS-CoV2 infection. 46. Section 5.5.3: Modified Table 4. Lymphopenia will not be included in hematological toxicity as this expected as part of PF- 06863135 mechanism of action. Added text and Table 8 for dose modifications for pomalidomide. 47. Section 5.9: Added drug-drug interaction (DDI) text for lenalidomide and pomalidomide. Section 5.9 and Appendix 12: Added DDI text for PF-06863135. 48. Section 5.9.10: Added cautionary text for the use of agents that may increase the risk

Document	Version Date	Summary of Changes
		of thrombosis in patients receiving lenalidomide. 49. Section 6.4: Replaced "study drug" with sasanlimab. 50. Section 7.2: Added text describing the disease response assessment. 51. Section 7.2.1: Added text to free light chain analysis describing timing for patients treated with daratumumab. Added this text to footnote #22 of Schedules of Activities A, B, and C to align. Deleted "only" from Beta-2 microglobulin bullet for clarity. 52. Section 7.2.2: Added that In case of suspected stringent Complete Response (sCR), the presence/absence of clonal cells on immunohistochemistry should also be evaluated to bone marrow biopsy paragraph. 53. Section 8.1.4.2: Added text specifying the start of the collection period for nonserious AEs and SAEs. Added instructional text for patients experiencing cytokine release syndrome. 54. Section 8.4.3.1: Replaced instance of "participant" with patient to align with protocol terminology. 55. Section 9.2.1: Added "If the MTD is not reached, then the MAD will be maximum dose that is evaluated in the study" for clarity. 56. Section 9.3: Updated sample size determination section for additional cohorts. 57. Section 9.5.1: Added Parts 1D and 2D to analysis of PF-06863135, replaced instance

Document	Version Date	Summary of Changes
		of "participants" with patients to align with other protocol sections. 58. Section 9.5.2: Added lenalidomide and pomalidomide, 1C and 2C and 1D and 2D as appropriate to the section title. Added lenalidomide and pomalidomide to the analysis of concentration-time data. 59. Section 9.5.6: Deleted first paragraph describing analysis of blood and bone marrow biomarker samples. Added paragraph for analysis and reporting of tertiary/exploratory analyses. 60. Section 9.6.2.1: Added that the severity of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) should be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria. 61. Section 13.1: Added reference to Section 6.6 for more information on how end of study is determined. 62. Appendix 2: Removed redundant text in IMWG criteria column in Progressive Disease (PD) row and added clarifying language prior to bulleted list. Corrected footnote number reference in third bullet in Clinical Relapse row. 63. Appendix 11: Added appendix to provide guidance for alternative measures during public emergencies. 64. Appendix 12: Added drug-drug interaction appendix.
Amendment 6 (Country specific	17 December 2020	The primary purpose of this amendment is to address requests received from regulatory agency Paul-Ehrlich-Institut

Document	Version Date	Summary of Changes
Amendment, Germany)		(PEI). The changes for Amendment 6 are specific only to Germany. 1. Removed Parts 1B and 2B (combination with Sasanlimab) throughout the protocol. 2. Section 3.2: Removed last bullet indicating that Infusion Related Reactions (IRRs) and Injection Site Reactions (ISRs) will not be adjudicated as DLTs. 3. Section 3.4: Section was updated with Recommended Phase 2 Dose for monotherapy and fixed (flat) dose additional details. 4. Section 5.5.3: Pomalidomide discontinuation criteria have been updated to include anaphylactic reactions, angioedema, progressive multifocal leukoencephalopathy (PML), or rash (Grade 4 or blistering). 5. Section 5.9.6: Removed last paragraph indicating that Infusion Related Reactions (IRRs) will not be considered as DLTs. 6. Section 5.9.7: Removed last paragraph indicating that Injection Site Reactions (ISRs) will not be considered as DLTs.
Amendment 7	15 January 2021	The primary purpose of this amendment is to incorporate changes previously included in country specific Amendment 6 (Germany). In addition, because dexamethasone is a key component of standard anti-myeloma therapies and its effect on the safety and efficacy of T-cell engaging bispecific agents is not known, PF-06863135 in combination with dexamethasone will be investigated in Parts 1E and 2E. Clarifications, administrative, and typographical modifications were made. 1. Changes previously included in country specific Amendment 6 (Germany) as described above.

Document	Version Date	Summary of Changes
		2. Protocol Summary (Study design) and Section 3.1: Added language to enable PF-06863135 combination with dexamethasone in Part 1E and expansion Part 2E, to evaluate its potential to mitigate immune effector cell-associated toxicities and modulate efficacy of PF-06863135. Part 1E will enroll ~ 9-16 patients. If the combination regimen with dexamethasone in Part 1E is well tolerated, Part 2E will enroll ~ 20 patients. 3. Study Objectives and Endpoints (Protocol Summary and Section 2.1): Update language to include evaluation PF-06863135 combination with dexamethasone and to clarify that plasma will be collected for PK analysis. 4. Protocol Summary (Study Design), Section 3.1.1, Section 3.1.1.3 and Section 3.1.1.4: For the purpose of clarity, added language to specify that patients will be hospitalized on C1D1 and removed 72 hrs, as hospitalization requirements are described in detail in Schedule of Activities for specific Parts of the study. 5. Section 3.1.1: Updated to clarify DLT observation period taking into account dosing schedule for cohorts that implement 4 weeks cycle with priming. 6. Protocol Summary (Study Design), Section 3.1 and Section 3.1.1.4: Update to indicate that if the combination regimen with dexamethasone in Part 1E is well tolerated as guided by mTPI, Part 2E may be initiated. 7. Protocol Summary, Section 3.1 (Study design) Section 3.1.1.4 and Section 9.3: Updated total patient numbers for the study, to account for addition of dexamethasone cohorts Part 1E and 2E. Approximately 120 patients are expected to be enrolled into Parts 1/1.1, 1C, 1D,

Document	Version Date	Summary of Changes
		and 1E and approximately 80 in combination cohorts of Part 2. 8. Schedule of Activities A, B, C: Added "Demography" as required assessment and provided additional information regarding MRD assessment requirements for clarity. 9. Schedule of Activities A, B, C: For the purpose of clarity, footnote 24 updated to include additional information regarding MRD assessment requirements for clarity. 10. Schedule of Activities A, B, and C: Footnote 25 updated to include that only MRI is allowed to be used as imaging modality for patients by sites in Germany. 11. Schedule of Activities B: Updated to include dexamethasone in combination with PF-06863135 in Parts 1E and 2E. 12. Schedule of Activities B and footnote 7: Updated to indicate that all patients receiving a priming dose will be hospitalized for at least 24hrs on C0D1 and for at least 24 hrs on C1D1. Hospitalization on C1D2 and C1D3 and C1D4 visits (including assessments) have been removed from Part 1.1 and any part using priming dose, followed by maintenance. 13. Schedule of Activities B (footnote 41): Added language to enable dexamethasone administration for Parts 1E and 2E as needed and provide further information regarding dosing, discontinuation, and duration of treatment. 14. Schedule of Pharmacokinetic, Soluble Factor and Cytokine Activities B (footnote 2): Updated to indicate that PK sample should be collected if the hospitalization period is extended beyond 24 hours on C0D1 or C1D1.

Document	Version Date	Summary of Changes
		15. Schedule of Pharmacokinetic, Soluble Factor and Cytokine Activities B: Updated to indicate that C1D4 and C2D4 visits (including assessments) have been removed. 16. Schedule of Pharmacokinetic, Soluble Factor and Cytokine Activities B (including footnote 5): Updated to provide instructions and clarification about blood sample collection for lenalidomide and pomalidomide concentration analysis. 17. Schedule of Pharmacokinetic, Soluble Factor and Cytokine Activities B (including footnote 6): Updated to provide instructions for blood sample collection for dexamethasone concentration analysis. 18. Schedule of Pharmacokinetic, Soluble Factor and Cytokine Activities C (footnote 3): Clarification provided about blood sample collection for lenalidomide and pomalidomide concentration analysis. 19. Section 1.2.3.1: Updated based on current safety data. Safety data for both IV and SC cohorts consolidated under Section 1.2.3.1. 20. Section 1.2.3.2: Updated based on current efficacy data. Efficacy data for both IV and SC cohorts consolidated under Section 1.2.3.2. 21. Section 1.2.6: Updated to indicate that lenalidomide can cause embryo-fetal toxicity. Removed reference to dexamethasone, as dexamethasone is enabled in Parts 1E and 2E to understand its effects on the safety and efficacy of PF-06863135. 22. Section 1.2.7: Updated to indicate that pomalidomide can cause embryo-fetal toxicity. Removed reference to dexamethasone, as dexamethasone is enabled in Part E to

Document	Version Date	Summary of Changes
		understand effects of this backbone anti-myeloma agent on the safety and efficacy of PF-06863135 23. Section 1.2.8: Introduced section to describe the rationale for combining PF-06863135 with dexamethasone. 24. Section 1.2.9.3: Updated section to indicate that Part 1E will evaluate the RP2D dose level of PF 06863135 with dexamethasone. 25. Section 3.1 (Study Schema/Figure 4): Updated to include combination with dexamethasone, Part 1E (≈9-16 patients) and Part 2E (≈20 patients). 26. Section 3.1 (Study Schema/Figure 4): Updated to describe Part 1.1 priming cohorts, including priming and maintenance (Q1W and Q2W). 27. Section 3.1.1: Updated heading with priming and maintenance cohorts for clarity. 28. Section 3.1.1.4: Updated to include RP2D for PF-06863135 as a single agent and a table detailing potential fixed doses to be administered in monotherapy and combination arms with pomalidomide, lenalidomide and dexamethasone. Provide detailed information for PF-06863135 administration in combination with dexamethasone. 29. Section 3.1.2 and 3.1.4: Added language to introduce Part 1E and 2E as needed and provide further information regarding dosing and de-escalation. 30. Section 3.1.1, 3.1.1.3, 3.2 and 3.2.1: Based on emerging data that there was no significant late toxicity, late toxicity evaluation of patients for a minimum of 60 days was

Document	Version Date	Summary of Changes
		removed as requirement for the purpose of MTD/MAD determination. 31. Section 3.1.1.3: Updated heading with priming and maintenance cohorts and removed dose escalation for clarity. 32. Section 3.4: Updated to include RP2D for PF-06863135 as a single agent and preliminary data suggesting that administration of priming dose reduces duration of CRS. 33. Section 4.1: Restricted Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) to 0-1 for Part 2A and to 0-2 for all other cohorts (inclusion 4). 34. Section 4.1: Clarified inclusion criteria for platelet counts for both Part 1E and Part 2E (inclusion 5). 35. Section 4.2: Provided clarity for requirement for systemic immune suppressive medication in (exclusion 12). 36. Section 4.2: Provided clarity regarding potential COVID vaccination (exclusion 18). 37. Section 4.3: Provided additional clarity regarding pregnancy prevention program for lenalidomide and pomalidomide. 38. Section 5 (study treatments), Section 5.2 and Section 5.3.1: Included dexamethasone as investigational medicinal product. 39. Section 5.5: Updated to include dexamethasone and clarify that if a dose of PF-06863135 is delayed or interrupted, then dexamethasone should not be administered until PF-06863135 administration is restarted. 40. Section 5.5.2 (Dose delays): Updated to include dexamethasone.

Document	Version Date	Summary of Changes
		41. Section 5.5.3 (Dose reductions): Updated to include guidance for dose delays for dexamethasone related toxicities, including Table 10. Updated to include guidance for dose modification for PF-06863135 related toxicities. Specifically, for any patient who receives fixed doses of PF-06863135, the next dose level of PF-06863135 will be 25% lower. 42. Section 5.9: Updated to introduce dexamethasone as moderate inducer of CYP 3A4. 43. Section 5.9.13: Updated to indicate that, except as specified in the protocol, corticosteroids for palliative or supportive purposes are permitted only following discussion and agreement between the investigator and sponsor. 44. Section 7.2.2: Updated to further clarify MRD assessment process and requirements. 45. Section 7.2.3: Updated to include that only MRI is allowed to be used as imaging modality by sites in Germany. 46. Section 9.3: Updated to include Part 1E and 2E in the sample size determination. 47. Section 9.4: Updated to enable independent central review for efficacy endpoints as needed. Section updated to clarify that confirmed responses are required, minimal response (MR) is not included in the ORR response definition and stable disease (SD) is not included in clinical benefit (CB) definition. 48. Section 9.5.1: Updated to include blood sample collection for PF-06863135 in Part 1E and 2E.

Document	Version Date	Summary of Changes
		49. Section 9.5.2: Updated to include blood sample collection for dexamethasone in Part 1E and 2E. 50. Section 16: Updated References as needed. 51. Appendix 1: Updated abbreviations as needed.
Amendment 8	06 June 2021	The primary purpose of this amendment is to incorporate changes related to peripheral neuropathy, including mitigation measures. 1. Protocol Summary (Study Design) and Study Overview (Study Design): Updated to clarify that enrollment in study C1071001 has been completed, as clinical development program for PF-06863135 has been expanded with dedicated studies that will further investigate both monotherapy and combination therapy. 2. Because lenalidomide belongs to the same drug class as pomalidomide, the maximum dose of lenalidomide was reduced to 15 mg, as described throughout the document. The dose adjustment tables (Table 6 and Table 7) in Section 5.5.3 were modified accordingly. 3. In order to focus on the data most important for investigators, Section 1.2.3.1 and Section 1.2.3.2 were updated with safety and efficacy data, respectively. 4. Clarified that neurological assessments occur at each physical examination in the SoAs and Section 7.1.4. 5. Schedule of Pharmacokinetic, Soluble Factor and Cytokine Activities B (footnote 5): Provided guidance about blood sample collection for lenalidomide and pomalidomide concentration analysis for

Document	Version Date	Summary of Changes
		patients transitioned to monotherapy with PF-06863135. 6. Clarification added for dose delays in Section 5.5.2 and 5.5.3. 7. Dose modifications of PF-06863135 for peripheral neuropathy were added to Table 5 in Section 5.5.3. 8. Considerations regarding concomitant medications were included in Section 5.9. 9. Section 5.9.1 and 5.9.4: Updated to describe premedication for CRS. 10. Recommended evaluation for peripheral neuropathy was added to Section 8.4.4. 11. Criteria for interruption of study treatment were added in Section 9.7. 12. Biomarker collections for MRD assessment by NGS were clarified in the the SoA. 13. Pregnancy tests and contraception checks, along with AE assessments were extended to 90 days after the last dose of investigational product. 14. The Title Page was updated to include the new Pfizer logo, the study name (MAGNETISMM-1), the generic name (elranatamab), and the NCT number. 15. Updated references as needed in Section 16. 16. For consistency between Appendix 5, Section 5.9.4 and rest of the protocol, it has been clarified throughout the document that CRS will be assessed according to the grading described by Lee et al. 2014 and 2019 (see Appendix 5) as initially described in protocol amendment 7.

Document	Version Date	Summary of Changes
		17. General formatting and copy editing were performed throughout the document.
Amendment 9	28 March 2023	The primary purpose of this amendment is to extend the duration of the study by ~ 6 months, reduce sample collections for exploratory endpoints, and extend contraception period post last dose.
		1. SoA A (footnote #37), SoA B (footnote #37), SoA C (footnote #36), Section 3.1 (Study Overview), Section 6.3 (Follow-up), Section 6.5 (End of Study): End of study for all patients will be death or up to approximately 30 months after last patient first dose, followed by any required follow-up visits; Survival follow-up has been updated accordingly. By revising end of study, active patients will continue receiving significant clinical benefit from therapy with elranatamab. 22 February 2023 PACL
		2. SoA A (footnote #20), SoA B (footnote #20), SoA C (footnote #19), Section 4.2 (Exclusion Criteria), Section 4.3 (Lifestyle Requirements): Revised contraception requirements based on recently updated PK data as described in IB.
		3. SoA A (footnote #21), SoA B (footnote #21), SoA C (footnote #20), Section 1.2.9.5 (Dosing Interval), Section 3.1.1.4 (Part 1 Combination Dose Finding), Section 5.4 (Administration): In order to reduce participant burden of frequent visits, dosing once per cycle (CXD1) is allowed upon consultation with the sponsor.
		4. SoA A (including footnotes #29, 31-33), SoA B (including footnotes #29, 31-33), SoA C (including footnotes #28, 30-32), Section 1.2.10 (Biomarkers), Section 2 (Study Objectives and Endpoints), Section 7.5 (Biomarkers and Pharmacodynamics Assessment; Table 12): In order to limit the burden of frequent sample collections, blood sample and bone marrow aspirate collections are reduced (exploratory endpoints). 19 August 2021 PACL
		5. In order to focus on the data most important for investigators, Section 1.2.3.1 and Section

Document	Version Date	Summary of Changes
		1.2.3.2 were updated with safety and efficacy data, respectively.
		6. In order to align with Pfizer processes and protocol template requirements, Sections 11.1, 11.3, 12.1, 15.1 and 15.2 were updated.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs) and any protocol administrative change letter(s).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

PROTOCOL SUMMARY

Background and Rationale

Despite a number of recent treatment advances for Multiple Myeloma (MM), most patients are expected to relapse. MM is not considered curable and each line of therapy renders the patient more refractory to treatment. For example, the median overall survival of patients with MM who relapsed following immunomodulatory drug (IMiD) and bortezomib (Velcade) therapies is 9 months.[1] It is therefore clear that additional treatment approaches are required for relapsed/refractory MM.

By directly targeting cytotoxic T-cells to tumors, bispecific antibodies offer a novel immunotherapeutic approach for cancer. These antibodies have two separate antigen recognition domains: a domain that recognizes a tumor antigen and another that recognizes cluster of differentiation (CD) 3 expressed on T-cells. Bispecific antibodies are therefore able to simultaneously bind to CD3 and the tumor antigen at the same time, thereby initiating a cytotoxic response towards the bound tumor cell. PF-06863135 is a heterodimeric humanized full-length bispecific antibody comprised of one B-cell Maturation Antigen (BCMA) binding arm and one CD3 binding arm paired through hinge mutation technology. Strategies to further enhance the immune effects of PF-06863135 have been supported by pre-clinical data showing enhanced tumor growth inhibition by combining PF-06863135 with an immunomodulatory drug (IMiD).

In this first in patient (FIP) clinical study, PF-06863135 will be evaluated for the treatment of adult patients with relapsed/refractory multiple myeloma, who have received a proteasome inhibitor, an IMiD and an anti CD38 monoclonal antibody (mAb) either in combination with lenalidomide, pomalidomide, dexamethasone, or as a single agent.

Study Design:

This is a Phase 1 open-label, multi-dose, multi-center, dose escalation, safety, pharmacokinetic (PK) and pharmacodynamic study of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide or dexamethasone in adult patients with advanced MM who have relapsed from or are refractory to standard therapy. This study will be divided into dose escalation/finding part (Part 1) and dose expansion part (Part 2).

Part 1 dose escalation/finding (with either monotherapy or combination therapies) in order to determine the recommended Phase 2 dose (RP2D) is further divided into:

- Part 1 intravenous (IV) monotherapy and Part 1 subcutaneous (SC) monotherapy cohorts as well as Part 1.1 priming and maintenance cohorts .
- Part 1C lenalidomide combination, Part 1D pomalidomide combination and Part 1E dexamethasone combination cohorts.

Part 2 dose expansion phase will be divided into 4 cohorts as follows:

- Part 2A (PF-06863135 as monotherapy).
- Part 2C (PF-06863135 in combination with lenalidomide).
- Part 2D (PF-06863135 in combination with pomalidomide).
- Part 2E (PF-06863135 in combination with dexamethasone).

After the single-agent PF-06863135 maximum tolerated dose (MTD) or maximum administered dose (MAD) and RP2D as well as preferred route of administration has been determined in the Part 1 monotherapy dose escalation, safety cohorts evaluating combinations of PF-06863135 with either lenalidomide, pomalidomide or dexamethasone may be initiated in Parts 1C, 1D or Part 1E respectively. Following identification of the MTD/MAD and RP2D as monotherapy and in each combination cohort, dose expansion cohorts testing monotherapy and combinations with lenalidomide, pomalidomide or dexamethasone will be initiated (expansion cohorts Parts 2A, 2C, 2D, or 2E respectively).

IV and SC administration of PF-06863135 will be evaluated during the Part 1 dose escalation. An alternative maintenance dose escalation phase (Part 1.1), which incorporates the usage of a priming dose during Cycle 0 Day 1 (C0D1) followed by a maintenance dose 1 week later at C1D1 for all subsequent doses, may also be initiated. Part 1 will be implemented as follows:

- Part 1 IV studies escalating doses of PF-06863135 administered intravenously (0.1, 0.3, 1, 3, 10, 30, 50 µg/kg or higher if indicated) weekly (see Section 3.1.1.3). Additional dose levels (lower, intermediate or higher) may be evaluated [see Section 3.1.4].
- After Part 1 IV 50 µg/kg dose was cleared, Part 1 SC administration (80, 130, 215, 360, 600, and 1000 µg/kg) weekly was opened based on the emerging clinical and PK data from Part 1 IV cohorts (see Section 3.1.1.3). Upon reaching MTD/MAD, up to 6-12 patients total at selected level(s) below the MTD/MAD weekly and Q2W dosing up to the same dose intensity as the MTD/MAD weekly regimen may be evaluated further to support the RP2D decision.
- An alternative Part 1.1 priming and maintenance dosing for monotherapy IV or SC administration may be triggered if ≥ Grade 3 cytokine release syndrome (CRS) events (lasting for >24 hours despite treatment with standard of care per the institution's, Investigator's, or treating physician's guidelines for the management of CRS) are observed (see Section 3.1.1.3). A priming dose (Cycle 0) would be given one week prior to Cycle 1 of maintenance dosing and include a mandatory overnight hospitalization on C0D1. Alternative strategies for increasing dosing such as a step-up regimen or prophylactic steroids may also be considered and implemented to further improve tolerability if needed.

- For all patients in monotherapy Part 1 cohorts, to closely manage and monitor acute toxicities, patients will be hospitalized on C1D1. The need for mandatory hospitalization as well as its length will be re-assessed for patients enrolled in Part 2A based on safety data from Part 1 after agreement of sponsor and investigators at the time of monotherapy MTD/MAD and RP2D determination.

- A staggered enrollment strategy will be applied for all patients in the monotherapy Part 1 cohort at each dose level: when a dose level opens for enrollment, the first patient will be dosed and observed for 48 hours. In Part 1, if no safety concerns arise during this 48 hr period from start of treatment, then subsequent patients will be enrolled into the same dose level. In Part 1.1, if no safety concerns arise 48 hrs after receiving the maintenance dose on C1D1, subsequent patients will be enrolled into the same maintenance dose level.

- All patients in the monotherapy cohorts of Part 1 will be monitored closely for dose limiting toxicities (DLTs, see Section 3.2), until the end of Cycle 1.

Either IV or SC administration of PF-06863135 either with or without a priming dose will be selected to move forward in combinations with lenalidomide, pomalidomide, or dexamethasone.

- Part 1C will investigate PF-06863135 in combination with lenalidomide, Part 1D will investigate PF-06863135 in combination with pomalidomide.

    - These safety cohorts (Parts 1C and 1D) will use a dose-escalation/de-escalation approach for PF-06863135 starting with the dose level MTD-1/MAD-1 or RP2D (whichever is lower) of PF-06863135 from Part 1 dose escalation combined with 15 mg lenalidomide, or 4 mg pomalidomide. If safe and well tolerated PF-06863135 will then be escalated to the monotherapy MTD/RP2D, if applicable, again in combination with 15 mg lenalidomide, or 4 mg pomalidomide in order to select the combination RP2D. If the combination regimen is not well tolerated due to PF-06863135, PF-06863135 may be de-escalated in combination according to mTPI design. Each cycle of the combination of PF-06863135 and lenalidomide or pomalidomide starting with Cycle 1 will be 28 days.

    - To closely manage acute toxicities, patients will be hospitalized on C1D1. The need for mandatory hospitalization as well as its length will be re-assessed for patients enrolled in Parts 2C and 2D based on safety data from Parts 1C and 1D, respectively.

    - A staggered enrollment strategy will be applied for Parts 1C and 1D: when a dose level opens for enrollment, the first patient will be dosed, and observed for 96 hours after C1D1. If no safety concerns arise during this 96 hr period from C1D1, subsequent patients will be enrolled into the same dose level and combination.

- Upon reaching MTD/MAD, up to approximately 6-12 patients total at selected level(s) below the MTD/MAD may be evaluated further to support the RP2D decision.

- Part 1E will investigate PF-06863135 in combination with dexamethasone. Dexamethasone would begin on C0D1 and it will be dosed as premedication prior to PF-06863135 administration.

  - This safety cohort will evaluate the RP2D of PF-06863135 with dexamethasone at a dose of 40 mg. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone premedication may be given prior to PF-06863135 at a dose of 20 mg. PF-06863135 may be de-escalated according to modified toxicity probability interval (mTPI) design. If the combination regimen is not well tolerated as guided by mTPI, Part 2E may not be initiated. Each cycle of the combination of PF-06863135 and dexamethasone starting with Cycle 1 will be 28 days.

  - To closely manage acute toxicities, patients in Part 1E will be hospitalized on C1D1. The need for hospitalization as well as its length will be re-assessed for patients enrolled in Part 2E based on safety data from Part 1E after agreement of sponsor and investigators.

  - For Part 1E or Part 2E, patients within these parts may enroll concurrently.

  - It is expected that Part 1E will enroll approximately 9-16 patients.

A modified toxicity probability interval (mTPI) method, targeting a DLT rate of 25% and an acceptable equivalence interval of 20%-30% will be utilized for dose escalation in Part 1. All patients will also be monitored closely for DLTs until the end of Cycle 1. All patients will be monitored for late toxicities following the initial DLT period up to Day 60 from first dose (see Section 3.2.1). Once a dose level has been declared safe, patients at lower dose levels who have completed the 60 day late toxicity observation period may escalate to the next higher dose level, if criteria outlined in Section 3.1.4.1 Criteria for Intrapatient Dose Escalation have been met. Additional intra-patient dose escalations will also be permitted after a minimal interval of 60 days. No crossover is allowed, however, between patients assigned to monotherapy PF-06863135 and the different combination regimens.

Following the determinations of the RP2D of monotherapy and combinations with lenalidomide or pomalidomide in Part 1, the respective expansion cohorts in Part 2 will commence. In addition, if the combination with dexamethasone in Part 1E is well tolerated as guided by mTPI, Part 2E may be initiated.

Part 2 dose expansion phase will be divided into 4 cohorts as follows: Part 2A (PF-06863135 as monotherapy), Part 2C (PF-06863135 in combination with lenalidomide), Part 2D (PF-06863135 in combination with pomalidomide) and Part 2E (PF-06863135 in

combination with dexamethasone) which will evaluate safety and anti-myeloma activity of PF-06863135 at RP2Ds determined in Part 1.

Approximately 120 patients had been planned to enroll into Parts 1/1.1, 1C, 1D, 1E with approximately 80 patients planned to enroll into Part 2. Parts 1C, 1D and 1E were planned to enroll approximately 9-16 patients with Parts 2A, 2C, 2D and 2E planned to enroll approximately 20 patients each.

The clinical development program for PF-06863135 has been expanded with dedicated studies that will further investigate both monotherapy and combination therapy. Therefore, the Sponsor has determined that enrollment in study C1071001 has been completed.

Study Objectives and Endpoints

Part 1 IV and SC monotherapy Dose Escalation, Part 1.1 Priming and Maintenance Dose Escalation and Parts 1C, 1D and 1E Combination DoseEscalation/Finding

Primary Objectives:	**Primary Endpoints:**
• To assess safety and tolerability at increasing dose levels of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone in successive cohorts of patients with multiple myeloma in order to estimate the Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAD) and select the Recommended Phase 2 Dose (RP2D).	• Number of DLTs following treatment with escalating doses of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.
Secondary Objectives:	**Secondary Endpoints:**
• To evaluate the overall safety profile.	• Adverse Events as characterized by type, frequency, severity as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, timing, seriousness, and relationship to PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone. The severity of cytokine release syndrome (CRS) will be assessed according to the grading described by Lee et al. (2014 and 2019,[2,3] See Appendix 5); • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.
• To evaluate anti-myeloma activity of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• Objective response rate (ORR) using the international myeloma working group (IMWG) response criteria for multiple myeloma[4,5] (see Appendix 2); • Time to event endpoints: time to response (TTR), complete response rate (CRR), duration of response (DOR), duration of complete

	response (DoCR), duration of stable disease (DOSD), progression-free survival (PFS), overall survival (OS), as assessed by IMWG criteria for response[4,5] (see Appendix 2); • Rate of patients with no minimal residual disease (MRD) after treatment with PF-06863135 using IMWG MRD criteria[5] (see Appendix 3).
• To evaluate single dose and multiple dose PK of PF-06863135 given as monotherapy and in combination with lenalidomide,pomalidomide, and dexamethasone. Additionally, PK of lenalidomide, pomalidomide, and dexamethasone will be evaluated when combined with PF-06863135 (Parts 1C, 1D, and 1E, respectively).	• Pharmacokinetic parameters of PF-06863135: Cycle 1 Day 1 dose and Cycle 2 Day 1 dose maximum concentration (C_{max}), area under the concentration versus time curve from time zero to the last quantifiable time point prior to the next dose (AUC_{last}) and if data permit, clearance (CL) or clearance after non-intravenous administration (CL/F), volume of distribution at steady state (Vss) or apparent volume of distribution after on-intravenous administration (Vss/F), and terminal elimination $t_{1/2}$. • Plasma lenalidomide, pomalidomide, and dexamethasone concentrations at selected time points (Parts 1C, 1D, and 1E, respectively).
• To evaluate immunogenicity of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone,.	• Incidence and titers of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against PF-06863135.
• To characterize the impact of PF-06863135 as a monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone on systemic soluble immune factors.	• Pre- and post-dose quantification of soluble cytokines in serum.
Tertiary/Exploratory Objectives:	**Tertiary/Exploratory Endpoints:**
• Evaluate the effect of PF-06863135 as a monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone on plasma cell, T and B cell compartments.	• BCMA expression on plasma cells in bone marrow, as assessed by multiparameter flow cytometry and immunohistochemistry; • Pre- and post-dose levels of soluble BCMA; • Enumeration of T, B, and natural killer (NK) subtypes in whole blood and bone marrow by flow cytometry analysis; • T-cell immunophenotyping, including but not limited to proliferation and activation markers in whole blood and bone marrow by flow cytometry analysis; • T-cell engagement, including but not limited to proliferation and activation markers in bone marrow by immunohistochemistry; • The relative expression of (ribonucleic acid) RNA transcripts, including but not limited to,

	those associated with immune activation and immune regulation in bone marrow; • The abundance and diversity of T-cell clones in bone marrow.
• To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens Section 7.7.

Part 2 Dose Expansion

Primary Objectives:	**Primary Endpoints:**
• To assess preliminary clinical efficacy at RP2D for PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• ORR and DOR, as assessed by IMWG criteria for response[4,5] (see Appendix 2)
Secondary Objectives:	**Secondary Endpoints:**
• To further characterize the safety and tolerability of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone. The severity of CRS will be assessed according to the grading described by Lee et al. (2014 and 2019,[2,3] See Appendix 5); • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.
• To further evaluate anti-myeloma efficacy of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• Time to event endpoints: CRR, DoCR, TTR, DOSD, PFS, OS, as assessed by IMWG criteria for response[4,5] (see Appendix 2); • Rate of patients with no minimal residual disease (MRD) after treatment with PF-06863135 using IMWG MRD criteria[5] (see Appendix 3).
• To evaluate PK of PF-06863135 at RP2D as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone. Additionally, to collect lenalidomide, pomalidomide, or dexamethasone concentration data when combined with PF-06863135.	• Concentrations of PF-06863135, lenalidomide, pomalidomide, or dexamethasone for selected time points.
• To evaluate immunogenicity of PF-06863135 as monotherapy and in combination with	• Incidence and titers of anti-drug antibodies (ADA and neutralizing antibodies (Nab) against PF-06863135.

lenalidomide, pomalidomide, or dexamethasone.	
• To characterize the impact of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide or dexamethasone on systemic soluble immune factors.	• Pre- and post-dose quantification of soluble cytokines in serum.
Tertiary/Exploratory Objectives:	**Tertiary/Exploratory Endpoints:**
• Evaluate the effect of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone on plasma cell, T and B cell compartments.	• BCMA expression on plasma cells in bone marrow, as assessed by multiparameter flow cytometry and immunohistochemistry; • Pre- and post-dose levels of soluble BCMA; • Enumeration of T, B, and NK subtypes in whole blood and bone marrow by flow cytometry analysis; • T-cell immunophenotyping, including but not limited to proliferation and activation markers in whole blood and bone marrow by flow cytometry analysis; • T-cell engagement, including but not limited to proliferation and activation markers in bone marrow by immunohistochemistry; • The relative expression of RNA transcripts, including but not limited to, those associated with immune activation and immune regulation in bone marrow; • The abundance and diversity of T-cell clones in bone marrow.
• To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens Section 7.7.

SCHEDULE OF ACTIVITIES A: PART 1 IV AND SC WEEKLY MONOTHERAPY (NO PRIMING DOSE)

The Schedule of Activities Table A provides an overview of the protocol visits and procedures. Refer to the ASSESSMENTS Section 7 of the protocol for detailed information on each assessment required for compliance with the protocol.

This schedule of activities is only applicable to Part 1 whenever weekly IV or SC monotherapy dosing is used without a priming dose. See Appendix 10 for alternative measure guidelines due to COVID-19.

The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table in order to conduct evaluations or assessments required to protect the well-being of the patient.

Schedule of Activities A Visit Identifier	**Screening[1] Days prior to enrollment**		**Treatment Period**														**1 month Follow-up[35]**	**Survival Follow-up[37]**
			Cycle 1 (1 Cycle = 3 weeks)						**Cycle 2**				**Cycle 3 onwards**			**EOT[36]**		
Study Day	**-28 to -1**	**-14 to -1**	**1**	**2**	**3**	**4***	**8**	**15**	**1**	**4***	**8**	**15**	**1**	**8**	**15**			
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2		+7	±14
Informed consent[2]	X																	
Myeloma history[3]	X																	
Medical history[4]	X																	
Demography	X																	
Baseline signs and symptoms[5]	X																	
Eligibility Criteria and Registration[6]		X																
Patient hospitalization[7]			X	X	X													
Clinical Evaluation																		
Physical examination[8]		X	X	X			X	X	X		X	X	X			X	X	
Weight[9]		X	X						X				X			X		
Vital signs (BP/pulse rate/Temp)[10]		X	X	X			X	X	X		X	X	X	X	X	X	X	
ECOG performance status[11]		X	X					X	X		X	X	X			X	X	
(12 lead) ECG[12]		X	X	X		(X)	X	X	X	(X)	X	X	X			X	X	
Echo or MUGA[13]	X		If there is a history of cardiac events, perform when clinically indicated.													X		
Safety Laboratory																		
Hematology[14]		X	X	X			X	X	X		X	X	X			X	X	
Blood Chemistry[15]		X	X	X			X	X	X		X	X	X			X	X	
Coagulation[16]		X	X				X	X	X		X	X	X			X	X	

Schedule of Activities A **Visit Identifier**	**Screening[1]** **Days prior to enrollment**		**Treatment Period**														**1 month Follow-up[35]**	**Survival Follow-up[37]**
			Cycle 1 (1 Cycle = 3 weeks)						**Cycle 2**				**Cycle 3 onwards**			**EOT[36]**		
Study Day	**-28 to -1**	**-14 to -1**	**1**	**2**	**3**	**4***	**8**	**15**	**1**	**4***	**8**	**15**	**1**	**8**	**15**			
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2		+7	±14
Hepatitis assessment[17]		X																
Multiplex cytokine assays (blood)[18]		Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments																
Urinalysis[19]		X	X													X	X	
Pregnancy test and contraception check[20]	X		X						X				X					
Treatment																		
Treatment with PF-06863135[21]			X				X	X	X		X	X	X	X	X			
Disease assessments																		
SPEP, SIFE, serum FLC ratio, beta2 microglobulin- (local)[22]		X	X						X				X			X	X	If obtained as SOC prior to subse-quent treat-ment[37]
UPEP, UIFE (local)[23]		X	X						X				X			X	X	
Bone marrow collection and assessments- aspirates (including NGS MRD assessment)[24]			X	At 1, 3, and 9 months after C1D1, every 6 months thereafter, at suspected CR and optional at disease progression. Collection at 9 months after C1D1 and onwards will be optional for patients who experience a plateau or CR. Central assessment of MRD by next-generation sequencing test is required at baseline (C1D1) and at all times bone marrow aspirates are obtained while a patient is in suspected or actual CR [24].															
Bone marrow collection and assessments- biopsies[24]			X	At 1, 3 (optional), and 9 (optional) months, every 6 months thereafter (optional), at suspected sCR and optional at disease progression. Collection at 9 months after C1D1 and onwards will be optional for patients who experience a plateau or CR.														
Disease assessments by PET/ CT[25]	X			At suspected CR or PD, and when clinically indicated for all patients. At 1, 3, and 9 months after C1D1 and every 6 months thereafter for patients with measurable target lesions at screening.												X		
Other clinical assessments																		
Serious and non-serious adverse event monitoring[26]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	

Schedule of Activities A **Visit Identifier**	**Screening[1]** **Days prior to enrollment**		**Treatment Period**														**1 month Follow-up[35]**	**Survival Follow-up[37]**
			Cycle 1 (1 Cycle = 3 weeks)						**Cycle 2**				**Cycle 3 onwards**			**EOT[36]**		
Study Day	**-28 to -1**	**-14 to -1**	**1**	**2**	**3**	**4***	**8**	**15**	**1**	**4***	**8**	**15**	**1**	**8**	**15**			
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2		+7	±14
Concomitant treatment(s)[27]			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Local Site Injection Tolerability Assessment (SC only)[38]			X				X	X										
Pharmacokinetic (PK) assessments																		
Blood sample for PF-06863135		Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments																
Immunogenicity assessments																		
Anti-drug antibodies and neutralizing antibodies against PF-06863135		Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments																
Pharmacodynamic assessments																		
Genetic analysis- bone marrow aspirate[28]			X															
BCMA+ expression on multiple myeloma cells from bone marrow aspirate- flow cytometry[29]			X	At 1, 3, and 9 months after C1D1 .														
BCMA expression on multiple myeloma cells (IHC) and additional PD assessments from bone marrow biopsy[29]			X	At 1, 3 (optional), and 9 (optional) months after C1D1.														
Soluble BCMA from blood[30]		Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments																
TBNK and immunophenotyping from blood[31]			X	X		X	X	X	X	X	X							
TBNK and immunophenotyping from bone marrow aspirate[31]			X	At 1 and 3months after C1D1														
Gene expression (RNA) profile from bone marrow aspirate[32]			X	At 1, 3, and 9 months after C1D1, every 6 months thereafter, at suspected CR and optional at disease progression if BM disease assessments are completed.														
TCR sequencing from bone marrow aspirate[33]			X	At 1, 3, and 9 months after C1D1, every 6 months thereafter, at suspected CR and optional at disease progression if BM disease assessments are completed.														
Other assessments																		
Genomic banked biospecimens Prep D1[34]			X															
Pharmacogenomic sample			X								X							
Post- Treatment																		
Survival follow-up[37]																		x

Abbreviations: → = ongoing/continuous event; BCMA = B-cell maturation antigen; BM = bone marrow; BP = blood pressure; CT = computed tomography; CR = complete response; Deoxyribonucleic acid = DNA; Echo = echocardiogram; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; end of treatment = EOT; IHC = immunohistochemistry; MM = multiple myeloma; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; NK = natural killer; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; qPCR = quantitative

Schedule of Activities A Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period														1 month Follow-up[35]	Survival Follow-up[37]
			Cycle 1 (1 Cycle = 3 weeks)						Cycle 2				Cycle 3 onwards			EOT[36]		
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	1	4*	8	15	1	8	15			
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2		+7	±14

polymerase chain reaction; RNA = ribonucleic acid; SIFE = serum immunofixation electrophoresis; SPEP = serum protein electrophoresis; TCR = T-cell receptor; TBNK = T, B, and NK lymphocytes; UIFE = 24 hr urine immunofixation electrophoresis ; UPEP = 24 hr urine protein electrophoresis.
*Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments A for additional assessments on Cycle 1 Day 4 (C1D4) and Cycle 2 Day 4 (C2D4).

Footnotes for Schedule of Activities A

1. **Screening:** To be completed within 28 days prior to start of study treatment.
2. **Informed Consent:** Must be obtained prior to undergoing any study specific procedures, and be completed within 28 days prior to start of study treatment.
3. **Myeloma History:** will be collected within 28 days during screening prior to start of study treatment. Includes history of disease under study including details of primary diagnosis, biopsy information, and treatment history.
4. **Medical History:** Includes history of disease process other than the cancer under study (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
5. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 28 days prior to C1D1. During the study, any new or worsened conditions since baseline will be recorded on the Adverse Events (AE) case report form (CRF) page.
6. **Registration**: Patient number and dose level allocation assigned by Pfizer Inc.
7. **Patient hospitalization:** All patients in Part 1 IV or SC monotherapy dose escalation will be hospitalized for 72 hrs from Cycle 1 Day 1 (C1D1). Hospitalization period may be extended if the patient experiences abnormal laboratory findings or ongoing adverse events that require further hospitalization.
8. **Physical examination (PE):** Physical examination includes neurological assessment and, at screening, will also include height.
9. **Weight:** Weight will be measured prior to dosing.
10. **Vital Signs:** Includes temperature (oral, tympanic, temporal or axillary), blood pressure (BP), and pulse rate to be recorded in the sitting position after 5 minutes of rest.
11. **Performance Status:** Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 4.
12. **12-Lead electrocardiogram (ECG)**: At screening, single 12-lead ECG will be performed. On C1D1 until C2D15, triplicate 12-lead ECGs will be performed to determine mean QTcF interval. On Day 1, 8, and 15 of Cycles 1 and 2, ECGs will be performed prior to investigational product administration (up to 60 minutes before dosing), and the end of infusion or subcutaneous injection. For subcutaneous administration only, triplicate 12-lead ECGs will also be performed on Day 4 of Cycles 1 and 2. From Cycle 3 onwards, single 12-lead ECG will be performed on Day 1 of each cycle prior to investigational product administration (up to 60 minutes before dosing). When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is

Schedule of Activities A Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period														1 month Follow-up[35]	Survival Follow-up[37]
			Cycle 1 (1 Cycle = 3 weeks)						Cycle 2				Cycle 3 onwards			EOT[36]		
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	1	4*	8	15	1	8	15			
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2		+7	±14

prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

13. **Echocardiogram (Echo) or multigated acquisition scan (MUGA)**: Echo or MUGA will be evaluated in patients with previous history of cardiac events. For these patients, an Echo or MUGA will be performed at screening, when clinically indicated and at the end of treatment (EOT) visit.
14. **Hematology**: No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Assessments Section 7.1.3 for Laboratory Tests list.
15. **Blood Chemistry**: No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Assessments Section 7.1.3 for Laboratory Tests list.
16. **Coagulation**: No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Assessments Section 7.1.3 for Laboratory Tests list.
17. **Hepatitis assessment**: Screening tests for hepatitis B (HBV) and C (HCV) should be performed including hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis C virus (HCV) antibody. In the case of apparent ongoing HBV or HCV infection, reflex serum DNA or RNA viral load testing, respectively, will be performed. See Assessments Section 7.1.3 for Laboratory Tests list.
18. **Multiplex cytokine assays**: see SCHEDULE OF PHARMACOKINETIC, SOLUBLE FACTOR AND CYTOKINE activities A table. See assessments Section 7.5.4 for laboratory tests list.
19. **Urinalysis**: Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. Following C1D1, only obtain as clinically indicated until EOT. See Assessments Section 7.1.3 for Laboratory Tests list.
20. **Pregnancy Test and contraception check**: Serum pregnancy test for females of child bearing potential (see Pregnancy Testing Section 7.1.1). Contraception use will be checked to confirm that contraception is used throughout the study and for 5 months after the last dose of study treatment consistently and correctly. Contraception only required for WOCBP.
21. **Treatment with investigational product PF-06863135**: Investigational product will be administered on Day 1, 8 and 15 of each cycle (see Administration Section 5.4). If a patient has received treatment with every week dosing (Q1W) PF-06863135 for at least 6 months, and disease assessments have remained stable over at least 2 months, consideration may be given to increasing dose intervals from weekly to every 2 weeks or once every three weeks (once per cycle; only CXD1 dosing and activities applicable) after consultation with sponsor. Cycles would remain the same length with any skipped weekly doses noted. If the patient subsequently begins to have increase of disease burden, dose intervals should return to weekly dosing.
22. **Serum immunofixation electrophoresis (SIFE), serum protein electrophoresis (SPEP), serum free light chain analysis (FLC) tests and beta-2 microglobulin tests**: No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. See Assessments Section 7.2.1 for

Schedule of Activities A Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period														1 month Follow-up[35]	Survival Follow-up[37]
			Cycle 1 (1 Cycle = 3 weeks)						Cycle 2				Cycle 3 onwards			EOT[36]		
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	1	4*	8	15	1	8	15			
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2		+7	±14

laboratory disease assessment tests list. Beta 2 microglobulin will be collected on C1D1 (other time points are optional). Note that SIFE will only be completed at baseline when electrophoresis shows no measurable protein, at suspected CR, and at suspected progression (clinical or biochemical). When a complete response (CR) or a clinical or biochemical progression is suspected, SPEP, SIFE, and serum free light chain analysis (FLC) tests will be repeated within 1 to 4 weeks. For patients scheduled to be dose escalated, samples will also be collected within 1 week prior to receiving the first higher dose. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. If patients were treated with daratumumab less than 114 days prior to planned treatment day, daratumumab will interfere with SPEP, UPEP, SIFE and UIFE assays. Therefore, for these patients, FLC assay should be completed at screening, C1D1, and all subsequent disease assessments. In these patients who previously received daratumumab serum and urine M-spike if measurable at baseline in these patients should also be followed at the same timepoints as FLC with the most representative marker of disease status used for determination IMWG assessment.

23. **24 hr urine immunofixation electrophoresis (UIFE), 24 hr urine protein electrophoresis (UPEP)**: No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. See Assessments Section 7.2.1 for laboratory disease assessment tests list. Note that UIFE will only be completed at baseline when electrophoresis shows no measurable protein, at suspected CR, and at suspected progression (clinical or biochemical). When a CR or a clinical or biochemical progression is suspected, UPEP and UIFE will be repeated within 1 to 4 weeks. For patients scheduled to be dose escalated, samples will also be collected within 1 week prior to receiving the first higher dose. If samples collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration.
24. **Bone Marrow Collection and Assessments**: For C1D1 and on treatment bone marrow collections and assessments, see- Section 7.2.2. Sample for Cycle 1 Day 1 (C1D1) may be taken up to 7 days before study treatment. Bone marrow collections and local plasma cell assessments should be fixed according to the calendar, regardless of treatment delays. Bone marrow evaluation consisting of bone marrow aspirate and/or bone marrow biopsies will be performed to follow disease response. When bone marrow plasmacell infiltration is assessed by both bone marrow aspirate and by bone marrow biopsy, the highest value of bone marrow -plasmacell infiltration should be utilized for response evaluation. Bone marrow aspirates will also be collected and plasma cells will be evaluated at time of suspected complete response (CR) and optional at time of suspected disease progression. Bone marrow biopsy will also be collected and plasma cells will be evaluated when confirmation of stringent complete response (sCR-) is required. For patients who experience a plateau or CR, additional BM aspirates at 9 months after C1D1 and onwards will be optional. Optional bone marrow aspirate and biopsy samples will also be taken at disease progression if a sample was not taken within the past 4 weeks. If a patient is scheduled for escalation to the next highest dose level cohort following 60day late toxicity evaluation, a bone marrow aspirate will be collected within 1 week before dose escalation, unless an -ontreatment- sample was collected within the past 28 days or the investigator assesses that there in an unjustifiable risk for the patient, and/or the patient refuses to undergo a bone marrow procedure. A bone marrow aspirate sample will be collected for central MRD assessment using the next generation sequencing (NGS) assay when patient is in suspected CR or actual CR. A C1D1 bone marrow aspirate must also be collected in all patients as the baseline MRD reference sample. Samples for MRD assessments should be aliquoted from the first bone marrow aspirate pull. Samples at 1 and 3 months after C1D1 will be collected ±7 days; samples at 9 months after C1D1 and later will be collected ±14 days.

Schedule of Activities A Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period														1 month Follow-up[35]	Survival Follow-up[37]
			Cycle 1 (1 Cycle = 3 weeks)						Cycle 2				Cycle 3 onwards			EOT[36]		
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	1	4*	8	15	1	8	15			
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2		+7	±14

25. **Disease assessments by fluorodeoxyglucose (FDG) positron emission tomography (PET)/ computerized tomography (CT):** See Assessments Section 7.2.3. Radiographic assessments obtained per the patient's standard of care prior to enrollment into the study do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 28 days before C1D1, (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. For all patients, images are required at screening, suspected CR, when disease progression is suspected (eg, symptomatic deterioration), end of treatment visit (if not done in previous 4 weeks) and when otherwise clinically indicated. In patients with measurable target lesions at screening, images at 1 and 3 months after C1D1 will be collected ±7 days; images at 9 months after C1D1 and every 6 months thereafter will be collected ±14 days. For sites in Germany: Only MRI is allowed to be used as imaging modality for participants.
26. **Adverse Event (AE) Assessments**: AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. However, the severity of cytokine release syndrome (CRS) will be assessed according to the grading described by Lee et al. (2014 and 2019[2,3] See Appendix 5) instead of CTCAE. In addition, American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading of CRS and immune effector cell-associated neurotoxicity (ICANS)[3]will be captured separately from the AE assessments (See Appendix 5). The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 90 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the case report form (CRF) ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
27. **Concomitant Treatments**: all concomitant medications and Nondrug Supportive Interventions should be recorded on the CRF.
28. **Genetic Analysis**: Bone marrow aspirates taken on C1D1 will be evaluated at local lab for t(4;14)(p16;q32), t(14;16)(q32;q23), 17p13 deletions, t(11;14)(q13;q32), chromosome 13 deletion, ploidy category, and chromosome 1 abnormalities. If some of these cytogenetic assessments cannot be done, site should provide patient's most recent cytogenetic testing results and enter into eCRF. Sample may be taken up to 7 days before the start of study treatment.
29. **BCMA+ expression on multiple myeloma cells in bone marrow:** Expression of BCMA will be evaluated on fresh bone marrow aspirates (by flow cytometry) and biopsies (by IHC). Expression of additional markers including CD138 will also be evaluated. Additional analyses may be performed on bone marrow biopsies, including immunophenotyping of infiltrating immune cells and exploratory molecular analyses. If the sample collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Sample for Cycle 1 Day 1 (C1D1) may be taken up to 7 days before study treatment; samples at 1 and 3 months after C1D1 will be collected pre-dose ±7 days; samples at 9 months after C1D1 will be collected pre-dose ±14 days. .
30. **Soluble BCMA**: See Schedule of Pharmacokinetic, Soluble Factor and Cytokine Activities A. Soluble BCMA will be measured in plasma by mass spectrometry.

Schedule of Activities A Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period														1 month Follow-up[35]	Survival Follow-up[37]
			Cycle 1 (1 Cycle = 3 weeks)						Cycle 2				Cycle 3 onwards			EOT[36]		
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	1	4*	8	15	1	8	15			
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2		+7	±14

31. **TBNK and Immunophenotyping:** enumeration and phenotypes of T-cell subsets by multiparameter flow cytometry. If sample collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Bone marrow sample for Cycle 1 Day 1 (C1D1) may be taken up to 7 days before study treatment; samples at 1 month or 3 months after C1D1 will be collected ±7 days.
.
32. **Gene expression ribonucleic acid (RNA) profile:** gene expression associated with activation state and anti-tumor activity will be measured by RNA sequencing in bone marrow. If sample collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Bone marrow sample for Cycle 1 Day 1 (C1D1) may be taken up to 7 days before study treatment; samples at 1 month or 3 months after C1D1 will be collected ±7 days; samples at 9 months after C1D1 will be collected ±14 days. When bone marrow aspirate samples are taken for disease response evaluation, samples for gene expression analysis will also be acquired.
33. **T-cell receptor (TCR) sequencing**: clonal expansion, contraction and diversity and its association with activity and durability will be assessed by deoxyribonucleic acid (DNA) sequencing of TCR in bone marrow. If sample collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Bone marrow sample for Cycle 1 Day 1 (C1D1) may be taken up to 7 days before study treatment; samples at 1 month or 3 months after C1D1 will be collected ±7 days; samples at 9 months after C1D1 will be collected ±14 days. When bone marrow aspirate samples are taken for disease response evaluation, samples for TCR sequencing will also be acquired.
34. **Genomic banked biospecimens Prep D1:** If not collected on C1D1, collect at the next available time point when biospecimens are being collected in conjunction with a patient visit.
35. **One month follow-up:** At least 28 calendar days, and no more than 35 calendar days, after discontinuation of treatment, patients will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. If the patient completes the follow-up visit prior to completion of the 60 day long term dose limiting toxicity (DLT) observation period, a follow up phone call will be completed on at least Day 60, and no more than Day 65.
36. **End of Treatment (EOT) Visit:** Obtain these assessments if not completed in the last week (last 4 weeks for disease assessments).
37. **Survival follow up:** Following discontinuation of study treatment (unless patients are lost to follow up, consent is withdrawn, or study is discontinued by the sponsor), survival status will be collected by telephone every 3 months until death, or up to approximately 30 months after last patient first dose, whichever comes first. Subsequent anti-cancer therapies and relevant transplant information will also be collected. Any standard of care (SOC) disease assessments obtained between EOT and subsequent anti-cancer therapy will be collected.
38. **Local Site Injection Tolerability Assessment (SC Administration Cohort Only):** Assessment of injection site should be conducted at 1 to 4 hours following treatment administration on Day 1, 8 and 15 for the first cycle. If injection site pain or injection site reaction (ISR) characteristics continue to persist after the first cycle, local site injection tolerability assessments should continue until the symptoms resolve.

SCHEDULE OF PHARMACOKINETIC, SOLUBLE FACTOR AND CYTOKINE ACTIVITIES A: PART 1 IV AND SC WEEKLY MONOTHERAPY (NO PRIMING DOSE)

The schedule of pharmacokinetic, soluble factor and cytokine activities table provides an overview of the protocol visits and procedures. This schedule of activities is applicable to Part 1 IV and SC monotherapy dose escalation cohorts. The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table in order to conduct evaluations or assessments required to protect the well-being of the patient. See Appendix 10 for alternative measure guidelines due to COVID-19.

Visit Identifier	Up to 7 days prior to C1D1	Treatment Period																					EOT
		Cycle 1											Cycle 2								Cycle 3 onwards		
Study Day		D1				D2	D4	D8			D15		D1			D4	D8		D15		D1		
Hours Pre/ after dosing[†]		0	2*	4*	8	24	72	0	2*	4*	0	2*	0	2*	4*	72	0	2*	0	2*	0	2*	
Visit window				±0.5 hr	±1 hr	±3 hrs	±24 hrs			±0.5 hr					±1 hr	±24 hrs							
Cytokine evaluation in serum[1]	X	X	X	X	X	X	X	X	X	X	X	X	X				X				3 (±7 days) and 9 months (±14 days) after C1D1		
Samples for PF-06863135 blood level[2]		X	X	X		X	X	X	X (IV only)	X (IV only)	X	X (IV only)	X	X (IV only)	X (IV only)	X	X	X (IV only)	X	X (IV only)	X[2]	X[2] (IV only)	X
Blood samples for ADA and NAb against PF-06863135[3]		X									X		X								X[3]		X
Soluble BCMA and other factors[4]	X	X	X	X		X	X	X	X (IV only)	X (IV only)	X	X (IV only)	X	X (IV only)	X (IV only)	X	X	X (IV only)	X	X (IV only)	X[4]	X[4] (IV only)	X

Abbreviations: Anti-PF-06863135 antibodies = ADA; BCMA = B-cell maturation antigen; D = Day; EOT = end of treatment; neutralizing antibodies =NAb.
* For intravenous (IV) administration, the 2-hour sample should be taken immediately (up to 15 minutes before) before the end of PF-06863135 infusion; if the infusion is longer than 2 hours (or shorter if a 1 hour infusion is tested), the collection time of this sample should be adjusted accordingly for the sample to

Visit Identifier	Up to 7 days prior to C1D1	Treatment Period																						EOT
		Cycle 1											Cycle 2								Cycle 3 onwards			
Study Day		D1				D2	D4	D8			D15		D1			D4	D8		D15		D1			
Hours Pre/ after dosing†		0	2*	4*	8	24	72	0	2*	4*	0	2*	0	2*	4*	72	0	2*	0	2*	0	2*		

be collected immediately before the actual end of PF-06863135 infusion. For subcutaneous administration, the 2-hour sample should be taken at 2 hours post-injection ±12 minutes; also for SC administration, with the exception of cytokine samples, 2 and 4 hr samples are not needed other than on Cycle 1 D1.
† Sampling times are related to the start of the infusion. All efforts will be made to obtain the pharmacokinetic (PK) samples at the exact nominal time relative to dosing. However, samples obtained within the window specified will be considered acceptable.

Footnotes for Schedule of Pharmacokinetic, Soluble Factors and Cytokine Activities A

1. **Cytokine evaluation in serum:** See Cytokine Assessments Section 7.5.4 for a full list of cytokine assessments. All samples will be analyzed centrally. All 0 hour samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. If CRS is suspected, an adhoc cytokine sample will be collected(see Section 7.1.3 Laboratory Safety Assessments). Should the site require cytokine information for patient management, the site will have the option of collecting an additional sample for local analysis. If a sample for cytokine panel evaluation is due to be collected on the same day as the day a suspected CRS event occurs, then an ad hoc sample for central analysis is not required/collected. However, an ad hoc sample for local analysis may still be collected for patient management.
2. **Blood sample for PF-06863135 blood level:** Approximately 5 mL sample of whole blood (to provide approximately 2 mL of serum) will be collected at each time point for PK analysis of PF-06863135. After Cycle 8, pre- and post-dose PK samples will be collected only on every 4th cycle (Cycle 8, Cycle 12, Cycle 16, etc.). An additional PK sample should also be taken if CRS is suspected, and a PK sample is not already scheduled to be taken (eg, Cycle 3 onwards).
3. **Anti PF-06863135 Antibodies (ADA) and Neutralizing Antibodies (NAb):** Collection of two 1 mL pre-dose serum samples (from 5 mL total whole blood) to detect the presence of antibodies to PF-06863135 is to be obtained prior to the start of treatment. Patients having an unresolved adverse event that is possibly related to anti-PF-06863135 antibodies at their last assessment will be asked to return to the clinic for ADA and drug concentration blood sampling at approximately 3-month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor. After Cycle 4, pre-dose ADA and NAb samples will be collected only on Cycles 6, 8, and every 4th cycle thereafter (Cycle 8, Cycle 12, Cycle 16, etc.).
4. **Soluble BCMA and other factors**: Approximately 3 mL sample of whole blood (to provide approximately 1 mL of plasma) will be collected at each time point for analysis of soluble BCMA and other factors by mass spectrometry. All 0 hour samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. After Cycle 8, pre- and post-dose PK samples will be collected only on

Visit Identifier	Up to 7 days prior to C1D1	Treatment Period																					EOT
		Cycle 1											Cycle 2								Cycle 3 onwards		
Study Day		D1				D2	D4	D8			D15		D1			D4	D8		D15		D1		
Hours Pre/ after dosing[†]		0	2*	4*	8	24	72	0	2*	4*	0	2*	0	2*	4*	72	0	2*	0	2*	0	2*	

every 4th cycle (Cycle 8, Cycle 12, Cycle 16, etc.). An additional soluble BCMA/other factor sample should also be taken if CRS is suspected, and a sample is not already scheduled to be taken (eg, Cycle 3 onwards).

SCHEDULE OF ACTIVITIES B: PART 1.1 AND ANY PART USING PRIMING DOSE AND MAINTENANCE

The Schedule of Activities Table B provides an overview of the protocol visits and procedures. Refer to the Assessments Section 7 of the protocol for detailed information on each assessment required for compliance with the protocol.

This schedule of activities is applicable to Part 1.1 if priming dose and maintenance is selected and any other parts of the study where a priming dose will be administered.

Grayed out columns should only be performed when every week dosing (Q1W) dosing of PF-06863135 is being used but not for Q2W dosing.

The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table in order to conduct evaluations or assessments required to protect the well-being of the patient. See Appendix 10 for alternative measure guidelines due to COVID-19.

Schedule of Activities B Visit Identifier	**Screening[1] Days prior to enrollment**		**Treatment Period**															**1 month Follow-up [35]**			**Survival Follow-up[37]**
			Priming Dose		**Maintenance Dose**																
			Cycle 0 (1 wk)		**Cycle 1 (1 Cycle = 4 weeks)**					**Cycle 2**				**Cycle 3 onwards**				**EOT [36]**			
Study Day	**-28 to -1**	**-14 to -1**	**1**	**2**	**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**		**28 d**	**90 d**	**120 d**	
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14
Informed consent[2]	X																					
Myeloma history[3]	X																					
Medical history[4]	X																					
Demography	X																					
Baseline signs and symptoms[5]	X																					
Eligibility Criteria and Registration[6]		X																				
Patient hospitalization[7]			X		X																	
Clinical Evaluation																						
Physical examination[8]		X	X	X	X	X	X	X	X	X	X	X	X	X				X	X			
Weight[9]		X	X							X				X				X				
Vital signs (BP/pulse rate/Temp)[10]		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			

Schedule of Activities B Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																1 month Follow-up [35]			Survival Follow-up[37]
			Priming Dose		Maintenance Dose																	
			Cycle 0 (1 wk)		Cycle 1 (1 Cycle = 4 weeks)					Cycle 2				Cycle 3 onwards				EOT [36]				
Study Day	-28 to -1	-14 to -1	1	2	1	2	8	15	22	1	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14
ECOG performance status[11]		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X			
(12 lead) ECG[12]		X	X	X	X	X	X	X	X	X	X	X	X	X				X	X			
Echo or MUGA[13]	X		If there is a history of cardiac events, perform when clinically indicated.															X				
Safety Laboratory																						
Hematology[14]		X	X	X	X		X	X	X	X	X	X	X	X				X	X			
Blood Chemistry[15]		X	X	X	X		X	X	X	X	X	X	X	X				X	X			
Coagulation[16]		X	X		X		X	X	X	X	X	X	X	X				X	X			
Hepatitis assessment[17]		X																				
Multiplex cytokine assays (blood)[18]			Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments																			
Urinalysis[19]		X	X															X	X			
Pregnancy test and contraception check[20]	X		X		Weekly during Cycle 1 starting at C1D1 for Parts 1C, 1D, 2C, and 2D					X				X					X	X	X	
Treatment																						
Treatment with PF-06863135[21]			X		X		X	X	X	X	X	X	X	X	X	X	X					
Treatment with dexamethasone (Part 1E and 2E) [41]			X		X		X	X	X	X	X	X	X	X	X	X	X					
Treatment with lenalidomide[39] (Part 1C and 2C only)					Daily on Days 1-21					Daily on Days 1-21				Daily on Days 1-21								
Treatment with pomalidomide[40] (Part 1D and 2D only					Daily on Days 1-21					Daily on Days 1-21				Daily on Days 1-21								

Schedule of Activities B Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																1 month Follow-up [35]			Survival Follow-up[37]
			Priming Dose		Maintenance Dose																	
			Cycle 0 (1 wk)		Cycle 1 (1 Cycle = 4 weeks)					Cycle 2				Cycle 3 onwards				EOT [36]				
Study Day	-28 to -1	-14 to -1	1	2	1	2	8	15	22	1	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14
Disease assessments																						
SPEP, SIFE, serum FLC ratio and beta-2 microglobulin (local)[22]		X	X		X					X				X				X	X			If obtained as SOC prior to subsequent treatment[37]
UPEP, UIFE (local)[23]		X	X		X					X				X				X	X			
Bone marrow collection and assessments - aspirate (including NGS MRD assessment)[24]			X			At 1, 3 and 9 months after C1D1, every 6 months thereafter, at suspected CR and optional at disease progression. Collection at 9 months after C1D1 and onwards will be optional for patients who experience a plateau or CR. Central assessment of MRD by next-generation sequencing test is required at baseline (C0D1) and at all times bone marrow aspirates are obtained while a patient is in suspected or actual CR[24].																
Bone marrow collection and assessments biopsies[24]			X			At 1, 3 (optional) and 9 (optional) months after C1D1, every 6 months thereafter (optional), at suspected sCR and optional at disease progression. Collection at 9 months after C1D1 and onwards will be optional for patients who experience a plateau or CR.																
Disease assessments by PET/CT[25]	X				At suspected CR or PD, and when clinically indicated for all patients. At 1, 3, and 9 months after C1D1 and every 6 months thereafter for patients with measurable target lesions at screening.													X				
Other clinical assessments																						
Serious and non-serious adverse event monitoring[26]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		→	→	→
Concomitant treatment(s)[27]			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		→	→	→
Local Site Injection Tolerability Assessment (SC only)[38]			X		X		X	X	X													

Schedule of Activities B Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																1 month Follow-up [35]			Survival Follow-up[37]
			Priming Dose		Maintenance Dose																	
			Cycle 0 (1 wk)		Cycle 1 (1 Cycle = 4 weeks)					Cycle 2				Cycle 3 onwards				EOT [36]				
Study Day	-28 to -1	-14 to -1	1	2	1	2	8	15	22	1	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14
Pharmacokinetic (PK) assessments																						
Blood sample for PF-06863135 (all Parts), lenalidomide (Parts 1C and 2C), pomalidomide (Parts 1D and 2D), and dexamethasone (Parts 1E and 2E)			Please see Schedule of Pharmacokinetic, Soluble Factor, and Cytokine Assessments																			
Immunogenicity assessments																						
Anti-drug antibodies and neutralizing antibodies against PF-06863135			Please see Schedule of Pharmacokinetic, Soluble Factor, and Cytokine Assessments																			
Pharmacodynamic assessments																						
Genetic analysis- bone marrow aspirate[28]			X																			
BCMA+ expression on multiple myeloma cells from bone marrow aspirate- flow cytometry[29]			X			At 1, 3 and 9 months after C1D1.																
BCMA expression on multiple myeloma cells (IHC) and additional PD assessments from bone marrow biopsy[29]			X			At 1, 3 (optional) and 9 (optional) months after C1D1.																
Soluble BCMA from blood[30]						Please see Schedule of Pharmacokinetic, Soluble Factor, and Cytokine Assessments																
TBNK and immunophenotyping from blood[31]			X		X	X (IV only)	X	X	X	X		X										
TBNK and immunophenotyping from bone marrow aspirate[31]			X			At 1 and 3 months after C1D1.																

Schedule of Activities B Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																1 month Follow-up [35]			Survival Follow-up[37]
			Priming Dose		Maintenance Dose																	
			Cycle 0 (1 wk)		Cycle 1 (1 Cycle = 4 weeks)					Cycle 2				Cycle 3 onwards				EOT [36]				
Study Day	-28 to -1	-14 to -1	1	2	1	2	8	15	22	1	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14
Gene expression (RNA) profile from bone marrow aspirate[32]			X		At 1, 3 and 9 months after C1D1, every 6 months thereafter, at suspected CR and optional at disease progression if BM disease assessments are completed.																	
TCR sequencing from bone marrow aspirate[33]			X		At 1, 3 and 9 months after C1D1, every 6 months thereafter, at suspected CR and optional at disease progression if BM disease assessments are completed.																	
Other assessments																						
Genomic banked biospecimens Prep D1[34]			X																			
Pharmacogenomic sample			X							X												
Post- Treatment																						
Survival follow-up[37]																						X

Abbreviations: → = ongoing/continuous event; BCMA = B-cell maturation antigen; BM = bone marrow; BP = blood pressure; CT = computed tomography; CR = complete response; Deoxyribonucleic acid = DNA; Echo = echocardiogram; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; end of treatment = EOT; IHC = immunohistochemistry; MM = multiple myeloma; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan ; NK = natural killer; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; qPCR = quantitative polymerase chain reaction ; RNA = ribonucleic acid; TCR = T-cell receptor; TBNK = T, B, and NK lymphocytes.

* Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments B for additional assessments on C1D4 and C2D4.

Activities in grayed out columns should only be done for PF-06863135 Q1W dosing schedule but skipped for Q2W dosing.

Footnotes for Schedule of Activities B

1. **Screening:** To be completed within 28 days prior to start of study treatment.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures, and be completed within 28 days prior to start of study treatment.
3. **Myeloma history:** will be collected within 28 days during screening prior to start of study treatment. Includes history of disease under study including details of primary diagnosis, biopsy information, and treatment history.
4. **Medical History:** Includes history of disease process other than the cancer under study (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.

Schedule of Activities B Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																1 month Follow-up [35]			Survival Follow-up[37]
			Priming Dose		Maintenance Dose																	
			Cycle 0 (1 wk)		Cycle 1 (1 Cycle = 4 weeks)					Cycle 2				Cycle 3 onwards				EOT [36]				
Study Day	-28 to -1	-14 to -1	1	2	1	2	8	15	22	1	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

5. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 28 days prior to C0D1. During the study, any new or worsened conditions since baseline will be recorded on the AE CRF page.
6. **Registration**: patient number and dose level allocation assigned by Pfizer Inc.
7. **Patient hospitalization:** All patients in receiving a priming dose will be hospitalized for at least 24 hrs on C0D1 and for at least 24 hrs from C1D1. Hospitalization period may be extended if the patient experiences abnormal laboratory findings or ongoing adverse events that require hospitalization. Hospitalization in Parts 2A, 2C, 2D and 2E at C1D1 may be optional based on safety data from Parts 1A, 1C, 1D and 1E, respectively.
8. **Physical examination (PE):** Physical examination includes neurological assessment and, at screening, will also include height.
9. **Weight:** Weight will be measured prior to dosing.
10. **Vital Signs:** Includes temperature (oral, tympanic, temporal or axillary), BP, and pulse rate to be recorded in the sitting position after 5 minutes of rest.
11. **Performance Status:** Use ECOG – see Appendix 4.
12. **Lead electrocardiogram (ECG)**: At screening, single 12-lead ECG will be performed. On C0D1 until C2D22, triplicate 12-lead ECGs will be performed to determine mean QTcF interval. On Days 1 and 2 of Cycle 0 and Days 1, 2, 8, 15 and 22 of Cycles 1 and 2, ECGs will be performed prior to investigational product administration (up to 60 minutes before dosing), and the end of infusion or subcutaneous injection. From Cycle 3 onwards, single 12-lead ECG will be performed on Day 1 of each cycle prior to investigational product administration (up to 60 minutes before dosing). When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
13. **Echocardiogram (Echo) or multigated acquisition scan (MUGA)**: Echo or MUGA will be evaluated in patients with previous history of cardiac events. For these patients, an Echo or MUGA will be performed at screening, when clinically indicated, and at the end of treatment (EOT) visit.
14. **Hematology**: No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Assessments Section 7.1.3 for Laboratory Tests list.
15. **Blood Chemistry**: No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Assessments Section 7.1.3 for Laboratory Tests list.

Schedule of Activities B Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																1 month Follow-up [35]			Survival Follow-up[37]
			Priming Dose		Maintenance Dose																	
			Cycle 0 (1 wk)		Cycle 1 (1 Cycle = 4 weeks)					Cycle 2				Cycle 3 onwards				EOT [36]				
Study Day	-28 to -1	-14 to -1	1	2	1	2	8	15	22	1	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

16. **Coagulation**: No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Assessments Section 7.1.3 for Laboratory Tests list.
17. **Hepatitis assessment**: Screening tests for hepatitis B (HBV) and C (HCV) should be performed including hepatitis B surface (HBs) antigen, hepatitis B core (HBc) antibody, and hepatitis C virus (HCV) antibody. In the case of apparent ongoing HBV or HCV infection, reflex serum DNA or RNA viral load testing, respectively, will be performed. See Assessments Section 7.1.3 for Laboratory Tests list.
18. **Multiplex cytokine assays**: See SCHEDULE OF PHAARAMACOKIETIC,SOLUBLE FACTOR AND CYTOKINE activities B. See Assessments Section 7.5.4 for Laboratory Tests list.
19. **Urinalysis**: Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. Following C0D1, only obtain as clinically indicated until EOT. See Assessments Section 7.1.3 for Laboratory Tests list.
20. **Pregnancy Test and contraception check**: Contraception only required for WOCBP. Contraception use will be checked to confirm that contraception is used throughout the study and for 5 months after the last dose of study treatment consistently and correctly. Serum pregnancy test for females of child bearing potential (see Pregnancy Testing Section 7.1.1). In addition, for Parts 1C, 1D, 2C, and 2D, pregnancy testing should occur at C1D1 and weekly during first cycle, and if menstrual cycles are irregular should occur every 2 weeks thereafter. Contraception use will be checked to confirm that contraception is used consistently and correctly. In addition, any risk evaluation and mitigation strategy (REMS), pregnancy prevention programs (PPP), or other applicable programs required per local regulations for lenalidomide and pomalidomide must be followed where applicable.
21. **Treatment with investigational product PF-06863135**: Priming dose will be administered on C0D1. Maintenance dose will be administered on starting on C1D1. If a patient has received treatment with Q1W PF-06863135 for at least 6 months and disease assessments have remained stable over at least 2 months, consideration may be given to increasing dose intervals from weekly to every 2 or once every four weeks (once per cycle; only CXD1 dosing and activities applicable) weeks after consultation with sponsor. For every 2 week (Q2W) dosing, it would be preferable to skip dosing of PF-06863135 on days 8 and 22 of each cycle (ie, omit activities in gray columns). If the patient subsequently begins to have increase of disease burden, dose intervals should return to weekly dosing.
22. **Serum immunofixation electrophoresis (SIFE), serum protein electrophoresis (SPEP), serum free light chain analysis (FLC) tests and beta-2 microglobulin tests:** No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. See Assessments Section 7.2.1 for laboratory disease assessment tests list. Beta 2 microglobulin will be collected on C0D1 (other time points are optional). Note that SIFE will only be completed at baseline when electrophoresis shows no measurable protein, at suspected CR, and at suspected progression (clinical or biochemical). When a CR or a clinical or biochemical progression is suspected, SPEP, SIFE, and serum FLC tests will be repeated within 1 to 4 weeks. For patients scheduled to be dose escalated, samples will also be collected within 1 week prior to receiving the first higher dose. All samples will be collected prior to investigational

Schedule of Activities B Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																1 month Follow-up [35]			Survival Follow-up[37]
			Priming Dose		Maintenance Dose																	
			Cycle 0 (1 wk)		Cycle 1 (1 Cycle = 4 weeks)					Cycle 2				Cycle 3 onwards				EOT [36]				
Study Day	-28 to -1	-14 to -1	1	2	1	2	8	15	22	1	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

product administration on days whereby investigational product is to be administered. If patients were treated with daratumumab less than 114 days prior to planned treatment day, daratumumab will interfere with SPEP, UPEP, SIFE and UIFE assays. Therefore, for these patients, FLC assay should be completed at screening, C1D1, and all subsequent disease assessments. In these patients who previously received daratumumab, serum and urine M-spike if measurable at baseline in these patients should also be followed at the same timepoints as FLC with the most representative marker of disease status used for determination IMWG assessment.

23. **24 hr urine immunofixation electrophoresis (UIFE), 24 hr urine protein electrophoresis (UPEP)**: No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. See Assessments Section 7.2.1 for laboratory disease assessment tests list. Note that UIFE will only be completed at baseline when electrophoresis shows no measurable protein, at suspected CR, and at suspected progression (clinical or biochemical). When a CR or a clinical or biochemical progression is suspected, UPEP and UIFE will be repeated within 1 to 4 weeks. For patients scheduled to be dose escalated, samples will also be collected within 1 week prior to receiving the first higher dose. If samples collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration.
24. **Bone marrow collection and assessments**: For C0D1 and on-treatment assessments, see- Section 7.2.2. Sample for Cycle 0 Day 1 (C0D1) may be taken up to 7 days before study treatment. Bone marrow collections and local plasma cell assessments should be fixed according to the calendar, regardless of treatment delays. Bone marrow evaluation consisting of bone marrow aspirate and/or bone marrow biopsies will be performed to follow disease response. When bone marrow plasmacell infiltration is assessed by both bone marrow aspirate and by bone marrow biopsy, the highest value of bone marrow plasmacell infiltration should be utilized for response evaluation. Bone marrow aspirates will also be collected and plasma cells will be evaluated at time of suspected complete response (CR) and optional at time of suspected disease progression. Bone marrow biopsy will also be collected and plasma cells will be evaluated when confirmation of stringent complete response (sCR) is required. For patients who experience a plateau or CR, additional BM aspirates at 9 months after C1D1 and onwards will be optional. Optional bone marrow aspirate and biopsy samples will also be taken at disease progression if a sample was not taken within the past 4 weeks. If a patient is scheduled for escalation to the next highest dose level cohort following 60day late toxicity evaluation, a bone marrow aspirate will be collected within 1 week before dose escalation, unless an ontreatment sample was collected within the past 28 days, or the investigator assesses that there in an unjustifiable risk for the patient, and/or the patient refuses to undergo a bone marrow procedure. This bone marrow aspirate sample will be collected for central MRD assessment using the next generation sequencing (NGS) assay when patient is in suspected CR or actual CR. A C0D1 bone marrow aspirate must also be collected in all patients as the baseline MRD reference sample. Samples for MRD assessments should be aliquoted from the first bone marrow aspirate pull. Samples at 1 and 3 months after C1D1 will be collected ±7 days; samples at 9 months after C1D1 and later will be collected ±14 days.
25. **Disease assessments by PET/CT:** See Assessments Section 7.2.3. Radiographic assessments obtained per the patient's standard of care prior to enrollment into the study do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 28 days before C0D1, (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (3) appropriate documentation indicating that these

Schedule of Activities B Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																1 month Follow-up [35]			Survival Follow-up[37]
			Priming Dose		Maintenance Dose																	
			Cycle 0 (1 wk)		Cycle 1 (1 Cycle = 4 weeks)					Cycle 2				Cycle 3 onwards				EOT [36]				
Study Day	-28 to -1	-14 to -1	1	2	1	2	8	15	22	1	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

radiographic tumor assessments were performed as standard of care is available in the patient's source notes. For all patients, images are required at screening, suspected CR, when disease progression is suspected (eg, symptomatic deterioration), end of treatment visit (if not done in previous 4 weeks) and when otherwise clinically indicated. In patients with measurable target lesions at screening, images at 1 and 3 months after C1D1 will be collected ±7 days; images at 9 months after C1D1 and every 6 months thereafter will be collected ±14 days. For sites in Germany: Only MRI is allowed to be used as imaging modality for participants.

26. **AE Assessments**: AEs should be documented and recorded at each visit using the NCI CTCAE version 4.03. The severity of CRS will be assessed according to the grading described by Lee et al. (2014 and 2019,[2,3] See Appendix 5) instead of CTCAE. In addition, ASTCT consensus grading of CRS and ICANS[3] will be captured separately from the AE assessments (See Appendix 5). The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 90 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
27. **Concomitant Treatments**: all concomitant medications and Nondrug Supportive Interventions should be recorded on the CRF.
28. **Genetic Analysis**: Bone marrow aspirates taken on C0D1 will be evaluated at local lab for t(4;14)(p16;q32), t(14;16)(q32;q23), 17p13 deletions, t(11;14)(q13;q32), chromosome 13 deletion, ploidy category, and chromosome 1 abnormalities. If some of these cytogenetic assessments cannot be done, site should provide patient's most recent cytogenetic testing results and enter into eCRF. Sample may be taken up to 7 days before the start of study treatment.
29. **BCMA+ expression on multiple myeloma cells in bone marrow:** Expression of BCMA will be evaluated on fresh bone marrow aspirates (by flow cytometry) and biopsies (by IHC). Expression of additional markers including CD138 will also be evaluated. Additional analyses may be performed on bone marrow biopsies, including immunophenotyping of infiltrating immune cells and exploratory molecular analyses. If the sample collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Sample for Cycle 0 Day 1 (C0D1) may be taken up to 7 days before study treatment; samples at 1 month and 3 months after C1D1 will be collected ±7 days; samples at 9 months after C1D1 will be collected ±14 days.
30. **Soluble BCMA**: See SCHEDULE OF PHARAMACOKINETIC,SOLUBLE FACTOR AND CYTOKINE activities B table. Soluble BCMA will be measured in plasma by mass spectrometry.
31. **TBNK and Immunophenotyping:** enumeration and phenotypes of T-cell subsets by multiparameter flow cytometry. If sample collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Bone marrow sample for Cycle 0 Day 1 (C0D1) may be taken up to 7 days before study treatment; samples at 1 month and 3 months after C1D1 will be collected ±7 days.

Schedule of Activities B Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																1 month Follow-up [35]			Survival Follow-up[37]
			Priming Dose		Maintenance Dose																	
			Cycle 0 (1 wk)		Cycle 1 (1 Cycle = 4 weeks)					Cycle 2				Cycle 3 onwards				EOT [36]				
Study Day	-28 to -1	-14 to -1	1	2	1	2	8	15	22	1	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

When bone marrow aspirate samples are taken for disease response evaluation, samples for TBNK and immunophenotyping will also be acquired. In the event of SC dose route, omit C1D2 collection.

32. **Gene expression RNA profile:** gene expression associated with activation state and anti-tumor activity will be measured by RNA sequencing in bone marrow. If sample collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Bone marrow sample for Cycle 0 Day 1 (C0D1) may be taken up to 7 days before study treatment; samples at 1 month and 3 months after C1D1 will be evaluated ±7 days; samples at 9 months after C1D1 will be evaluated ±14 days. When bone marrow aspirate samples are taken for disease response evaluation, samples for gene expression analysis will also be acquired. In the event of SC dose route, omit C1D2 collection.
33. **TCR sequencing**: clonal expansion, contraction and diversity and its association with activity and durability will be assessed by deoxyribonucleic acid (DNA) sequencing of TCR in bone marrow. If samples collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Bone marrow sample for Cycle 0 Day 1 (C0D1) may be taken up to 7 days before study treatment; samples at 1 month and 3 months after C1D1 will be collected ±7 days; samples at 9 months after C1D1 will be collected ±14 days. When bone marrow aspirate samples are taken for disease response evaluation, samples for TCR sequencing will also be acquired.
34. **Genomic banked biospecimens Prep D1:** If not collected on C0D1, collect at the next available time point when biospecimens are being collected in conjunction with a patient visit.
35. **One month follow-up:** At least 28 calendar days, and no more than 35 calendar days, after discontinuation of treatment, patients will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. If the patient completes the follow-up visit prior to completion of the 60 day long DLT observation period, a follow up phone call will be completed on at least Day 60, and no more than Day 65.
36. **End of treatment (EOT) visit:** Obtain these assessments if not completed in the last week (last 4 weeks for disease assessments).
37. **Survival follow up:** Following discontinuation of study treatment (unless patients are lost to follow up, consent is withdrawn, or study is discontinued by the sponsor), survival status will be collected by telephone every 3 months until death, or up to approximately 30 months after last patient first dose, whichever comes first. Subsequent anti-cancer therapies and relevant transplant information will also be collected. Any SOC disease assessments obtained between EOT and subsequent anti-cancer therapy will be collected.
38. **Local Site Injection Tolerability Assessment (SC Administration Cohort Only):** Assessment of injection site should be conducted at 1 to 4 hours following treatment administration on Day 1, 8 15 and 22 for the first cycle. If injection site pain or ISR characteristics continue to persist after the first cycle, local site injection tolerability assessments should continue until the symptoms resolve.

Schedule of Activities B Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period															1 month Follow-up [35]			Survival Follow-up[37]
			Priming Dose		Maintenance Dose																
			Cycle 0 (1 wk)		Cycle 1 (1 Cycle = 4 weeks)					Cycle 2				Cycle 3 onwards				EOT [36]			
Study Day	-28 to -1	-14 to -1	1	2	1	2	8	15	22	1	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

39. **Treatment with lenalidomide:** An oral dose of 15 mg of lenalidomide will be administered daily on Days 1-21 over a 28 day cycle. Subsequent cycles will be dosed every 4 weeks. Day 1 safety laboratory test results need to be reviewed by the investigator prior to dosing at the beginning of each cycle for dosing confirmation.
40. **Treatment with pomalidomide:** A dose of 4 mg of pomalidomide will be administered orally on Days 1-21 over a 28 day cycle. Day 1 safety laboratory test results need to be reviewed by the investigator prior to dosing at the beginning of each cycle for dosing confirmation.
41. **Treatment with dexamethasone:** For patients receiving dexamethasone, administer dexamethasone 40 mg orally 60 ± 30 minutes before every dose of PF-06863135 beginning with C0D1; the dose of dexamethasone may be reduced to 20 mg for patients who are older than 75 years of age or who have a body-mass index (the weight in kilograms divided by the square of the height in meters) of less than 18.5. If a dose of PF-06863135 is held or skipped, then dexamethasone should not be administered. Dose adjustments for dexamethasone are provided in Table 10 and, following discussion and agreement between the investigator and sponsor, the dose of dexamethasone may be adjusted for tolerability if needed for a specific patient. For patients receiving dexamethasone premedication, dexamethasone should be discontinued after 6 months unless clinical rationale to continue dexamethasone is provided by investigator and approved by sponsor.

SCHEDULE OF PHARMACOKINETIC, SOLUBLE FACTOR AND CYTOKINE ACTIVITIES B: PART 1.1 AND ANY OTHER PART USING PRIMING DOSE AND MAINTENANCE

The schedule of pharmacokinetic, soluble factor and cytokine activities table provides an overview of the protocol visits and procedures. This schedule of activities is applicable to Part 1.1 and any other parts of the study where a priming dose will be administered. If priming dose and maintenance is selected, this table should be followed.

Grayed out columns should only be performed when Q1W dosing of PF-06863135 being used but not for Q2W dosing.

The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table in order to conduct evaluations or assessments required to protect the well-being of the patient. See Appendix 10 for alternative measure guidelines due to COVID-19.

Visit Identifier	**Up to 7 days prior to C0D1**	**Treatment Period**																										**EOT**
		Priming Cycle					**Maintenance Dose**																						
		Cycle 0 (1 wk)					**Cycle 1 (1 Cycle = 4 weeks)**											**Cycle 2**									**Cycle 3 onwards**		
Study Day		**1**				**2**	**D1**				**D2**	**D8**			**D15**		**D22**		**D1**			**D8**		**D15**		**D22**		**D1**		
Hours Pre/after dosing†		**0**	**2**	**4**	**8**	**24**	**0**	**2***	**4***	**8**	**24**	**0**	**2* (IV only)**	**4* (IV only)**	**0**	**2* (IV only)**	**0**	**2* (IV only)**	**0**	**2* (IV only)**	**4* (IV only)**	**0**	**2* (IV only)**	**0**	**2* (IV only)**	**0**	**2* (IV only)**	**0**	**2* (IV only)**	
Visit window				±0.5 hr	±1 hr	±3 hrs			±0.5 hr	± 1 hr	±3 hrs			±0.5 hr							±1 hr									
Cytokine evaluation in serum[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X					X				3 (±7 days) and 9 months (±14 days) after		

Visit Identifier	Up to 7 days prior to C0D1	Treatment Period																										EOT
		Priming Cycle					Maintenance Dose																					
		Cycle 0 (1 wk)					Cycle 1 (1 Cycle = 4 weeks)											Cycle 2								Cycle 3 onwards		
Study Day		1				2	D1				D2	D8			D15		D22		D1			D8		D15		D22		D1		
Hours Pre/after dosing[†]		0	2	4	8	24	0	2*	4*	8	24	0	2* (IV only)	4* (IV only)	0	2* (IV only)	0	2* (IV only)	0	2* (IV only)	4* (IV only)	0	2* (IV only)	0	2* (IV only)	0	2* (IV only)	0	2* (IV only)	
																												C1D1		
Samples for PF-06863135 blood level[2]		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]	X[2]	X
Blood samples for ADA and Nab against PF-06863135[3]		X													X				X									X[3]		X
Samples for lenalidomide blood level (Parts 1C and 2C only)[5]							X					X			X									X					
Samples for pomalidomide blood level (Parts 1D and 2D only)[5]							X					X			X									X					
Samples for dexamethasone blood level (Parts 1E and 2E only)[6]		X				X					X																			

Visit Identifier	Up to 7 days prior to C0D1	Treatment Period																												EOT
		Priming Cycle					Maintenance Dose																							
		Cycle 0 (1 wk)					Cycle 1 (1 Cycle = 4 weeks)												Cycle 2										Cycle 3 onwards		
Study Day		1				2	D1				D2	D8			D15		D22		D1			D8		D15		D22		D1		
Hours Pre/after dosing†		0	2	4	8	24	0	2*	4*	8	24	0	2* (IV only)	4* (IV only)	0	2* (IV only)	0	2* (IV only)	0	2* (IV only)	4* (IV only)	0	2* (IV only)	0	2* (IV only)	0	2* (IV only)	0	2* (IV only)	
Soluble BCMA and other factors[4]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]	X[4]	X

Abbreviations: Anti-drug antibodies = ADA; BCMA = B-cell maturation antigen; D = Day; EOT = end of treatment; neutralizing antibodies =Nab.

* For IV administration, the 2-hour sample should be taken immediately (up to 15 minutes before) before the end of PF-06863135 infusion; if the infusion is longer than 2 hours (or shorter if a 1 hour infusion is tested), the collection time of this sample should be adjusted accordingly for the sample to be collected immediately before the actual end of PF-06863135 infusion. For subcutaneous administration, the 2-hour sample should be taken at 2 hours post-injection ±12 minutes. For Part 2 IV administration lead-in cohort, C2D1 end of infusion sample will be taken at 1 hr immediately (up to 15 minutes) before the end of PF-06863135 infusion. Also for SC administration, 2 and 4 hr samples are not needed other than on Cycle 0 D1 and Cycle 1 D1.

† Sampling times are related to the start of the infusion. All efforts will be made to obtain the pharmacokinetic (PK) samples at the exact nominal time relative to dosing. However, samples obtained within the window specified will be acceptable.

Activities in grayed out columns should only be done for PF-06863135 Q1W dosing schedule but skipped for Q2W dosing.

Footnotes for Schedule of Pharmacokinetic, Soluble Factors and Cytokine Activities B

1. **Cytokine evaluation in serum:** See Cytokine Assessments Section 7.5.4 for a full list of cytokine assessments. All samples will be analyzed centrally. All 0 hour samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. If CRS is suspected, an adhoc cytokine sample will be collected (see Section 7.1.3 Laboratory Safety Assessments). Should the site require cytokine information for patient management, the site will have the option of collecting an additional sample for local analysis. If a sample for cytokine panel evaluation is due to be collected on the same day as the day a suspected CRS event occurs, then an ad hoc sample for central analysis is not required/collected. However, an ad hoc sample for local analysis may still be collected for patient management.

Visit Identifier	Up to 7 days prior to C0D1	Treatment Period																												EOT
		Priming Cycle					Maintenance Dose																							
		Cycle 0 (1 wk)					Cycle 1 (1 Cycle = 4 weeks)													Cycle 2									Cycle 3 onwards		
Study Day		1				2	D1				D2	D8			D15		D22		D1			D8			D15		D22		D1		
Hours Pre/after dosing[†]		0	2	4	8	24	0	2*	4*	8	24	0	2* (IV only)	4* (IV only)	0	2* (IV only)	0	2* (IV only)	0	2* (IV only)	4* (IV only)	0	2* (IV only)	0	2* (IV only)	0	2* (IV only)	0	0	2* (IV only)	

2. **Blood sample for PF-06863135 blood level:** Approximately 5 mL sample of whole blood (to provide approximately 2 mL of serum) will be collected at each time point for PK analysis of PF-06863135. After Cycle 8, pre- and post-dose PK samples will be collected only on every 4th cycle (Cycle 8, Cycle 12, Cycle 16, etc.). An additional PK sample should also be taken if CRS is suspected or if the hospitalization period is extended beyond 24 hours on C0D1 or C1D1for any reason, and a PK sample is not already scheduled to be taken.

3. **Anti-drug Antibodies (ADA) and Neutralizing Antibodies (Nab) against PF-06863135:** Collection of two 1 mL pre-dose serum samples (from 5 mL total whole blood) to detect the presence of antibodies to PF-06863135 is to be obtained prior to the start of treatment. Patients having an unresolved adverse event that is possibly related to anti-PF-06863135 antibodies at their last assessment will be asked to return to the clinic for ADA and drug concentration blood sampling at approximately 3-month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor. After Cycle 4, pre-dose ADA and Nab samples will be collected only on Cycles 6, 8, and every 4th cycle thereafter (Cycle 8, Cycle 12, Cycle 16, etc.).

4. **Soluble BCMA and other factors**: Approximately 3 mL sample of whole blood (to provide approximately 1 mL of plasma) will be collected at each time point for analysis of soluble BCMA and other factors by mass spectrometry. All 0 hour samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. After Cycle 8, pre- and post-dose PK samples will be collected only on every 4th cycle (Cycle 8, Cycle 12, Cycle 16, etc.). An additional soluble BCMA/other factor sample should also be taken if CRS is suspected, and a sample is not already scheduled to be taken (eg, Cycle 3 onwards).

5. **Blood sample for lenalidomide and pomalidomide blood levels**: Approximately 3 mL sample of whole blood (to provide approximately 1.5 mL of plasma) will be collected into a 3 mL K2EDTA vacutainer tube at each time point within 2 hours prior to the administration of lenalidomide and pomalidomide, respectively, for PK analysis of lenalidomide and pomalidomide. Blood sample collection for lenalidomide and pomalidomide blood levelsanalysis will not be required for any patient transitioned to PF-06863135 monotherapy treatment.

6. **Blood sample for dexamethasone blood levels**: Approximately 3 mL sample of whole blood (to provide approximately 1.5 mL of plasma) will be collected into a 3 mL K2EDTA vacutainer tube on C0D1 (within 2 hours prior to the administration of dexamethasone) and on C0D2 and C1D2 (within 24±2 hours after the administration of dexamethasone on C0D1 and C1D1, respectively) for PK analysis of dexamethasone.

SCHEDULE OF ACTIVITIES C: PARTS 1 SC Q2W, 1C, AND 1D (DOSE ESCALATION COMBINATION) AND 2A, 2C AND 2D (DOSE EXPANSION COHORTS) WITHOUT PRIMING DOSE

The Schedule of Activities Table C provides an overview of the protocol visits and procedures. Refer to the Assessments Section 7 of the protocol for detailed information on each assessment required for compliance with the protocol.

This schedule of activities is applicable to Parts 1C, 1D, 2A, 2C, and 2D, which would dose PF-06863135 either on a Q1W or Q2W schedule depending on Part 1 monotherapy data, as well as Part 1 SC Q2W dosing without a priming dose. Please refer to Schedule of Activities B if priming dose and maintenance is selected.

Grayed out columns should only be performed if Q1W dosing of PF-06863135 is selected but not for Q2W dosing.

The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table in order to conduct evaluations or assessments required to protect the well-being of the patient. See Appendix 10 for alternative measure guidelines due to COVID-19.

Schedule of Activities C Visit Identifier	**Screening[1] Days prior to enrollment**		**Treatment Period**																**EOT[35]**	**1 month Follow-up [34]**			**Survival Follow-up[36]**
			Cycle 1 (1 Cycle = 4 weeks)							**Cycle 2**					**Cycle 3 onwards**								
Study Day	**-28 to -1**	**-14 to -1**	**1**	**2**	**3**	**4***	**8**	**15**	**22**	**1**	**4***	**8**	**15**	**22**	**1**	**8**	**15**	**22**		**28 d**	**90 d**	**120 d**	
Visit Window (days)							±1	±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14
Informed consent[2]	X																						
Myeloma history[3]	X																						
Medical history[4]	X																						
Demography	X																						
Baseline signs and symptoms[5]	X																						
Eligibility Criteria and Registration[6]		X																					
Patient hospitalization[7]			X	X	X																		
Clinical Evaluation																							
Physical examination[7]		X	X	X			X	X	X	X		X	X	X	X				X	X			
Weight[8]		X	X							X					X				X				
Vital signs (BP/pulse rate/Temp)[9]		X	X	X			X	X	X	X		X	X	X	X	X	X	X	X	X			
ECOG performance status[10]		X	X					X	X	X		X	X	X	X	X	X	X	X	X			
(12 lead) ECG[11]		X	X	X		(X)	X	X	X	X	(X)	X	X	X	X				X	X			
Echo or MUGA[12]	X		If there is a history of cardiac events, perform when clinically indicated.																X				

Schedule of Activities C Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																EOT[35]	1 month Follow-up [34]			Survival Follow-up[36]
			Cycle 1 (1 Cycle = 4 weeks)							Cycle 2					Cycle 3 onwards								
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	22	1	4*	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14
Safety Laboratory																							
Hematology[13]		X	X	X			X	X	X	X		X	X	X	X				X	X			
Blood Chemistry[14]		X	X	X			X	X	X	X		X	X	X	X				X	X			
Coagulation[15]		X	X				X	X	X	X		X	X	X	X				X	X			
Hepatitis assessment[16]		X																					
Multiplex cytokine assays (blood)[17]	Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments																						
Urinalysis[18]		X	X																X	X			
Pregnancy test and contraception check[19]	X		X	Weekly during Cycle 1 starting at C1D1 for Parts 1C, 1D, 2C, and 2D						X					X					X	X	X	
Treatment																							
Treatment with PF-06863135[20]			X				X	X	X	X		X	X	X	X	X	X	X					
Treatment with lenalidomide[38] (Parts 1C and 2C only)			Daily on Days 1-21							Daily on Days 1-21					Daily on Days 1-21								
Treatment with pomalidomide (Parts 1D and 2D only)[39]			Daily on Days 1-21							Daily on Days 1-21					Daily on Days 1-21								
Disease assessments																							
SPEP, SIFE, serum FLC ratio, beta-2 microglobulin (local)[21]		X	X							X					X				X	X			If obtained as SOC prior to subsequent treatment[36]
UPEP, UIFE (local)[22]		X	X							X					X				X	X			
Bone marrow collection and assessments- aspirates (including NGS MRD assessment)[23]			X	At 1, 3 and 9 months after C1D1, every 6 months thereafter, at suspected CR and optional at disease progression. Collection at 9 months after C1D1 and onwards will be optional for patients who experience a plateau or CR. Central assessment of MRD by next-generation sequencing test is required at baseline (C1D1) and at all times bone marrow aspirates are obtained while a patient is in suspected or actual CR.																			
Bone marrow collection and assessments- biopsies[23]			X	At 1, 3 (optional) and 9 (optional) months after C1D1, every 6 months thereafter (optional), at suspected sCR and optional at disease progression. Collection at 9 months after C1D1 and onwards will be optional for patients who experience a plateau or CR.																			
Disease assessments by PET/ CT[24]	X			At suspected CR or PD, and when clinically indicated for all patients. At 1, 3, and 9 months after C1D1 and every 6 months thereafter for patients with measurable target lesions at screening.															X				

Schedule of Activities C Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																EOT[35]	1 month Follow-up [34]			Survival Follow-up[36]
			Cycle 1 (1 Cycle = 4 weeks)							Cycle 2					Cycle 3 onwards								
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	22	1	4*	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14
Other clinical assessments																							
Serious and non-serious adverse event monitoring[25]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Concomitant treatment(s)[26]			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Local Site Injection Tolerability Assessment (SC only)[37]			X				X	X	X														
Pharmacokinetic (PK) assessments																							
Blood sample for PF-06863135 (all Parts), lenalidomide (Parts 1C and 2C), or pomalidomide (Parts 1D and 2D)			Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments																				
Immunogenicity assessments																							
Anti-drug antibodies and neutralizing antibodies against PF-06863135			Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments																				
Pharmacodynamic assessments																							
Genetic analysis- bone marrow aspirate[27]			X																				
BCMA+ expression on multiple myeloma cells from bone marrow aspirate- flow cytometry[28]			X	At 1, 3 and 9 months after C1D1.																			
BCMA expression on multiple myeloma cells (IHC) and additional PD assessments from bone marrow biopsy[28]			X	At 1, 3 (optional) and 9 (optional) months after C1D1.																			
Soluble BCMA from blood[29]			Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments																				
TBNK and immunophenotyping from blood[30]			X	X (IV only)		X	X	X	X	X			X										
TBNK and immunophenotyping from bone marrow aspirate[30]			X	At 1 and 3 months after C1D1.																			
Gene expression (RNA) profile from bone marrow aspirate[31]			X	At 1, 3 and 9 months after C1D1, every 6 months thereafter, at suspected CR and optional at disease progression if BM disease assessments are completed.																			

Schedule of Activities C Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																EOT[35]	1 month Follow-up [34]			Survival Follow-up[36]
			Cycle 1 (1 Cycle = 4 weeks)							Cycle 2					Cycle 3 onwards								
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	22	1	4*	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14
TCR sequencing from bone marrow aspirate[32]			X	At 1, 3 and 9 months after C1D1, every 6 months thereafter, at suspected CR and optional at disease progression if BM disease assessments are completed.																			
Other assessments																							
Genomic banked biospecimens Prep D1[33]			X																				
Pharmacogenomic sample			X							X													
Post- Treatment																							
Survival follow-up[36]																						x	

Abbreviations: → = ongoing/continuous event; BCMA = B-cell maturation antigen; BM = bone marrow; BP = blood pressure; CT = computed tomography; CR = complete response; Deoxyribonucleic acid = DNA; Echo = echocardiogram; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; end of treatment = EOT; IHC = immunohistochemistry; MM = multiple myeloma; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; NK = natural killer; PD = pharmacodynamic; positron emission tomography = PET; pharmacokinetic =PK; quantitative polymerase chain reaction = qPCR; ribonucleic acid = RNA; serum immunofixation electrophoresis = SIFE; SOC = standard of care; serum protein electrophoresis =SPEP; TCR = T-cell receptor; T, B, and NK lymphocytes = TBNK; 24 hr urine immunofixation electrophoresis = UIFE; 24 hr urine protein electrophoresis = UPEP.

*Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments C for assessments on Cycle 1 Day 4 (C1D4) and Cycle 2 Day 4 (C2D4).

Activities in grayed out columns should only be done for SCPF-06863135 Q1W dosing schedule but skipped for Q2W dosing.

Footnotes for Schedule of Activities C

1. **Screening:** To be completed within 28 days prior to start of study treatment.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures, and be completed within 28 days prior to start of study treatment.
3. **Myeloma history:** will be collected within 28 days during screening prior to start of study treatment. Includes history of disease under study including details of primary diagnosis, biopsy information, and treatment history.
4. **Medical History:** Includes history of disease process other than the cancer under study (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
5. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 28 days prior to C1D1. During the study, any new or worsened conditions since baseline will be recorded on the Adverse Events (AE) case report form (CRF) page.

Schedule of Activities C Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																EOT[35]	1 month Follow-up [34]			Survival Follow-up[36]
			Cycle 1 (1 Cycle = 4 weeks)							Cycle 2					Cycle 3 onwards								
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	22	1	4*	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

6. **Registration**: Patient number and dose level allocation assigned by Pfizer Inc.

7. **Patient hospitalization:** All patients in Parts 1 SC Q2W, 1C, and 1D dose escalation will be hospitalized for 72 hrs from Cycle 1 Day 1 (C1D1). Hospitalization period may be extended if the patient experiences abnormal laboratory findings or ongoing adverse events that require further hospitalization. Hospitalization in Parts 2A, 2C, and 2D at C1D1 may be optional based on safety data from Parts 1A, 1C, or 1D respectively.

7. **Physical examination (PE):** Physical examination includes neurological assessment and, at screening, will also include height.
8. **Weight:** Weight will be measured prior to dosing.

9. **Vital Signs:** Includes temperature (oral, tympanic, temporal or axillary), blood pressure (BP), and pulse rate to be recorded in the sitting position after 5 minutes of rest.

10. **Performance Status:** Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 4.

11. **12-Lead electrocardiogram (ECG)**: At screening, single 12-lead ECG will be performed. On C1D1 until C2D22, triplicate 12-lead ECGs will be performed to determine mean QTcF interval. On Days 1, 8, 15 and 22 of Cycles 1 and 2, ECGs will be performed prior to investigational product administration (up to 60 minutes before dosing), and the end of infusion or subcutaneous injection. For subcutaneous administration only, triplicate 12-lead ECGs will also be performed on Day 4 of Cycles 1 and 2. From Cycle 3 onwards, single 12-lead ECG will be performed on Day 1 of each cycle prior to investigational product administration (up to 60 minutes before dosing). When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

12. **Echocardiogram (Echo) or multigated acquisition scan (MUGA)**: Echo or MUGA will be evaluated in patients with previous history of cardiac events. For these patients, an Echo or MUGA will be performed at screening, when clinically indicated and at the end of treatment (EOT) visit.

13. **Hematology**: No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Assessments Section 7.1.3 for Laboratory Tests list.

14. **Blood Chemistry**: No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Assessments Section 7.1.3 for Laboratory Tests list.

Schedule of Activities C Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																EOT[35]	1 month Follow-up [34]			Survival Follow-up[36]
			Cycle 1 (1 Cycle = 4 weeks)							Cycle 2					Cycle 3 onwards								
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	22	1	4*	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

15. **Coagulation**: No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Assessments Section 7.1.3 for Laboratory Tests list.

16. **Hepatitis assessment**: Screening tests for hepatitis B (HBV) and C (HCV) should be performed including hepatitis B surface (HBs) antigen, hepatitis B core (HBc) antibody, and hepatitis C virus (HCV) antibody. In the case of apparent ongoing HBV or HCV infection, reflex serum DNA or RNA viral load testing, respectively, will be performed. See Assessments Section 7.1.3 for Laboratory Tests list.

17. **Multiplex cytokine assays**: see SCHEDULE OF PHARMACOKINETIC, SOLUBLE FACTOR AND CYTOKINE activities C table. See assessments Section 7.5.4 for laboratory tests list.

18. **Urinalysis**: Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. Following C1D1, only obtain as clinically indicated until EOT. See Assessments Section 7.1.3 for Laboratory Tests list.

19. **Pregnancy Test and contraception check**: Contraception only required for WOCBP. Contraception use will be checked to confirm that contraception is used throughout the study and for 5 months after the last dose of study treatment consistently and correctly. Serum pregnancy test for females of child bearing potential (see Pregnancy Testing Section 7.1.1). In addition, for Parts 1C, 1D, 2C, and 2D, pregnancy testing should occur at C1D1 and weekly during first cycle, and if menstrual cycles are irregular should occur every 2 weeks thereafter. Contraception use will be checked to confirm that contraception is used consistently and correctly. In addition, any risk evaluation and mitigation strategy (REMS), pregnancy prevention programs (PPP), or other applicable programs required per local regulations for lenalidomide and pomalidomide must be followed where applicable.

20. **Treatment with investigational product PF-06863135**: Investigational product will be administered on Day 1, 8, 15 and 22 of each cycle (see Administration Section 5.4). If a patient has received treatment with Q1W PF-06863135 for at least 6 months, and disease assessments have remained stable over at least 2 months, consideration may be given to increasing dose intervals from weekly to every 2 weeks or once every four weeks (once per cycle; only CXD1 dosing and activities applicable) after consultation with sponsor. Cycles would remain the same length with any skipped weekly doses noted. For Q2W dosing, it would be preferable to skip dosing of PF-06863135 on Days 8 and 22 of each cycle (ie, omit activities in gray columns). If the patient subsequently begins to have increase of disease burden, dose intervals should return to weekly dosing.

21. **Serum immunofixation electrophoresis (SIFE), serum protein electrophoresis (SPEP), serum free light chain analysis (FLC) tests and beta-2 microglobulin tests:** No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. See Assessments Section 7.2.1 for laboratory disease assessment tests list. Beta 2 microglobulin will be collected on C1D1 (other time points are optional). Note that SIFE will only be completed at baseline when electrophoresis shows no measurable protein, at suspected CR, and at suspected progression (clinical or biochemical). When a complete response (CR) or a clinical or biochemical progression is suspected, SPEP, SIFE, and serum free light chain analysis (FLC) tests will be repeated within 1 to 4 weeks. For patients scheduled to be dose escalated, samples will also be collected within 1 week prior to receiving the first higher dose. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. If patients were

Schedule of Activities C Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																1 month Follow-up [34]			Survival Follow-up[36]
			Cycle 1 (1 Cycle = 4 weeks)							Cycle 2					Cycle 3 onwards				EOT[35]			
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	22	1	4*	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

treated with daratumumab less than 114 days prior to planned treatment day, daratumumab will interfere with SPEP, UPEP, SIFE and UIFE assays. Therefore, for these patients, FLC assay should be completed at screening, C1D1, and all subsequent disease assessments. In these patients who previously received daratumumab serum and urine M-spike if measurable at baseline in these patients should also be followed at the same timepoints as FLC with the most representative marker of disease status used for determination IMWG assessment.

22. **24 hr urine immunofixation electrophoresis (UIFE), 24 hr urine protein electrophoresis (UPEP)**: No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. See Assessments Section 7.2.1 for laboratory disease assessment tests list. Note that UIFE will only be completed at baseline when electrophoresis shows no measurable protein, at suspected CR, and at suspected progression (clinical or biochemical). When a CR or a clinical or biochemical progression is suspected, UPEP and UIFE will be repeated within 1 to 4 weeks. For patients scheduled to be dose escalated, samples will also be collected within 1 week prior to receiving the first higher dose. If samples collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration.

23. **Bone Marrow Collection and Assessments**: For C1D1 and on-treatment bone marrow collections and assessments, see Section 7.2.2. Sample for Cycle 1 Day 1 (C1D1) may be taken up to 7 days before study treatment. Bone marrow collections and local plasma cell assessments should be fixed according to the calendar, regardless of treatment delays. Bone marrow evaluation consisting of bone marrow aspirate and/or bone marrow biopsies will be performed to follow disease response. When bone marrow plasma-cell infiltration is assessed by both bone marrow aspirate and by bone marrow biopsy, the highest value of bone marrow plasma-cell infiltration should be utilized for response evaluation. Bone marrow aspirates will also be collected and plasma cells will be evaluated at time of suspected complete response (CR) and optional at time of suspected disease progression. Bone marrow biopsy will also be collected and plasma cells will be evaluated when confirmation of stringent complete response (sCR) is required. For patients who experience a plateau or CR, additional BM aspirates at 9 months after C1D1 and onwards will be optional. Optional bone marrow aspirate and biopsy samples will also be taken at disease progression if a sample was not taken within the past 4 weeks. If a patient is scheduled for escalation to the next highest dose level cohort following 60-day late toxicity evaluation, a bone marrow aspirate will be collected within 1 week before dose escalation, unless an on-treatment sample was collected within the past 28 days or the investigator assesses that there in an unjustifiable risk for the patient, and/or the patient refuses to undergo a bone marrow procedure. A bone marrow aspirate sample will be collected for central MRD assessment using the next generation sequencing (NGS) assay when patient is in suspected CR or actual CR. A C1D1 bone marrow aspirate must also be collected in all patients as the baseline MRD reference sample. Samples for MRD assessments should be aliquoted from the first bone marrow aspirate pull. Samples at 1 and 3 months after C1D1 will be collected ±7 days; samples at 9 months after C1D1 and later will be collected ±14 days.

24. **Disease assessments by fluorodeoxyglucose (FDG) positron emission tomography (PET)/ computerized tomography (CT):** See Assessments Section 7.2.3. Radiographic assessments obtained per the patient's standard of care prior to enrollment into the study do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 28 days before C1D1, (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. For all patients, images are required at screening, suspected CR, when disease progression is

Schedule of Activities C Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																EOT[35]	1 month Follow-up [34]			Survival Follow-up[36]
			Cycle 1 (1 Cycle = 4 weeks)							Cycle 2					Cycle 3 onwards								
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	22	1	4*	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

suspected (eg, symptomatic deterioration), end of treatment visit (if not done in previous 4 weeks) and when otherwise clinically indicated. In patients with measurable target lesions at screening, images at 1 and 3 months after C1D1 will be collected ±7 days; images at 9 months after C1D1 and every 6 months thereafter will be collected ±14 days. For sites in Germany: Only MRI is allowed to be used as imaging modality for participants.

25. **Adverse Event (AE) Assessments**: AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The severity of cytokine release syndrome (CRS) will be assessed according to the grading described by Lee et al. (2014 and 2019,[2,3] See Appendix 5) instead of CTCAE. In addition, ASTCT consensus grading of CRS and ICANS[3] will be captured separately from the AE assessments (See Appendix 5). The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 90 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the case report form (CRF) ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.

26. **Concomitant Treatments**: all concomitant medications and Nondrug Supportive Interventions should be recorded on the CRF.

27. **Genetic Analysis**: Bone marrow aspirates taken on C1D1 will be evaluated at local lab for t(4;14)(p16;q32), t(14;16)(q32;q23), 17p13 deletions, t(11;14)(q13;q32), chromosome 13 deletion, ploidy category, and chromosome 1 abnormalities. If some of these cytogenetic assessments cannot be done, site should provide patient's most recent cytogenetic testing results and enter into Ecrf. Sample may be taken up to 7 days before the start of study treatment.

28. **BCMA+ expression on multiple myeloma cells in bone marrow:** Expression of BCMA will be evaluated on fresh bone marrow aspirates (by flow cytometry) and biopsies (by IHC). Expression of additional markers including CD138 will also be evaluated. Additional analyses may be performed on bone marrow biopsies, including immunophenotyping of infiltrating immune cells and exploratory molecular analyses. If the sample collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Sample for Cycle 1 Day 1 (C1D1) may be taken up to 7 days before study treatment; samples at 1 and 3 months after C1D1 will be collected ±7 days; samples at 9 months after C1D1 will be collected ±14 days.

29. **Soluble BCMA**: See Schedule of Pharmacokinetic, Soluble Factor and Cytokine Activities C. Soluble BCMA will be measured in plasma by mass spectrometry.

30. **TBNK and Immunophenotyping:** enumeration and phenotypes of T-cell subsets by multiparameter flow cytometry. If sample collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Bone marrow sample for Cycle 1 Day 1 (C1D1) may be taken up to 7 days before study treatment; samples at 1 month or 3 months after C1D1 will be collected ±7 days.

Schedule of Activities C Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																EOT[35]	1 month Follow-up [34]			Survival Follow-up[36]
			Cycle 1 (1 Cycle = 4 weeks)							Cycle 2					Cycle 3 onwards								
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	22	1	4*	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

When bone marrow aspirate samples are taken for disease response evaluation, samples for TBNK and immunophenotyping will also be acquired. In the event of SC dose route, omit C1D2 collection.

31. **Gene expression ribonucleic acid (RNA) profile:** gene expression associated with activation state and anti-tumor activity will be measured by RNA sequencing in bone marrow. If sample collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Bone marrow sample for Cycle 1 Day 1 (C1D1) may be taken up to 7 days before study treatment; samples at 1 month or 3 months after C1D1 will be collected ±7 days; samples at 9 months after C1D1 will be collected ±14 days. When bone marrow aspirate samples are taken for disease response evaluation, samples for gene expression analysis will also be acquired. In the event of SC dose route, omit C1D2 collection.

32. **T-cell receptor (TCR) sequencing**: clonal expansion, contraction and diversity and its association with activity and durability will be assessed by deoxyribonucleic acid (DNA) sequencing of TCR in bone marrow. If sample collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration. Bone marrow sample for Cycle 1 Day 1 (C1D1) may be taken up to 7 days before study treatment; samples at 1 month or 3 months after C1D1 will be evaluated ±7 days; samples at 9 months after C1D1 will be collected ±14 days. When bone marrow aspirate samples are taken for disease response collected, samples for TCR sequencing will also be acquired.

33. **Genomic banked biospecimens Prep D1:** If not collected on C1D1, collect at the next available time point when biospecimens are being collected in conjunction with a patient visit.

34. **One month follow-up:** At least 28 calendar days, and no more than 35 calendar days, after discontinuation of treatment, patients will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. If the patient completes the follow-up visit prior to completion of the 60 day long term dose limiting toxicity (DLT) observation period, a follow up phone call will be completed on at least Day 60, and no more than Day 65.

35. **End of Treatment (EOT) Visit:** Obtain these assessments if not completed in the last week (last 4 weeks for disease assessments).

36. **Survival follow up:** Following discontinuation of study treatment (unless patients are lost to follow up, consent is withdrawn, or study is discontinued by the sponsor), survival status will be collected by telephone every 3 months until death, or up to approximately 30 months after last patient first dose, whichever comes first. Subsequent anti-cancer therapies and relevant transplant information will also be collected. Any SOC disease assessments obtained between EOT and subsequent anti-cancer therapy will be collected.

37. **Local Site Injection Tolerability Assessment (SC Administration Cohort Only):** Assessment of injection site should be conducted at 1 to 4 hours following treatment administration on Day 1, 8 and 15 for the first cycle. If injection site pain or injection site reaction (ISR) characteristics continue to persist after the first cycle, local site injection tolerability assessments should continue until the symptoms resolve.

Schedule of Activities C Visit Identifier	Screening[1] Days prior to enrollment		Treatment Period																1 month Follow-up [34]			Survival Follow-up[36]
			Cycle 1 (1 Cycle = 4 weeks)							Cycle 2					Cycle 3 onwards				EOT[35]			
Study Day	-28 to -1	-14 to -1	1	2	3	4*	8	15	22	1	4*	8	15	22	1	8	15	22		28 d	90 d	120 d	
Visit Window (days)							±1	±1	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2		+7	+7	+7	±14

38. **Treatment with lenalidomide:** A dose of 15 mg of lenalidomide will be administered orally on days 1-21 over a 28 day cycle. For subsequent cycles, dosing will be every 4 weeks. Day 1 safety laboratory test results need to be reviewed by the investigator prior to dosing at the beginning of each cycle for dosing confirmation.

39. **Treatment with pomalidomide**: A dose of 4 mg of pomalidomide will be administered orally on Days 1-21 over a 28 day cycle. Day 1 safety laboratory test results need to be reviewed by the investigator prior to dosing at the beginning of each cycle for dosing confirmation.

SCHEDULE OF PHARMACOKINETIC, SOLUBLE FACTOR AND CYTOKINE ACTIVITIES C: PARTS 1 SC Q2W, 1C AND 1D (DOSE ESCALATION COMBINATION) AND 2A, 2C AND 2D (DOSE EXPANSION COHORTS) WITHOUT PRIMING DOSE

The schedule of pharmacokinetic, soluble factor and cytokine activities table provides an overview of the protocol visits and procedures. This schedule of activities (both gray and white columns) is applicable to Parts 1C, 1D, 2A, 2C and 2D as well as Part 1 SC Q2W dosing without a priming dose. Please refer to Schedule of Activities B for if priming dose and maintenance is selected.

Grayed out columns should only be performed if Q1W dosing of PF-06863135 is selected but not for Q2W dosing.

The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table in order to conduct evaluations or assessments required to protect the well-being of the patient. See Appendix 10 for alternative measure guidelines due to COVID-19.

Visit Identifier	**Up to 7 days prior to C1D1**	**Treatment Period**																								**EOT**
		Cycle 1												**Cycle 2**										**Cycle 3 onwards**		
Study Day		**D1**				**D2**	**D4**	**D8**			**D15**		**D22**		**D1**			**D4**	**D8**		**D15**		**D22**		**D1**		
Hours Pre/after dosing[†]		**0**	**2**	**4**	**8**	**24**	**72**	**0**	**2**	**4**	**0**	**2**	**0**	**2**	**0**	**2**	**4**	**72**	**0**	**2**	**0**	**2**	**0**	**2**	**0**	**2**	
Visit window				±0.5 hr	±1 hr	±3 hrs	±24 hrs			±0.5 hr							±0.5 hr	±24 hr									
Cytokine evaluation in serum[1]	X	X	X	X	X	X	X	X	X	X	X	X	X		X						X				3 (±7 days) and 9 months (±14 days) after C1D1		
Samples for PF-06863135 blood level (Parts 1 SC, 1C, and 1D only)[2]		X			X	X	X	X			X		X		X			X	X		X		X		X[2]		X

Visit Identifier	Up to 7 days prior to C1D1	Treatment Period																								EOT
		Cycle 1												Cycle 2										Cycle 3 onwards		
Study Day		D1				D2	D4	D8			D15		D22		D1			D4	D8		D15		D22		D1		
Hours Pre/after dosing[†]		0	2	4	8	24	72	0	2	4	0	2	0	2	0	2	4	72	0	2	0	2	0	2	0	2	
Samples for PF-06863135 blood level (Parts 2A, 2C, 2D only)[2]		X			X	X	X	X			X		X		X			X	X		X		X		X		X
Samples for lenalidomide blood level (Parts 1C and 2C only)[3]		X						X			X										X						
Samples for pomalidomide blood level (Parts 1D and 2D only)[3]		X						X			X										X						
Blood samples for PF-06863135 ADA and Nab[4]		X									X				X										X[4]		X
Soluble BCMA and other factors (Parts 1 SC, 1C, and 1D only)[5]	X	X			X	X	X	X			X		X		X			X	X		X		X		X[4]		X
Soluble BCMA and	X	X				X	X	X			X		X		X						X				X[4]		X

Visit Identifier	Up to 7 days prior to C1D1	Treatment Period																									EOT
		Cycle 1												Cycle 2										Cycle 3 onwards			
Study Day		D1				D2	D4	D8			D15		D22		D1			D4	D8		D15		D22		D1			
Hours Pre/after dosing†		0	2	4	8	24	72	0	2	4	0	2	0	2	0	2	4	72	0	2	0	2	0	2	0	2	
other factors (Parts 2A, 2C, and 2D only)[5]																											

ADA = Abbreviations: Anti-drug antibodies; BCMA = B-cell maturation antigen; D = Day; EOT = end of treatment; Nab = neutralizing antibodies.

† Sampling times are related to the start of the infusion/injection. All 0 hr samples should be taken prior to dose administration. All efforts will be made to obtain the pharmacokinetic (PK) samples at the exact nominal time relative to dosing. However, samples obtained within the window specified will be acceptable.

Activities in grayed out columns should only be done for SCPF-0863135 Q1W dosing schedule but skipped for Q2W dosing.

Footnotes for Schedule of Pharmacokinetic, Soluble Factors and Cytokine Activities C

1. **Cytokine evaluation in serum:** See Cytokine Assessments Section 7.5.4 for a full list of cytokine assessments. All samples will be analyzed centrally. All 0 hour samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. If CRS is suspected, an adhoc cytokine sample will be collected(see Section 7.1.3 Laboratory Safety Assessments). Should the site require cytokine information for patient management, the site will have the option of collecting an additional sample for local analysis. If a sample for cytokine panel evaluation is due to be collected on the same day as the day a suspected CRS event occurs, then an ad hoc sample for central analysis is not required/collected. However, an ad hoc sample for local analysis may still be collected for patient management

2. **Blood sample for PF-06863135 blood levels:** Approximately 3 Ml sample of whole blood (to provide approximately 1.5 Ml of serum) will be collected into a 3 Ml vacutainer tube at each time point for PK analysis of PF-06863135. After Cycle 8, pre- and post-dose PK samples will be collected only on every 4th cycle (Cycle 8, Cycle 12, Cycle 16, etc.). An additional PK sample should also be taken if CRS is suspected, and a PK sample is not already scheduled to be taken (eg, Cycle 3 onwards).

3. **Blood sample for lenalidomide and pomalidomide blood levels:** Approximately 3 Ml sample of whole blood (to provide approximately 1.5 Ml of plasma) will be collected into a 3 Ml K_2EDTA vacutainer tube at each time point within 2 hours prior to the administration of lenalidomide and pomalidomide, respectively, for PK analysis of lenalidomide and pomalidomide.

Visit Identifier	Up to 7 days prior to C1D1	Treatment Period																									EOT
		Cycle 1												Cycle 2											Cycle 3 onwards		
Study Day		D1				D2	D4	D8			D15		D22		D1			D4	D8		D15		D22			D1		
Hours Pre/after dosing[†]		0	2	4	8	24	72	0	2	4	0	2	0	2	0	2	4	72	0	2	0	2	0	2	0	2	

4. **Anti PF-06863135 Antibodies (ADA) and Neutralizing Antibodies (Nab):** Two 1 Ml pre-dose serum samples (from 5 Ml total whole blood) to detect the presence of antibodies to PF-06863135 is to be obtained prior to the start of dose administration. Patients having an unresolved adverse event that is possibly related to anti-PF-06863135 antibodies at the End of Treatment visit will be asked to return to the clinic for ADA and drug concentration blood sampling at approximately 3-month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor. After Cycle 4, pre-dose ADA and Nab samples will be collected only on Cycles 6, 8, and every 4th cycle thereafter (Cycle 8, Cycle 12, Cycle 16, etc.).

5. **Soluble BCMA and other factors**: Approximately 3 Ml sample of whole blood (to provide approximately 1 Ml of plasma) will be collected at each time point for analysis of soluble BCMA and other factors by mass spectrometry. All 0 hour samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. After Cycle 8, pre- and post-dose PK samples will be collected only on every 4th cycle (Cycle 8, Cycle 12, Cycle 16, etc.). An additional soluble BCMA/other factor sample should also be taken if CRS is suspected, and a sample is not already scheduled to be taken (eg, Cycle 3 onwards).

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06863135 is a bispecific monoclonal antibody against B-cell maturation antigen (BCMA, also known as tumor necrosis factor receptor superfamily member 17 [TNFRSF17] or cluster of differentiation [CD] 269) and CD3. Targeted T-cell mediated cytotoxicity follows the binding of one epitope of PF-06863135 to CD3 expressing T-cells, and a second epitope to BCMA expressing multiple myeloma cells. In this clinical study, PF-06863135 will be evaluated for the treatment of adult patients with relapsed or refractory multiple myeloma as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.

1.2. Background and Rationale

1.2.1. Multiple Myeloma

Multiple myeloma (MM) is a hematological malignancy that is characterized by uncontrolled expansion of bone marrow plasma cells. Approximately 114,000 new cases of MM are diagnosed worldwide each year, and 80,000 patients will die from their disease.[6] In the US, the incidence of MM has increased from 4.91 per 100,000 in 1975, to 6.79 per 100,000 in 2013.[7] More patients are diagnosed at an older age; 34.4 per 100,000 diagnosed at age 65 and over, whilst 2.4 per 100,000 are diagnosed under the age of 65.

MM is a disease that evolves from a pre-malignant stage of monoclonal gammopathy of undetermined clinical significance (MGUS), to asymptomatic smoldering myeloma, to symptomatic active myeloma.[8] During the active stage of disease, a majority of patients develop painful bone lesions and organ dysfunction, leading to anemia, renal insufficiency and hypercalcemia. Whilst patients with smoldering myeloma do not require primary therapy, the treatment regimen for patients with active disease is currently dependent on the patient's eligibility to receive an autologous stem cell transplant (ASCT). For patients <70 years old with no comorbidities, induction therapy (either proteasome inhibitor-based or immunomodulation-based regimens) combined with an ASCT is the suggested approach, with 2-year survival achieved in 80% of patients.[8,9] Still, even in this younger age group, the rate of toxicity following transplant is high, with 5% mortality due to adverse events reported in clinical studies.[10] In older patients ie, those >70 years, adverse event related mortalities following ASCT is a staggering 19%.[10] Though in theory allogeneic stem cell transplant has a curative potential, it is not a recommended regimen for this population as no survival advantages have been demonstrated in randomized studies due to increased toxicities.[11] For transplant ineligible patients, immunomodulation based regimen of bortezomib, lenalidomide, and dexamethasone is the primary preferred treatment option as it was demonstrated in the Phase III Southwest Oncology Group (SWOG) S0777 study that an objective response rate (ORR), of 71%, and progression free survival of 43 months can be achieved.[9,12] However, toxicity remains to be a concern, with Grade 3 or higher neuropathy reported in 24% of patients.

Despite a number of recent advances, the majority of patients are expected to relapse, even for those who respond initially to treatment. Even for patients who are eligible to receive autologous stem cell transplants, the median time to relapse was 17.2 months.[13] Similarly, for patients that are treated with novel proteasome inhibitor-based or immunomodulation-based combination regimens as front line treatment, the median time to relapse is 16.4 months.[14]

Patients with relapsed refractory multiple myeloma who respond poorly to proteasome inhibitor-based or immunomodulation-based regimens show a median overall survival of only 1.5 years.[15] In this relapsed setting, approximately 50% treatment-related adverse events (AE) and 20% serious adverse events (SAE) have been reported.[16] Furthermore, each subsequent line of therapy renders the patient more refractory to treatment. For example, patients who are double-refractory to proteasome inhibitor-based or immunomodulation regimens have a median overall survival of 9 and 5 months.[17] It is therefore clear that additional treatment approaches are required for relapsed/ refractory MM.

1.2.2. Bispecific Antibodies

Functional local and systemic immunity is often suppressed in a MM patient. Impaired immunity results from the disruption of normal hematopoiesis following bone marrow invasion by plasma clones. The potential for T-cell based immunotherapy for MM has been highlighted by the ability for graft immune reactive T-cells to eradicate myeloma cells following allogeneic stem cell transplantation.[18] It may therefore be possible to restore immune-reactive T-cells, prevent malignant cell growth and decrease disease recurrence with immunotherapeutic approaches.

Bispecific antibodies offer a novel immunotherapeutic approach that allows the direct targeting of cytotoxic T-cells to tumor cells. These antibodies are engineered with two separate antigen recognition domains; one that recognizes a tumor antigen and another that recognizes CD3 expressed on T-cells. Simultaneous binding of CD3 and the tumor antigen initiates a cytotoxic response towards the bound tumor cell. Unlike normal T-cell cytotoxicity, bispecific antibody mediated cytotoxicity is independent to the presence of antigen presenting cells (APCs), expression of major histocompatibility complex (MHC) I molecules by the tumor, and the presence of costimulatory molecules. Blinatumomab, a CD19/CD3 bispecific antibody, was the first bispecific antibody to be approved by the United States (US) Food and Drug Administration (FDA).[19] In a Phase 2 trial of relapse or refractory B cell acute lymphoblastic leukemia (ALL) patients, 33% achieved complete response (CR) and 10% achieved CR with incomplete hematological recovery.[19] It may therefore be possible to use the same approach for MM with a myeloma-restricted antigen.

B-cell maturation antigen (BCMA, also known as TNFRSF17 and CD269) is a candidate for bispecific antibody based immunotherapy. BCMA expression is upregulated during B-cell maturation into plasma blasts and plasma cells, but it is not expressed on naïve B cells, hematopoietic stem cells or normal tissues such as the heart, lung, kidney, or tonsil.[20,21] BCMA knockout mice show normal development, and are able to elicit a normal humoral immune response.[22,23] In multiple myeloma, BCMA expression was identified at each disease stage, and on patients with differing cytogenetic risks.[20] Furthermore, BCMA

expression was not influenced by treatment with autologous stem cell transplant (ASCT) or chemotherapy.[20,21] In vivo, bispecific antibodies against BCMA have been shown to induce T-cell activation, reduce tumor burden and prolong survival.[24-26] A Phase 1 dose escalation study with a BCMA bispecific antibody (BI 836909) has been initiated. As of August 2019, 43 patients have been enrolled.[26]

1.2.3. PF-06863135

PF-06863135 is a heterodimeric humanized full-length bispecific antibody comprised of one B-cell Maturation Antigen (BCMA) binding arm and one cluster of differentiation (CD3) binding arm paired through hinge mutation technology. It utilizes a modified human IgG2Da fragment crystallizable (Fc) region. The half-life of PF-06863135 was 3 days in a non-human primate model, and PF-06863135 has a projected terminal half-life of 10 days in humans.

1.2.3.1. Safety

The safety, efficacy, and PK of elranatamab were initially evaluated in Phase 1 study (C1071001) as monotherapy (IV and SC) or in combination with lenalidomide or pomalidomide.

As of the 22 June 2022 data cutoff date, 101 participants have been enrolled in the study as follows: 23 in Part 1 IV dose escalation, 30 in Part 1 SC dose escalation, 20 in Part 1.1 SC priming dose cohorts, 15 in Part 2A: SC dose dose expansion, 4 in Part 1C: elranatamab + lenalidomide and 9 in Part 1D: elranatamab + pomalidomide. In Part 1.1, to mitigate the risk of CRS and ICANS, participants received a priming dose of 600 µg/kg elranatamab (equivalent to 44 mg) on Day 1 prior to the first full dose of 1000 µg/kg (equivalent to 76 mg) on Day 8. In Part 2A, in addition to the priming dose of elranatamab, participants received pre-medication with dexamethasone, acetaminophen and diphenhydramine prior to the first 2 doses, priming dose and first full dose respectively.

Based on the data from this study, 76 mg QW administered SC was selected as the RP2D of elranatamab for future studies. This section will focus on safety data from participants who received elranatamab monotherapy at the full 1000 µg/kg or 76 mg [QW or Q2W] dosing regimen (N=41) regardless of priming dose or premedication.

In the 41 participants who received elranatamab monotherapy at the full 1000 µg/kg or 76 mg [QW or Q2W] dosing regimen , the most common all causality TEAEs (frequency ≥20%) were CRS (87.8%), neutropenia (78.0%), anemia (63.4%), ISR (56.1%), thrombocytopenia and fatigue (each 48.8%), diarrhea, hypophosphatemia and lymphopenia (each 39.0%), decreased appetite and dry skin (each 36.6%), back pain (34.1%), nausea and hypomagnesaemia (each 31.7%), AST increased and leukopenia (each 26.8%), ALT increased, fall, hypokalemia, pyrexia, vomiting, pain in extremity and weight decreased (each 24.4%), arthralgia, cough, dyspnoea, headache and pneumonia (each 22.0%).

For additional information, refer to the single reference safety document (SRSD), which for this study is the Investigator's Brochure.

1.2.3.2. Efficacy

Clinical activity has been observed in Study C1071001. As of the 22 June 2022 data cutoff date, the confirmed objective response rate at the full 1000 µg/kg or 76 mg [QW or Q2W dosing regimen (N=41)] was 63.4% (95% CI, 48.1, 76.4), per IMWG criteria. Responses were durable and deepened over time. Median duration of follow-up for all 41 patients treated at the full 1000 µg/kg or 76 mg (QW or Q2W dosing regimen) was 10.94 months (0.30, 24.41). For responding participants, the median duration of response (95% CI) was 11.6 (7.2, NE) months. The median progression-free survival (95% CI) was 10.4 (4.7, 15.2) months.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure.

1.2.3.3. Monoclonal Antibody Interference of Laboratory Evaluation of Myeloma

With the increasing use of therapeutic immunoglobulin G kappa (IgG_k) mAbs, either as a treatment for multiple myeloma itself, or for other reasons, the issue of mAb interference and associated false-positive results in the monoclonal spike (M-spike) assay for patients with IgG_k multiple myelomas has been noted. On both serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis (SIFE) methods, a visible and quantifiable myeloma protein (M-protein) corresponding to the therapeutic antibody may migrate with similar characteristics to the patient's own M-spike. This has prompted the international myeloma working group (IMWG) to issue an updated definition of CR that when looking at detectable myeloma protein (M-protein) in peripheral blood, the presence or absence of monoclonal bands by SPEP and SIFE must be made only in reference to the patient's original M-protein secreted by pathologic plasma cells.[27] This speaks to the importance of having a baseline sample from the patient's original disease clone and also the need for experienced readers who can recognize characteristic migration patterns of certain therapeutic mAbs. Studies report the detection limit in SPEP and SIFE assays using samples spiked with therapeutic mAbs to be 100 µg/ml; a concentration that is well exceeded in the circulation at therapeutic doses.[28] PF-06863135, however, is predicted to reach a maximal serum concentration of 100 µg/ml only at doses of 2500 µg/kg and above; hence there is no expectation of therapeutic mAb interference in the M-spike assay in this instance.

1.2.4. Nonclinical Safety Information

In nonclinical safety studies conducted in cynomolgus monkeys with PF-06863135 administered by either the IV or SC route for up to 1-month in duration, the key effects were cytokine elevations that were occasionally accompanied by emesis during the first 6 hours after the first drug administration and minimal to moderate inflammation at the injection site. Decreases in B cells and plasma cells as well as fluctuations in peripheral T-cell numbers were observed in IV studies where immunophenotyping measurements were included. All of these effects were considered related to the mechanism of action. In addition, red skin discoloration was noted in a subset of animals administered PF-06863135 by the IV route. None of the effects were considered adverse. Thus, the no observed adverse effect level (NOAEL) in the pivotal toxicity study was ≥0.3 mg/kg in monkeys [highest dose

tested; maximum concentration (C_{max}) of 10.4 µg/mL and area under the curve (AUC_{168}) of 715 µg·h/mL]. A detailed summary of the nonclinical safety programs are provided in the current Investigator's Brochure.

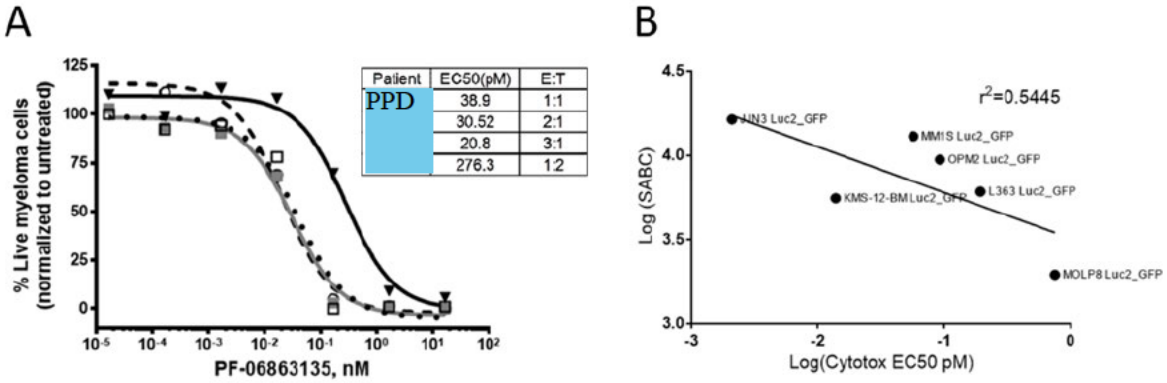
1.2.5. PF-06863135 Preclinical Efficacy

Efficacy of PF-06863135 has been demonstrated in vitro and in vivo, as summarized below.

1.2.5.1. In Vitro Activity of PF-06863135

Using fresh bone marrow aspirates from myeloma patients, PF-06863135 eliminated myeloma cells in a dose-dependent manner (see Figure 1A). There was a modest correlation between effective concentration 50 (EC50) and number of BCMA receptors on the cell surface when multiple myeloma cell lines with varying BCMA cell surface receptor levels were used in a cytotoxicity assay (Figure 1B). BCMA is shed from the surface of myeloma cells, and soluble BCMA in patient serum may decrease activity of PF-06863135 by acting as a sink. Bone marrow stromal cells are known to protect MM cells from drug treatment and induce myeloma cell growth. In the case that either of these suppressive mechanisms negatively impact PF-06863153 activity, the protocol allows dosing up to 60 fold over the predicted clinical efficacious dose.

Figure 1. PF-06863135 Activity In Vitro



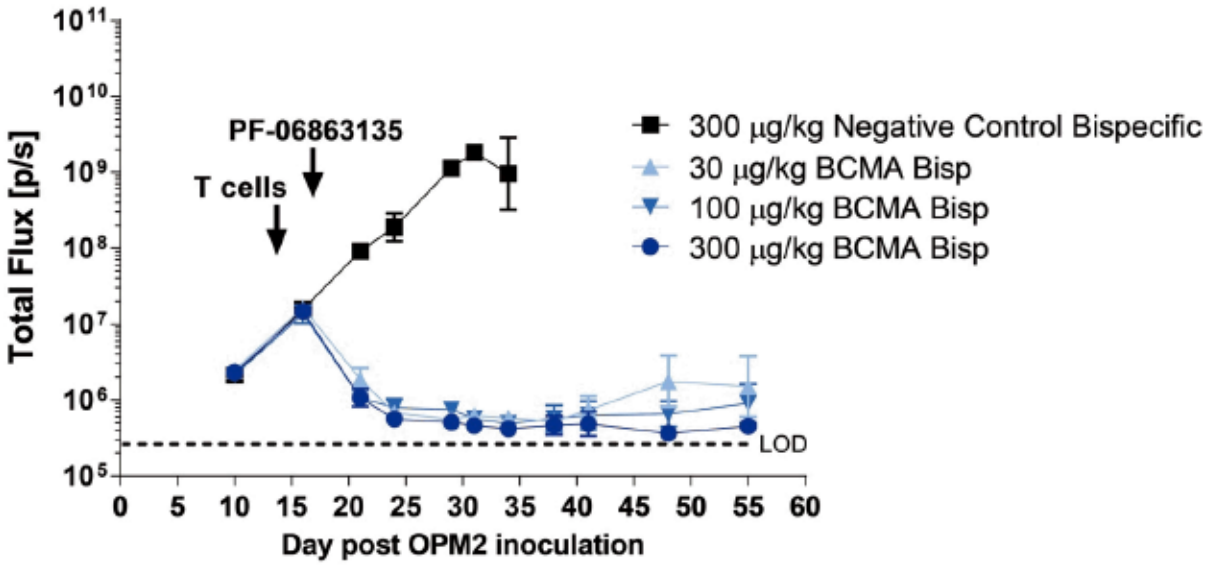
Abbreviations: EC50 = half maximal effective concentration; E:T = effector (T cells) to target (myeloma cells) ratio; nM = nanomolar; pM = picomolar; sABC = specific antibody-binding capacity

1.2.5.2. Single Agent Anti-tumor Efficacy of PF-06863135 in Orthotopic Multiple Myeloma Models Tumor Models

Activity of PF-06863135 was also evaluated in MM orthotopic tumor models. Multiple myeloma cell line (OPM-2), myeloma cells were injected into NOD scid gamma (NSG) mice. Fourteen days following OPM-2 injection, the mice received an intraperitoneal injection of CD3+ T-cells and a single dose of PF-06863135 two additional days later. As shown in Figure 2, PF-06863135 dose dependently inhibited tumor growth, and elimination of myeloma cells was observed on Day 24. At the highest dose level of 300 µg/kg, tumor growth reduction was sustained up to Day 55 when the study was terminated. Similar results were observed using MM1.S (a glucocorticoid sensitive multiple myeloma cell line) and

MOLP-8 (a multiple myeloma cell line with t(11;14)(q13;q32) chromosomal abnormality and negative for CD28) tumor models.

Figure 2. PF-06863135 Activity in an OPM-2 MM Orthotropic Tumor Model



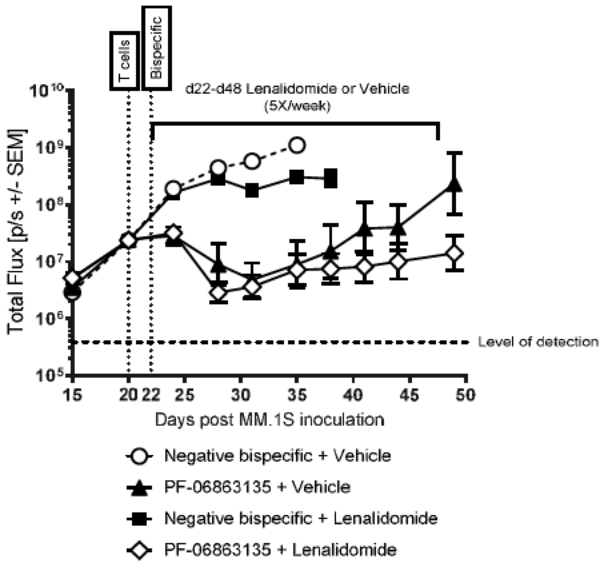
1.2.5.3. Anti-tumor Efficacy of PF-06863135 in Combination with the Immunomodulatory Drug Lenalidomide in Orthotopic and Subcutaneous Myeloma Models

In vivo studies were performed in T cell engrafted human myeloma orthotopic tumor-bearing mice to evaluate the combination of PF-06863135 with the immunomodulatory drug (IMiD) lenalidomide (PF-06863135_29Apr19_093404).

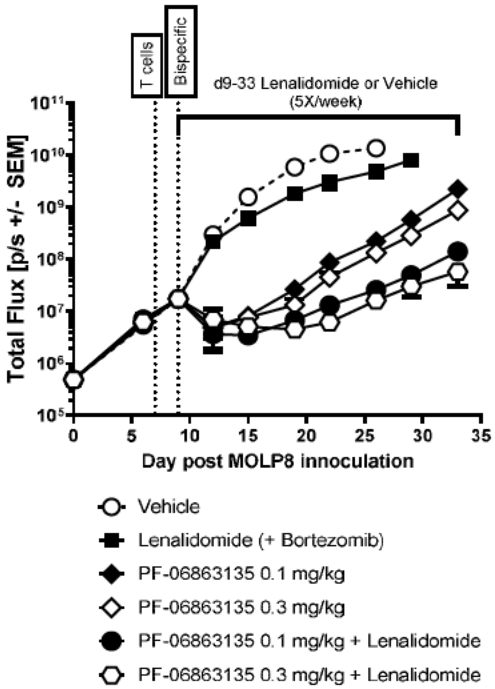
In the high BCMA expressing MM.1S model, PF-06863135 treatment resulted in superior anti-tumor response versus lenalidomide alone. Tumor growth inhibition induced by PF-06863135 was enhanced when given in combination with lenalidomide compared to single agent treatments, although it was not statistically significant (Figure 3A). Using body weight as a measurement of potential for toxicity, there were no indications that the single-agent or combinations therapies had negative effects on the general health of the animals during the study. In the MOLP-8 model, which expresses low levels of BCMA, tumor growth inhibition was statistically significantly enhanced in the PF-06863135 + lenalidomide combination compared to other treatments (Figure 3B). The human T cell engrafted myeloma models have a limited repertoire of human immune cells engrafted and therefore they cannot be used to comprehensively recapitulate all potential mechanisms of action of lenalidomide. Perhaps because of this, the enhancement in anti-tumor activity was not statistically significant in the MM.1S model compared to single agent PF-06863135 treatment groups. Even so, enhanced tumor activity of the combination of PF-06863135 and lenalidomide was observed in both the MM.1S and MOLP-8 models, suggesting the potential for synergy in the human setting.

Figure 3. Efficacy of PF-06863135 in Combination with Lenalidomide in MM.1S and MOLP-8 Orthotopic Tumor Models

A. MM.1S



B. MOLP8



A. 20 x 10^6 pre-activated and expanded T cells were administered on Day 20 after MM.1S-Luc tumor cell inoculation IV. Single dose PF-06863135 (10 ug/kg) or negative bispecific (7 µg/kg) was administered IV on Day 22 after tumor cell inoculation. Lenalidomide was administered at 15 mg/kg orally (PO) 5x/week starting on Day 22 after tumor inoculation. N = 9-10 animals per group.

B. 20 x 10^6 pre-activated and expanded T cells were administered on Day 7 after MOLP-8-luc tumor cell inoculation IV. Single dose PF-06863135 (0.1 or 0.3 mg/kg) was administered IV on Day 9 after tumor cell inoculation. Lenalidomide was administered at 50 mg/kg PO 5x/week and bortezomib (a proteasome inhibitor) was administered at 1 mg/kg IP 2x/week starting on Day 9 after tumor inoculation. N = 6-7 animals per group. Tumor cell bioluminescence captured as Total Flux serves as a measure of tumor burden and was measured 2x a week. Plot depicts mean logarithmic luminescence (p/s ± SEM). 2x = twice; 5x = five times; d = day post MM1.S-Luc tumor cell inoculation; IV = Intravenous; kg = kilogram; mAb = Monoclonal antibody; µg = micrograms; mg = milligram; N = number of mice; PO = per os or oral gavage administration; p/s = photons/second; SEM = standard error of the mean.

1.2.6. Lenalidomide

Lenalidomide (Revlimid®) is a thalidomide analogue which has immunomodulatory, antiangiogenic, and antineoplastic properties that induces apoptosis of certain hematopoietic tumor cells including multiple myeloma, mantle cell lymphoma, and del (5q) myelodysplastic syndromes in vitro.[29] Lenalidomide is indicated for patients with Multiple myeloma (MM) in combination with dexamethasone. It is also indicated as a maintenance for patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT). Most common side effects include fatigue, neutropenia, constipation, diarrhea, muscle cramp, anemia, pyrexia, peripheral edema, nausea, back pain, upper respiratory tract

infection, dyspnea, dizziness, thrombocytopenia, tremor and rash. Lenalidomide, a thalidomide analogue, can cause embryo-fetal toxicity.

Lenalidomide will be dosed at 15 mg orally daily days 1-21 of every 28 days starting C1D1. Complete information for this compound can be found in the Celgene USPI, Revlimid® (lenalidomide), Summit, New Jersey which is the SRSD for this study.[30] In the EU, Revlimid® can be found at the European Medicines Agency SPC.[31] In Canada this compound can be found in the Celgene Product Monograph, Revlimid® (lenalidomide) Mississauga, Ontario.[32]

1.2.7. Pomalidomide

Pomalidomide (Pomalyst® in the US and Imnovid in the EU) is a thalidomide analogue which has direct anti-myeloma tumoricidal activity, inhibits stromal cell support for MM tumor cell growth and has immunomodulatory activities.[33] Additionally, pomalidomide induces tumor cell death in both, lenalidomide-sensitive and lenalidomide-resistant cell lines. Pomalidomide is indicated in combination with dexamethasone for patients with MM who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy. Most common side effects include fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper-respiratory tract infections, back pain, and pyrexia. Rash, cough, peripheral edema, muscle spasms, and hypothyroidism can also be common side effects. Pomalidomide, a thalidomide analogue, can cause embryo-fetal toxicity.

A dose of 4 mg of pomalidomide will be administered orally on Days 1-21 of every 28 days starting C1D1. Complete information for this compound can be found in the Celgene USPI, Pomalyst® (pomalidomide), Summit, New Jersey (the SRSD for this study).[34] In the EU, Imnovid® can be found at the European Medicines Agency SPC.[35] In Canada this compound can be found in the Celgene Product Monograph, Pomalyst® (pomalidomide), Mississauga, Ontario.[36]

1.2.8. Dexamethasone

Dexamethasone is a corticosteroid which has immunomodulatory properties and anti-neoplastic activity against lymphoid malignancies including multiple myeloma.[37] Dexamethasone has been used in the prevention and treatment of immune effector cell-associated toxicities including cytokine release syndrome.[38,39] In addition to its immunomodulatory properties, dexamethasone exhibits anti-myeloma activity and has been integrated into standard combination regimens such as bortezomib/lenalidomide/dexamethasone and daratumumab/lenalidomide/dexamethasone.[40,41] Because the effect of dexamethasone on the safety and efficacy of T-cell engaging bispecific agents is not known, the addition of dexamethasone to PF-06863135 will be investigated in Part 1E and Part 2E. The most common adverse reactions are cardiovascular, dermatologic, endocrine, fluid and electrolyte disturbances, gastrointestinal, metabolic, musculoskeletal, neurological/psychiatric, ophthalmic, abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, and weight gain.

Dexamethasone will be dosed as premedication at 40 mg orally 60 ± 30 minutes prior to PF-06863135 administration. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone may be dosed as premedication at 20 mg orally 60 ± 30 minutes prior to PF-06863135 administration. If a dose of PF-06863135 is held or skipped, then dexamethasone should not be administered. For patients receiving dexamethasone premedication, dexamethasone should be discontinued after 6 months unless clinical rationale to continue dexamethasone is provided by investigator and approved by sponsor.

1.2.9. Starting Dose Rationale

1.2.9.1. Intravenous (IV) Starting Dose Rationale

The selection of the starting dose for this first-in-patient (FIP) study was based on the minimum anticipated biological effect level (MABEL) in accordance with the International Conference on Harmonization (ICH) S9 Guidance, given that PF-06863135 is a bi-specific T-cell-engaging agent with immune agonistic properties. The in vitro biological activities for PF-06863135 were determined via T-cell activation, cytokine release, and cytotoxicity experiments. Based on exposure-response analyses, eight out of ten assay measures achieved 20% maximal effect (effective concentration [EC]20) above 1.9 ng/mL. All ten assay measures also achieved 50% maximal effect (EC50) above 1.9 ng/mL. This EC20 value in combination with the projected PF-06863135 human pharmacokinetics (PK) based on allometric scaling of monkey PK data were used for projecting the MABEL dose. Specifically, the MABEL dose was calculated by setting the maximum (or peak) serum concentration (C_{max}) less than or equal to the 1.9 ng/mL threshold (assuming peak cytokine release and CD3+ T-cell activation is driven by maximum drug exposure). In addition, receptor occupancy (RO) was calculated based on in vitro binding affinities (equilibrium dissociation constant or K_D) of PF-06863135 (38 pM against BCMA and 17 nM against CD3) to further ensure that the recommended MABEL starting dose will result in minimum receptor binding.

Based on this MABEL approach, the clinical starting dose selected for the study is 0.1 µg/kg given as a 2-hour intravenous infusion given weekly in 3 week cycles. As PF-06863135 has a projected half-life of 3.5 days in humans, a weekly regimen, with a projected <1.33-fold exposure accumulation ratio at steady state across the planned dose escalation range was chosen to maintain a higher average concentration over the dosing interval (a potential driver of efficacy) relative to C_{max}. The human C_{max} for unbound PF-06863135 at the starting dose of 0.1 µg/kg is projected to be approximately 1.1 ng/mL, which is expected to result in minimal biological effect. This free concentration projection accounts for binding to typical levels of serum soluble BCMA (2.57 ng/mL) in healthy humans. Because the serum soluble BCMA levels are elevated in relapsed/refractory MM patients, the unbound PF-06863135 concentrations at C_{max} may be lower. In addition, the recommended starting dose of 0.1 µg/kg is expected to result in minimum receptor binding, as the theoretical receptor occupancy (RO) values at the projected C_{max} are less than 17% for BCMA and 0.05% CD3.

A body weight-based dosing approach (µg/kg) will be applied for the dose-escalation part (Part 1) of FIP study of PF-06863135 with the goal to reduce inter-individual variations in PK exposure. Fixed-dosing approach will be applied in dose-finding for combination and

also in all expansion parts of the study (see Section 1.2.9.4 for more details). Pfizer intends to conduct population PK analysis of PF-06863135 after sufficient data have been collected to inform optimal dosing approach for future studies.

1.2.9.2. Subcutaneous (SC) Starting Dose Rationale

The proposed starting dose for SC administration is 80 µg/kg, one dose level higher ("Dose IV +1") than the previously tested IV dose level (50 µg/kg) in Part 1 IV administration that is deemed safe. Taking expected bioavailability for SC versus IV into consideration, the 80 µg/kg SC dose is expected to have lower exposure than 50 µg/kg IV. Available and emerging safety data from completed and initiated IV administration cohorts in the dose escalation Part 1 IV informed and supported the decision to initiate SC administration. Based on an assumed bioavailability ≤100% and slowed uptake to the systemic circulation with SC administration, the systemic exposure C_{max} and area under the curve (AUC) after SC administration at the starting dose did not exceed exposures of "Dose IV -+1" for SC dose escalation. Consequently, relative to the next proposed dose level in Part 1 IV, the SC starting dose cohort is expected to exhibit comparable or less severe systemic adverse events, including CRS. This should reduce the potential for toxicity with the initial transition from IV to SC dosing. The sponsor may decide to discontinue or pause the IV dose escalation and only determine an MTD/MAD for the SC route.

In cynomolgus monkeys, PF-06863135 was well tolerated following repeated IV doses up to 300 µg/kg or following repeated SC doses up to 300 µg/kg. For reference, following SC administration of PF-06863135 at 100 µg/kg weekly in humans and assuming 100% bioavailability, the systemic maximum concentration (C_{max}) is predicted to be approximately 33.4% and 57.0% of the C_{max} observed following administration of 300 µg/kg IV and 300 µg/kg SC, respectively in cynomolgus monkeys. Similarly, the area under the concentration-time curve for the first dosing interval (AUC_{0-168}) following single SC administration of PF-06863135 at 100 µg/kg weekly in humans is predicted to be approximately 57.6% and 49.8% of the AUC determined following the administration of 300 µg/kg IV and 300 µg/kg SC, respectively, in cynomolgus monkeys. Thus, exposures of PF-06863135 following SC administration up to 100 µg/kg are projected to be lower than those observed to be well tolerated in cynomolgus monkey.

1.2.9.3. Starting Dose for Combination Safety Cohorts (Parts 1C, 1D and 1E)

The dose finding evaluation with PF-06863135 in combination with lenalidomide or pomalidomide is planned to be initiated after the PF-06863135 monotherapy dose escalation, and the MTD/MAD and RP2D of PF-06863135 monotherapy has been determined. The starting dose of PF-06863135 for the combination with lenalidomide or pomalidomide therapy will be 1 dose level below the MTD/MAD if the MTD/MAD and RP2D of monotherapy PF-06863135 are equal, and the dose of PF-06863135 will be dose escalated to the monotherapy MTD/MAD or RP2D. If the monotherapy RP2D is already at least 1 dose level below the MTD/MAD, then the RP2D will be used as the starting dose of PF-06863135 in combination with lenalidomide or pomalidomide, and no dose escalation will be planned. Lenalidomide will be dosed at 15 mg orally daily days 1-21 of every 28 days starting C1D1. Pomalidomide will be dosed at 4 mg orally daily Days 1-21 of every 28 days starting C1D1.

Part 1E will investigate PF-06863135 in combination with dexamethasone. Dexamethasone would begin on C0D1 and it will be dosed as premedication prior to PF-06863135 administration. Due to non-overlapping toxicity between PF-06863135 and dexamethasone, this safety cohort will evaluate the RP2D of PF-06863135 monotherapy and a fixed dose of dexamethasone, at a dose of 40 mg. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone premedication may be given prior to PF-06863135 at a fixed dose of 20 mg. If a dose of PF-06863135 is held or skipped, then dexamethasone should not be administered. For patients receiving dexamethasone premedication, dexamethasone should be discontinued after 6 months unless clinical rationale to continue dexamethasone is provided by investigator and approved by sponsor.

1.2.9.4. Fixed Dosing Approach

A fixed-dose approach will be applied for PF-06863135 in Parts 1C, 1D and 1E and Part 2 given that a fixed dosing approach was shown to provide similar PK variability compared to body-weight adjusted dosing when evaluated for monoclonal antibodies, therapeutic peptides, and proteins.[42,43] In addition, fixed dosing offers ease of preparation and less chance of dosing errors. Based on the preliminary population PK analysis of PF-06863135 in 41 patients up to 360 µg/kg dose, there is no clinically meaningful effect of body weight (range: 47.9 to 120 kg) or body surface area (range: 1.37 to 2.36 m^2), on the PF-06863135 clearance and further justifies fixed dosing approach for expansion parts of the ongoing study. Also, age (range: 47 to 82 years) or sex (20 males vs 21 females) were not clinically meaningful covariates on PF-06863135 exposure.

1.2.9.5. Dosing Interval

The initial Q1W dosing frequency of PF-06863135 in this study was selected based on the projected $t_{1/2}$ of 4-8 days in humans. Based on emerging PK, PD, and safety data, regimens with alternative dosing frequencies (eg, Q2W or Q4W) may also be considered. In order to reduce the burden of weekly visits, if a patient has received treatment with Q1W PF-06863135 for at least 6 months, and disease assessments have remained stable over at least 2 months, consideration may be given to increasing dose intervals from weekly to every 2 weeks or once per cycle (CXD1) after consultation with the sponsor. Cycles would remain the same length. It would be preferable to skip dosing of PF-06863135 on days 8 and 22 of each cycle if cycles are 4 weeks in length. If the patient subsequently begins to have an increase of disease burden, dose intervals should return to weekly dosing.

In addition, if PK data at any point during SC Q1W dose escalation suggests that a Q2W dose schedule may be able to achieve sufficient trough concentrations and provide adequate systemic exposure, a Q2W dosing schedule would replace Q1W at the next higher dose level if MTD or MAD have not been reached. If it is possible and warranted to continue dose escalation with SC Q2W even if MTD/MAD has been reached for SC Q1W, Part 1.1 may be used with priming dose at the MTD/MAD of SC Q1W and subsequent escalation to next higher dose level with SC Q2W dosing as maintenance, provided that the next higher dose level given Q2W would not exceed the overall exposure that had been achieved at MTD/MAD of SC Q1W.

Cycles for Q2W dosing would be 4 weeks. Both Q1W and Q2W dosing will be considered for RP2D determination from Part 1.

1.2.9.6. Priming and Maintenance Dose Rationale

In a Phase 2 trial of blinatumomab in adults patients with relapse/refractory acute lymphoblastic leukemia (ALL), dose limiting toxicities of Grade 4 cytokine release syndrome (CRS) were reported in 2 out of 7 patients treated at 15 μg/m2/day.[44] It was found that if treatment was interrupted for 1-2 weeks, patients recovered sufficiently for treatment to resume. This led to the implementation of a lower starting dose (priming dose) of 5 μg/m2/day for the first week, escalating to 15 and 30 $\mu g/m^2$ per day subsequently. Of the 11 patients treated with this approach within the same study, 2 patients developed Grade 3 CRS, but no dose limiting Grade 4 or 5 CRS was observed.[44] When this stepwise approach was applied to a second Phase 2 study, only 3 patients out of 189 treated experienced CRS (Grade 3) but no Grade 4 or 5 CRS was observed.[18] Thus, it was concluded that the implementation of a priming dose approach is effective in ameliorating CRS through building tolerance, and it has become the recommended treatment regimen for ALL patients. Based on priming followed by maintenance being demonstrated to be potentially successful in reducing CRS, this approach may be evaluated prior to reaching an MTD/MAD (see Section 3.1.1.3). This approach may be implemented to reduce CRS related toxicities if indicated for patient safety.

1.2.10. Biomarker Rationale

The objectives of the biomarker assessments will be to understand the relationship between the pharmacokinetics (PK), target load, immune cell phenotypes, and pharmacodynamic activity of PF-06863135, with and without combination partners, and its anti-tumor activity and safety profile. This understanding will in turn inform the selection of a therapeutic dose, as well as potentially identify a phenotypic profile that maximizes anti-tumor activity while minimizing the risk of toxicity.

Target load will be assessed using a flow cytometry assay to measure cell surface BCMA on multiple myeloma cells in fresh bone marrow aspirates at baseline. Levels of circulating soluble BCMA will be measured from plasma samples before and after PF-06863135 using mass spectrometry. The relationship between target load and the pharmacokinetics of PF-06863135 will provide guidance for dose selection for PF-06863135. The goal of this analysis will be to select doses that exhibit an acceptable safety profile, and potentially provide evidence of anti-tumor activity. The pharmacodynamic effect of BCMA: CD3 engagement by PF-06863135 will be investigated in the bone marrow for all patients. Potential effects of PF-06863135 on T-cell subset percentages, proliferation and survival, and activation markers will be assessed by flow cytometry. In addition to these flow cytometry analyses, bone marrow biopsy tissue samples will be assessed for similar endpoints including BCMA expression and T-cell subset immunophenotyping by immunohistochemistry (IHC). The spatial relationship of myeloma cells and T-cells may be interrogated. Thereafter, material and assay permitting, additional exploratory analyses may be undertaken to further evaluate mechanism of action and/or resistance.

To monitor for potential immune activation or inflammation resulting from the immunostimulatory effects of dosing with PF-06863135, serum will be collected to measure cytokines and chemokines, and whole blood absolute cell counts (T, B, and NK [natural killer] lymphocytes or TBNK) will be measured.

The most challenging objective of the biomarker plan will be to discover markers that identify patients at baseline most likely to respond to PF-06863135 therapy with minimal risk of toxicity. Exploratory analyses may be undertaken to understand the biological basis for response to BCMA: CD3 engagement. These measures will attempt to address whether baseline levels or changes in bone marrow ribonucleic acid (RNA) expression, and T-cell clonal diversity correlate with tumor response. Bone marrow sample may be submitted to RNA profiling analysis to interrogate the balance between immune transcripts associated with immune activation and immune regulation. T-cell repertoire diversity may be assessed by high throughput sequencing of T-cells from bone marrow tissue and/or peripheral blood. Whole blood and, sample permitting, a portion of the bone marrow sample may be used for deoxyribonucleic acid (DNA) isolation for exploratory analyses such as pharmacogenomics. These assessments may be analyzed in the context of clinical response data to potentially identify patients with the highest probability of responding to BCMA: CD3 engagement. All of these measures will be correlated with measures of toxicity and anti-tumor activity to ascertain their usefulness as potential biomarkers of clinical benefit.

1.2.10.1. Banked Biospecimens

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens Section 7.7. Comparing the DNA, RNA, protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

Banked biospecimens retained in the BBS also can be used in research on MM.

Providing these biospecimens is a required study activity for study sites and patients, unless prohibited by local regulations or ethics committee (EC) decision.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Part 1 IV and SC monotherapy Dose Escalation, Part 1.1 Priming and Maintenance Dose Escalation and Parts 1C, 1D and 1E Dose Escalation/Finding

Primary Objectives:	**Primary Endpoints:**
• To assess safety and tolerability at increasing dose levels of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone in successive cohorts of patients with multiple myeloma in order to estimate the Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAD) and select the Recommended Phase 2 Dose (RP2D).	• Number of DLTs following treatment with escalating doses of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.
Secondary Objectives:	**Secondary Endpoints:**
• To evaluate the overall safety profile.	• Adverse Events as characterized by type, frequency, severity as graded by NCI CTCAE version 4.03, timing, seriousness, and relationship to PF-06863135 treatment as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone . The severity of CRS will be assessed according to the grading described by Lee et al. (2014 and 2019,[2,3] See Appendix 5); • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.
• To evaluate anti-myeloma activity of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• Objective response rate (ORR) using the international myeloma working group (IMWG) response criteria for multiple myeloma[4,5] (see Appendix 2); • Time to event endpoints: time to response (TTR), complete response rate (CRR), duration of response (DOR), duration of complete response (DoCR), duration of stable disease (DOSD), progression-free survival (PFS), overall survival (OS), as assessed by IMWG criteria for response[4,5] (see Appendix 2); • Rate of patients with no MRD after treatment with PF-06863135 using IMWG MRD criteria[5] (see Appendix 3).
• To evaluate single dose and multiple dose PK of PF-06863135 given as monotherapy and in combination with lenalidomide or pomalidomide. Additionally, PK of lenalidomide, pomalidomide, and	• Pharmacokinetic parameters of PF-06863135: Cycle 1 Day 1 dose and Cycle 2 Day 1 dose maximum concentration (C_{max}), area under the concentration versus time curve from time zero to the last quantifiable time point prior to the next dose (AUC_{last}) and if data permit,

dexamethasone will be evaluated when combined with PF-06863135 (Parts 1C, 1D, and 1E, respectively).	clearance (CL or CL/F), volume of distribution at steady state (Vss or Vss/F), and terminal elimination $t_{1/2}$. • Plasma lenalidomide, pomalidomide, and dexamethasone concentrations at selected time points (Parts 1C, 1D, and 1E, respectively).
• To evaluate immunogenicity of PF-06863135 as monotherapy and in combination with , lenalidomide, pomalidomide. or dexamethasone.	• Incidence and titers of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against PF-06863135.
• To characterize the impact of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone, on systemic soluble immune factors.	• Pre- and post-dose quantification of soluble cytokines in serum.
Tertiary/Exploratory Objectives:	**Tertiary/Exploratory Endpoints:**
• Evaluate the effect of PF-06863135 as a monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone on plasma cell, T and B cell compartments.	• BCMA expression on plasma cells in bone marrow, as assessed by multiparameter flow cytometry and immunohistochemistry; • Pre- and post-dose levels of soluble BCMA; • Enumeration of T, B, and NK subtypes in whole blood and bone marrow by flow cytometry analysis; • T-cell immunophenotyping, including but not limited to proliferation and activation markers in whole blood and bone marrow by flow cytometry analysis; • T-cell engagement, including but not limited to proliferation and activation markers in bone marrow by immunohistochemistry; • The relative expression of RNA transcripts, including but not limited to, those associated with immune activation and immune regulation in bone marrow; • The abundance and diversity of T-cell clones in bone marrow.
• To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens Section 7.7.

2.2. Part 2 Dose Expansion

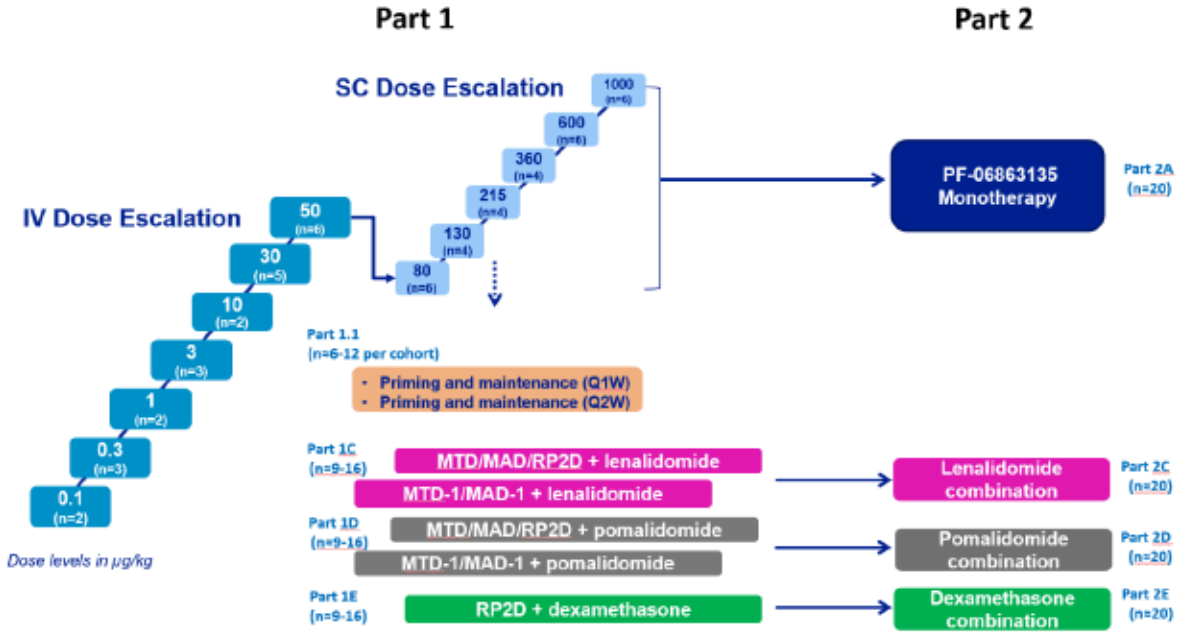
Primary Objectives:	Primary Endpoints:
• To assess preliminary clinical efficacy at RP2D for PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• ORR and DoR, as assessed by IMWG criteria for response[4,5] (see Appendix 2).
Secondary Objectives:	**Secondary Endpoints:**
• To further characterize the safety and tolerability of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to PF-06863135 treatment as monotherapy and in combination with pomalidomide, lenalidomide, or dexamethasone. The severity of CRS will be assessed according to the grading described by Lee et al. (2014 and 2019,[2,3] See Appendix 5); • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.
• To further evaluate anti-myeloma efficacy of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• Time to event endpoints: CRR, DoCR, TTR, DOSD, PFS, OS, as assessed by IMWG criteria for response[4,5] (see Appendix 2); • Rate of patients with no MRD after treatment with PF-06863135 using IMWG MRD criteria[5] (see Appendix 3).
• Evaluate PK of PF-06863135 at RP2D as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone. Additionally, to collect lenalidomide, pomalidomide, and dexamethasone concentration data when combined with PF-06863135.	• Concentrations of PF-06863135, lenalidomide, pomalidomide, and dexamethasone at selected time points.
• To evaluate immunogenicity of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• Incidence and titers of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against PF-06863135.
• To characterize the impact of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone on systemic soluble immune factors.	• Pre- and post-dose quantification of soluble cytokines in serum.
Tertiary/Exploratory Objectives:	**Tertiary/Exploratory Endpoint):**
• Evaluate the effect of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or	• BCMA expression on plasma cells in bone marrow, as assessed by multiparameter flow cytometry and immunohistochemistry;

dexamethasone on plasma cell, T and B cell compartments.	• Pre- and post-dose levels of soluble BCMA; • Enumeration of T, B, and NK subtypes in whole blood and bone marrow by flow cytometry analysis; • T-cell immunophenotyping, including but not limited to proliferation and activation markers in whole blood and bone marrow by flow cytometry analysis; • T-cell engagement, including but not limited to proliferation and activation markers in bone marrow by immunohistochemistry; • The relative expression of RNA transcripts, including but not limited to, those associated with immune activation and immune regulation in bone marrow; • The abundance and diversity of T-cell clones in bone marrow.
• To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens Section 7.7.

3. STUDY DESIGN

3.1. Study Overview

Figure 4. C1071001 Study Design



This is a Phase 1, open-label, multi-dose, multi-center, dose escalation, safety, pharmacokinetic (PK) and pharmacodynamic (PD) study of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide or dexamethasone in adult patients with advanced multiple myeloma who have relapsed from or are refractory to standard therapy. This study will be divided into dose escalation/finding (Part 1) and dose expansion (Part 2). Intravenous (IV) and subcutaneous (SC) administration of PF-06863135 will be evaluated during the Part 1 dose escalation. An alternative maintenance dose escalation phase (Part 1.1), which incorporates the usage of a priming dose during Cycle 0 Day 1 (C0D1) 1 week prior to a maintenance dose for all subsequent doses may also be initiated if excessive toxicity occurs or the MTD/MAD is reached earlier than desired (see Section 3.1.1.3). Upon reaching MTD/MAD, up to approximately 6-12 patients total at selected level(s) below the MTD/MAD weekly and Q2W dosing up to the same dose intensity as the MTD/MAD weekly regimen may be evaluated further to support the RP2D decision. The route of PF-06863135 administration for Parts 1C, 1D and Part 1E and Part 2 will be decided once the IV and SC dose escalations have been completed, and an RP2D has been selected.

Following the determinations of the RP2D of monotherapy and combinations with lenalidomide or pomalidomide in Part 1, the respective expansion cohorts in Part 2 will commence. In addition, if the combination regimen with dexamethasone is well tolerated as guided by mTPI in Part 1E , Part 2E may be initiated.

The Part 2 dose expansion phase will be divided into 4 cohorts as follows: Part 2A (PF-06863135 as monotherapy), Part 2C (PF-06863135 in combination with lenalidomide), Part 2D (PF-06863135 in combination with pomalidomide), and Part 2E (PF-06863135 in combination with dexamethasone), which will evaluate safety and anti-myeloma activity of PF-06863135 at the RP2Ds determined in Part 1 (see Section 3.1.1, 3.1.1.3 and 3.1.2).

Approximately 120 patients had been planned to enroll into Parts 1/1.1, 1C, 1D and 1E with approximately 80 patients planned to enroll into Part 2. Parts 1C,1D and 1E were planned to enroll approximately 9-16 patients with Parts 2A, 2C, 2D and 2E planned to enroll approximately 20 patients each.

The clinical development program for PF-06863135 has been expanded with dedicated studies that will further investigate both monotherapy and combination therapy. Therefore, the Sponsor has determined that enrollment in study C1071001 has been completed.

All patients will complete up to 4 weeks of screening for all Parts.

Following the initial dose, treatment with investigational product will continue until disease progression, patient withdrawal of consent or unacceptable toxicity occurs. A follow-up visit approximately 4 weeks after the last dose for adverse event (AE) and serious AE (SAE) collection will be conducted. If the patient completes the 1 month follow-up visit prior to completion of the 60 day long term DLT observation period (see Section 3.2.1), a follow up phone call will be completed on at least Day 60, and no more than Day 65. Patients found to have anti-drug antibodies (ADA) at their final study visit and an ongoing AE possibly related to ADA will be asked to return to the clinic for ADA assessment at approximately 3 month

intervals (if feasible given the underlying disease) until the adverse event or its sequelae return to baseline or stabilize at a level acceptable to the investigator and sponsor.

Following discontinuation of study treatment (unless patients are lost to follow up, consent is withdrawn, or study is discontinued by the sponsor), survival status will be collected by telephone every 3 months until death, or up to approximately 30 months after first treatment of the last patient, whichever comes first. Subsequent anti-cancer therapies and relevant transplant information will also be collected.

Treatment with investigational product will continue until disease progression, patient refusal or unacceptable toxicity occurs. The last study treatment will be up to approximately 30 months after first treatment of the last patient, and the study would then end after any additional follow-up visits required after the last study treatment.

3.1.1. Part 1 Monotherapy Dose Escalation and Part 1.1 Priming and Maintenance Cohorts

SCHEDULE OF ACTIVITIES A and SCHEDULE OF PHARMACOKINETIC, SOLUBLE FACTOR AND CYTOKINE activities A will be utilized in Part 1.

To closely manage acute toxicities, all patients enrolled into Part 1 dose escalation phase will be hospitalized on C1D1 (Also for at least 24 hrs if a priming dose is given on C0D1). The hospitalization period may be extended if the patient experiences abnormal laboratory findings or ongoing adverse events that require further hospitalization. The need for mandatory hospitalization as well as its length will be re-assessed for patients enrolled in Parts 2A, 2C, and 2D based on safety data from Part 1 after agreement of sponsor and investigators at the time of monotherapy MTD/MAD/ and RP2D determination

For safety reasons, a staggered enrollment strategy will be applied for Parts 1 and 1.1 at each dose level; the first patient will be dosed and observed for 48 hours. If no safety concerns arise during this 48 hr period from start of treatment, then subsequent patients will be enrolled into the same dose level. All patients in Part 1 and Part 1.1 will be monitored closely for dose limiting toxicities (DLTs, see Section 3.2). Decisions for dose escalation will be made based on DLTs observed within the DLT observation period. A modified toxicity probability interval (mTPI) method, targeting a DLT rate of 25% and an acceptable equivalence interval of 20%-30% will be utilized for dose escalation Part 1 (see Section 3.1.4). At least 6, up to 16 patients must be enrolled into a dose level that is determined to be MTD/MAD. Upon reaching MTD/MAD, up to approximately 6-12 patients total at selected level(s) below the MTD/MAD weekly and Q2W dosing up to the same dose intensity as the MTD/MAD weekly regimen may be evaluated further to support the RP2D decision.

Assessment of late toxicities will also be completed after the DLT observation period to 60 days after C1D1 for all patients. Once a dose level has been declared safe, patients at lower dose levels who have completed the 60 day late toxicity observation period may escalate to the next higher dose level, if criteria outlined in Section 3.1.4.1 Criteria for Intrapatient Dose Escalation have been met. Additional intra-patient dose escalations will

also be permitted after a minimal interval of 60 days. No crossover is allowed, however, between monotherapy PF-06863135 and the different combination regimens.

3.1.1.1. Part 1 Intravenous (IV) Administration

In Part 1, PF-06863135 will initially be studied as an IV formulation in sequential dose levels (0.1, 0.3, 1, 3, 10, 30, 50 μg/kg or higher if indicated) in adult patients with relapsed/refractory multiple myeloma, who have received a proteasome inhibitor, an immunomodulatory drug (IMiD) and an anti CD38 monoclonal antibody (mAb) where approved and available either in combination or as a single agent. Additional dose levels (lower, intermediate or higher) may be evaluated. If toxicity is observed at the starting dose level of 0.1 μg/kg, 0.03 μg/kg will be evaluated. Subsequent to the starting dose level, if dose de-escalation is recommended by the mTPI model after DLT evaluation, intermediate dose levels between the previous dose and current dose may be studied. Depending on the observed safety and tolerability profile of PF-06863135, dose levels above 50 μg/kg or higher if indicated may be explored. All patients will also be monitored from Day 22 to Day 60 for late toxicities (see Section 3.2.1).

If within 21 days after the initial infusion a dose level induces symptoms consistent with ≥ Grade 3 CRS and lasts for >24 hours despite standard of care treatment for the management of CRS per the guidelines of the institution, Investigator, or treating physician, and it is considered not to be due to an IRR, allergic reaction, anaphylaxis or other causes, evaluation of Part 1 SC or Part 1.1 IV Maintenance administration may be initiated.

3.1.1.2. Part 1 Subcutaneous (SC) Administration

Part 1 SC administration has been triggered based on the emerging clinical and PK data from IV cohorts at 80 μg/kg, one dose level higher ("Dose IV +1") than the tested IV dose level of 50 μg/kg in Part 1 IV administration that is deemed safe and has not experienced a Grade 3 CRS event.

Depending on the observed safety and tolerability profile of PF-06863135, each dose level for SC administration will be increased by a maximum of 3-fold.

Depending on evaluation of immunogenicity, safety, efficacy, PK and/or PD data the SC administration portion may be placed on hold or discontinued and Part 1.1 Priming and Maintenance Dose Escalation administration may be re-initiated if appropriate.

3.1.1.3. Part 1.1 Priming and Maintenance Cohorts

Part 1.1 is an alternative dosing regimen that will be initiated only if a priming dose for IV or SC has been declared in Part 1. The decision to evaluate a regimen that includes a priming dose may be made by the investigators and sponsor prior to reaching an MTD/MAD using the following criteria as guidance:

- If a dose level induces symptoms consistent ≥ Grade 3 CRS lasting for >24 hours (despite treatment with standard of care per the institution's, Investigator's, or treating physician's guidelines for the management of CRS) considered not to be due to an infusion related reaction (IRR), allergic reaction, anaphylaxis or other causes, then a lower dose, which has been evaluated in at least 2-4 patients, will be chosen as a priming dose (Dose Prime) for subsequent cohorts.

- If a Dose Prime is selected, dose escalation will continue to determine the MTD/MAD of a dose regimen that includes a priming dose.

- If a dose level induces confirmed CRS of Grade 4 considered not to be due to an IRR, allergic reaction, anaphylaxis or other causes, then a lower dose, which has been evaluated in at least 2-4 patients, will be chosen as a priming dose (Dose Prime) for subsequent cohorts.

- In addition, observation of a confirmed CRS event that meets the above qualifications following later infusions (ie, after Cycle 1 Day 1) or CRS events that are approaching the limit of tolerability may prompt the investigators and sponsor to include evaluation of a Dose Prime for subsequent cohorts.

After confirmation of the safety of Dose Prime, the treatment schedule will implement the inclusion of the fixed priming dose as the first dose (C0D1) followed by a maintenance dose 1 week later (C1D1) that will continue to be escalated in subsequent cohorts following an mTPI method. The starting maintenance dose level will be no greater than 2-fold above the priming dose (see Section 3.1.4). Depending on the observed safety and tolerability profile of PF-06863135, each maintenance dose level administration will be increased by a maximum of 2-fold. After the MTD/MAD has been established, the priming dose may potentially be further verified in connection to the established MTD/MAD/RP2D, including consideration of more than one priming step, if indicated, using information from all patients who were included in the initial priming dose determination as well as those enrolled in subsequent dosing cohorts.

SCHEDULE OF ACTIVITIES B: WITH PRIMING DOSE AND SCHEDULE OF PHARMACOKINETIC, SOLUBLE FACTOR AND CYTOKINE ACTIVITIES B will then be utilized in Part 1.1. In Part 1.1, patients will receive the priming dose on C0D1 during the priming dose portion of Cycle 0. The priming dose will remain the same for all dose level cohorts. The maintenance dose will be administered one week later on C1D1 and for subsequent cycles.

To closely manage acute toxicities, all patients receiving a priming dose will be hospitalized for at least 24 hrs on both C0D1, and C1D1. The hospitalization period may be extended if the patient experiences abnormal laboratory findings or ongoing adverse events that require further hospitalization.

For safety reasons, a staggered start will be employed at each dose level; the first patient will be dosed, and observed for 48 hours. The 48 hr observation period for the first patient in each dose level in Part 1.1 will begin on C1D1 during the second hospitalization period. If no safety concerns arise during this 48 hr period from start of treatment, then subsequent patients will be enrolled into the same maintenance dose level.

Decisions for maintenance dose escalation will be made based on toxicities observed within the DLT observation period (Cycles 0 and 1). Subsequent to starting the maintenance dose level, if dose de-escalation is recommended by the mTPI model after evaluation, intermediate dose levels between the previous dose and current dose may be studied. At least 6, up to approximately 16 patients must be enrolled into a maintenance dose level that is determined to be the maximum tolerated dose (MTD)/MAD.

Once a dose level has been declared safe, patients at lower dose levels who have completed 60 day late toxicity observation period may escalate to the next higher dose level, if criteria outlined in Section 3.1.4.1 Criteria for Intrapatient Dose Escalation have been met. Additional intra-patient maintenance dose escalations will also be permitted after a minimal interval of 60 days from first administration of maintenance dose.

Alternative strategies for increasing dosing such as a step-up regimen or prophylactic steroids may also be considered and implemented to further improve tolerability if needed.

3.1.1.4. Part 1 Combination Dose Finding

Parts 1C, 1D and 1E, are dose finding safety cohorts for PF-06863135 in combination with lenalidomide, pomalidomide or dexamethasone, respectively. Upon determining the PF-06863135 RP2D/MTD/MAD and route of administration as monotherapy either with or without priming dose in Part 1, Parts 1C, 1D and 1E will be initiated to study the safety of PF-06863135 in combination with lenalidomide, pomalidomide, or dexamethasone. Parts 1C and 1D will be started with PF-06863135 one dose level below the MTD/MAD and escalated one dose level unless the RP2D is below the MTD/MAD in which case the RP2D will be used as the starting dose of PF-06863135. If in Parts 1C, or 1D, the combination is not well tolerated, doses of PF-06863135 may be de-escalated to a lower dose level below the starting dose of PF-06863135 used in combination. Part 1E will be a combination of PF-06863135 at RP2D/MTD/MAD and dexamethasone. If this combination is not well tolerated, Part 2E may not be initiated.

As described in Section 3.4, a dose of 1000 µg/kg SC weekly has been selected as the RP2D for PF-06863135 as a single agent. This single agent RP2D will be administered as a fixed dose of 76 mg (a fixed dose equivalent of 1000 µg/kg; see Section 1.2.9.4 for rationale) following a priming dose of 44 mg (a fixed dose equivalent of 600 µg/kg) administered one week earlier. Similarly, Part 1 combination dose finding (Part 1C and Part 1D) will be

administered as fixed doses for PF-06863135 with maintenance doses started one week after the priming dose; the starting dose is one dose level below the single agent RP2D as described in Table 1:

Table 1. Table of Potential Fixed Dose Levels

Dose level[a]	Priming Dose (mg)	Maintenace Dose (mg)
0	24	32
1 (starting)	32	44
2[b]	44	76

a. Dose level refers to designated dose levels for Part 1C and Part 1D
b. Designated dose level for Part 1E

Part 1C will investigate PF-06863135 in combination with lenalidomide in sequentially escalating doses of PF-06863135. This safety cohort will start with the dose level MTD-1/MAD-1 or RP2D (whichever is lower) of PF-06863135 from the Part 1 dose escalation and 15 mg dose of lenalidomide in order to select the combination RP2D. If the combination regimen is not well tolerated, a dose that is lower than the RP2D determined for single-agent PF-06863135 may be evaluated in combination before proceeding to Part 2. If necessary, de-escalation will be guided by an mTPI design. PF-06863135 will be administered on C1D1 and weekly or every 2 weeks or once per cycle (CXD1) thereafter with or without a priming dose. A dose of 15 mg of lenalidomide will be administered orally on Days 1-21. PF-06863135 and lenalidomide will be administered over a cycle of 28 days. A staggered enrollment strategy will be applied at each dose level: when a dose level opens for enrollment, the first patient will be dosed, and observed for 96 hours beyond C1D1. If no safety concerns arise during this 96 hr period from C1D1 of PF-06863135 and lenalidomide, subsequent patients will be enrolled into the same dose level. To closely manage acute toxicities, patients will be hospitalized on C1D1. It is expected that Part 1C will enroll approximately 9-16 patients.

Part 1D will investigate PF-06863135 in combination with pomalidomide in de-escalation doses. This safety cohort will evaluate the MTD-1/MAD-1 or RP2D dose level (whichever is lower) of PF-06863135 from Part 1 dose escalation and a standard of care dose of pomalidomide in order to select the combination RP2D. If the combination regimen is not well tolerated, a dose that is lower than the RP2D determined for single-agent PF-06863135 may be evaluated in combination before proceeding to Part 2. If necessary, de-escalation will be guided by mTPI. The first dose of PF-06863135 will be administered on C1D1 and weekly thereafter. A dose of 4 mg of pomalidomide will be administered orally on Days 1-21. PF-06863135 and pomalidomide will be administered over a cycle of 28 days. A staggered enrollment strategy will be applied at each dose level: when a dose level opens for enrollment, the first patient will be dosed, and observed for 96 hours. If no safety concerns arise during this 96 hr period from C1D1 of PF-06863135 and pomalidomide, subsequent patients will be enrolled into the same dose level. To closely manage acute toxicities,

patients will be hospitalized on C1D1. It is expected that Part 1D will enroll approximately 9-16 patients.

Part 1E will investigate PF-06863135 in combination with dexamethasone. This safety cohort will evaluate the RP2D fixed dose level of PF-06863135 monotherapy and a fixed dose of dexamethasone, at a dose of 40 mg. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone premedication may be given prior to PF-06863135 at a dose of 20 mg. If the combination regimen is not well tolerated due to PF-06863135, PF-06863135 may be de-escalated in combination according to modified toxicity probability interval (mTPI) design. Each cycle of the combination of PF-06863135 and dexamethasone starting with Cycle 1 will be 28 days. If the combination regimen is not well tolerated as guided by mTPI, Part 2E may not be initiated. Dexamethasone would begin on C0D1 and it will be dosed as premedication prior to PF-06863135 administration. If a patient has received dexamethasone for 6 months or PF-06863135 is discontinued, then dexamethasone should be discontinued unless clinical rationale to continue dexamethasone is provided by investigator and approved by sponsor. Patients who need to discontinue treatment with dexamethasone may continue to receive treatment with PF-06863135. If a dose of PF-06863135 is held or skipped, then dexamethasone should not be administered until PF-06863135 is restarted. It is expected that Part 1E will enroll approximately 9-16 patients.

3.1.2. Part 2 Dose Expansion

Part 2 dose expansion phase will be divided into 4 cohorts as follows: Part 2A (PF-06863135 as monotherapy), Part 2C (PF-06863135 in combination with lenalidomide), Part 2D (PF-06863135 in combination with pomalidomide), and Part 2E (PF-06863135 in combination with dexamethasone) which will evaluate safety and anti-myeloma activity of PF-06863135 at the monotherapy/combination RP2D.

Based on emerging clinical data from the Part 1 dose escalation, either IV or SC administration including priming and maintenance dose Q1W or Q2W will be selected for the Part 2 dose expansion.

If the SC administration is selected for Part 2 dose expansion, all patients in 2C, 2D and 2E will receive a subcutaneous fixed dose of PF-06863135 at the Q1W RP2D (with or without a priming dose given at C0D1 1 week prior to C1D1). Part 2A patients will also receive a subcutaneous fixed dose of PF-06863135 at either the RP2D Q1W or Q2W schedule, depending on emerging clinical data in Part 1.

For lenalidomide, Part 2C, 15 mg orally (PO) will be administered daily on days 1–21 of a 28 day cycle starting C1D1 in combination with the MTD/MAD or RP2D of PF-06863135 determined in Part 1C (with or without a priming dose of PF-06863135 given at C0D1, 1 week prior to C1D1).

For pomalidomide, Part 2D, 4 mg PO will be administered daily on days 1–21 of a 28-day cycle starting C1D1 in combination with the MTD/MAD or RP2D of PF-06863135 determined in Part 1D (with or without a priming dose of PF-06863135 given at C0D1 1 week prior to C1D1).

For dexamethasone, Part 2E, 40 mg PO will be administered as premedication 60 ± 30 minutes prior to PF-06863135 starting C0D1 in combination with the MTD/MAD/RP2D fixed dose of PF-06863135 determined in Part 1. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone premedication may be given 60 ± 30 minutes prior to PF-06863135 at a dose of 20 mg.

The RP2D selected will be based on the MTD or the MAD, and further evaluation of other covariates such as disease burden, soluble plasma BCMA level, and body size information will also be utilized. Selection of 1 hr or 2 hr intravenous administration (if utilized in Part 2) will be based on the incidence of IRRs. Approximately 80 patients may be enrolled into Part 2 (see Section 9.3 Sample Size Determination) with approximately 20 patients in Parts 2A, 2C, 2D, and 2E. Patients from the dose finding combination cohorts of Parts 1C, and 1D treated at the dose levels selected for Part 2 may be counted towards sample size of the corresponding cohorts of Part 2.

Preliminary data from the Part 2 dose expansion may provide guidance in the Sponsor's decision to adjust the sample size of each arm, to add other available treatment combinations in a future amendment, or to initiate additional clinical studies.

3.1.3. Starting Dose

The starting dose for Part 1 IV administration will be 0.1 μg/kg given weekly in 3 week cycles.

3.1.4. Criteria for Dose Escalation/De-Escalation

The study has been designed to establish the MTD/MAD defined as the dose that yields approximately 25% probability of DLT and considers equivalent doses that yield probability of DLT in the interval (Equivalence Interval) 20% to 30%.

All dose escalation/de-escalations will be guided by the mTPI design and therefore 2-4 patients will be enrolled in each cohort (see Section 3.1 Study Overview).

The potential dose levels to be evaluated for Part 1 IV administration are listed in Table 2. The potential dose levels to be evaluated for Part 1 SC administration are listed in Table 3.

Dose escalation for Part 1 IV and SC will start at dose level 1 for each (Table 2 and Table 3).

In Part 1, for both IV and SC administration, the maximum dose increase will be approximately 3 fold if no DLTs are observed; per mTPI, intermediate or higher doses may be evaluated based on clinical findings.

Table 2. Table of Potential Dose Levels in Part 1 IV Administration

Dose level	Dose (µg/kg)
1	0.1
2	0.3
3	1.0
4	3.0
5	10.0
6	30.0
7	50.0

Table 3. Table of Potential Dose Levels in Part 1 SC Administration

Dose level	Dose (µg/kg)
0	50
1	80
2	130
3	215
4	360
5	600
6	1000

In Part 1.1, the starting maintenance dose will be no more than 2-fold above the priming dose established from Part 1. Maximum maintenance dose increases will be 2-fold (100%).

Q2W dosing would be evaluated upon reaching MTD/MAD. Cycles for Q2W dosing would be 4 weeks rather than the 3 weeks with Q1W dosing. Both Q1W and Q2W dosing may be considered for Part 2A expansion from Part 1.

Once the first DLT is observed, the maximum increase would increase no more than 2-fold up to 3 µg/kg, and no more than 67% beyond 3 µg/kg.

Parts 1C, and 1D will combine escalating doses of PF-06863135 starting at the monotherapy MTD-1/MAD-1 or RP2D (whichever is lower) dose level and increasing to the monotherapy RP2D/MTD, if applicable, in combination with a standard dose of lenalidomide or pomalidomide, respectively. De-escalation of PF-06863135 to a lower dose level may occur if necessary.

In Part 1E, the cohort that includes dexamethasone will evaluate PF-06863135 at a priming dose of 44 mg followed by a maintenance dose of 76 mg administered. De-escalation of PF-06863135 to a lower dose level may occur if necessary.

The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same dose level to determine (Decision Rules) where future cohorts should involve dose escalation, no change in dose, or dose de-escalation as presented in Table 4 (see also Section 9.2 Statistical Methods and Properties and Appendix 8).

Table 4. Decision Rules

Number of Patients Having DLT	Number of Patients Treated at a Dose Level										
	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10	n=11	n=12
0	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E
2	U	D	D	S	S	S	S	S	S	S	E
3		U	U	U	D	S	S	S	S	S	S
4			U	U	U	U	D	S	S	S	S
5				U	U	U	U	U	U	D	S
6					U	U	U	U	U	U	U

D: De-escalate the dose; E: Escalate the dose; S: Stay at the dose; U: Unacceptable toxicity
Note: If one patient has a DLT event observed in a dose cohort with 2 patients enrolled, additional patients may be enrolled for dose escalation assessment. Any DLT observed accounts for decision rules.

Dose escalation will stop under any of the following conditions:

- The maximum sample size has been achieved;
- Approximately 6-16 patients have been enrolled at a dose that is predicted to be the MTD/MAD;
- All doses explored appear to be overly toxic and the MTD/MAD cannot be determined.

3.1.4.1. Criteria for Intrapatient Dose Escalation

Intrapatient dose escalation to the next dose-level will be permitted in this study for patients in dose escalation phase. Data gathered from patients following intra-patient dose escalation will be excluded from MTD/MAD evaluation. Intrapatient dose-escalation to the next dose level is permitted if all of the following conditions are met. Further intrapatient dose escalations are permitted, and will be based on the same criteria for each escalation.

1. The next dose level is safe after DLT observation in all patients for a minimum of 60 days;
2. The candidate for intra-patient dose-escalation tolerated the current dose level well, with highest drug-related toxicity observed being Grade 2 or below;
3. A bone marrow aspirate and disease staging lab tests can be performed within 1 week before start of treatment with the escalated dose (a bone marrow aspirate is mandatory unless the investigator assesses that there in an unjustifiable risk for it

and/or the patient refuses to undergo a bone marrow procedure; if a bone marrow aspirate or biopsy was performed within the past 28 days prior to planned start of escalated dose, only disease staging lab tests must be performed);

4. A discussion between the investigator and sponsor has been completed, and it is agreed that this will be in the patient's best interest.

A patient whose dose has been escalated will not contribute to the assessment of the number of DLTs at the escalated dose level.

3.2. Dose Limiting Toxicity (DLT) Definition

Monitoring for DLTs will occur during Part 1. Severity of adverse events (AEs) will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The severity of cytokine release syndrome (CRS) will be assessed according to the grading described by Lee et al. (2014 and 2019,[2,3] See Appendix 5). For the purpose of dose escalation, the DLT observation period will be up to the end of Cycle 1 in each patient. For those patients receiving a priming dose, Cycle 0 and Cycle 1 would be included in the DLT observation period. DLT evaluable patients will include patients that have experienced a DLT in the DLT observation period or. DLT evaluable patients will also include those who received all of their planned doses of PF-06863135 in the initial DLT observation period if Q2W dosing is being evaluated or at least all but one of their planned doses of PF-0686135 if Q1W dosing is being evaluated, provided a dose was not missed due to toxicity attributed to study drug. Safety information from any patients that do not meet DLT evaluable criteria could still be considered for overall dose escalation decisions although they would not factor into mTPI decision rules.

Any of the following adverse events observed within the DLT observation period considered related to PF-06863135 or PF-06863135 in combination with lenalidomide, pomalidomide, dexamethasone,will be classified as DLTs:

Hematological:

- Grade 4 neutropenia lasting >5 days. Except in lenalidomide combination cohort where it can be managed by dose reduction of lenalidomide in the next cycle.
- Febrile neutropenia (defined as an absolute neutrophil count [ANC] <1000/mm^3 with a single temperature of >38.3°C [101°F], or a sustained temperature of ≥38°C [100.4°F] for more than one hour). If fever is determined to be a symptom of CRS confirmed by clinical course and cytokine levels and resolves in a manner consistent with CRS, this would no longer be considered a DLT, and the patient may resume treatment.
- Grade ≥3 neutropenia with infection.
- Grade 4 thrombocytopenia (unless the study entry baseline count was ≥25,000 and <50,000 to take into account bone marrow suppression due to multiple myeloma, in

this case grade 4 thrombocytopenia needs to be accompanied by ≥ Grade 2 bleeding to be a DLT). For subjects who experience a platelet count <10,000/mm^3, this is considered a DLT irrespective of other factors with the exception of lenalidomide-related Grade 4 thrombocytopenia manageable by platelet transfusions and lenalidomide dose reduction in the next cycle.

- Grade 3 thrombocytopenia with ≥ Grade 2 bleeding.

Non-hematological:

- Grade 4 Adverse Events (AEs).
- Grade 3 AE lasting ≥5 days despite optimal supportive care, with the exception of AE attributed to a CRS event (ie, Grade 3 transaminitis).
- Grade 3 CRS, except those CRS that have i) not been maximally treated (ie, lack of administration of standard of care treatment per the institution's, Investigator's, or treating physician's guidelines for the management of CRS) or ii) improved to ≤ Grade 1 within 48 hours.
- Grade 4 CRS.
- Confirmed drug-induced liver injury (DILI) meeting Hy's law criteria outlined in Section 8.4.1.
- Grade 4 laboratory abnormalities deemed clinically significant by the investigator shall be reported as Grade 4 AE as described in Section 8.2.2.
- Clinically important or persistent toxicities (eg, toxicities responsible for significant dose delay) that are not included in the above criteria may also be considered a DLT following review by the investigators and the Sponsor. All DLTs need to represent a clinically significant shift from baseline.

The following AEs will not be adjudicated as DLTs:

- Isolated Grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset or deemed clinically insignificant by the investigator.

3.2.1. Late Toxicities

Late toxicities are AEs that meet the same grading criteria as DLT criteria and occur from Cycle 2 Day 1 through the 60 day assessment period. If late toxicities occur those may be incorporated in the mTPI approach and enrollment into any higher dose level cohorts may be placed on temporarily hold. All safety data will be reviewed, and a decision will be made to either:

- Continue enrollment in higher dose level cohorts.
- Increase the number of patients at the dose level in which the late toxicities occurred to satisfy the mTPI decision rules (Section 3.1.4). All patients will be followed for at least 60 days to assess safety at this dose level. If the mTPI decision rule of dose-escalation is reached, enrollment in higher dose level cohorts may resume. If after the enrollment of additional subjects the mTPI recommends to de-escalate the dose, the option to de-escalate the dose will be discussed.
- Permanently stop enrollment in higher dose level cohorts, and declare the dose level to be above MTD/MAD. Increase the number of patients at the dose level in which the late toxicities occurred to satisfy the mTPI decision rules (Section 3.1.4).
- Stop the study.

For any given patient that is on-treatment at dose levels that are subsequently considered to be above the MTD/MAD, the option to dose reduce will be discussed. If a patient tolerated the above MTD/MAD dose level well and is benefiting, continuation of treatment at the above MTD/MAD dose level will require re-consenting.

3.3. Maximum Tolerated and Maximum Administered Dose (MTD and MAD) Definitions

The MTD is defined as the highest dose with true toxicity probabilities in the equivalence interval (EI) where the EI is defined as 20%-30%.

Even though the mTPI model may select an MTD with an incidence of DLTs that is higher than 30% since mTPI decision rules are based on unit probability mass (UPM) and not on point estimates of the DLT rate (see Section 9.2.1), doses with an incidence of DLT >30% (eg, 3 out of 9) cannot be declared as the MTD. In practice, model recommendations may be overridden by clinical judgment, and MTD with an incidence of DLTs that is higher than 30% will not be considered acceptable to be selected as MTD. The MTD will be the highest dose associated with the occurrence of DLTs ≤30% (eg, <3 of 9 evaluable patients experience a DLT).

If the MTD is not reached, then the MAD will be maximum dose that is evaluated in the study.

3.4. Recommended Phase 2 Dose (RP2D) Definition

Based on preliminary safety, efficacy, PK, and pharmacodynamics data from Part 1 (monotherapy dose escalation), a dose of 1000 µg/kg SC weekly has been selected as the RP2D for PF-06863135 as a single agent. Briefly, single-agent anti-myeloma activity has been observed at doses ≥215 µg/kg SC with an acceptable safety profile across all dose levels. The overall response rate (ORR) for the 215, 360, 600, and 1000 µg/kg SC dose levels was 75% (3/4), 75% (3/4), 66.7% (4/6) and 83% (5/6), respectively. In addition, preliminary exposure-efficacy analyses indicated that higher PF-06863135 exposure (average concentration at steady state) may be associated with higher probability of objective response, especially in patients with high baseline soluble BCMA. Overall, the data support 1000 µg/kg SC weekly as a tolerable dose that provides clinical benefit for the majority of patients with relapsed or refractory MM, including those with high baseline soluble BCMA.

Although only Grade 1 or Grade 2 CRS was reported during dose escalation, 2 of 6 patients experienced Grade 1 CRS events that lasted for 9 days with the first dose of 1000 µg/kg. The longest duration of CRS in the 600 µg/kg SC cohort was 4 days, which occurred in 1 patient and was Grade 1. Therefore, Part 1.1 of this study evaluates whether the duration of CRS can be mitigated by a single priming dose of 600 µg/kg given one week prior to 1000 µg/kg maintenance dosing (see Section 1.2.9.6 for rationale). Based on preliminary safety data from Part 1.1, administration of a priming dose (600 µg/kg) reduces duration of CRS associated with subsequent maintenance dosing (1000 µg/kg). Therefore, a priming strategy will be adopted for both PF-06863135 monotherapy and combination therapy in this study as well as other studies.

For monotherapy dosing with PF-06863135, the RP2D of 1000 µg/kg will be administered as a fixed dose of 76 mg SC weekly (see Section 1.2.9.4 for rationale) following a single priming dose of 44 mg (fixed dose equivalent of 600 µg/kg) administered one week before initiation of maintenance dosing.

The combination RP2D for PF-06863135 will be determined separately for each combination therapy.

3.5. Stopping Criteria in Part 2 Dose Expansion

If the following criteria listed below are met in any of the cohorts in Part 2 dose expansion, further enrollment into the cohort meeting the criteria will be placed on hold, and a decision to stop the cohort may be made following a review of all safety information:

- Grade 5 treatment-related AE ≥10%; or
- Grade 4-5 treatment-related non-hematological AE >25%.

Adverse event information collected during dose escalation of patients treated at the same dose levels will be included in the evaluation.

4. PATIENT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Patients with relapsed or refractory multiple myeloma, as defined by the international myeloma working group (IMWG) updated criteria 2014[45] (see Appendix 6), and measurable disease on enrollment (study entry) as defined by one or more of the abnormalities listed in a to c below:

   a. Serum myeloma (M)-protein greater than or equal to 0.5 g/dL (5 g/L).

   b. Urine M-protein greater or equal to 200 mg/24 h.

   c. For patients without measurable serum and urine M-protein levels or if the serum and urine M-protein levels are uninterpretable due to assay interference by prior treatment with daratumumab only: free light chain (FLC) is considered to be measurable in patients whose involved light chain (either kappa or lambda) is >100 mg/L (10 mg/dL) and who have an abnormal kappa:lambda ratio (abnormal is outside the range .26 to 1.65).

2. Patients must have progressed on or are intolerant of established therapies known to provide clinical benefit in multiple myeloma including proteasome inhibitor, an IMiD drug and an anti-CD38 mAb, where approved and available, either in combination or as a single agent. Patients must not be candidate for regimens known to provide clinical benefit in relapse or refractory multiple myeloma based on the investigator's judgment. If a patient declines such therapy, this must be recorded in the study files.

3. Female or male patients age ≥18 years.

4. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)(see Appendix 4).

   - For Part 2A: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1.

   - For all other Parts: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1. PS-2 is permitted if PS is due to underlying myeloma.

5. Adequate hematological function including:
   - Absolute neutrophil count (ANC) ≥1,000/mm^3.
   - For PF-06863135 monotherapy, Part 1E and 2E : Platelet count ≥25,000/mm^3 (transfusion support is permitted if completed prior to planned start of dosing). For Parts 1C and 2C platelet count ≥30,000/mm^3. For Parts 1D and 2D platelet count ≥50,000/mm^3.
   - Hemoglobin ≥8.0 g/dL (transfusion support is permitted if completed prior to planned start of dosing).
6. Adequate Renal Function, including:
   - For non-lenalidomide parts of the study: Estimated creatinine clearance ≥30 mL/min as calculated using the method standard for the institution. (If an estimated creatinine clearance [CrCl] is believed to be inaccurate for a patient, 24-hour urine collection with actual assessment of CrCl is allowed); For Parts 1C and 2C, estimated creatinine clearance ≥60 mL/min.
   - Serum creatinine ≤2.5 mg/dL;
   - Not dialysis-dependent.
7. Adequate Liver Function, including:
   - Aspartate and alanine aminotransferase (AST and ALT) ≤2.5 x upper limit of normal (ULN); ≤5.0 x ULN if there is liver involvement by the tumor.
   - Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in case of bone metastasis).
   - Total bilirubin ≤2.0 mg/dL, except in patients with Gilbert Syndrome who must have a total bilirubin less than 3.0 mg/dL.
8. No active hepatitis B (HBV) or hepatitis C (HCV) infection.
9. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1, with the exception of peripheral neuropathy attributable to bortezomib in the limit of Grade ≤2.
10. Serum pregnancy test (for females of childbearing potential) negative at screening.
11. Female patients of non-childbearing potential must meet at least 1 of the following criteria:
    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or

physiological cause; status may be confirmed with a serum follicle stimulating hormone (FSH) level confirming the postmenopausal state.

- Have undergone a documented hysterectomy and/or bilateral oophorectomy.
- Have medically confirmed ovarian failure.
- All other female patients (including female patients with tubal ligations) are considered to be of childbearing potential.

12. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

13. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Patients with other malignancies in addition to multiple myeloma are not eligible if the other malignancy has required treatment within the past 3 years or is not in complete remission with the exceptions of successfully treated non-metastatic basal cell or squamous cell skin carcinoma.

2. History of active autoimmune disorders (including but not limited to: Crohn's disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Grave's disease) and other conditions that compromise or impair the immune system.

3. Any form of primary immunodeficiency (such as Severe Combined Immunodeficiency Disease).

4. Patients with active uncontrolled bacterial, fungal or viral infection, including known human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) related illness. See Appendix 10 for additional clarification as it relates to SARS-CoV2 infection.

5. Patients with evidence of active mucosal or internal bleeding.

6. History of CTCAE Grade ≥3 immune-mediated adverse event (including hepatitis, pancreatitis, colitis, pneumonitis, carditis, and cytokine release syndrome) that was considered related to prior immune-modulatory therapy (exceptions: immune-related adverse events secondary to checkpoint inhibitors that have been appropriately managed or resolved such as hypophysitis and hypothyroidism).

7. Major surgery within 4 weeks prior to study entry.

8. Radiation therapy within 2 weeks prior to study entry (bone lesions requiring radiation may be treated with limited [ie, ≤25% of bone marrow in field] radiation therapy during this period).

9. Patients with a history of stem cell transplant (autologous or allogeneic) within 100 days prior to study enrollment.

10. Donor Lymphocyte Infusion (DLI) within 30 days prior to study entry.

11. Time between the last doses of previous systemic anti-cancer therapy is less than 5 times the elimination half-life of previous therapy or less than 30 days after last dose of antibody based therapies (eg, elotuzumab, daratumumab).

12. Requirement for systemic immune suppressive medication except as permitted in the study protocol.

13. Current requirement for chronic blood product support.

14. Patients with known relapse following BCMA targeted therapy (except for PF-06863135) may be eligible following discussion with the sponsor. However, patients who had received alemtuzumab previously or who have not recovered white blood cell counts to baseline after conditioning chemotherapy for prior chimeric antigen receptor (CAR) T cell therapy are excluded.

15. Patient known to be refractory to platelet or red blood cell transfusions.

16. Baseline 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect patient safety or interpretation of study results (eg, baseline corrected QT [QTc] interval >470 msec, complete left bundle branch block [LBBB], signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of active myocardial ischemia, second- or third-degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >470 msec, this interval should be rate-corrected using the Fridericia method and the resulting Corrected QT interval by Fredericia (QTcF) should be used for decision making and reporting. If QTc exceeds 470 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the patients eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants. Cases must be discussed in detail with sponsor's medical monitor to judge eligibility.

    Any of the following in the previous 6 months: myocardial infarction, long QT syndrome, Torsade de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), serious conduction system abnormalities (eg, left anterior hemiblock, left bundle branch block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF, New York Heart Association class III or IV), cerebrovascular accident, transient

ischemic attack, symptomatic pulmonary embolism, and/or other clinical significant episode of thromboembolic disease, ongoing cardiac dysrhythmias of National Cancer Institute (NCI) CTCAE > Grade 2, atrial fibrillation of any grade (> Grade 2 in the case of asymptomatic lone atrial fibrillation). If a participant has a cardiac rhythm device/pacemaker placed and QTcF >470 msec, the participant can be considered eligible. Subjects with cardiac rhythm device/pacemaker must be discussed in detail with sponsor's medical monitor to judge eligibility.

17. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

18. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry. Patient may be included if 5 times elimination half-life of drug has passed. Note: COVID-19 vaccination may be considered an exception and should be discussed with the sponsor on an individual basis.

19. Known or suspected hypersensitivity to murine and bovine products.

20. Fertile male patients and female patients of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol.

21. Other acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

22. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

23. For enrollment in lenalidomide combination cohorts Parts 1C and 2C, patients who had previously received lenalidomide and were dose reduced to less than 25 mg daily for thrombocytopenia, neutropenia or renal impairment.

24. For enrollment in pomalidomide combination cohorts Parts 1D and 2D, patients who had previously received pomalidomide and were dose reduced to less than 4 mg daily for thrombocytopenia, neutropenia, severe renal impairment, or hepatic impairment.

25. For enrollment in pomalidomide combination cohorts Parts 1D and 2D, patients who are receiving strong CYP1A2 inhibitors (eg, ciprofloxacin and fluvoxamine).

26. For patients on pomalidomide combination Parts 1D and 2D, patients who have any level of hepatic impairment (Child-Pugh A-C) that would require dose reduction of pomalidomide.

4.3. Lifestyle Requirements

All fertile female patients who are of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 5 months after the last dose of PF-06863135.

No contraception methods are required for male participants who receive PF-06863135 in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the estimated MABEL (minimal anticipated biological effect level) used as conservative estimate of exposure that may result in serious manifestations of developmental toxicity.

In addition to contraception requirements to PF-06863135, for Parts 1C, 2C, 1D and 2D, the manufacturer's (Bristol Meyers Squibb's) pregnancy prevention programs (PPP) for lenalidomide and pomalidomide must be followed. All females of childbearing potential, as defined per PPP, must use at least 2 acceptable methods of contraception as specified in the PPP including at least one highly effective method (tubal ligation, IUD, hormonal [birth control pills, hormonal patches, injections, vaginal rings, or implants], or partner's vasectomy) and at least one additional effective method of birth control (male latex or synthetic condom, diaphragm, or cervical cap every time they have sex with a male, or abstaining from sex with a male) for at least 4 weeks before lenalidomide or pomalidomide therapy (including during dosing interruptions), during lenalidomide or pomalidomide therapy, and until at least 4 weeks after the last dose of lenalidomide or pomalidomide therapy, and men must always use a latex or synthetic condom during any sexual contact with females of childbearing potential during lenalidomide or pomalidomide therapy (including during dosing interruptions) and until at least 4 weeks after discontinuing lenalidomide or pomalidomide. In addition, PPP requirements related to prohibition of blood, semen, and sperm donation during lenalidomide and pomalidomide treatment and for at least 4 weeks after discontinuing treatment must be followed.

The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected an appropriate method of contraception for the individual patient and his or her partner(s) from the permitted list of contraception methods (see below) and will confirm that the patient has been instructed in its consistent and correct use. At time points indicated in the SCHEDULE OF ACTIVITIES (including the required contraception period [through 5 months post last dose of PF-06863135 for WOCBP]), the investigator or designee will inform the patient of the need to use highly effective contraception consistently and correctly and document the conversation and the patient's affirmation in the patient's chart (patients need to affirm their consistent and correct use of the selected methods of contraception). In addition, the investigator or designee will instruct the patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the patient or partner. In addition to reporting requirements outlined in Sections

8.4.2 and 8.4.2.1, for Parts 1C, 2C, 1D and 2D, additional reporting requirements as defined in the PPP for lenalidomide and pomalidomide must be followed, including immediate reporting of potential pregnancy exposure to the manufacturer, follow-up reporting to the manufacturer each trimester until outcome, and infant follow-up to the manufacturer every quarter for 1 year after birth (pending consent of the female participant or female partner). Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the patient or male patient's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the patient.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the

established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational medicinal products include PF-06863135, lenalidomide, pomalidomide and dexamethasone. For dose level information, please see Section 3.1.

5.1. Allocation to Treatment

Dose level allocation will be performed by the sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will e-mail a complete Registration Form to the designated sponsor study team member or designee. The sponsor will assign a patient identification number and supply this number to the site. The patient identification number will be used on all study-related documentation at the site.

No patient shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the patient's enrollment;
- Specification of the dose level for that patient and;
- Permission to proceed with dosing the patient.

The sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

5.2. Patient Compliance

All doses of PF-06863135 will be administered by the appropriately designated study staff at the investigational site. Oral medications lenalidomide,pomalidomide, and dexamethasone, if applicable, will be taken by the patient either at the site or at home.

The site will complete required dosage Preparation Record located in the Investigational Product manual (IP manual). The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the

preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

5.3. Investigational Product Supplies

5.3.1. Pharmaceutical Form(s) and Packaging

PF-06863135 is presented as a sterile aqueous buffered solution for intravenous/subcutaneous administration. Please consult the Investigational Product Manual (IP manual) and Investigator's Brochure for further details.

Lenalidomide (Revlimid®) is an oral medication approved in the US, EU, and Canada for the treatment of multiple myeloma. Please consult the Revlimid® US package Insert (USPI) or EU Package Insert or SPC for further details.[30-32]

Pomalidomide (US Pomalyst®, EU and Canada Imnovid®) is an oral medication approved in the US, EU, and Canada for the treatment of multiple myeloma. Please consult the Pomalyst® US package Insert (USPI) or EU package insert or SPC for further details.[34-36]

Dexamethasone is an oral medication approved in the US, EU, and Canada.[37]

5.3.2. Preparation and Dispensing

For PF-06863135, see the IP manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of biotherapy agents.

5.4. Administration

5.4.1. IV Administration PF-06863135

PF-06863135 will be administered on Day 1, 8 and 15 of each cycle per the IP manual as an intravenous (IV) infusion over 2 hrs (±15 minutes). If the patient is assigned to the lead-in cohort in Part 2 that is specifically designed to evaluate reduced infusion time, PF-06863135 may be administered as an IV infusion over 1 hr (±10 minutes). For monotherapy, each cycle will be 3 weeks in duration, and each patient will be treated 3 times during each cycle, unless dose delays or interruptions occur (see Sections 5.5.1 and 5.5.2). On C1D1 for all patients, and on C0D1 for patients receiving a priming dose, PF-06863135 will be administered on an inpatient basis. On all other days, PF-06863135 will be administered on an outpatient basis.). On C1D1 for all patients, and on C0D1 for patients receiving a priming dose, PF-06863135 will be administered on an inpatient basis. On all other days, PF-06863135 will be administered on an outpatient basis.

Details for PF-06863135 infusion are provided in the current PF-06863135 IP Manual. The dose level will be assigned by the sponsor (see Section 5.1 Allocation to Treatment). For monotherapy Part 1, all patients should be weighed within 72 hours prior to Day 1 of each cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of PF-06863135 required for dose preparation. If the patient experienced either a weight loss or gain >10% compared to the prior weight used to calculate the initial dose or dose in the previous cycle, the amount of PF-06863135 required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained. Should the institutional policy be such that the dose is required to be calculated if a patient experiences a weight gain of <10%, this will be allowed. Fixed dosing approach will be applied in dose-finding for combination and also-dosing approach will be applied in dose-finding for combination and also in all expansion parts of the study (See Section 1.2.9.4).

The use of an infusion or syringe pump is the preferred method of administration to ensure accurate delivery of the investigational product. Please refer to the IP manual for infusion rate and duration.

Each patient may receive PF-06863135 until disease progression, unacceptable toxicity, withdrawal of consent, or study termination. If a patient has received treatment with Q1W PF-06863135 for at least 6 months, and disease assessments have remained stable over at least 2 months, consideration may be given to increasing dose intervals from weekly to every 2 weeks or once per cycle (only CXD1 dosing and activities applicable) after consultation with sponsor. Cycles would remain the same length with any skipped weekly doses noted. If the patient subsequently begins to have increase of disease burden, dose intervals should return to weekly dosing.

5.4.2. SC Administration PF-06863135

Qualified and trained investigator site personnel will administer PF-06863135 to patients by SC injection. Ideally, each injection may be up to 2 mL in volume. However, if the maximum volume allowed per institution's policy is lower, the number of injections may increase to accommodate this difference in volume to ensure the correct final dose is delivered.

Study drug should be administered to the abdomen (with preference given to the lower quadrants when possible). Refer to Appendix 9 for details on administration of multiple injections to the abdomen. Study staff should refer to the IP Manual for specific instructions on the handling and preparation of study drug.

Similar to IV dosing, during monotherapy dose escalation with Q1W SC PF-06863135 only each cycle will be 3 weeks in duration, and each patient will be treated 3 times during each cycle, unless dose delays or interruptions occur (see Sections 5.5.1 and 5.5.2. If patients are enrolled into Q2W SC dosing cohorts during dose escalation, each cycle will be 4 weeks in duration, and each patient will be treated twice during each cycle. On C1D1 for all patients, and on C0D1 for patients receiving a priming dose, PF-06863135 will be administered on an inpatient basis. On all other days, PF-06863135 will be administered on an outpatient basis).

If patients are enrolled into Q2W SC dosing cohorts during dose escalation, each cycle will be 4 weeks in duration, and each patient will be treated twice during each cycle. On C1D1 for all patients, and on C0D1 for patients receiving a priming dose, PF06863135 will be administered on an inpatient basis. On all other days, PF06863135 will be administered on an outpatient basis.

Details for PF-06863135 injections are provided in the current PF-06863135 IP Manual. The dose level will be assigned by the sponsor (see Section 5.1 Allocation to Treatment). For monotherapy Part 1, all patients should be weighed within 72 hours prior to Day 1 of each cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of PF-06863135 required for dose preparation. If the patient experienced either a weight loss or gain >10% compared to the prior weight used to calculate the initial dose or dose in the previous cycle, the amount of PF-06863135 required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained. Should the institutional policy be such that the dose is required to be calculated if a patient experiences a weight gain of <10%, this will be allowed. Fixed-dosing approach will be applied in dose-finding for combination and also in all expansion parts of the study (See Section 1.2.9.4).

Each patient may receive PF-06863135 until disease progression, unacceptable toxicity, withdrawal of consent, patient no longer willing to participate in trial, or study termination. If a patient has received treatment with Q1W PF-06863135 for at least 6 months, and disease assessments have remained stable over at least 2 months, consideration may be given to increasing dose intervals from weekly to every 2 weeks or once per cycle (only CXD1 dosing and activities applicable) after consultation with sponsor. Cycles would remain the same length with any skipped weekly doses noted. If the patient subsequently begins to have increase of disease burden, dose intervals should return to weekly dosing.

For Parts 1C, 1D, 1E and Part 2 dose expansion: PF-06863135 will be administered as described for monotherapy PF-06863135, and each cycle will be 4 weeks in duration. On C1D1 for all patients and C0D1 for patients receiving a priming dose, PF-06863135 will be administered on an inpatient basis. On all other days, PF-06863135 will be administered on an outpatient basis.

If a patient has received treatment with Q1W PF-06863135 for at least 6 months, and disease assessments have remained stable over at least 2 months, consideration may be given to increasing dose intervals from weekly to every 2 weeks or once per cycle (only CXD1 dosing and activities applicable) after consultation with sponsor. Cycles would remain the same length with any skipped weekly doses noted. For every 2 week dosing, it would be preferable to skip dosing of PF-06863135 on days 8 and 22 of each cycle. If the patient subsequently begins to have increase of disease burden, dose intervals should return to weekly dosing.

5.5. Recommended Dose Modifications

Every effort should be made to administer investigational product on the planned dose and schedule.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications of PF-06863135, lenalidomide, pomalidomide and dexamethasone, may occur in one of three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

In Parts 1E and 2E, if a dose of PF-06863135 is delayed or interrupted, then dexamethasone should not be administered until PF-06863135 administration is restarted.

5.5.1. Dosing Interruptions

Patients experiencing Grade 3 or 4 potentially treatment-related toxicity or intolerable drug-related Grade 2 toxicity despite supportive care should have their treatment interrupted.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in the Dose Delays Section 5.5.2.

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions Section 5.5.3, unless expressly agreed otherwise following discussion between the investigator and the sponsor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >3 weeks, treatment resumption will be decided in consultation with the sponsor.

5.5.2. Dose Delays

Re-treatment following treatment interruption for treatment-related toxicity or at the start of any new cycle should not occur until all of the following parameters have been met:

- ANC $\geq$1,000/mm^3 for PF-06863135, dexamethasone, and lenalidomide; $\geq$500/mm^3 for pomalidomide;
- Platelets count $\geq$25,000/mm^3 for PF-06863135 and dexamethasone; $\geq$30,000/mm^3 for lenalidomide; $\geq$50,000/mm^3 for pomalidomide;
- Non-hematologic toxicities have returned to baseline or Grade $\leq$1 severity (or, at the investigator's discretion, Grade $\leq$2 if not considered a safety risk for the patient).
- Recovery of treatment-emergent peripheral neuropathy to Grade $\leq$1 severity.

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If these conditions are met within 3 weeks of treatment interruption or cycle delay, study treatment may be resumed. Refer to the Dose Reductions Section 5.5.3 for adverse events requiring dose reduction at the time of treatment resumption.

If these conditions are not met, treatment resumption must be delayed up to a maximum of 3 weeks. If patients require discontinuation of study treatment for more than 42 days of Day 1 of the current cycle, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the Sponsor's medical monitor.

If a treatment interruption continues beyond the last day of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

Recommended guidelines for dose delays of PF-06863135 for participants who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV2 infection can be found in Appendix 10.

5.5.3. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the PF-06863135 dose may need to be reduced when treatment is resumed.

No specific dose adjustments for PF-06863135 are recommended for Grade 1/2 treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level of PF-06863135 once recovery to Grade $\leq$1 or baseline is achieved.

Dose reduction of PF-06863135 by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered. Patients enrolled in the first (0.1 μg/kg) cohort will be allowed 1 dose reduction if required. Patients requiring more than 2 dose reductions (or 1 dose reduction for the first cohort) will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor. If dose reduction of PF-06863135 is needed for any patient who receives fixed doses of PF-06863135 (Parts 1C, 1D, 1E, 2A, 2C, 2D, 2E), the next dose level of PF-06863135 will be 25% lower than the current dose level (eg, from 32 mg to 24 mg, or from 24 mg to 16 mg). All dose modifications/adjustments must be clearly documented in the patient's source notes and case report form (CRF).

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intrapatient dose re-escalation is not allowed.

Patients experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved. Patients experiencing a DLT of prolonged myelosuppression (>42 days) may not resume treatment even if adequate recovery is achieved. No dose reductions are planned for patients experiencing toxicities other than those listed as DLTs. However, patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved. Patients whose hematologic indices improve prior to meeting the criteria for prolonged myelosuppression >42 days may resume dosing at the next lower dose level or permanently discontinue from treatment at the discretion of the investigator.

Recommended dose reductions for PF-06863135 are described in Table 5.

Table 5. Dose Modifications for PF-06863135 Product-Related Toxicity and for Peripheral Sensory or Motor Neuropathy***

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic (excluding peripheral neuropathy-see below)	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose by 1 level.*	Permanently discontinue.*
Hematologic except for lymphopenia, which is expected as part of PF-06863135 mechanism of action	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level.** If toxicity reoccurs, dosing may be reduced by 1 dose level. If	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment.** If toxicity reoccurs despite dose reduction, dosing may be reduced by

Table 5. Dose Modifications for PF-06863135 Product-Related Toxicity and for Peripheral Sensory or Motor Neuropathy*

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
			toxicity reoccurs after a maximum of 2 dose level reductions (1 for patients in first cohort), patient may be permanently discontinued from treatment. For platelets, withhold dose if toxicity ≤25,000 mm3 and re-start when platelets have returned to ≥25,000 mm3 or baseline	1 more dose level. If toxicity reoccurs, patient may be permanently discontinued from treatment.
Peripheral sensory or motor neuropathy (all causality) See Section 8.4.4 for recommended work-up.	Continue at the same dose level. Continue to monitor the participant for signs of worsening neuropathy	Withhold dose until resolution to Grade ≤1, then resume at a reduced dose level. Continue to monitor the participants for signs of worsening neuropathy. If Grade ≥2 neuropathy reoccurs, permanently discontinue elranatamab.	Permanently discontinue elranatamab.	Permanently discontinue elranatamab

* Nausea, vomiting, or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification.
** Cycle will not be extended to cover for the missing doses.
*** Dose reductions for lenalidomide should also follow the recommendations in this table.

Doses may be held as needed until toxicity resolution. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator.

Dose modifications for lenalidomide (ie, for neutropenia, thrombocytopenia, renal impairment, grade 3 or 4 toxicities judged to be related to lenalidomide) per manufacturer's guidelines is permitted. Please see, Table 7 and Table 8 hematologic toxicities and renal impairment for dose modifications. Please consult the Revlimid® US package Insert (USPI)

for further details.[30] For Europe, please consult the Revlimid® Summary of Product Characteristics (SPC) for further details.[31] For Canada, please consult the Revlimid® Product Monograph for further details.[32]

Table 6. Lenalidomide Dose Adjustment for Thrombocytopenia

Platelet Count	Recommended Course of Action
• When count first falls to <30,000 mcL. • When count returns to ≥30,000 mcL.	• Interrupt lenalidomide treatment, follow complete blood count (CBC) weekly. • Resume lenalidomide at 10 mg.
• For each subsequent drop in count to <30,000 mcL. • When count returns to ≥30,000 mcL.	• Interrupt lenalidomide treatment. • Resume lenalidomide at the next lower dose level (5 mg) once daily. Do not decrease dose below 5 mg once daily.

Table 7. Lenalidomide Dose Adjustment for Neutropenia

Neutrophil Count	Recommended Course of Action
• When count first falls to <1,000/mcL. • When count returns to ≥1,000/mcL and neutropenia is the only observed toxicity. • When count returns to ≥1,000/mcL and other toxicity is observed.	• Interrupt lenalidomide treatment, start G-CSF treatment, follow CBC weekly. • Resume lenalidomide at 15 mg once daily. • Resume lenalidomide at 10 mg once daily.
• For each subsequent drop in count to <1,000/mcL. • When count returns to ≥1,000/mcL.	• Interrupt lenalidomide treatment. • Resume lenalidomide at the next lower dose level (10 mg or 5 mg) once daily. Do not decrease dose below 5 mg once daily.

Table 8. Lenalidomide Dose Adjustment for Renal Impairment

Category	Renal Function	Dose
Moderate renal impairment	CrCl[a] 30-60 mL/min	10 mg every once daily
Severe renal impairment	CrCl[a] <30 mL/min (not requiring dialysis)	15 mg every other day
End-stage renal disease	CrCl[a] <30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose after dialysis

Key: CrCl = creatinine clearance.
a Estimated by creatinine clearance as calculated by the Cockcroft-Gault equation.

For recommended lenalidomide dose modifications for peripheral neuropathy (all causality), refer to Table 5.

Dose modifications for pomalidomide (ie, for neutropenia, thrombocytopenia, strong CYP1A2 inhibitors, severe renal impairment, or hepatic impairment) per manufacturer's guidelines is permitted. Please see Table 9 hematologic toxicities for dose modifications. Please consult the Pomalyst® US package Insert (USPI) for further details.[34] For Europe, please consult the Imnovid® Summary of Product Characteristics (SPC) for further details.[35] For Canada, please consult the Pomalyst® Product Monograph for further details.[36]

Table 9. Dose Modification Instructions for Pomalidomide for Hematologic Toxicities

Interruption/resumption threshold	Dose Modification
Neutropenia	
ANC* <500 per mcL or Febrile neutropenia (fever ≥ to 38.5°C and ANC <1,000 per mcL) ANC return to ≥500/mcL	Interrupt pomalidomide treatment, follow CBC weekly. Resume pomalidomide at 3 mg daily.
For each subsequent drop <500/mcL Return to ≥500/mcL	Interrupt pomalidomide treatment. Resume pomalidomide at 1 mg less than the previous dose
Thrombocytopenia	
Platelets <25,000/mcL Platelets return to >50,000/mcL	Interrupt pomalidomide treatment, follow CBC weekly. Resume pomalidomide treatment at 3 mg daily.
For each subsequent drop <25,000/mcL Return to more than or equal to 50,000/mcL	Interrupt pomalidomide treatment. Resume pomalidomide at 1 mg less than previous dose.

*Note: ANC = Absolute Neutrophil Count

For other Grade 3 or 4 toxicities (except as noted below), hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician's discretion. For anaphylactic reactions, angioedema, progressive

multifocal leukoencephalopathy (PML), or rash (Grade 4 or blistering), pomalidomide should be permanently discontinued.

To initiate a new cycle of pomalidomide, the neutrophil count must be at least 500 per mcL, the platelet count must be at least 50,000 per mcL. If toxicities occur after dose reductions to 1 mg, then discontinue pomalidomide.

- Dosage Adjustment for Strong CYP1A2 Inhibitors:
  - Avoid concomitant use of pomalidomide with strong inhibitors of CYP1A2. Consider alternative treatments. If a strong CYP1A2 inhibitor must be used, reduce pomalidomide dose by 50%.
- Dosage Adjustment for Patients with Severe Renal Impairment on Hemodialysis:
  - For patients with severe renal impairment requiring dialysis, the recommended starting dose is 3 mg daily (25% dose reduction). Take pomalidomide after completion of dialysis procedure on hemodialysis days.
- Dosage Adjustment for Patients with Hepatic Impairment:
  - For patients with mild or moderate hepatic impairment (Child-Pugh classes A or B), the recommended starting dose is 3 mg daily (25% dose reduction). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose is 2 mg (50% dose reduction).

Dexamethasone will be administered at a dose of 40 mg weekly. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), the dexamethasone dose may be administered at a dose of 20 mg weekly. Dexamethasone may be reduced, if necessary, according to Table 10.

Table 10. Dose Modification Instructions for Dexamethasone Toxicities

CTACAE Category	Toxicity	Dose Modification
Gastrointestinal	Grade 1-2 Dyspepsia, gastric or duodenal ulcer, gastritis requiring medical management	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measure, decrease dexamethasone dose by 50%.
	≥Grade 3 requiring hospitalization or surgery	Hold dexamethasone until symptoms adequately controlled. Restart at 50% of current dose along with concurrent therapy with H2 blockers, sucralfate or omeprazole. If symptoms persist despite above measure, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume

Table 10. Dose Modification Instructions for Dexamethasone Toxicities

CTACAE Category	Toxicity	Dose Modification
Cardiovascular	≥ Grade 3 Edema limiting function and unresponsive to therapy or anasarca	Diuretics as needed and decrease dexamethasone dose by 25%; if edema persists despite above measures, decrease dose to 50% of initial dose; discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction
Neurology/Psychiatric	≥ Grade 2 interfering with function but not interfering with activities of daily living	Hold dexamethasone until symptoms adequately controlled. Restart at 50% of current dose. If symptoms persist despite above measure, discontinue dexamethasone and do not resume
Musculoskeletal	≥ Grade 2 Muscle weakness Symptomatic and interfering with function but not interfering with activities of daily living	Decrease dexamethasone dose by 25%; if weakness persists despite above measures, decrease dose to 50% of initial dose; discontinue dexamethasone and do not resume if symptoms persist despite 50%
Metabolic	≥Grade 3 Hyperglycemia	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measure, decrease dose by 25% decrements until levels are satisfactory

5.5.4. Intra-Patient Dose Escalation for PF-06863135

Once a patient completes their 60 day late toxicity observation period, if the patient did not experience any ≥ Grade 3 drug related toxicities, the patient may escalate to the next higher dose level if the higher dose level is already been declared safe following 60-day late toxicity evaluation, and criteria outlined in Section 3.1.4.1 Criteria for Intrapatient Dose Escalation have been met.

Additional intra-patient dose escalations will also be permitted once additional 60 day late toxicity evaluation has been completed, and if the patient did not experience any ≥ Grade 3 drug related toxicities. No crossover is allowed, however, between monotherapy PF-06863135 and the different combination regimens.

A maintenance dose level will be declared safe following DLT evaluation of patients for a minimum of 60 days. Once a maintenance dose level has been declared safe, patients at lower dose levels who have completed the 60 day late toxicity observation period may escalate to the next higher dose level, if criteria outlined in Section 3.1.4.1 Criteria for Intrapatient Dose Escalation have been met. No crossover is allowed, however, between monotherapy PF-06863135 and the different combination regimens.

5.6. Permanent Discontinuation

The study will stop if all doses explored appear to be overly toxic as determined by study sponsor and investigators. For other sponsor discontinuation criteria, please refer to Section 14. For patient withdrawal criteria, please refer to Section 6.6.

Note that disease progression as determined by laboratory assessments completed within the first cycle cannot be a reason for study withdrawal.

Dose escalation may also stop if:

- The maximum sample size has been achieved;
- Approximately 6-16 patients have been enrolled at a dose that is predicted to be the MTD/MAD;
- All doses explored appear to be overly toxic and the MTD/MAD cannot be determined.

5.7. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

See the IP manual for storage conditions of the product once reconstituted.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage

conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until the Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.8. Investigational and Non-Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational and non-investigational product supplies. All investigational and non-investigational products will be accounted for using a drug accountability form/record.

5.8.1. Destruction of Investigational and Non-Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational and non-investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.9. Concomitant Treatment(s)

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as nondrug interventions received by patients from screening until the end of study visit will be recorded on the CRF.

PF-06863135 has been demonstrated to transiently increase cytokine levels (eg, IL-6) in vivo in monkeys and humans (also demonstrated via in vitro assays) which is expected with CD3-targeted bispecifics. Cytokines have been shown to result in modest inhibition of some cytochrome P450 enzymes. Therefore, treatment with PF-06863135 has a potentialto increase the exposure of concomitant medications that are substrates for these enzymes. Caution should be used upon concomitant use of sensitive substrates of cytochrome P450 enzymes with narrow therapeutic index (eg, CYP3A4: alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus;

CYP2C9: phenytoin, warfarin) especially during the initial treatment cycle. Additional details are provided in Appendix 11.

Lenalidomide when co-administered with digoxin has demonstrated an increase in digoxin C_{max} and AUC_{inf} by 14%.[30] Levels of digoxin for patients receiving both drugs must be monitored in Parts 1C and 2C in accordance with clinical judgment and based on standard clinical practice in patients receiving digoxin. Refer to lenalidomide label regarding drugs that are prohibited for use concomitantly.

Pomalidomide exposure may be increased by strong CYP1A2 inhibitors (eg, ciprofloxacin and fluvoxamine). If co-administration is unavoidable in Parts 1D and 2D, reduce the pomalidomide dose per instructions in Pomalyst label[34] and Section 5.5.3.

Drugs which induce CYP 3A4 enzyme activity (e.g., barbiturates, phenytoin, carbamazepine, rifampin) may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased. Drugs which inhibit CYP 3A4 (e.g., ketoconazole, macrolide antibiotics such as erythromycin) have the potential to result in increased plasma concentrations of corticosteroids. Dexamethasone is a moderate inducer of CYP 3A4. Co-adminstration with other drugs that are metabolized by CYP 3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentration.

All COVID-19 vaccines are permitted and should be recorded as concomitant medications (standard AE collection and reporting processes should be followed). The timing of COVID-19 vaccine administration relative to study intervention is at the discretion of the investigator, although, if possible, it is best to avoid vaccine administration within 48 hours before or after the first and second doses of study intervention.

The administration of drugs known to cause peripheral neuropathy should be carefully considered, and if possible, avoided by the investigator.

5.9.1. Premedication Required for Cytokine Release Syndrome Prophylaxis

For both the priming doses and first full dose (76 mg), administer these medications 60 minutes (±15 minutes) prior to elranatamab dose:

- acetaminophen 650 mg (or paracetamol 500 mg)*
- diphenhydramine 25 mg (or equivalent)*, oral or IV
- dexamethasone 20 mg (or equivalent), oral or IV

* Different but comparable doses due to local strength variations are permissible.

Similar premedications for doses at other time points may be given at the discretion of the investigator.

See Appendix 5 for management of CRS and ICANS.

5.9.2. Other Anti-tumor/Anti-cancer or Experimental Drugs

No additional anti-cancer therapy will be permitted while patients are receiving study treatment. Additionally, the concurrent use of select vitamins or herbal supplements is not permitted. Palliative radiotherapy on study is permitted for the treatment of painful bony lesions provided that the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of PF-06863135 with radiotherapy, PF-06863135 treatment should be interrupted during palliative radiotherapy, stopping 7 days before and resuming treatment after 7 days.

5.9.3. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

Allopurinol/rasburicase may be administered as needed for tumor lysis prophylaxis or treatment.

5.9.4. Cytokine Release Syndrome

Symptoms associated with CRS vary greatly and may be difficult to distinguish from other conditions. The more common symptoms include fever, nausea, headache, tachycardia, hypotension, rash and shortness of breath. The severity of symptoms can be mild to life threatening and thus there should be a high suspicion for CRS if these symptoms occur. If CRS is suspected, cytokines will be analyzed at central laboratories to determine if cytokine elevation consistent with CRS is observed (see Section 7.1.3). The severity of cytokine release syndrome (CRS) will be assessed according to the modified grading described by Lee et al. in 2014[2] as well as the more recent consensus grading from the American Society for Transplantation and Cellular Therapy (ASTCT)[3] but only ASTCT will be used for management of CRS[38,39] (Appendix 5).

For CRS DLT criteria, please see Section 3.2.

5.9.5. Immune Effector Cell-Associated Neurotoxicity Syndrome ICANS

ICANS is defined as "a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.[3] It has been observed following administration of some chimeric antibody receptor (CAR) T cells and bispecific antibodies and can occur independently of CRS. The severity of ICANS should be graded according to the ASTCT consensus criteria,[3] and management guidelines are provided in Appendix 5.[38,39]

5.9.6. Tumor Lysis Syndrome (TLS)

Tumor lysis is a group of metabolic complications that can occur after treatment of cancer. Tumor lysis syndrome (TLS) occurs when tumor cells release their contents into the bloodstream, either spontaneously or in response to therapy, leading to the characteristic findings of hyperuricemia, hyperkalemia, hypophosphatemia, and hypocalcemia. These electrolyte and metabolic disturbances can progress to clinical toxic effects, including renal insufficiency, cardiac arrhythmias, seizures, and death due to multi-organ failure. The incidence and severity of the TLS depend on the cancer mass, the potential for lysis of tumor cells, the characteristics of the patient, and supportive care.

Optimal management of TLS should involve preservation of renal function. Management should also include prevention of dysrhythmias and neuromuscular irritability. All patients who are at risk for TLS should receive intravenous hydration to rapidly improve renal perfusion and glomerular filtration and to minimize acidosis. Reducing the level of uric acid, with the use of allopurinol and particularly with the use of rasburicase, can preserve or improve renal function and reduce serum phosphorus levels as a secondary beneficial effect.

Hyperkalemia remains the most dangerous component of TLS because it can cause sudden death due to cardiac dysrhythmia. Patients should limit potassium and phosphorus intake during the risk period for TLS. Frequent measurement of potassium levels (every 4 to 6 hours), continuous cardiac monitoring, and the administration of oral sodium polystyrene sulfonate are recommended in patients with TLS and acute kidney injury. Hypocalcaemia can also lead to life-threatening dysrhythmias and neuromuscular irritability; controlling the serum phosphorus level may prevent hypocalcemia. Symptomatic hypocalcemia should be treated with calcium at the lowest dose required to relieve symptoms. Hypocalcemia not accompanied by signs or symptoms does not require treatment.

5.9.7. Infusion Related Reactions (IRR)

Following the first infusion of some monoclonal antibody therapeutics, some patients experience fever, headache, nausea, vomiting or hypotension. These adverse events (AEs) are generally ascribed to lysis of cellular targets, cytokine release, or complement activation.

Infusion related reaction is characterized by fever and chills, and less commonly hypotension, either experienced by a particular patient or if seen in other patients, pretreatment medication should be administered to reduce the incidence and severity. A regimen is suggested here; however, if local standard of care is a different regimen, this will be allowed. In cases of infusion reactions, patients should be pretreated with acetaminophen and diphenhydramine (or other antihistamine) approximately 0.5 to 2 hours before investigational product administration. The pretreatment medications will not be supplied by Pfizer. Suggested starting doses are 650 to 1000 mg acetaminophen and 50 mg diphenhydramine (or equivalent for other antihistamines) either IV or oral. Two (2) additional doses of acetaminophen may be administered approximately every 4-6 hours after the initial pretreatment or as needed.

Detailed guidance on treatment, dose interruptions and potential retreatment is provided in Appendix 7.

5.9.8. Injection Site Reactions (ISR)

ISR is a type of hypersensitivity reaction that may be immediate, although it usually appears within 24-48 hrs after injection. ISR, by definition, includes the following erythema, pruritus, pain, inflammation, rash, induration, itching and edema at the injection site. To evaluate ISRs, site tolerability assessments will be performed per SCHEDULE OF ACTIVITIES .

5.9.9. Hypersensitivity Types 1 and 3

Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein. Immune complex mediated Type 3 hypersensitivity reactions are similar to the adverse events (AEs) of Type 1 reactions but are likely to be delayed from the time of infusion and may include symptoms such as rash, urticaria, polyarthritis, myalgia, polysynovitis, fever, and, if severe, glomerulonephritis.

All patients should be closely observed while receiving investigational product infusions and monitoring for clinical signs of a systemic reaction will continue thereafter for clinical signs of allergic reactions/hypersensitivity.

In the case of a hypersensitivity reaction, the subject will be treated symptomatically with supportive care, further monitoring, and treatment with anti-histamines and/or corticosteroids. Study infusions may be stopped and the subject will be followed until the end of the study.

Detailed guidance on treatment, dose interruptions and potential retreatment is provided in Appendix 7.

5.9.10. Extravasation

In the event of extravasation, infusion should be stopped immediately and the investigator needs to be consulted immediately. Treatment of extravasation should follow local standard of care.

5.9.11. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during Cycle 1, but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology guidelines.[46]

Use of erythropoietin growth factors is allowed as needed to treat anemia. Erythropoietic agents or other agents that may increase the risk of thrombosis should be used with caution after making a benefit-risk assessment in patients receiving lenalidomide.

5.9.12. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is permitted in the first cycle. Primary prophylaxis in subsequent cycles is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor approval assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatment(s) Section 5.9.

5.9.13. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatment(s) Section 5.9.

5.9.14. Corticosteroids

Chronic systemic corticosteroid use for palliative or supportive purposes, except as specified in the protocol, is permitted only following discussion and agreement between the investigator and sponsor. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

5.9.15. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06863135 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06863135 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-06863135 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.9.16. Transfusion Support

Primary prophylactic use of transfusion support for anemia is allowed to treat anemia, as indicated by the current American Society of Clinical Oncology and American Association of Blood Banks (AABB) guidelines.[47]

Primary prophylactic use of transfusion support for thrombocytopenia is allowed during screening if the transfusion is completed prior to planned study treatment start. Primary prophylactic use of transfusion support for thrombocytopenia is allowed to treat thrombocytopenia, as indicated by the current American Society of Clinical Oncology.[48]

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see the SCHEDULE OF ACTIVITIES and Assessments Section 7.

All patients being considered for the study and eligible for screening must sign an informed consent for the study before completing any study-specific procedures. A patient identification number will be assigned. The investigator (or appropriate delegate at the site)

will obtain informed consent from each patient in accordance with the procedures described in the SCHEDULE OF ACTIVITIES and on Informed Consent.

All patients will be screened within 28 days prior to administration of the first dose to confirm that they meet the patient selection criteria for the study.

The required screening assessments and laboratory tests are summarized in the SCHEDULE OF ACTIVITIES and Section 7.1.3. Following completion of the screening assessments and confirmation of eligibility, patients may be enrolled.

6.2. Study Period

For the treatment period procedures, see the SCHEDULE OF ACTIVITIES and Section 7.

6.3. Follow-up

For follow-up procedures see the SCHEDULE OF ACTIVITIES and Assessments Section 7.

At least 28 calendar days, and no more than 35 calendar days, after discontinuation of treatment, patients will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. Patients found to have ADA at their final study visit and an ongoing AE possibly related to ADA will be asked to return to the clinic for ADA assessment at approximately 3 month intervals (if feasible given the underlying disease) until the adverse event or its sequelae return to baseline or stabilize at a level acceptable to the investigator and sponsor. If the patient completes the 1 month follow up visit prior to completion of the 60 day long term DLT observation period, a follow up phone call will be completed on Day 60 and no more than Day 65.

Following discontinuation of study treatment (unless patients are lost to follow up, consent is withdrawn, or study is discontinued by the sponsor), survival status will be collected by telephone every 3 months until death, or up to approximately 30 months after first treatment of the last patient, whichever comes first. Subsequent anti-cancer therapies and relevant transplant information will also be collected.

6.4. End of Treatment

End of treatment is defined as the date in which the patient completes the end of treatment (EOT) visit (unless patients are lost to follow up, consent is withdrawn, or study is discontinued by the sponsor). Note that the patient may continue on the study for their follow up and survival follow up visits.

6.5. End of Study

End of study for all patients will be death or up to approximately 30 months after last patient first dose, followed by any required follow-up visits.

6.6. Patient Withdrawal

Withdrawal of consent:

Patients who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him or her or persons previously authorized by the patient to provide this information. Patients should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate case report form (CRF) page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the patient to 1 registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a sponsor -retained third-party representative to assist site staff with obtaining the patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the patient's medical records.

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the patient to comply with the protocol -required schedule of study visits or procedures at a given investigator site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression (note that disease progression as determined by laboratory assessments completed within the first cycle cannot be a reason for study withdrawal);

- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

Note that discontinuation of study treatment does not represent withdrawal from the study. If study treatment is definitively discontinued, the participant will remain in the study If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed for survival unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study-specific evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol -required tests and procedures are completed as described. However, it is anticipated that from time to time there may be

circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol -required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety Assessment

Safety assessments will include collection of AEs, serious adverse events (SAEs), vital signs and physical examination, electrocardiogram (ECG [12-lead]), laboratory assessments, including pregnancy tests and verification of concomitant treatments. See Appendix 10 for alternative measure guidelines due to COVID-19.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening and on Day 1 of each cycle.

A negative pregnancy test result is required before the patient may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

In addition, for Parts 1C, 1D, 2C, and 2D, pregnancy testing should occur at C1D1 and weekly during first cycle, and if menstrual cycles are irregular should occur every 2 weeks thereafter. In addition, pregnancy prevention programs (PPP) for lenalidomide and pomalidomide must be followed.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the National Cancer Institute [NCI] CTCAE version 4.03) timing, seriousness, and relatedness. The severity of cytokine release syndrome (CRS) will be assessed according to the grading described by Lee et al. (2014 and 2019,[2,3] see Appendix 5).

Patients who have undergone allogeneic stem cell transplant >100 days before the first dose of study treatment will be monitored for chronic graft-versus-host disease (GvHD) according to institutional guidelines.

7.1.3. Laboratory Safety Assessment

Hematology, blood chemistry, viral, coagulation and pregnancy assessments will be drawn at the time points described in the SCHEDULE OF ACTIVITIES and analyzed at local laboratories. If CRS is suspected, an ad hoc cytokine sample will be collected and evaluated centrally (See Section 7.5.4). Should the site require cytokine information for patient management, the site will have the option of collecting an additional sample for local analysis. If a sample for pharmacodynamic cytokine panel evaluation is due to be collected on the same day as a suspected CRS event occurs, then an ad hoc sample for central analysis is not required/collected. However, an ad hoc sample for local analysis may still be collected for patient management. Local cytokine analysis may include interleukin (IL)-6, IL-1β, tumor necrosis factor –alpha (TNFα), and/or IL-10 or other cytokines that will help the investigator with patient management.

If TLS is suspected, a sub-set of chemistry tests will be completed (ie, total calcium, creatinine, phosphorus or phosphate, potassium and uric acid) to confirm diagnosis if the tests were not performed within the last 24 hrs.

Table 11. Safety Laboratory Tests

Hematology	Chemistry	Viral	Coagulation	Urinalysis	Pregnancy Test	Ad hoc Central Lab Cytokine Analysis†
Hemoglobin	ALT	HBsAg and HBcAb) with reflexive DNA testing	PT or INR	Urine dipstick for urine protein: If positive, collect 24-hr and microscopic (Reflex Testing)	For female patients of childbearing potential, serum.	IL-6, IL-10, IL-2, sIL2R, IL-12, IL-4, IL-5, IL--13, IL-17, IL-1b, IL-8, IFNγ, and TNF-α
Platelets	AST	HCV antibody with reflexive RNA testing.	PTT			
WBC	bicarbonate					
Absolute Neutrophils	CRP					
Absolute Lymphocytes	Alk Phos					
Absolute Monocytes	Sodium					
Absolute Eosinophils	Potassium					**Optional Ad hoc Local Lab Cytokine Analysis†**
Absolute Basophils	Magnesium			Urine dipstick for urine blood: If positive, collect a microscopic (Reflex Testing)		
	Chloride					IL-6
	Total calcium					IL-1β
	Total bilirubin***					IL-10
	Total Protein					TNFα
	BUN or Urea					Other cytokines
	Creatinine					

Table 11. Safety Laboratory Tests

Hematology	Chemistry	Viral	Coagulation	Urinalysis	Pregnancy Test	Ad hoc Central Lab Cytokine Analysis†
	Uric Acid					
	Glucose (nonfasted)					
	LDH					
	Albumin					
	Phosphorus or Phosphate					

Abbreviations: Alkaline phosphatase = Alk Phos; alanine Aminotransferase = ALT; aspartate aminotransferase = AST; blood urea nitrogen = BUN; C-reactive protein = CRP; hepatitis B = HBV; hepatitis C = HCV; interferon-gamma = IFNγ; IL = interleukin; International Normalized = INR; lactate dehydrogenase = LDH; partial thromboplastin time = PTT;; TNFα = Tumor necrosis factor- alpha; white blood cells=WBC.

*** For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

† Adhoc cytokines for central lab evaluation will be collected if CRS is suspected and coincides with a day pharmacodynamic samples are not collected per the Schedule of Activities. Local lab evaluation of cytokine is only required if the site require this information for patient management.

7.1.4. Vital Signs and Physical Examination

Patients will have a physical examination to include neurological assessment, weight, vital signs, pulse rate, assessment of ECOG performance status (Appendix 4) and height; height will be measured at screening only.

7.1.5. (12-Lead) Electrocardiogram

Electrocardiogram (ECG): Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for ECGs collected in Cycles 1 and 2. Single ECGs will be collected at screening and from Cycle 3 onwards. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point in Cycles 1 and 2 (see the SCHEDULE OF ACTIVITIES), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 500 msec. If QTcF interval reverts to less than ≤480 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec the investigational product will be held until the QTcF interval decreases to 480 msec. Patients will then restart the

investigational product at the next lowest dose level. If the QTcF interval has still not decreased to ≤480 msec after 2 weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study unless the investigator believes that it is in the best interest of the patient to continue and it has been agreed upon after discussion with the sponsor. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If a patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

When matched with PK sampling, the ECG should be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections overrides the timing of the ECG collections).

7.1.6. Echocardiogram (Echo) or Multigated Acquisition Scan (MUGA)

Echocardiogram (Echo) or multigated acquisition scan (MUGA) will be evaluated in patients with previous history of cardiac events. For these patients, an echocardiogram or MUGA will be performed at screening, when clinically indicated, and at the end of treatment (EOT) visit. The following parameters will be evaluated: ventricular function (including left ventricular ejection fraction [LVEF], end systolic volume [ESV] and end diastolic volume [EDV]), qualitative evaluation of chamber size, and wall motion. A Doppler examination will be completed and should include an assessment of mitral valve, atria, right ventricle, tricuspid valve, aortic valve, pulmonic valve, great vessels, and pericardium.

7.1.7. Local Site Injection Tolerability Assessment (SC Only)

Assessments made of the injection sites in the abdominal fat fold to monitor local tolerability to PF-06863135 SC injections will be performed 1 to 4 hours following study drug administration, as per the SCHEDULE OF ACTIVITIES . If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted. Refer to Appendix 9 for more details.

Site tolerability assessments should continue at regularly scheduled visits if injection site pain or injection site reaction (ISR) characteristics continue to persist. The assessments should continue until the symptoms resolve. The injection sites will be assessed for erythema, induration, ecchymosis, injection site pain, injection site pruritus, or other observed characteristics after study drug dosing. The diameter of the affected area will be measured and the condition of the injection site will be recorded on the SC Injection Site Assessment CRF. Any observed abnormality at the injection site will be judged by the investigator to determine whether a corresponding AE should be reported. ISRs should be immediately photographed in color, with scaled ruler placed by the reaction, and these

photographs should be included in the patient's source documentation. When appropriate, at the discretion of the investigator, a patient with an ISR may be referred for a dermatological consultation and skin biopsy may be obtained for future examination of the ISR. The dermatology consultation is expected to take place at the dermatologist's practice location, or may occur within the same institution where this study is conducted.

7.2. Disease Response Assessment

Anti-cancer assessments and response will be assessed according to the International Myeloma Working Group (IMWG) response criteria for multiple myeloma[4,5] (MM, See Appendix 2). Disease response assessment should be continued to end of treatment if end of treatment reason is disease progression. Patients that end treatment without progression and remain in follow-up on study should continue to have disease response assessments that are obtained per standard of care reported until disease progression, start of new anti-myeloma therapy, or end of follow-up on study with response assessments recorded in the study database.

7.2.1. Laboratory Evaluation of Disease Response

Laboratory tests for disease response will be used to explore early signals of anti-cancer activity (see Appendix 2).[4,5] These laboratory tests will be completed per SCHEDULE OF ACTIVITIES, including assessments at suspected CR, whenever disease progression is suspected (eg, symptomatic deterioration), and at withdrawal from treatment if not done in the previous 4 weeks. For patients scheduled to be dose escalated, samples will also be collected within 1 week before the planned start of the escalated dose. Assessments will include:

- Serum protein electrophoresis (SPEP) for the measurement of serum albumin and M-proteins (alpha1 globulins, alpha2 globulins, beta1 globulins, beta2 globulins [beta globulins if lab is unable to separate beta1 and beta2 globulins], and/or gamma globulins).

- Serum immunofixation electrophoresis (SIFE) for definitive identification of specific M-proteins (including immunoglobulin [Ig]G, IgA, IgM, and two light chains kappa and lamda). SIFE will only be completed at baseline when electrophoresis shows no measurable protein at suspected CR, and at suspected progression (clinical or biochemical).

- 24 hr urine protein electrophoresis (UPEP) for the measurement of urine albumin and M- proteins (alpha1 globulins, alpha2 globulins, beta1 globulins, beta2 globulins, [beta globulins if lab is unable to separate beta1 and beta2 globulins], and/or gamma globulins).

- 24 hr urine immunofixation electrophoresis (UIFE) for definitive identification of specific M-proteins (including IgG, IgA, IgM, and two light chains kappa and lamda). UIFE will only be completed at baseline when electrophoresis shows no measurable protein at suspected CR, and at suspected progression (clinical or biochemical).

- Involved and uninvolved serum free light chain analysis (FLC) only when both serum and urine M-components are deemed non-measurable (including at suspected CR). Serum free kappa, free lambda and free kappa/lambda ratio should be recorded.

    - If patients were treated with daratumumab less than 114 days prior to planned treatment day, daratumumab will interfere with SPEP, UPEP, SIFE and UIFE assays. Therefore, for these patients, FLC assay should be completed at screening, C1D1, and all subsequent disease assessments. In these patients who previously received daratumumab serum and urine M-spike if measurable at baseline in these patients should also be followed at the same timepoints as FLC with the most representative marker of disease status used for determination IMWG assessment.

- Beta-2 microglobulin. This will be collected on the first day of treatment.

All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. In patients with two M-protein bands at the start of therapy, unless the second band is due to daratumumab or other therapeutic mAb interference, the sum of the two spikes should be used for monitoring of disease. When a complete response (CR), or a clinical or biochemical progression is suspected, SPEP, serum SIFE, UPEP, UIFE and FLC tests will be repeated within 1 to 4 weeks.

Note that if a patient had measurable serum or urine M-spike at baseline, unless the band is due to daratumumab or measurement of M-spike is confounded by the presence of daratumumab or other therapeutic mAb, progression cannot be defined by increases in serum FLC alone. Serum FLC levels should only be used for response assessment when both the serum and urine M-component levels are deemed not measurable or uninterpretable. Furthermore, careful attention should be given to new positive immunofixation results appearing in patients who have achieved a CR, when the isotype is different. This may represent oligoclonal immune reconstitution and should not be confused with relapse; these bands typically disappear over time.

7.2.2. Bone Marrow Plasma Cell Evaluation and Bone Marrow Sample Collection

Bone marrow evaluation of plasma cells in bone marrow aspirate and/or bone marrow biopsies will be performed to follow disease response.

Unilateral bone marrow aspirate samples will be collected and the percentage of plasma cells will be evaluated at the following times:

a. First pre-dose first day of study treatment or up to 7 days before study treatment);

b. At 1 month after C1D1 ±7 days;

c. At 3 months after C1D1 ±7 days;

d. When subject is found immunofixation negative in both serum and urine to confirm any complete response (CR);

e. At time of suspected disease progression (optional);

f. Within 1 week prior to escalating to the next higher dose level cohort following 60-day late toxicity evaluation (unless the investigator assesses that there in an unjustifiable risk for it and/or the patient refuses to undergo a bone marrow procedure; if a bone marrow aspirate or biopsy was performed within the past 4 weeks prior to planned start of escalated dose, only disease staging lab tests must be performed);

g. At 9 months after C1D1 and every 6 months thereafter unless a plateau or CR is observed. For patients who experience a plateau or CR, additional samples at 9 months after C1D1 and onwards will be optional. A ±14 day window applies for these collections.

Bone marrow biopsies will also be collected and the percentage of plasma cells within the biopsy samples will also be evaluated at the following times. In case of suspected stringent Complete Response (sCR), the presence/absence of clonal cells on immunohistochemistry should also be evaluated.

a. First day of study treatment (or up to 7 days before study treatment);

b. At 1 month after C1D1 ±7 days;

c. At 3 months (optional) after C1D1 ±7 days;

d. At 9 months ± 14 days (optional) after C1D1 and every 6 months ±14 days thereafter (optional);

e. At suspected stringent Complete Response (sCR);

f. At time of suspected disease progression (optional).

Assessments should be fixed according to the calendar, regardless of treatment delays. When bone marrow plasma cell infiltration is assessed by both bone marrow aspirate and by bone marrow biopsy, the highest value of bone marrow plasma cell infiltration should be utilized for response evaluation.

The same bone marrow location used for characterization at baseline should be employed in post-baseline bone marrow sampling if clinically feasible.

When bone marrow aspirate and biopsy samples are taken for disease response evaluation, samples for biomarker analysis will also be acquired (see Bone Marrow Biomarkers Section 7.5.1). In addition, if a subject is immunofixation negative in both serum and urine

and flow cytometry is not available, biopsy sample will be required for IHC staining to assess clonality.

Bone marrow aspirates will also be evaluated centrally for minimal residual disease (MRD, see Appendix 3)[5] using a next generation sequencing (NGS) assay when a patient is in suspected CR or actual CR. Bone marrow aspirates will be collected following the sample collection schedule described in Schedule of Activities A, B, and C. A C1D1 (patients without priming dose) or C0D1 (patients with priming dose) bone marrow aspirate must also be collected and submitted for all patients as the baseline reference of the NGS MRD test. Samples for MRD assessments should be aliquoted from the first bone marrow aspirate pull. Local MRD testing is not encouraged. In the case that MRD assessment is performed locally using an analytically validated flow cytometry MRD assay that meets the IMWG sensitivity criteria (i.e. sensitivity of one in 10^5 nucleated cells), results of such test should be provided to the sponsor by recording in the study database. NGS MRD testing should not be performed locally..

7.2.3. Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/Computed Tomography (CT) Imaging

Fluorodeoxyglucose-PET/CT (^{18}F-FDG-PET/CT) imaging will be used to explore early signals of anti-cancer activity. FDG-PET/CT is a functional imaging method in which the uptake of 18F-FDG by cells reflects the tissue uptake of glucose, thus revealing specific types of tissue metabolism. In MM, functional imaging on hybrid scanners (combination of PET and CT imaging) rather than on PET scanners alone are required. The association of abnormal FDG uptake provided by PET imaging and the assessment of bone structure provided by CT imaging leads to an optimal evaluation of disease.

Imaging studies will be collected per SCHEDULE OF ACTIVITIES. For all patients, images are required at screening, suspected CR, when disease progression is suspected (eg, symptomatic deterioration), end of treatment visit (if not done in previous 4 weeks) and when otherwise clinically indicated. In patients with measurable target lesions at screening, images are required at 1, 3, and 9 months after C1D1 and every 6 months thereafter.

The screening PET/CT will be used to determine evaluable target lesions for each patient. Tumor background ratios (TBRs) and development of new sites of abnormality will be recorded.

If imaging is used in disease assessment, the same imaging technique used to characterize each identified and reported lesion at baseline will be employed in post-baseline disease assessments. Any soft tissue plasmacytoma documented at baseline must undergo serial monitoring; otherwise, the patient will be classified as unevaluable. Plasmacytoma that has been irradiated will not be suitable for response assessment; however, it must be monitored for progressive disease.

Radiographic studies are not required to satisfy response and MRD requirements, except if CR or imaging MRD -negative status is suspected (see Appendix 3).

Disease response assessments will be based upon IMWG criteria[4,5] (see Appendix 2).

All patients' files and radiologic images and pathology samples must be available for source verification and for potential peer review or independent central review.

Radiographic assessments obtained per the patient's standard of care prior to enrollment into the study do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 28 days before start of study treatment, (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

Note: For sites in Germany, only MRI is allowed to be used as imaging modality for participants with extramedullary disease.

7.3. Pharmacokinetics Assessments

Blood samples for the analysis of PF-06863135 concentrations will be collected into appropriately labeled tubes at the times specified in the SCHEDULE OF ACTIVITIES of the protocol. If CRS is suspected, and if a PK sample is not already scheduled to be taken (eg, from Cycle 3 onwards), a PK sample should also be taken. For each analysis, approximately 5 mL of blood samples will be collected to provide approximately 2 mL serum. The PK sampling schedule may be modified based on emerging PK data. Blood samples (approximately 3 mL) to provide approximately 1.5 mL plasma for the analysis of lenalidomide, pomalidomide, and dexamethasone concentrations will be collected in Parts 1C and 2C, Parts 1D and 2D, and Parts 1E and 2E, respectively, of the study as outlined in the SCHEDULE OF ACTIVITIES.

In addition to samples collected at the scheduled times, an additional blood sample for PF-06863135 should be collected from patients experiencing unexpected and/or serious AEs and the date and time of blood sample collection and of last dosing prior to PK collection should be documented in the CRF. Where noted in the SCHEDULE OF ACTIVITIES, blood samples for PF-06863135 concentrations will be collected at approximately the same time as other assessments such as pharmacodynamic samples whenever possible.

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. All blood samples should be taken from the contralateral infusion arm on dosing days. However, the exact time of the sample collection will always be noted on the CRF. Samples obtained within the specified visit window will be not be captured as a protocol deviation. The 2 hr samples should be collected immediately before the infusion ends (not more than 15 minutes prior) from the contra-lateral arm of the infusion. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor. Additional instructions for sample collection, processing, storage and shipping will be provided in the lab manual.

PK samples will be assayed for PF-06863135, lenalidomide, and pomalidomide using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

As part of understanding the pharmacokinetics of the investigational product samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the clinical study report.

7.4. Immunogenicity Analyses

Bioanalysis to assess for anti-drug (PF-06863135) antibodies (ADA) will be performed. Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs). All samples that are positive in a screening assay will be further characterized in terms of antibody specificity. A tiered approach to screening, confirmation and titer/quantitation will be utilized. A screening assay with competitive confirmatory steps followed by a titer assay will be used. Samples may also be analyzed in neutralizing antibody (NAb) assays. Patients found to have anti-drug antibodies at their final study visit and an ongoing AE possibly related to ADA will be asked to return to the clinic for ADA and drug concentration blood sampling at approximately 3 month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.

Blood samples (approximately 5 mL) to provide approximately 1 mL of serum each for ADA and NAb against PF-06863135 analysis will be collected into appropriately labeled tubes at times specified in the schedule of activities of this protocol. Additional instructions for sample collection, processing, storage, and shipping will be provided in the lab manual.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the immunogenicity of the investigational product, samples may be used for evaluation of the bioanalytical method and/or additional characterization of an observed immunogenicity response. These data will be used for internal exploratory purposes and will not be included in the clinical study report (CSR). Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.5. Biomarker and Pharmacodynamic Assessments

One of the key elements of this study is the possibility to evaluate potential molecular targets that could be modified by PF-06863135, as a monotherapy and in combination. Tissue

samples (including but not limited to bone marrow biopsy, bone marrow aspirate, peripheral blood, serum and plasma) will be collected before and after PF-06863135 dosing for biomarker evaluation and pharmacodynamic assessments. Samples obtained pre and post PF-06863135 administration will be mandatory for all patients (except for bone marrow biopsy samples collected at 1, 3 and 9 months after C1D1(optional) and every 6 months thereafter (optional), or for bone marrow aspirate samples from 9 months after C1D1 and every 6 months thereafter for patients who experience a plateau or CR). If the collection of a bone marrow biopsy is not required for disease response assessment, and the investigator determines that the risk associated with the bone marrow biopsy is not appropriate for a research setting eg, based on complications during a previous procedure, after consultation with the sponsor's medical monitor, the collection of any impending bone marrow biopsies may be omitted.

Table 12 summarizes representative assays to be used and the sample source. Refer to the SCHEDULE OF ACTIVITIES for details pertaining to specific days and times of sample collection and to the Lab Manual for details of sample preparation, storage, and shipment. The biomarker studies will be used to help understand the mechanism of action of PF-06863135 alone and in combination as well as potential mechanisms of resistance. The studies may help in the future development of PF-06863135.

Table 12. Biomarker Assays and Sample Sources

Biomarker	Matrix	Assay
Soluble immune factors	Serum	Immunoassay
Soluble BCMA/related factors	Plasma	Mass spectrometry
BCMA expression	BM aspirate	Flow cytometry
	BM biopsy	IHC
TBNK	Whole blood	Flow cytometry
	BM aspirate	Flow cytometry
Immune cell phenotyping	Whole blood	Flow Cytometry
	BM aspirate	Flow Cytometry
	BM biopsy	IHC
RNA profiling	BM aspirate and/or biopsy (possible)	RNA Sequencing
T-cell repertoire analysis	Whole blood	DNA Sequencing
	BM aspirate and/or Biopsy (possible)	DNA Sequencing

Abbreviations: BCMA = B-cell maturation antigen; BM = bone marrow; deoxyribonucleic acid = DNA; T, B, and NK cells = TBNK

7.5.1. Bone Marrow Biomarkers

Patients will be required to provide bone marrow biopsy and aspirate samples for biomarker analysis at times specified in the SCHEDULE OF ACTIVITIES (see also Section 7.2.2 Bone Marrow Evaluation). When bone marrow aspirate and biopsy samples are taken for disease response evaluation, samples for biomarker analysis will also be acquired. This includes bone marrow taken following a CR, sCR or following disease progression.

Analyses will be conducted at flow cytometry and IHC reference labs to assess target expression and enumeration and phenotyping of plasma cells, infiltrating T-cell subsets and additional immune cells. Further IHC, immunofluorescence or multiplex imaging assays for additional immune cell populations and/or immune activation and regulation markers, and/or epigenetic assays for immune cell quantification may be performed to assess additional pharmacodynamic effects, if biopsy materials suffice. Tumor tissue may also be submitted to RNA, T-cell receptor (TCR), and other molecular profiling of drug response by nucleotide sequencing.

Instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.

7.5.2. Whole Blood Pharmacodynamic Markers

Whole blood samples for circulating T, B, NK lymphocyte assay (TBNK), and T-cell immunophenotyping will be collected at times specified in the SCHEDULE OF ACTIVITIES of this protocol. The TBNK assay determines the absolute counts and percentages for T, B, NK lymphocyte populations as well as CD4+ and CD8+ T-cell subset ratios in peripheral blood. T-cell immunophenotyping will use multiparameter flow cytometry to evaluate markers such as proliferation and survival, activation, and exhaustion in CD4+ and CD8+ naïve and memory T-cell subsets.

Whole blood samples for exploratory molecular analysis and biobanking will be collected at times specified in the SCHEDULE OF ACTIVITIES of this protocol.

Instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.

Samples may be used for flow assay development. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.5.3. Shipment of Pharmacodynamic Samples

The shipment address and assay lab contact information are provided in the laboratory manual.

7.5.4. Cytokine Assessments

Samples will be collected for central evaluation of cytokines at the time points specified in the SCHEDULE OF ACTIVITIES and Section 7.1.3. Instructions for sample collection,

processing, storage and shipment will be provided in the study manual. All samples will be analyzed centrally. If CRS is suspected and coincides with a day pharmacodynamic samples are not collected per the Schedule of Activities, an ad hoc cytokine sample should be collected (see Section 7.1.3 Laboratory Safety Assessments). In addition, should the site require cytokine information for patient management, the site will have the option of collecting an additional sample for local analysis.

7.5.5. Soluble BCMA Assessments

Whole blood samples (approximately 3 mL) to provide approximately 1 mL plasma for soluble BCMA assessment will be collected at the times specified in the SCHEDULE OF ACTIVITIES of this protocol. An additional soluble BCMA/other factor sample should also be taken if CRS is suspected, and a sample is not already scheduled to be taken (eg, from Cycle 3 onwards). Instructions for sample collection, processing, storage and shipment will be provided in the study manual.

Soluble BCMA levels will be determined by a mass spectrometry assay, and samples may be used for further evaluation of the bioanalytical method, as well as for other internal exploratory purposes including determination of related soluble factors such as A Proliferation-Inducing Ligand (APRIL). These data will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.6. Pharmacogenomics

7.6.1. Genotyping Analysis

Blood samples for genotyping may be examined to assess the impact of allelic variants of genes proposed to impact response to PF-06863135, as well as mechanisms of action and/ or resistance. Additionally, these samples may also be used for retrospective evaluation of additional genetic variants associated with variation in PK or to explore AEs should these be observed. Samples will be retained for a period of up to 3 years after regulatory approval.

A 4-mL blood sample will be collected from each patient into a plastic dipotassium edetic acid ethylenediaminetetraacetic acid (K_2EDTA) tube at times specified in the SCHEDULE OF ACTIVITIES section of the protocol.

Samples will be analyzed using a non-characterized assay (non-validated). These data will be used for internal exploratory purposes and will not be included in the CSR.

The pharmacogenomic (PGx) samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PGx processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

7.6.2. Genetic Analysis

Bone marrow aspirates taken before the start of study treatment will be evaluated at local lab for t(4;14)(p16;q32), t(14;16)(q32;q23), 17p13 deletions, t(11;14)(q13;q32), chromosome 13 deletion, ploidy category, and chromosome 1 abnormalities. If some of these cytogenetic assessments cannot be done, site should provide patient's most recent cytogenetic testing results and enter into eCRF. Samples may be taken up to 7 days before the start of study treatment.

7.7. Banked Biospecimens

Banked biospecimens will be collected from patients for exploratory research relating to the drug response and MM. These collections are not typically associated with a planned assessment described in the protocol. They will be handled in a manner that protects each patient's privacy and confidentiality. Banked biospecimens will be assigned the patient's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the patient's ID and the patient's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also post-marketing research. Patients may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses.

Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen **Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole-blood collection optimized for DNA analysis)** will be collected at the time specified in the SCHEDULE OF ACTIVITIES section of the protocol to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response and MM. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

The banked biospecimens will be collected from all patients unless prohibited by local regulations or IRB/EC decision.

It is possible that the use of these biospecimens may result in commercially viable products. Patients will be advised in the informed consent document that they will not be compensated in this event.

7.7.1. Additional Research

Unless prohibited by local regulations or IRB/EC decision, patients will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Banked Biospecimens Section 7.7 will be used. Patients may still participate in the study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: 1) SAEs; 2) non-serious adverse events (AEs); and 3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the clinical trial serious adverse event (CT SAE) Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately,

irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events Section 8.2.3 below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events

See also the Patient Withdrawal Section 6.6.

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 90 calendar days after the last administration of PF-06863135. If the 1-month follow up visit is completed before the 60 day late toxicity evaluation period is completed, the AE/SAE collection period will be extended until the late toxicity evaluation is completed.

For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a patient during the active collection period, which begins after obtaining informed consent as described in Section 8.1.4, will be recorded on the AE section of the CRF. Any signs and symptoms entirely due to CRS (eg, fever, hypoxia, hypotension) should be recorded within the CRS assessment CRF. A single term of Cytokine release syndrome graded by modified Lee et al 2014 criteria[2] should then be recorded in the AE CRF. Any signs and symptoms entirely due to ICANS (eg, confusion, seizure) should be recorded within the ICANS assessment CRF. A single term of Immune cell- associated neurotoxicity graded by ASTCT criteria[3] should then be recorded in the AE CRF. Injection site assessments containing AEs should have the term of Injection site reaction recorded with CTCAE 4.03 grading in the AE CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above -indicated active collection period.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Section 8.3 Severity Assessment).

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Patients who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value

>2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For patients with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

  - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function tests (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.2.1. Exposure During Pregnancy (EDP)

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.2.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.3. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Such medication errors occurring to a study patient are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.4.4. Peripheral neuropathy

Peripheral neuropathy is a common complication of MM and its treatment. Peripheral neuropathy can be caused by MM itself, either by the paraneoplastic effects of the monoclonal protein (polyneuropathy is an essential feature of POEMS syndrome) or in the form of radiculopathy from direct compression, and particularly by certain therapies, including IMiDs and proteasome inhibitors. Symptoms are usually symmetric and include paresthesias, numbness, burning sensation and muscle weakness; these are generally mild, but in rare cases can be disabling or even life-threatening. Treatment-emergent peripheral neuropathy symptoms are usually symmetric, distal and progressive.[49] Recently, peripheral neuropathy has been described following administration of BCMA-directed bispecific T-cell engagers.[50]

Peripheral neuropathy (including GBS) is considered an important potential risk of elranatamab.

Work-up for new or worsening Grade ≥2 peripheral neuropathy should include a neurology consult, imaging (eg, MRI of the spine), NCV/EMGs, and lumbar puncture to assess CSF. In consultation with a neurologist, appropriate therapy for peripheral neuropathy (eg, steroids and/or IV immunoglobulin) should be considered.

Closely monitor participants for signs and symptoms of neuropathy following infections or following the administration of any vaccine.

For recommended dose modifications for peripheral neuropathy (all causality), refer to Table 5.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Analysis Sets

Treated patient safety analysis set:

The safety analysis set includes all enrolled patients who receive at least one dose of study treatment.

Full analysis set:

The full analysis set includes all enrolled patients.

Per-protocol analysis set (evaluable for MTD/MAD):

The per-protocol analysis set includes all enrolled patients who receive at least one dose of study treatment and who do not have major treatment deviations during DLT observation period. Patients with major treatment deviations during DLT observation period are not evaluable for the MTD/MAD assessment and will be replaced as needed to permit MTD/MAD estimation.

PF-06863135 PK analysis sets:

The PK parameter analysis population is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest.

The PK concentration population is defined as all enrolled patients who are treated with PF-06863135, have no protocol deviations affecting the PK assessment, and have at least 1 post-dose concentration measurement.

Biomarker analysis set(s):

The biomarker analysis set includes all enrolled patients with at least one of the pharmacodynamic/biomarker parameters evaluated at pre- or post-dose.

Efficacy modified intent to treat (ITT) analysis set:

Includes all Patients who have received at least one dose of study treatment.

Efficacy Per-Protocol analysis set:

The efficacy per-protocol analysis set includes all treated patients who do not have major treatment deviations and are evaluable at least for the first tumor assessment.

PF-06863135 Immunogenicity analysis set:

The immunogenicity analysis set is defined as patients who receive at least 1 dose of study treatment and have at least 1 ADA sample collected.

9.2. Statistical Methods and Properties

9.2.1. Statistical Methods for Dose Escalation/De-Escalation

This study has been designed to establish the Maximum Tolerated Dose (MTD)/MAD. The MTD is defined as the dose that yields approximately 25% probability of DLT and considers equivalent doses that yield probability of DLT in the interval (Equivalence Interval) 20% to 30%. The 25% target was chosen based on safety considerations and is considered appropriate based on simulations and expert input.

The mTPI design[51-53] uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (target probability [pT] = 0.25). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to pT, the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model.

Being a model-based design, mTPI automatically and appropriately tailors dose-escalation and de-escalation decisions for different studies with different toxicity parameters. More importantly, all the dose-escalation decisions for a given study can be pre-calculated under the mTPI design and presented in a two-way table (see Appendix 8). Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement.

Decision rules are based on calculating unit probability mass (UPM) of 3 dosing intervals corresponding to under, proper, and over dosing in terms of toxicity. Specifically, the

underdosing interval is defined as (0; pT-e_1), the over-dosing interval (pT+e_2, 1), and the proper-dosing interval (pT- e_1, pT+ e_2), where e_1 and e_2 are small fractions. In study, e_1 and e_2 are selected as 0.05, therefore, the target interval for the DLT rate is (0.20, 0.30). The 25% target, the symmetry of the Equivalence Interval and its upper limit were chosen based on safety considerations. The prior distribution of DLT is set as a beta (0.5, 0.5), and the threshold probability for early termination and dose exclusion is set to 0.95.

The 3 dosing intervals are associated with 3 different dose-escalation decisions. The underdosing interval corresponds to a dose-escalation (E), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to remaining at the current dose (R). Given a dosing interval and a probability distribution, the unit probability mass (UPM) of that dosing interval is defined as the probability of a patient belonging to that dosing interval divided by the length of the dosing interval. Even though the mTPI may select an MTD/MAD with an incidence of DLTs that is higher than 30%, doses with an incidence of DLT >30% (eg, 4 out of 9) cannot be declared as the MTD/MAD.

If the MTD is not reached, then the MAD will be maximum dose that is evaluated in the study.

9.2.2. Statistical Method for Estimating the MTD/MAD

As previously described, the estimated MTD is the highest tested dose level with DLT rate ≤0.30 in at least 6 DLT-evaluable patients (ie, per protocol analysis set). It is assumed that higher doses result in higher toxicity rates. But, due to the relatively low number of patients that may be potentially allocated to any dose, this assumption may be violated.

To estimate the MTD/MAD the study will continue accruing until one of the three stopping conditions below is triggered:

1. The maximum sample size has been achieved.
2. MTD/MAD has been identified with sufficient accuracy: 6 to 16 patients have been accumulated on a dose that is currently estimated to be the MTD/MAD; or
3. All doses explored appear to be overly toxic and the MTD/MAD cannot be determined.

Clinical judgment will be exercised in taking forward doses to the expansion cohort(s), in case no clear choice exists between more than 1 competing MTD/MAD. This decision will be based upon the combination of data related to safety, anti-tumor activity, and clinical judgment of the investigators and the sponsor.

9.3. Sample Size Determination

Due to the dynamic nature of the Bayesian allocation procedure, the sample size of the mTPI approach cannot be determined in advance. It is estimated approximately 100 DLT evaluable patients may be enrolled in the dose escalation stage in order to have a reliable and accurate estimate of the MTD/MAD and RP2D. At least 6 and up to 16 patients should be enrolled at a dose level that is predicted to be the MTD/MAD as per the mTPI method. However, additional cohorts below MTD/MAD may also be considered for enrollment up to approximately 6-12 patients for the purpose of confirming the RP2D.

It is anticipated that Parts 1C, 1D and 1E will each have approximately 9-16 patients enrolled. However, the total number of patients will depend on the number of dose levels needed to determine the MTD/MAD for each combination and number of patients evaluable for DLT at each cohort.

Subsequent patients will enter an expansion component, Part 2, aimed at evaluating safety and anti-myeloma activity of PF-06863135 at the RP2D in monotherapy (Part 2A) and in combination with lenalidomide, pomalidomide, or dexamethasone (Parts 2C, 2D and 2E, correspondingly). Approximately 20 patients are expected to be enrolled into each of Parts 2A, 2C, 2D and 2E, but enrollment of patients may be discontinued earlier if minimal or no anti-tumor activity is observed.

Cohort sample size is determined as follows.

Part 2A - monotherapy: Assuming a non-informative prior (ie, Jeffrey's prior) if 12 out of 20 participants have tumor response, this would predict a posterior probability (Beta Binomial) equal to 0.814 that true response rate is not inferior to target response rate of 50% and a posterior probability equal to 0.003 that true response rate is inferior to benchmark rate of 30%.

Parts 2C, 2D, and 2E – combination with lenalidomide, pomalidomide, and dexamethasone respectively: Assuming a non-informative prior (ie, Jeffrey's prior) if 14 out of 20 participants have tumor response, this would predict a posterior probability (Beta Binomial) equal to 0.818 that true response rate is not inferior to the target response rate of 60% and a posterior probability equal to 0.0001 that true response rate is inferior to benchmark rate of 30%.

9.4. Efficacy Analysis

In this First in Patient study, anti-myeloma activity is a secondary objective in Part 1 dose escalation. Objective response rate (ORR) and duration of response (DOR) are primary objectives in Part 2 dose expansion. Other efficacy endpoints are secondary objectives in Part 2. The analysis population is defined in Section 9.1 Analysis Sets.

Imaging studies, relevant laboratory assessments, and bone marrow pathology may be collected to support independent central review for efficacy endpoints.

Disease response will be presented in the form of patient data listings that include, but are not limited to starting dose, disease response at each visit, and best overall response. In addition, progression date, death date, date of first response and last disease assessment date, and date of last contact will be listed.

Best overall response (BOR) will be assessed based on reported overall responses at different evaluation time points using IMWG response criteria (see Appendix 2).[4,5]

- **Complete Response** will encompass confirmed stringent Complete Response (sCR) and Complete Response (CR).
- **Overall Response** (OR) will encompass confirmed sCR, CR, VGPR (very good partial response) and partial response (PR).
- **Clinical Benefit** (CB) will encompass confirmed sCR, CR, VGPR, PR and MR.

Progression -free survival (PFS) is the time from start date of study treatment to date of first documentation of progression, or death due to any cause. Progression is defined as the appearance of local, regional or distant disease of the same type after complete response or progression of pre-existing lesions. It does not include second primary malignancies of unrelated types.

Overall survival (OS) is the time from start date of study treatment to date of death due to any cause.

Duration of Complete Remission is defined for patients with confirmed complete response (sCR, CR) as the time from the first documentation of complete response to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first.

Duration of Response (DOR) is defined for patients with confirmed objective response (as defined above in overall response) as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first.

Duration of Stable Disease (DOSD) is defined for patients with confirmed stable disease as the time from the first documentation of objective stable disease to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first.

Time to Response (TTR) is defined for patients with confirmed objective response (as defined above in overall response) as the time from the first documentation of objective tumor response.

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. PF-06863135 PK Analysis

The concentrations of PF-06863135 will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum maximum, and geometric mean) by dosing cohort, cycle, and nominal time. Individual patient and median profiles of the concentration-time data will be plotted by dosing cohort and cycle using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

For patients from Parts 1, 1.1, 1C, 1D, and 1E, individual concentration-time data of PF-06863135 following the Cycle 0 Day 1 dose (only for patients receiving priming dose), Cycle 1 Day 1 dose and Cycle 2 Day 1 dose (IV only) will be analyzed separately using non-compartmental analysis to estimate the PK parameters. The PK parameters estimated will include C_{max}, time to maximum concentration (T_{max}), and concentration versus time curve (AUC_{last}). If data permit or if considered appropriate, minimum concentration (C_{min}), terminal elimination half-life ($t_{1/2}$), clearance (CL or CL/F), volume of distribution at steady state (V_{ss} or $V_{ss/F}$), and accumulation ratio (Rac) will be also estimated for Cycle 1 Day 1 and Cycle 2 Day 1. Actual sample collection times will be used for the parameter calculations. The PK parameters will be summarized descriptively by dosing cohort, and cycle.

For patients enrolled in Parts 2A, 2C, 2D, and 2E of the study, trough PF-06863135 concentrations will be summarized descriptively by cycle.

9.5.2. Lenalidomide, Pomalidomide, and Dexamethasone Pharmacokinetic Analysis (Parts 1C and 2C, Parts 1D and 2D, Parts 1E and 2E as appropriate)

The concentration-time data of lenalidomide, pomalidomide, and dexamethasone will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean) according to dosing cohort and time for each part of the study.

9.5.3. Population Pharmacokinetic Analysis of Pharmacokinetics (PK)/Pharmacodynamic Modeling

PK and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between PF-06863135 exposure and biomarkers or significant safety and/or efficacy endpoints. The results of these analyses, if performed, may be reported separately from the clinical study report.

9.5.4. Analysis of Immunogenicity

For the immunogenicity data, the percentage of patients with ADA will be summarized. Listings and summary tabulations of the ADA data at baseline and post-randomization will be generated. Samples may also be analyzed for the presence of NAb, and any data will be similarly summarized. For patients with positive ADA or NAb, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described, if data permit. The potential impact of immunogenicity on PK and clinical response including pharmacodynamic markers, safety/tolerability and efficacy of ADA will be explored, if warranted by the data.

9.5.5. Analysis of Pharmacodynamics

Pharmacodynamic endpoints being measured include cellular BCMA expression, plasma soluble BCMA, endogenous patient immune cell populations, peripheral blood gene expression profiles and T-cell receptor (TCR) clonality. These endpoints will be subject to analysis by summary statistics of values at baseline as well as change from baseline on study. Gene expression profiling and TCR clonal analysis will also be subject to specialized, fit-for-purpose analysis algorithms used to interrogate high dimensional data sets.

9.5.6. Analysis of Biomarker Endpoints

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance. The statistical approach will examine correlations of biomarker results with PK parameters and measures of anti-cancer efficacy.

Results from tertiary/exploratory analyses will be reported in the CSR where possible. However, given the exploratory nature of exploratory objectives and endpoints, the analyses may not be complete at the time of the CSR. Results from exploratory analyses that are not included in the CSR will be shared with the scientific community through publication at a scientific conference and/or in a peer-reviewed scientific journal. Detailed analysis for the tertiary and exploratory endpoints will be specified in a separate technical document outside of the SAP.

9.6. Safety Analysis

Summaries and analyses of safety parameters will include all patients in the Safety Analysis Set. For patients who undergo intra-patient dose escalation, safety analysis of their initial assigned dose will be censored at time of intra-patient dose escalation (or maintenance dose escalation for Part 1.1). This will allow at least 60 days of safety analysis for all patients at their initial assigned dose levels.

9.6.1. Analysis of the Primary Endpoint for Part 1

DLT is the primary endpoint of the dose escalation component of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD/MAD as described in the Study Design Section 3. Adverse Events constituting DLTs will be listed per dose level.

9.6.2. Analysis of Secondary Safety Endpoints

9.6.2.1. Adverse Events

AEs (except CRS) will be graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). CRS will be assessed according to the grading described by Lee et al. (2014 and 2019,[2,3] See Appendix 5)and coded using MedDRA. The severity of ICANS should be graded according to the ASTCT consensus criteria[3] (Appendix 5). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized

according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).

9.6.2.2. Laboratory Test Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

9.6.2.3. Electrocardiogram

The analysis of ECG results will be based on patients in the safety analysis set with baseline (sample taken prior to first dosing) and on-treatment ECG data. ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT (time between the start of the Q wave and the end of the T wave) intervals will be corrected for heart rate (HR, QTc) using standard correction factors (ie, Fridericia's [default correction], Bazett's, and possibly a study -specific factor, as appropriate). Data will be summarized and listed for QT, HR, response rate (RR), partial response (PR), QRS, QTcF (and other correction factors, eg, corrected QT interval by Bazett (QTcB) as appropriate), and by study arm and dose. Individual QT (all evaluated corrections) intervals will be listed by study arm, time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by study arm, dose and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT (one or more correction methods will be used) using maximum CTCAE Grade. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment (yes, no, not done: (n, %)). Patients experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration -corrected QT analyses may be performed. Data may

be pooled with other study results and/or explored further with PK/pharmacodynamic models.

9.7. Interim Analysis

No formal interim analysis will be performed. Patients' safety and disease progression will be monitored continuously.

The criteria below guiding interruption of study treatment are based on Bayesian posterior probabilities using a non-informative Beta (0.5, 0.5) prior distribution. The probabilities will be calculated for total number of participants assigned or transitioned to monotherapy with elranatamab across its efficacious dose range, including Part 1 SC doses ≥215 ug/kg, Part 1.1, Part 2A, and any patient from Part 1D transitioned to monotherapy.

If the number of evaluable participants observed to have treatment-related Grade 3-4 GBS (including variants) results in a posterior probability that the true rate of such events exceeding 3% is ≥0.80, study treatment will be interrupted for all active participants pending review of all safety information. For example, if the total number of participants enrolled in the cohorts described above is 62, observing 3 or more participants with treatment-related Grade 3-4 GBS (including variants) will result in the interruption of study treatment for all active participants.

If the number of evaluable participants observed to have treatment-related Grade 4 sensory neuropathy, Grade 4 immune-related neurologic AEs (excluding ICANS), or Grade 3-4 peripheral motor neuropathy results in a posterior probability that the true rate of such events exceeding 10% is ≥0.80, study treatment will be interrupted for all active participants pending review of all safety information. For example, if the total number of participants enrolled in the cohorts described above is 62, observing 9 or more participants with treatment-related Grade 4 sensory neuropathy, Grade 4 immune-related neurologic AEs (excluding ICANS), or Grade 3-4 peripheral motor neuropathy will result in the interruption of study treatment for all active participants.

If a participant enrolled on the combination with lenalidomide arm develops ≥ Grade 3 peripheral motor neuropathy (including GBS), that participant will be managed according to Table 5 and the remaining participants on the combination arm will be transitioned to monotherapy with single agent PF-06863135.

In addition, if any of the following adverse events occur, study treatment will be interrupted for all active participants:

- 1 Grade 5 event of CRS
- 1 Grade 5 event of ICANS
- 1 Grade 5 treatment-related peripheral neuropathy or IR neurologic event

- Any 2 treatment-related Grade 5 events (excluding CRS and ICANS and peripheral neuropathy/IR neurologic event).

9.8. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source

documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

11.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password-protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of

disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

12. ETHICS

12.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.

- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

12.2. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study patients. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The informed consent documents and any patient recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws. Potential benefit and risks of alternative procedures will not be outlined in the consent for patients on this study per ICH GCP Section 4.8.10 (i), if the outline of this information is not in alignment with institute's policies.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.3. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new

information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as last subject last visit (LSLV). For more information on how end of study is determined, please see Section 6.5.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06863135 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 2 business days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant level data or full CSRs for the purposes of "bona fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials avalable 18 months after study completion. Participant level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes..

15.2. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study intervention or Pfizer related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication. The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

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Appendix 1. ABBREVIATIONS

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AABB	American Association of Blood Banks
ACRIN	American College of Radiology Imaging Network
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
ADL	activities of daily living
AE	adverse event
AHA	American Heart Association
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
APCs	antigen presenting cells
APRIL	a proliferation-inducing ligand
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
AUC_{168}	area under the curve measured to 168 hours
AUC_{inf}	area under the concentration versus time curve to infinity
AUC_{last}	area under the plasma concentration-time curve from time zero to time of last measurable concentration
$AUC_{sd,\tau}$	area under the single dose concentration-time curve over dosing interval τ
AUC_{τ}	area under the plasma concentration-time curve from time zero to time t
auto-HSCT	autologous hematopoietic stem cell transplantation
AV	Atrioventricular
BBS	biospecimen banking system
BCMA	B-cell maturation antigen
BID	twice daily
BM	bone marrow
BMI	body mass index
BNP	B-type natriuretic peptide
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen

Abbreviation	Term
C	Cycle
CBC	complete blood count
C0D1	Cycle 0 Day 1
C1D1	Cycle 1 Day 1
CAR	chimeric antigen receptors
C_{av}	average concentration
CB	clinical benefit
CBR	clinical benefit rate
CD	cluster of differentiation
CEA	carcinoembryonic antigen
Ceff	efficacious concentration
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase MB
CL	clearance
CL/F	clearance after non-intravenous administration
C_{max}	maximum (or peak) concentration
C_{min}	minimum concentration
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRAB	calcium elevation, renal failure, anemia, lytic bone lesions;
Cranial nerve VI	abducens nerve
CrCl	creatinine clearance
CRF	case report form
CRh	complete remission with partial hematological recovery
CRP	C-reactive protein
CRR	complete response rate
CRS	cytokine release syndrome
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CT SAE	clinical trial serious adverse event
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CXD1	Cycle X Day 1
CYP3A4	Cytochrome P450 3A4
CV	coefficient of variation
DCR	disease control rate

Abbreviation	Term
DDI	drug-drug interaction
DFS	disease free survival
DILI	drug-induced liver injury
DLI	Donor Lymphocyte Infusion
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoCR	duration of complete response
DOR	duration of response
DOSD	duration of stable disease
DU	dispensable unit
EBV	epstein-barr virus
EC	ethics committee
EC20	effective concentration 20
EC50	effective concentration 50
ECG	Electrocardiogram
echo	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDV	end-diastolic volume
EEG	Electroencephalogram
eg	for example
EGFR	epidermal growth factor receptor
EI	equivalence interval
EMG	electromyography
EOS	end of study
EOT	end of treatment
ESC	European Society of Cardiology
ESV	end-systolic volume
Etc	'and other things' or 'and so forth'
EU	European Union
EudraCT	European Clinical Trials Database
FAP	final approved protocol
Fc	fragment crystallizable
FDA	Food and Drug Administration (United States)
FDG-PET/CT	fluorodeoxyglucose positron emission tomography/computed tomography
FIP	first in patient
FISH	fluorescence in situ hybridization
FLC	free light chain analysis

Abbreviation	Term
FSH	follicle-stimulating hormone
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GH	growth hormone
GI	gastrointestinal tract
GLP	Good Laboratory Practice
GM-CSF	granulocyte- macrophage colony stimulating factor
GnRH	gonadotropin-releasing hormone agonist
GvHD	graft-versus-host disease
HbA1c	hemoglobin A1c
HBc	hepatitis B core
HBcAb	hepatitis B core antibody
HBs	hepatitis B surface
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	Hemoglobin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLH	Lymphohistiocytosis
HR	heart rate
hrs	Hours
HTLV	human T-cell lymphotropic virus
IB	investigator's brochure
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICD	Informed consent document
ICE	Immune Effector Cell-Associated Encephalopathy
ICH	International Conference on Harmonization
ICP	Intracranial pressure
ICU	intensive care unit
ID	Identification
ie	that is
IFNγ	interferon gamma
Ig	Immunoglobulin
IGF-1	Insulin-like growth factor 1
IgG2Δa	immunoglobulin G 2Δa
IgG_k	immunoglobulin G kappa
IHC	Immunohistochemistry
IL-	Interleukin
IMiD	immunomodulatory drug
IMWG	international myeloma working group

Abbreviation	Term
IND	investigational new drug application
INR	international normalized ratio
IP manual	Investigational Product manual
IR	Immune-related
IRB	institutional review board
IRC	internal review committee
IRR	infusion related reaction
ISR	injection site reaction
ITT	intent to treat
IUD	intrauterine device
IV	Intravenous
K_2EDTA	dipotassium edetic acid ethylenediaminetetraacetic acid
K_D	equilibrium dissociation constant
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LPFV	last patient first visit
LSLV	last subject last visit
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
M	Monoclonal
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MAD	maximum administered dose
MAD-1	1 dose level below the MAD
MAS	macrophage activation syndrome
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MFC	multiparametric flow cytometry
MFD	maximum feasible dose
MGUS	monoclonal gammopathy of undetermined clinical significance
MHC	major histocompatibility complex
MM	multiple myeloma
MM1.S	a glucocorticoid sensitive multiple myeloma cell line
MOLP-8	a multiple myeloma cell line with t(11;14)(q13;q32) chromosomal abnormality and negative for CD28
M-Protein	myeloma protein
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging

Abbreviation	Term
M-spike	monoclonal spike
MTD	maximum tolerated dose
MTD-1	1 dose below the MTD
mTPI	modified toxicity probability interval
MUGA	multigated acquisition scan
N	number
N/A	not applicable
NAb	neutralizing antibody
NCI	National Cancer Institute
NCT	National Clinical Trial
NCV	Nerve conduction velocity
NGF	next generation flow cytometry
NGS	next generation sequencing
NK	natural killer
NOAEL	no observed adverse effect level
NSAIDS	nonsteroidal anti-inflammatory drugs
NSCLC	non-cell small cell lung cancer
NSG	NOD scid gamma
OBD	optimal biological dose
OPM-2	a type of multiple myeloma cell line
OR	objective response or overall response
ORR	objective response rate
OS	overall survival
PACL	Protocol Administrative Change Letter
PaO_2	partial pressure of oxygen
PCD	primary completion date
PD	pharmacodynamic, progressive disease
PET	positron emission tomography
PFS	progression-Free Survival
PGx	pharmacogenomics
PI	principal investigator
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	by mouth
POEMS	polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes
PP	posterior probability
PPP	pregnancy prevention program
PR	partial response
PRL	Prolactin
PS	performance status
PT	prothrombin time

Abbreviation	Term
PTT	partial thromboplastin time
Q1W	every week
Q2W	every 2 weeks
Q3W	every three weeks
Q4W	every four weeks
QD	every day
qPCR	quantitative polymerase chain reaction
QT	time between the start of the Q wave and the end of the T wave
QTc	corrected QT interval
QTcB	corrected QT interval by Bazett
QTcF	Corrected QT interval by Fridericia
R_{ac}	accumulation ratio
RCL	replication competent lentivirus
RD	response/remission duration
REMS	risk evaluation and mitigation strategy
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose
RR	response rate
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SBP	systolic blood pressure
SC	Subcutaneous
SCCHN	squamous cell cancer of head and neck
scFv	single-chain variable fragment
SCLC	small cell lung cancer
sCR	stringent complete response
SCT	stem cell transplant
SD	stable disease
SIFE	serum immunofixation electrophoresis
sIL2Rα	soluble interleukin-2 receptor alpha
SLAMF7	Signaling lymphocytic activation molecule F7
SoA	Schedule of Activities
SOC	standard of care
SOP	standard operating procedure
SPC	Summary of Product Characteristics
SPD	sum of the products of the maximal perpendicular diameters of measured lesions
SPEP	serum protein electrophoresis

Abbreviation	Term
SRSD	single reference safety document
STR	short tandem repeat
SUV	standard uptake value
SWOG	southwest oncology group
$T_{1/2}$	terminal elimination half-life
TALEN	transcription activator-like effector nucleases
TBD	to be determined
TBili	total bilirubin
TBNK	T-, B-, and natural killer lymphocytes
TBR	tumor background ratio
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
TNF	tumor necrosis factor
TNFα	tumor necrosis factor –alpha
TNFRSF17	tumor necrosis factor receptor superfamily Member 17
TRAC	T-cell receptor alpha constant
TRAEs	Treatment-emergent treatment-related adverse events
Tregs	T regulatory cells
$T_{ss,max}$	time to maximum concentration
TTP	time to progression
TTR	time to response
UC	urothelial carcinoma
UK	United Kingdom
UIFE	urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	urine protein electrophoresis
UPM	unit probability mass
US	United States
USPI	United States package insert
UVB	ultraviolet B
VCN	vector copy number
VGPR	very good partial response
V_{ss}	volume of distribution at steady state
V_{ss}/F	apparent volume of distribution after non-intravenous administration
WBC	white blood cell
wks	Weeks

Appendix 2. THE INTERNATIONAL MYELOMA WORKING GROUP (IMWG) RESPONSE CRITERIA FOR MULTIPLE MYELOMA

All response categories require two consecutive assessments made any time before starting any new therapy. Patients must have measurable disease at enrollment (study entry). Measurable disease is defined as:

- Serum M-protein ≥0.5 g/dL (5 g/L); (See inclusion criteria for modifications);
- Urine M-protein ≥200 mg/24 h;
- Serum FLC assay: involved FLC level ≥10 mg/dL provided serum FLC ratio is abnormal.

Whenever more than one parameter is used to assess response, the overall assigned level of response is determined by the lower or lowest level of response. Patients will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; patients cannot move to a lower response category.

Response	IMWG Criteria
Stringent Complete Response (sCR)	• Complete response as defined below plus normal free light chain (FLC) ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells).[2] • In patients whereby the only measurable disease is by serum FLC levels, sCR is defined as normal FLC ratio of 0.26 to 1.65 plus absence of clonal cells in bone marrow as defined above.
Complete Response (CR)	• Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates.[1] • In patients whereby the only measurable disease is by serum FLC levels, CR is defined as normal FLC ratio of 0.26 to 1.65 plus criteria listed above.
Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis. or • ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24 hr. • In patients whereby the only measurable disease is by serum FLC levels, VGPR is defined as a >90% decrease in the difference between involved (tumor) and uninvolved (non-tumor) serum FLC levels.

Response	IMWG Criteria
Partial Response (PR)	• ≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 hr. • If the serum and urine M-protein are unmeasurable,[4] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • In patients whereby the only measurable disease is by serum FLC levels, PR is defined as 50% reduction in difference between involved and uninvolved FLC. • In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)[2] of soft tissue plasmacytomas is also required.
Minimal Response (MR)	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a 50% reduction in the size (sum of the products of the maximal perpendicular diameters of measured lesions [SPD])[3] of soft tissue plasmacytomas is also required.
No Change/Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, MR or progressive disease.

Progressive Disease (PD)[5]	Any one or more of the following criteria:
	• Increase of ≥25% from lowest response value in any one or more of the following:
	  • Serum M-component and/or (the absolute increase must be ≥0.5 g/dL);[4]
	  • Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL;
	  • Urine M-component and/or (the absolute increase must be ≥200 mg/24 hr.
	  • 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);
	• Appearance of a new lesion(s), ≥50% increase from nadir in SPD[1] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis.

Clinical Relapse	Clinical relapse requires one or more of the following criteria:

Response	IMWG Criteria
	• Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD^3 of the measurable lesion; • Hypercalcemia (>11 mg/dL); • Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein.

CRAB features=calcium elevation, renal failure, anemia, lytic bone lesions; IMWG=International Myeloma Working Group; FLC=free light chain; M-protein=myeloma protein; SPD=sum of the products of the maximal perpendicular diameters of measured lesions.

Footnotes:

1. Confirmation with repeat bone marrow biopsy not required. Careful attention should be given to new positive immunofixation results appearing in patients who have achieved a complete response, when the isotype is different. This probably represents oligoclonal immune reconstitution and should not be confused with relapse; these bands typically disappear over time.
2. Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.
3. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or dedicated CT scans where applicable. Measurement of tumor size will be determined by the SPD.
4. All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. To confirm response or progressive disease, two discrete samples are required and testing cannot be based upon the splitting of a single sample. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression free survival. Patients will be considered to have progressive disease if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for patients who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in serum FLC alone.
5. For progressive disease, serum M-component increases of ≥1 mg/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

Appendix 3. IMWG MINIMAL RESIDUAL DISEASE (MRD) Criteria

Assess for MRD (at least by centrally collected flow cytometry and sequencing) for all bone marrow aspirates obtained while a patient is in suspected or actual CR. Confirmation with two consecutive assessments is not required.

Response	IMWG Criteria
Sustained MRD-negative[1]	MRD negativity in the marrow (NGS) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years).
Flow MRD-negative[2]	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 105 nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 105 nucleated cells or higher.
Imaging-positive MRD-negative	MRD negativity as defined by NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue.

CT = computed tomography; IMWG=International Myeloma Working Group; MRD = minimal residual disease; NGF = next-generation flow cytometry; NGS = next generation sequencing; positron emission tomography = PET; SUV = standardized uptake value.

Footnotes

1. Sustained MRD negativity, when reported, should also annotate the method used (eg, sustained sequencing MRD- negative).
2. Bone marrow multiparametric flow cytometry MFC should follow NGF guidelines. The reference NGF method is an eight-color two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The complete eight-color method should use a lyophilized mixture of antibodies. 5 million cells should be assessed. The method employed should have a sensitivity of detection of at least 1 in 105 plasma cells.

Appendix 4. ECOG PERFORMANCE STATUS

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

*As published in Am J Clin Oncol 5:649-655, 1982.[53]

Appendix 5. CRS AND ICANS MITIGATION AND MANAGEMENT

CRS is a non-antigen-specific cytokine-associated toxicity that occurs as a result of high-level immune activation. CRS is a potentially life-threatening toxicity that has been observed following administration of immune-base therapies for cancer (antibodies and adoptive T-cell therapies). CRS is likely to be a common toxicity that can be managed through supportive care and anti-cytokine interventions.

In cases of suspected cytokine release syndrome, a serum sample should be provided for cytokine release assay analysis by the local lab (see Section 7.1.3) so as long as the sampling does not interfere with the medical treatment of the patient.

Early intervention should be undertaken at the first sign of CRS; signs may include pyrexia, tachycardia, tachypnea and/or hypotension and are temporally related to PF-06863135 in the absence of alternative etiologies.

The original CRS grading system proposed by Lee et al in 2014[2] (Table 13) should be used only for the purposes of grading of CRS on the adverse event case report form (CRF), but not for management of CRS. Grading by the more recent ASTCT CRS criteria[3] (Table 15) will be captured along with the Lee et al 2014 criteria on the CRS CRF, and management guidelines will follow ASTCT CRS grading. These treatment guidelines[39] may be modified as needed by the responsible Investigator according to the best practices at their institute.

Table 13. Lee et al 2014 CRS revised grading system[2]

Toxicity Grade	Characteristics
1	Symptoms are not life threatening and require symptomatic treatment only, eg, Fever, nausea, fatigue, headache, myalgia, malaise.
2	Grade 2 hypoxia* [decreased oxygen saturation with activity (eg, pulse oximeter <88%); intermittent supplemental oxygen]; or Hypotension responsive to fluids or low-dose of one vasopressor (Table 14) or Grade 2 organ toxicity.
3	Grade 3 hypoxia* [decreased oxygen saturation at rest (eg, pulse oximeter <88% or partial pressure of oxygen (PaO2) <=55 mm Hg)]; or Hypotension requiring high-dose vasopressors or multiple vasopressors (Table 14); or Grade 3 organ toxicity (except transaminitis); or Grade 4 transaminitis.
4	Life-threatening symptoms; Grade 3 hypoxia* [decreased oxygen saturation at rest (eg, pulse oximeter <88% or partial pressure of oxygen (PaO2) <=55 mm Hg)]or Grade 4 organ toxicity (excluding transaminitis).
5	Death.

*Modification to the Lee et al CRS Revised Grading System according to the CTCAE v4.03. Transient decreases in oxygen levels below 88% will not be considered to have met the criteria.

The definitions for high-dose vasopressors are shown in Table 14.

Table 14. Definition of High Dose Vasopressor

Pressor	High Dose (doses less than these would be considered low)
Norepinephrine monotherapy	≥20 μg/min
Dopamine monotherapy	≥10 μg/kg/min
Phenylephrine monotherapy	≥200 μg/min
Epinephrine monotherapy	≥10 μg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥10 μg/min*
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥20 μg/min*

** VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (μg/min)]*
+ [dopamine (μg/kg/min) ÷ 2] + [epinephrine (μg/min)] + [phenylephrine (μg/min) ÷10

Table 15. ASTCT CRS revised grading system[3]

CRS parameter:	Fever*	With Hypotension	And/or† Hypoxia
Grade 1	Temp. ≥38°C	None	None
Grade 2	Temp. ≥38°C	Not requiring vasopressors	Requiring low-flow‡ nasal cannula, low-flow‡ facemask or blow-by
Grade 3	Temp. ≥38°C	Requiring a vasopressor with or without vasopressin	Requiring high-flow‡ nasal cannula, high-flow‡ facemask, nonrebreather mask, or Venturi mask
Grade 4	Temp. ≥38°C	Requiring multiple vasopressors (excluding vasopressin)	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS should still be graded according to CTCAE v4.03 and do not influence CRS grading.

* Fever is defined as temperature ≥38°C and not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula or facemask is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula or facemask is defined as oxygen delivered at >6 L/min. This is modified from original ASTCT criteria to differentiate between low-flow and high-flow facemask.

CRS management guidelines[38,39]

ASTCT Grade 1 CRS:

- Monitor vital signs for worsening of condition.

Fever

- Acetaminophen/paracetamol and hypothermia blanket for the treatment of fever.
- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen can be used as second treatment option for fever if not contraindicated.
- Assess for infection using blood and urine cultures, and chest radiography.
- Empiric broad-spectrum antibiotics and filgrastim if neutropenic.
- Maintenance IV fluids for hydration.
- Symptomatic management of constitutional symptoms or organ toxicity.
- Consider tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV for persistent (lasting >3 days) and refractory fever.

ASTCT Grade 2 CRS:

- Monitor vital signs every 4 hours for worsening of condition.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV fluid bolus of 500-1000 ml of normal saline. Can give second IV fluid bolus if systolic blood pressure remains <90 mmHg.
- Consider tocilizumab 8 mg/kg (maximum dose 800 mg) IV or siltuximab 11 mg/kg IV for treatment of hypotension refractory to fluid boluses; tocilizumab can be repeated after 6 h if needed.
- If hypotension persists after 2 fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to intensive care unit (ICU), obtain echocardiogram (ECHO), and initiate other methods of hemodynamic monitoring.

- In patients at high-risk (bulky disease, older age or comorbidities) or if hypotension persists after 1-2 doses of anti-IL-6 therapy, dexamethasone can be used at 10 mg IV every 6 hrs.

Hypoxia

- Supplemental oxygen.

  Tocilizumab or siltuximab ± corticosteroids and supportive care, as indicated for hypotension.

ASTCT Grade 3 CRS:

- Monitor patient (including continuous ECG monitoring) in an ICU and obtain ECHO if not done already.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV boluses, as needed, as recommended for Grade 2 CRS.
- Tocilizumab and siltuximab as recommended for Grade 2 CRS if not administered previously.
- Vasopressors as needed.
- Dexamethasone 10 mg IV every 6 hrs; if refractory, increase to 20 mg IV every 6 hrs.

Hypoxia

- Supplemental oxygen including high-flow oxygen delivery.
- Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above.

ASTCT Grade 4 CRS:

- Monitor patient (including continuous ECG monitoring) in an ICU and obtain ECHO if not done already.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV boluses, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as recommended for grade 3 CRS.
- Methylprednisolone 1 g/day IV.

Hypoxia

- Supplemental oxygen via positive pressure/mechanical ventilation.
- Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Although less commonly seen than CRS, ICANS has been observed with some T-cell directed therapies and may manifest as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and cerebral edema.[3] If ICANS is observed in relation to PF-06863135, the ASTCT criteria[3] should be followed for its grading and management.[38,39] These treatment guidelines may be modified as needed by the responsible Investigator according to the best practices at their institute.

Table 16. Immune Effector Cell-Associated Encephalopathy (ICE) Score

Category	Task	Points
Orientation	Orientation to year, month, city, hospital	4
Naming	Ability to name 3 objects	3
Following commands	Ability to follow simple commands	1
Writing	Ability to write a standard sentence	1
Attention	Ability to count backwards from 100 by 10	1

Table 17. ASTCT ICANS Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging⁂	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI (abducens nerve) palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure[ICP]/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v4.03, but they do not influence ICANS grading.

⁂ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v4.03.

ICANS Management guidelines[38,39]

ASTCT ICANS Grade 1:

- Vigilant supportive care; aspiration precautions; intravenous (IV) hydration.
- Withhold oral intake of food, medicines, and fluids, and assess swallowing.
- Convert all oral medications and/or nutrition to IV if swallowing is impaired.
- Avoid medications that cause central nervous system depression.
- Neurology consultation.
- Evaluate elevated intracranial pressure (ICP), if suspected, with fundoscopic exam for papilledema and lumbar puncture for cerebrospinal fluid opening pressure.
- Magnetic resonance imaging (MRI)MRI of the brain with and without contrast; CT scan of the brain can be performed if MRI of the brain is not feasible.
- Daily 30 min electroencephalogram (EEG) until toxicity symptoms resolve; if no seizures are detected on EEG, continue levetiracetam 750 mg every 12 hrs.
- Consider anti-IL-6 therapy with tocilizumab 8 mg/kg (maximum 800 mg) IV or siltuximab 11 mg/kg IV, if there is concurrent CRS.

ASTCT ICANS Grade 2:

- Supportive care and neurological work-up as described for grade 1 ICANS.
- Anti-IL-6 therapy if associated with concurrent CRS, as described for grade 1 ICANS and if not administered previously.
- Dexamethasone 10 mg IV every 6 h or methylprednisolone 1 mg/kg IV every 12 h if refractory to anti-IL-6 therapy, or for ICANS without concurrent CRS.
- Consider transferring patient to intensive-care unit (ICU) if ICANS associated with grade ≥2 CRS.

ASTCT ICANS Grade 3:

- Supportive care and neurological work-up as indicated for grade 1 ICANS.
- ICU transfer is recommended.

- If EEG shows non-convulsive status epilepticus:
  - Assess airway, breathing, and circulation; check blood glucose.
  - Lorazepam 0.5 mg intravenously (IV), with additional 0.5 mg IV every 5 min, as needed, up to a total of 2 mg to control electrographical seizures.
  - Levetiracetam 500 mg IV bolus, as well as maintenance doses.
  - If seizures persist, transfer to intensive-care unit (ICU) and treat with phenobarbital loading dose of 60 mg IV.
  - Maintenance doses after resolution of non-convulsive status epilepticus are as follows: lorazepam 0.5 mg IV every 8 h for three doses; levetiracetam 1,000 mg IV every 12 hr; phenobarbital 30 mg IV every 12 hr.
  - Lacosamide may also be considered for treatment of seizures should the seizures persist but should not be used in patients with concurrent CRS in order to avoid arrhythmias and hypotension.
- For convulsive status epilepticus:
  - Convulsive status epilepticus.
  - Assess airway, breathing, and circulation; check blood glucose.
  - Transfer to ICU.
  - Lorazepam 2 mg IV, with additional 2 mg IV to a total of 4 mg to control seizures.
  - Levetiracetam 500 mg IV bolus, as well as maintenance doses.
  - If seizures persist, add phenobarbital treatment at a loading dose of 15 mg/kg IV.
  - Maintenance doses after resolution of convulsive status epilepticus are: lorazepam 0.5 mg IV every 8 h for three doses; levetiracetam 1,000 mg IV every 12 h; phenobarbital 1–3 mg/kg IV every 12 h.
  - Lacosamide may also be considered for treatment of seizures should the seizures persist but should not be used in patients with concurrent CRS in order to avoid arrhythmias and hypotension.
  - Continuous electroencephalogram monitoring should be performed, if seizures are refractory to treatment.

- High-dose methylprednisolone IV 1 g/day for focal/local edema.
- Anti-IL-6 therapy if associated with concurrent CRS, as described for grade 1 ICANS and if not administered previously.
- Corticosteroids as outlined for grade 2 ICANS if symptoms worsen despite anti-IL-6 therapy, or for ICANS without concurrent CRS; continue corticosteroids until improvement to grade 1 ICANS and then taper.

ASTCT ICANS Grade 4:

- Supportive care and neurological work-up as outlined for grade 1 ICANS.
- ICU monitoring; consider mechanical ventilation for airway protection.
- Anti-IL-6 therapy and repeat neuroimaging as described for grade 3 ICANS.
- High-dose methylprednisolone IV 1 g/day continued until improvement to grade 1 ICANS and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 h for 2 days, and 60 mg every 12 h for 2 days.
- For seizures, treat as described for grade 3 ICANS.
- MRI of the spine should be obtained for focal motor weakness.
- To manage elevated ICP:
  - Elevate head end of the patient's bed to an angle of 30 degrees.
  - Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mmHg, but maintained for no longer than 24 hrs to lower.
  - Hyperosmolar therapy with either mannitol (20 g/dl solution) or hypertonic saline (3% or 23.4%, as detailed below):
    - Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 hrs while monitoring metabolic profile and serum osmolality every 6 hrs, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40.
    - Hypertonic saline: initial 250 ml of 3% hypertonic saline; maintenance at 50-75 ml/h while monitoring electrolytes every 4 hrs, and withhold infusion if serum Na levels reach ≥155 mEq/l.
    - For patients with imminent herniation: initial 30 ml of 23.4% hypertonic saline; repeat after 15 min, if needed.

- Consider neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema and IV anesthetics for burst-suppression pattern on EEG.

- Metabolic profiling every 6 h and daily CT scan of head, with adjustments in usage of the aforementioned medications to prevent rebound cerebral oedema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension.

Appendix 6. INTERNATIONAL MYELOMA WORKING GROUP (IMWG) MULTIPLE MYELOMA DIAGNOSIS CRITERIA[45]

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma defining events:

1. Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
   a. Hypercalcemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL).
   b. Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL).
   c. Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L.
   d. Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT.‡
2. Any one or more of the following biomarkers of malignancy:
   e. Clonal bone marrow plasma cell percentage* ≥60%.
   f. Involved: uninvolved serum free light chain ratio§ ≥100 >1 focal lesions on MRI studies.

PET-CT=^{18}F-fluorodeoxyglucose PET with CT.

* Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

† Measured or estimated by validated equations.

‡ If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

§ These values are based on the serum freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. Each focal lesion must be 5 mm or more in size.

Relapse is defined as progression of disease after an initial response to previous treatment, more than six months after cessation of treatment.

Refractory is defined as resistance to treatment due to lack of response or progression of disease during treatment or within six months after cessation of treatment.

Appendix 7. MANAGEMENT OF INFUSION RELATED REACTIONS, INCLUDING ALLERGIC REACTIONS OR ANAPHYLAXIS

In the event of infusion related reactions, Investigators should institute treatment measures according to best medical and nursing practice.

The following treatment guidelines should be employed:

If chills and fever (>100.4°F/38.0°C) occur, the infusion should be interrupted. Patients may be treated symptomatically (as described in Section 5.5.2 Dose Delay) and the infusion should be restarted at 50% of the original rate.

Hypersensitivity reactions:

1. NCI-CTCAE Grade 1 allergic reaction:
    - Monitor for worsening condition. If the reaction worsens, stop the infusion. Institute premedication for subsequent infusions as per Section 5.5.2 Dose Delay.
2. NCI-CTCAE Grade 2 allergic reaction:
    - Stop PF-06863135 infusion.
    - Administer bronchodilators, oxygen, acetaminophen, etc. as medically indicated.
    - Resume infusion at 50% of previous rate once reaction has decreased to Grade 1 in severity. Monitor closely for any worsening. If the reaction recurs, stop infusion. Institute premedication for subsequent infusions as per Section 5.5.2 Dose Delay.
3. NCI-CTCAE Grade 3 or Grade 4 allergic reaction or anaphylaxis:
    - A Grade 3 anaphylaxis (hypersensitivity reaction) consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergy-related edema/angioedema, or hypotension.
    - A Grade 4 anaphylaxis (hypersensitivity reaction) is a life-threatening event requiring urgent intervention.
4. Treatment of Grade 3 or Grade 4 allergic reaction or anaphylaxis:
    - Stop the PF-06863135 infusion immediately and disconnect infusion tubing from the patient.
    - Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc. as medically indicated.

- Telephone Sponsor or designated representative to report an SAE as per Section 8 Adverse Event Reporting.
- For a NCI-CTCAE Grade 3 or 4 hypersensitivity reaction, study treatment will be discontinued.

5. Re-treatment following Grade 1 or Grade 2 allergic reactions:

   - Once the PF-06863135 infusion rate has been decreased due to an allergic reaction or cytokine release syndrome, it will remain decreased for all subsequent infusions.
   - If the patient has a second reaction at the lower infusion rate, the infusion should be stopped and the patient should receive no further PF-06863135.
   - If the patient experiences a Grade 3 or 4 allergic reaction or anaphylaxis at any time, the patient should receive no further PF-06863135.
   - If there are questions concerning whether an observed reaction is consistent with an allergic reaction, cytokine release syndrome, or anaphylaxis, the medical monitor should be contacted immediately to assist with grading the reaction.

PK, pharmacodynamic and ADA sampling should continue as long as the sampling does not interfere with the medical treatment of the patient.

Appendix 8. DETAILED DOSE ESCALATION/DE-ESCALATION SCHEME FOR mTPI DESIGN

	Number of Patients Treated at a Dose Level										
Number of Patients Having DLT	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10	n=11	n=12
0	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E
2	U	D	D	S	S	S	S	S	S	S	E
3		U	U	U	D	S	S	S	S	S	S
4			U	U	U	U	D	S	S	S	S
5				U	U	U	U	U	U	D	S
6					U	U	U	U	U	U	U

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to a lower dose
U = The dose is Unacceptably toxic
MTD/MAD = The highest dose yields the probability of DLT within the equivalence interval (20%, 30%).

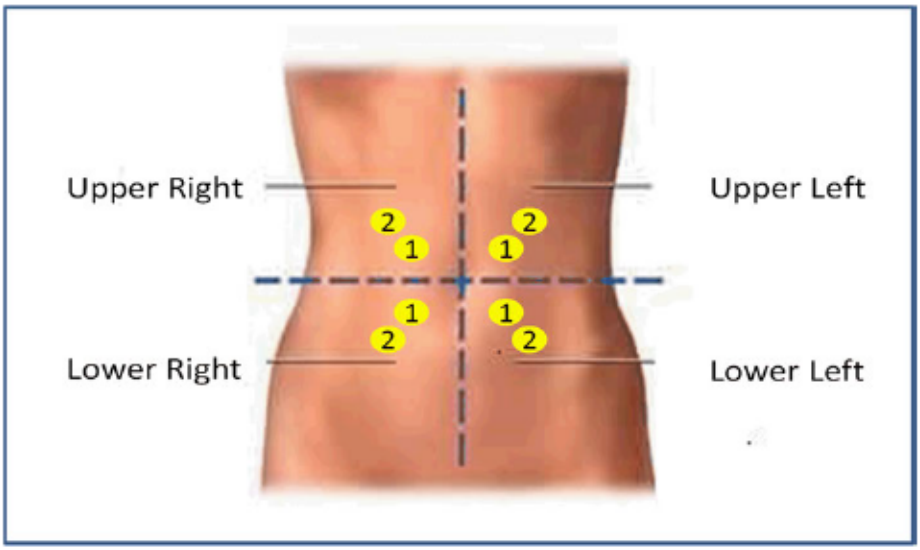
Escalation/De-escalation algorithms for total number of patients treated at the current dose level (current and previous cohorts):

- With 1 patient treated at current dose level:
  - 0 DLT -> escalate;
  - 1 DLT or other toxicities occur (ie, those that have the potential to be DLTs if more severe) -> may add additional patients to asses safety on a cohort size of n=2-4.
- With 2 patients treated at current dose level:
  - 0 DLT -> escalate;
  - 1 DLT -> remain at the same dose;
  - 2 DLTs -> de-escalate and consider current dose as intolerable.
- With 3 patients treated at current dose level:
  - 0 DLT -> escalate;
  - 1 DLT -> remain at the same dose;
  - 2 DLTs -> de-escalate;

    - 3 DLTs -> de-escalate and consider current dose as intolerable.
- With 4 patients treated at current dose level:
    - 0 DLT -> escalate;
    - 1 DLTs -> remain at the same dose;
    - 2 DLTs -> de-escalate;
    - 3-4 DLTs -> de-escalate and consider current dose as intolerable.
- With 5 patients treated at current dose level:
    - 0 or 1 DLT -> escalate;
    - 2 DLTs -> remain at the same dose;
    - 3-5 DLTs -> de-escalate and consider current dose as intolerable.
- With 6 patients treated at current dose level:
    - 0-1 DLT -> escalate;
    - 2 DLTs -> remain at the same dose;
    - 3 DLTs -> de-escalate;
    - 4-6 DLTs -> de-escalate and consider current dose as intolerable.
- With 7 patients treated at current dose level:
    - 0-1 DLT -> escalate;
    - 2-3 DLTs -> remain at the same dose;
    - 4-7 DLTs -> de-escalate and consider current dose as intolerable.
- With 8 patients treated at current dose level:
    - 0-1 DLT -> escalate;
    - 2-3 DLTs -> remain at the same dose;
    - 4 DLTs -> de-escalate;
    - 5-8 DLTs -> de-escalate and consider current dose as intolerable.

- With 9 patients treated at current dose level:
  - 0-1 DLT -> escalate;
  - 2-4 DLTs -> remain at the same dose;
  - 5-9 DLTs -> de-escalate and consider current dose as intolerable.
- With 10 patients treated at current dose level:
  - 0-1 DLT -> escalate;
  - 2-4 DLTs -> remain at the same dose;
  - 5-10 DLTs -> de-escalate and consider current dose as intolerable.
- With 11 patients treated at current dose level:
  - 0-1 DLT -> escalate;
  - 2-4 DLTs -> remain at the same dose;
  - 5 DLTs -> de-escalate (mTPI suggests "remain at the same dose");
  - 6-11 DLTs -> de-escalate and consider current dose as intolerable.
- With 12 patients treated at current dose level:
  - 0-2 DLTs -> escalate;
  - 3-5 DLTs -> remain at the same dose;
  - 6-12 DLTs -> de-escalate and consider current dose as intolerable.

Appendix 9. SUBCUTANEOUS INJECTION SITE LOCATIONS



Injection site locations include a maximum of 8 unique administration sites distributed across 4 abdominal quadrants with a possibility of up to 2 injection locations per quadrant. Location 1 is proximal to the umbilicus and Location 2 is distal to the umbilicus.

Administer the required number of injections in the following order:

1. Lower Left Quadrant Location 1;
2. Lower Right Quadrant Location 1;
3. Lower Left Quadrant Location 2;
4. Lower Right Quadrant Location 2;
5. Upper Right Quadrant Location 1;
6. Upper Left Quadrant Location 1;
7. Upper Right Quadrant Location 2;
8. Upper Left Quadrant Location 2.

Injections to the abdomen are preferred. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted.

Track the patient's injection site(s) sequentially on this diagram with a red pen and mark the injection sites on the patient's abdomen according to your clinic's standard practice.

Record the location, time of each injection and any injection site reactions in the patient's source records and study CRF. Complete one CRF per injection

Appendix 10. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic in participating countries and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

Eligibility

Regarding eligibility, while SARS-CoV2 testing is not mandated for this study you should follow local clinical practice standards for testing. If a participant has a positive test result for active SARS-CoV2 infection, is known to have asymptomatic infection or is suspected of having SARS-CoV2, he/she should be excluded at this time. Please note the protocol excludes patients with active infections:

Exclusion Criteria:

4. Patients with active uncontrolled bacterial, fungal or viral infection, including known human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) related illness.

When the infection resolves, the patient could be considered for re-screening, if allowed by study protocol.

Telehealth Visits

In the event that in-clinic follow-up study visits cannot be conducted where sample collection is not performed or treatment not given, every effort should be made to follow up on the safety of study patients at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess patient safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.1.4.2.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the patient is adhering to the contraception method(s) required in the protocol.

Study participants must be reminded to promptly notify site staff about any change in their health status.

Alternative Facilities for Safety Assessments

Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations as listed in Table 11 may be performed at a local laboratory if necessary:

- Hematology;
- Blood chemistry;
- Coagulation;
- Urinalysis;
- Pregnancy test.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Dose Delays

The following is recommended for the administration of PF-06863135 for participants who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV2 infection:

- For symptomatic participants with active SARS-CoV2 infection, investigational treatment should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions as described Section 5.9 and Appendix 11 for any concomitant medication administered for treatment of SARS-CoV2 infection.

Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

Appendix 11. Prohibited Concomitant Medications which may Result in Drug-Drug Interaction (DDI)

The prohibited concomitant medications listed below should not be taken with PF-06863135 for the period of time at least equal to the required washout period listed in the table below, and throughout the conduct of the study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgement on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Drug Category	Drugs	Required Washout Period Requirement
CYP3A4 Substrate	alfentanil cyclosporine dihydroergotamine ergotamine fentanyl pimozide quinidine sirolimus tacrolimus	2 weeks or 5 half-lives whichever is longer
CYP2C9 Substrate	phenytoin warfarin	2 weeks or 5 half-lives whichever is longer

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

Also, investigators should consult the product label for lenalidomide and pomalidomide for information regarding medication that is prohibited for concomitant use during the conduct of Parts 1C/2C and 1D/2D, respectively.