PROTOCOL C1071001

A PHASE I, OPEN LABEL STUDY TO EVALUATE THE SAFETY, PHARMACOKINETIC, PHARMACODYNAMIC AND CLINICAL ACTIVITY OF 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)

STATISTICAL ANALYSIS PLAN AMENDMENT (SAP)

Version: 3

Author: PPD

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

1.1. Amendment 3

This amendment updates some response endpoint definitions and changes in Protocol Amendment 8. Texts taken directly from the Protocol Amendment 8 dated 06 Jun 2021 are *Italicized.*

1.2. Amendment 2

This amendment incorporates the added subcutaneous administration cohorts in the amended protocol (amendment 2, V.25Apr2018) study design. Discussions of detailed study conduct features are referred to the amendment. Discussions on combination treatment in the original SAP were found not applicable and were removed in this amendment. In this amendment, the interim study monitoring using Bayesian predictive probability is clarified.

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol C1071001 latest amendment, dated 06 Jun 2021. This SAP is meant to supplement the study protocol. This SAP supersedes the statistical considerations identified in the protocol and, where considerations are substantially different, they will be identified as such. Any deviations from this analysis plan will be described in the clinical study report (CSR). Any post-hoc, or unplanned analyses performed that are not specified in this SAP will be clearly identified in the CSR. This plan is developed and finalized prior to database lock of the clinical database. This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline (Guidance for Industry: Statistical Principles for Clinical Trials) and on the ICH E3 Guideline (Guidance for Industry: Structure and Content of Clinical Study Reports).

Interim data may be analyzed and reported in an interim CSR at any timepoint (including at the primary completion date [PCD]) before the final ORR collection are complete. The following CSRs will contain any updated data collected after the interim CSR cutoff date.

2.1. 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).*

Approximately 120 patients are expected to be enrolled into Parts 1/1.1, 1C, 1D, 1E and approximately 80 patients are expected to enroll into Part 2. Parts 1C, 1D and 1E will enroll approximately 9-16 patients into each safety cohort. Actual number of patients enrolled will depend on the combination tolerability with lenalidomide, pomalidomide and the number of dose levels that are required to select the combination RP2Ds. Patients from the combination cohorts of Parts 1C, 1D, 1E treated at the dose levels selected for Part 2 may be counted towards the sample size of the corresponding cohorts of Part 2. Parts 2A, 2C, 2D and 2E will enroll approximately 20 patients each.

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. Once a dose level has been declared safe following the 60-day evaluation, 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 of the protocol 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.

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 on C1D1 and observed for 48 hours. If no safety concerns arise during this 48-hr. period, 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 of the protocol) during the first 21-day period for weekly dosing and 28-day period for Q2W dosing.

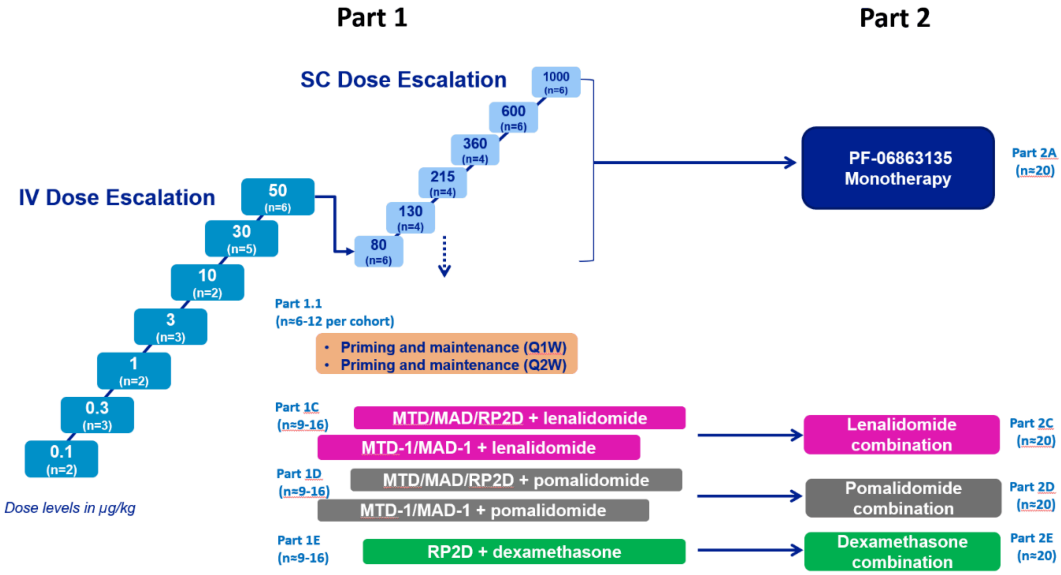
Following the initial dose, treatment with investigational product will continue until disease progression, subject withdrawal of consent or unacceptable toxicity occurs. A follow up visit approximately 4 weeks after the last dose for adverse event (AE) and serious AE (SAE) collection will be conducted. If the subject 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 later 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 subjects 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 24 months after first treatment of the last subject, whichever comes first. Subsequent anti-cancer therapies and relevant transplant information will also be collected.

Treatment with investigational product will continue until disease progression, subject refusal or unacceptable toxicity occurs. It is estimated that subjects will remain on treatment for approximately 4-12 weeks (exclusive of survival follow-up). Actual duration can be longer, if a subject derives benefit from study treatment. The last study treatment will be up to 24 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.

Figure 1 C1071001 Study Design



2.2. Study Objectives and Endpoint

2.2.1. 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

Type	Primary Objectives:	Primary Endpoints:
Safety	• To assess safety and tolerability at increasing dose levels of PF-06863135 as	• Number of DLTs following treatment with escalating doses of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or

	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).	dexamethasone. DLT is observed up to the end of Cycle 1 in each participant
	Secondary Objectives:	**Secondary Endpoints:**
Safety	• 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. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.

Efficacy	• To evaluate anti-myeloma activity of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• ORR defined using the International Working Group (IMWG) response criteria for multiple myeloma and is the percentage of participants with best overall confirmed BOR of sCR, CR, VGPR, or PR relative to the appropriate analysis set.
		• Time to event endpoints as follows:
		  • TTR defined as the time from date of first dose to the first documentation of objective treatment response (PR, VGPR, CR, or sCR, whichever is earlier in participants with BOR of PR, VGPR, CR or sCR).
		  • CRR defined as the proportion of subjects with confirmed stringent Complete Response (sCR) and Complete Response (CR).
		  • CBR defined as proportion of subjects with a BOR of sCR, CR (with or without MRD negativity) VGPR, PR, and MR.
		  • DOR, defined as the time from the first documentation of OR to the first documentation of objective PD of progression, clinical relapse or to death due to any cause, whichever occurs first.
		  • DoCR or sCR, defined as the time from the

		first documentation of complete response to the first documentation of objective progression, clinical relapse or death due to any cause, whichever occurs first. • DOSD is defined for patients with 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. • PFS, defined as the time from date of first dose to date of first documentation of objective PD of progression, or death due to any cause (progression as defined by IMWG response criteria for PD). • OS, defined as the time from date of first dose to date of death due to any cause. Subjects are censored at the time of last follow-up. • Rate of patients with no MRD (by lab data) after treatment with PF-06863135 using IMWG MRD criteria
PK	• 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 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 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).
Immunogenicity	• 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.
Biomarker	• 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:**
Biomarker	• 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 and peripheral blood; • The abundance and diversity of T-cell clones in bone marrow and peripheral blood.
Biomarker	• 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.

2.2.2. Part 2 Dose Expansion

Type	Primary Objectives:	Primary Endpoints:
Efficacy	• To assess preliminary clinical efficacy at RP2D for PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• ORR (as Part 1) • DOR (as Part 1)
	Secondary Objectives:	**Secondary Endpoints:**
Safety	• 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]; • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.
Efficacy	• To further evaluate anti-myeloma efficacy of PF-06863135 as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone.	• Time to event endpoints (as Part 1) • Rate of patients with no MRD after treatment with PF-06863135 using IMWG MRD criteria[4].
PK	• 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.
Immunogenicity	• 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.

Biomarker	• 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):**
Biomarker	• 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 and peripheral blood; • The abundance and diversity of T-cell clones in bone marrow and peripheral blood.
Biomarker	• 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.

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

There are no formal interim statistical analyses in this open-label, unblinded clinical trial. Treatment safety and effectiveness are to be monitored continuously.

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:

- Number of patients with *Grade 5 treatment-related AE ≥ 10%, or*
- Number of patients with *Grade 4-5 treatment-related non-hematological AE >25%.*

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

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Of the dose-escalation phase of the study, a Bayesian procedure is implemented to determine the MTD.

4.2. Statistical Decision Rules

The initial Study Decision rules are described in the following table:

Table 1. Decision Rules

Number of Subjects 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

D: De-escalate the dose; E: Escalate the dose; S: Stay at the dose; U: Unacceptable toxicity

Note: If one subject has a DLT event observed in a dose cohort with 2 subjects enrolled, additional subjects 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;
- 6-12 subjects have been enrolled at a dose that is predicted to be the MTD;
- All doses explored appear to be overly toxic and the MTD cannot be determined.

5. ANALYSIS SETS

Analysis Set	Description	Applicable Analysis (for additional information refer to section 6)
Full Analysis Set (FAS)	all enrolled participants.	Primary endpoint, main analysis (section 6.1.1.1)
DLT Evaluable Set	patients that have experienced a DLT in the DLT observation period or 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.	DLT (see section 8.2.1)
Safety Analysis Set	all subjects who receive at least 1 full or partial dose of study medication.	DLT (see section 8.2.1) Safety (see Section 8.2.3) Demography and Baseline characteristics
PK Concentration Analysis Set	PF-06863135 PK Concentration Analysis Set is defined as all subjects randomized and treated who have at least 1 measurable PF-06863135 concentration.	PK Analysis (see Section 8.2.5.)
PK Parameter Analysis Set	PF-06863135 PK parameter analysis population is defined as all enrolled subjects treated who have sufficient information to estimate at least 1 of the PF-06863135 PK parameters of interest.	PK Analysis (see Section 8.2.5.)
PD/Biomarker Analysis Set	all enrolled subjects with at least 1 of the PD/Biomarkers evaluated at pre- and/or post-dose.	PD/Biomarker Endpoints (see Section 8.2.5.4)
Immunogenicity Analysis Set	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.	Immunogenicity Analysis(see Section 8.2.5.5.)
mITT Analysis Set (for evaluation of efficacy)	all subjects who have received at least one dose of study treatment. If the FAS is same as the mITT, the analysis should be run on FAS.	Efficacy Analysis (see Section 8.2.3)
Response Evaluable Set	all patients who have received at least one dose of the study treatment, and has at least one post baseline efficacy assessment.	Efficacy Analysis (see Section 8.2.3)

5.1. Treatment Misallocations

This is an unblinded MTD dose finding study. Subjects will be included in the cohort defined by their initial dose.

5.2. Protocol Deviations

Protocol deviations will be defined and this analysis plan to be updated before database lock.

5.2.1. Deviations Assessed Prior to Randomization

At Screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

5.2.2. Deviations Assessed Post-randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

6. ENDPOINTS AND COVARIATES

Baseline is defined as the last planned visit measurement on or prior to the first dose of study medication administration; otherwise, the last available measurement on or prior to the first dose of study medication administration is to be adopted as Baseline. The start date is defined as the first day of dosing.

6.1. Efficacy Endpoints

In this First in Patient study anti-tumor activity is a secondary objective for Part 1 and the primary objective for Part 2. All responses are as per investigator reported responses.

Endpoints are as shown in Section 2.2.

- **Complete Response** includes confirmed stringent Complete Response (sCR) and Complete Response (CR). CR Rate (CRR) is defined as the percentage of subjects meeting criterion for CB relative to the mITT analysis set.

- **Clinical Benefit** (CB) includes confirmed response of sCR, CR (with and without MRD negativity), VGPR, PR, and MR. CB Rate (CBR) is defined as the percentage of subjects meeting criterion for CB relative to the mITT analysis set.

- The **OR Rate** (ORR) is defined as the percentage of subjects meeting criterion for OR relative to mITT analysis set.

6.2. Safety Endpoints

- DLT is the primary endpoint of the dose escalation component of the study. The occurrence of DLTs observed in the dosing cohort is used to estimate the MTD. Adverse Events constituting DLTs will be listed per dose level.

- Adverse Events (AEs): Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study medication.

- AEs will be graded by the investigator according to CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects 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.

- Laboratory abnormalities.

- Vital signs.

- ECGs.

- Cytokine Release Syndrome: The severity of cytokine release syndrome (CRS) will be assessed according to the modified grading described by Lee et al 2019 for SC cohorts and Lee et al 2014 for IV cohorts. (Appendix 5 of the protocol).

6.2.1. DLT Evaluability Criteria

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.

The following criteria will be used to assess adequate dosing for DLT evaluability:

- Part 1 (no priming): At least 1 dose of the PF-06863135.

- Part 1.1 Q1W: 75% of the planned PF-06863135 dose regimen in cycle 1, i.e. 28 days from C1D1. The total planned dose as per protocol = (maintenance dose * 4).
    - Dose administered dose will be the sum of Calculated Dose Administered=Volume of PF-06863135 administered * Concentration of PF-06863135 formulation /body weight for the first 28 days.
- Part 1.1 Q2W: 75% of the planned dose regimen in cycle 1, i.e. 28 days from C1D1. The total planned dose as per protocol = (maintenance dose * 2).
    - Dose administered dose will be the sum of Calculated Dose Administered=Volume of PF-06863135 administered * Concentration of PF-06863135 formulation/ body weight for the first 28 days.

- Part 1C and 1D: [(75% of the planned PF-06863135 dose) AND (75% of the planned combination drug dose)] in cycle 1, i.e., 28 days from C1D1.
    - The total planned PF-06863135 dose = (maintenance dose * 4).
    - The total planned Lenalidomide dose = (planned Lenalidomide dose in mg * 21).
    - The total planned Pom dose = (planned Pomalidomide dose in mg * 21).
    - Dose administered should be the sum of calculated actual dose administered for the first 28 days.
- Part 1E: [(75% of the planned PF-06863135 dose) AND (75% of the planned Dexamethasone dose)] in cycle 1, i.e., 28 days from C1D1.
    - The total planned PF-06863135 dose = (maintenance dose * 4).
    - The total planned Dexamethasone dose = (planned Dexamethasone dose in mg * 4). *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* in the protocol.

Relative dose intensity at each cycle will be calculated as follows:

- Part 1 (no priming): Cycle length is determined as entered by the site.
    - Dose administered will be the sum of "Calculated Dose Administered" for the cycle.
    - The total planned dose will be the (assigned dose of PF-06863135 *3)
    - If patient discontinues before end of the cycle, the planned dose for the will be based on dosing for number of days on the last cycle based on the dosing page. For example, if patient discontinues after CXD2, the planned dose will be (assigned dose of PF-06863135 *1).

- Part 1.1 Q1W and Part 2A: Cycle length is determined as entered by the site.
    - The total planned dose = (maintenance dose of PF-06863135 * 4).
    - Dose administered will be the sum of "Calculated Dose Administered" for the cycle.
    - If patient discontinues before end of the cycle, the planned dose for the will be based on dosing for number of days on the last cycle based on the dosing page.

- Part 1.1 Q2W: Cycle length is determined as entered by the site.
    - The total planned dose = (maintenance dose of PF-06863135 * 2).
    - Dose administered will be the sum of "Calculated Dose Administered" for the cycle.
    - If patient discontinues before end of the cycle, the planned dose for the will be based on dosing for number of days on the last cycle based on the dosing page.

- Part 1C and 1D: Cycle length is determined as entered by the site.
    - The total planned PF-06863135 dose = (maintenance dose * 4).
    - The total planned Lenalidomide dose = (assigned dose of Lenalidomide in mg * 21).
    - The total planned Pomalidomide dose = (assigned Pomalidomide dose of mg * 21.
    - Dose administered should be the sum of "calculated actual dose" for the cycle.
    - If patient discontinues before end of the cycle, the planned dose for the lenalidomide/pomalidomide will be based on daily dosing for min(number of days on the cycle, 21) as entered in the dosing page .

- Part 1E: Cycle length is determined as entered by the site.
    - The total planned PF-06863135 dose = (maintenance dose * 4).
    - The total planned Dexamethasone dose = (assigned dose of Dexamethasone * 4).
    - Dose administered should be the sum of "calculated actual dose" for the cycle.
    - If patient discontinues before end of the cycle, the planned dose for the will be based on dosing for number of days on the last cycle based on the dosing page.

6.3. Pharmacokinetics Endpoints

Drug concentrations of PF-06863135 will be measured using validated methods. For patients from Parts 1, 1.1, 1C, and 1D, PK parameters following the Cycle 1 Day 1 dose and Cycle 2 Day 1 dose will be determined separately from the respective concentration-time data using standard noncompartmental methods. Actual sample collection times will be used for the parameter calculations. For PF-06863135, PK parameters including maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve over 1 dosing interval (AUC_{τ}), area under the concentration-time curve from time 0 to the last measurable concentration (AUC_{last}), and, if data permit or if considered appropriate, area under the concentration-time curve from time 0 extrapolated to infinity time (AUC_{inf}), terminal elimination half-life ($t_{½}$), clearance (CL or CL/F), volume of distribution at steady state (V_{ss}), and accumulation ratio (R_{ac}) will be calculated. PK parameters will be derived from the concentration-time data as follows:

Table 2. PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the concentration-time profile from time zero to the time of the last quantifiable concentration	Linear/Log trapezoidal method
AUC_{τ}	Area under the concentration-time	Linear/Log trapezoidal method

Parameter	Definition	Method of Determination
	profile from time zero to the time τ, the dosing interval	
AUC_{inf}	Area under the concentration-time profile from time zero extrapolated to infinite time	$AUC_{(0\text{-}t[last])}$ + (Clast*/kel), where Clast* is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{min}	Lowest concentration observed during interval	Observed directly from data
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$T_{½}$	Terminal elimination half-life	$Log_e(2)$/kel, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL (IV) or CL/F (SC)	Clearance (IV) or apparent clearance (SC)	Dose/ AUC_{inf} for cycle 1; Dose/ AUC_{τ} for cycle 2
V_{ss}	Volume of distribution at steady state	CL×MRT
R_{ac}	Observed accumulation ratio	$AUC_{cycle\ 2,\ \tau}$/ $AUC_{cycle\ 1,\ \tau}$

For patients enrolled in Part 2A, 2B 2C, and 2D of the study, trough PF-06863135 concentrations will be summarized descriptively by cycle.

Drug concentrations of lenalidomide (Parts 1C and 2C only), and pomalidomide (Parts 1D and 2D only) will be measured using validated methods and 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. No PK parameters will be determined for lenalidomide, or pomalidomide.

6.4. PD/Biomarker Endpoints

The biomarker endpoints will be used to help understand the in mechanism of action as well as potential mechanisms of resistance of PF-06863135 either as a monotherapy or in combination therapy.

Table 3. 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

Table 3. Biomarker Assays and Sample Sources

Biomarker	Matrix	Assay
	BM biopsy (possible)	IHC
RNA profiling	Whole blood	RNA Sequencing
	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

- BCMA expression and enumeration of CD138+ benign and malignant plasma cell populations in bone marrow pre- and post-dose, as assessed by multiparameter flow cytometry;
- Pre- and post-dose levels of soluble BCMA;
- Enumeration of T, B, and NK subtypes in whole blood;
- T cell immunophenotyping, including but not limited to proliferation and activation markers in whole blood and bone marrow by flow cytometry analysis;
- The relative expression of RNA transcripts, including but not limited to, those associated with immune activation and immune regulation in bone marrow and peripheral blood;
- The abundance and diversity of T cell clones in bone marrow and peripheral blood;
    - BCMA expression on plasma cells and their spatial relationship to T cells by immunohistochemistry.
    - 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 Protocol C1071001.

6.4.1. Immunogenicity Endpoints

For the immunogenicity data, the percentage of subjects with positive ADA of PF-06863135 and Nab each will be further characterized in terms of antibody specificity and summarized by dose level (Part 1) or by treatment arms. For subjects with positive ADA or Nab, categorization as treatment-emergent or treatment-boosted, the magnitude (titer), time of onset, and duration of ADA or Nab response will also be described, if data permit. Potential impact of immunogenicity on PK and clinical response including PD markers, safety/tolerability and efficacy of PF-06863135 will be explored, if warranted by the data).

6.4.2. Outcomes Research Endpoints

Not applicable

6.5. Covariates

The analyses of the MTD do not use covariates, and none will be defined. There are no planned comparisons between dose groups.

7. HANDLING OF MISSING VALUES

Missing data will be excluded from the tabular summaries.

7.1. Pharmacokinetics

7.1.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification).

7.1.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of the median values at each time point, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (i.e., not done) or NS (i.e., no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

7.1.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (i.e., not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

Overview of analysis:

- Continuous data will be summarized using descriptive statistics (mean, median, SD, minimum, maximum, and 2-sided 95% CI where applicable)

- Categorical data (including point estimates) will be summarized by frequency counts, percentages and binomial 95% CIs using the Clopper-Pearson[5] method.

- Kaplan-Meier estimates (product-limit estimates) will be presented and displayed graphically where appropriate, together with a summary of associated statistics (including 2-sided 95% C is using log(-log) method according to Kalbfleisch and Prentice[8]).

8.1. Statistical Methods

The statistical summaries are non-inferential. The data are summarized by cohort defined by the initial dose, and route of administration of the study drug.

8.1.1. Analyses for Continuous Data

Continuous data will be summarized with the mean, median, minimum, maximum and standard deviation.

8.1.2. Analyses for Categorical Data

Categorical data will be summarized by number of unique subject incidence.

8.1.3. Analyses for Binary Endpoints

Binary data will be summarized using number of unique subject incidence, and Wilson's confidence interval for binomial proportions will be presented

8.1.4. Analyses for Time-to-event Data

The median, percentiles, and probabilities at particular points in time are estimated using the method of Kaplan and Meier. Kaplan-Meier estimates (product-limit estimates) will be presented and displayed graphically where appropriate, together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley, 1982.6

8.2. Statistical Analyses

8.2.1. Primary Analysis

The primary analysis will be based on the Safety Analysis Set. The analysis objective is to summarize the adverse event incidence and will implement Pfizer standard summaries for adverse events. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in the Study Design section. Adverse Events constituting DLTs will be listed per dose level. Because the intent is to find a desirable dose that meets the tolerability criteria based on DLT rate while demonstrating clinical activity based on response rate, descriptive statistics (n, frequency, and percentage) will be reported.

Corresponding listings of data will be generated. Adverse events and cytokine release syndrome will be summarized by dose cohorts and in aggregate.

8.2.2. Efficacy Analyses

No formal hypothesis testing will be performed on analysis of efficacy endpoints.

Efficacy analysis will be summarized by dose cohorts. Analysis of progression free survival and time to progression are defined as time from the date of first dose. Summaries of the n and % of subjects with PFS, and TTR and data listing by tumor type and dose will be generated. If applicable, the PFS may also be summarized using the Kaplan-Meier method at all or some of the following timepoints:

- OS at 6, 9, 12, 18, 24 months timepoints
- PFS, DOR, DoSD and DoCR at 3, 6, 9, 12, 18 months timepoints
- Reverse KM Follow-up probability is 3, 6, 9 months timepoints

The 95% confidence intervals will be generated. Confidence intervals for medians and quartiles will be based on the Brookmeyer-Crowley method. Confidence intervals for the estimated probability of an event at a particular time point will be generated using the Greenwood formula. Duration of response will be summarized with number of responders, number and percentage of event/censorship, mean, standard deviation, minimum, maximum and median of duration in unit of months. ORR and CBR will be summarized by number of subjects meeting respective criteria, percentage. The 95% confidence intervals will be generated for PFS, TTR, ORR, and CBR. Definitions of PFS, TTR, DoR, ORR, and CBR are outlined below.

8.2.2.1. Progression-Free Survival (PFS)

PFS is the time from date of first dose to date of first documentation of PD in a progression or death due to any cause. PD or death after no more than 1 missing tumor assessment or date of first dose will be counted as an event according to the disease assessment date or date of death, as appropriate. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of progression free survival. Subjects will be considered to have progressive disease if they meet the criteria for progression even by a variable that was not considered as a measurable marker at baseline; however, for subjects who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in serum FLC alone. In the IMWG criteria, clinical relapse subjects 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.

Clinical relapse will be equivalent to PD. Note that a progression is defined as:

- 2 consecutive assessments of PD,
- or 1 PD as last efficacy assessment followed by permanent treatment discontinuation,

- or 1 PD following treatment discontinuation (EOT for both treatments in combined therapy - Part 1C and Part 1D). If the discontinuation is after PD but before the next response, then it is considered PD. If there are better responses before discontinuation, it is not considered PD to allow for possible pseudo progression from the treatment which is clinically possible and accepted.

The mITT analysis set will be used.

Censoring: Subjects without an event or with an event after 2 or more missed tumor assessments will be censored as described in Table 4. In addition, if a new anti-cancer therapy is started prior to an event, the subject will be censored on the date of the last adequate tumor assessment that documented no progression prior to the start of the new anti-cancer therapy.

An adequate post-baseline assessment is defined as an assessment where a response of sCR, CR, VGPR, PR, MR, SD, Relapse or PD can be determined based on IMWG response criteria for multiple myeloma. Subjects with no baseline disease assessment (including subjects with an inadequate baseline assessment) or with no adequate post-baseline disease assessments within 46 days for cohorts with 21 day cycles and 60 days for cohorts with 28 day cycles after the date of first dose will be censored on the date of first dose, unless the subject dies within 46 days for cohorts with 21 day cycles and 60 days for cohorts with 28 day cycles of the date of the first dose, in which case, death will be an event on date of death. Subjects will be considered to have progressive disease if they meet the criteria for progression by a variable that was not considered measurable at baseline.

Events and censoring rules are summarized in Table 4.

Table 4. Progression Free Survival

Situation	Date of Progression/Censoring[1]	Outcome
Inadequate baseline assessment	First dosing date in Cycle 1 (or Cycle 0 for priming cohorts)	Censored
No on-study assessments	First dosing date in Cycle 1(or Cycle 0 for priming cohorts)	Censored
Alive, on treatment[2] and no Progression	Date of last objective tumor assessment[3]	Censored
New anti-cancer therapy	Date of last adequate disease assessment that documented no progression prior to new anti-cancer therapy	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation[2]	Date of first objective tumor assessment showing objective progression	Progressed (Event)
Withdrawal of consent prior and refusal to follow-up	Date of last objective tumor assessment prior to	Censored

	discontinuation[2]	
Treatment discontinuation for undocumented progression, toxicity or other reason	Date of last objective tumor assessment prior to discontinuation[2]	Censored
Death prior to first planned tumor assessment	Date of death	Death (Event)
Death without objective progression prior to treatment discontinuation[2]	Date of death	Death (Event)
Death or progression after 2 or more missed tumor assessments[4]	Date of last objective tumor assessment prior to the event	Censored
Lost to follow-up	Date of last objective tumor assessment[3]	Censored

1. For date of censorship, if a tumor assessment takes place over a number of days (e.g., superficial lesions one day, scans another), the last date is used as the assessment date.
2. or within 28 days of discontinuation of treatment.
3. Date of last adequate disease assessment that documented no progression
4. This would be 46 days for cohorts with 21 day cycles and 60 days for cohorts with 28 day cycles

Reasons for censoring should be summarized according to the categories in Table 5.

Table 5. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy before event.	Start of new anti-cancer therapy
3	Event after 2 or more missed tumor assessments/start date	Event after missing assessments [a]
4	No event and [withdrawal of consent date ⩾ date of first dose OR End of study (EOS) = Subject refused further FU]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any EPOCH after screening says subject will not continue into any subsequent phase of the study] and no adequate post-baseline disease assessment	No adequate post-baseline disease assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missed tumor assessment.

Disease Assessment Date: The Date of Disease Assessment at each nominal timepoint as provided by the investigator on the IMWG response CRF page will be utilized for the respective analyses.

Adequate Baseline Disease Assessment: Adequate baseline is defined using the following criteria:

- All baseline disease assessments (IMWG responses) must be within 28 days prior to and including the date of first dose;

- Measurable disease based on IMWG criteria as defined by at least 1 of the following:
  - Serum M-protein ≥0.5 g/dL by SPEP;
  - Urinary M-protein excretion ≥200 mg/24 hours by UPEP;
  - Serum immunoglobulin FLC >10 mg/dL (>100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65).

Adequate Post-baseline Disease Assessment: An adequate disease assessment is defined as an assessment where a time-point response of sCR, CR, VGPR, PR, minimal response (MR), Stable Disease (SD) or PD has been provided.

Timepoints where the response is not evaluable or no assessment was performed will not be used for determining the censoring date for time-to-event endpoints including PFS, DOR and DOCR.

8.2.2.2. Overall Survival (OS)

OS is defined as the time from the date of first dose until death due to any cause and will be calculated in months as follows:

OS (months) = [date of death or censoring – date of first dose +1] / 30.4375

Survival status is expected to be collected irrespective of study intervention discontinuation or participant's request to discontinue study procedures. All participants who have not withdrawn consent for further participation in the study should be followed for survival until the end of the study. OS for participants not known to have died are censored on the date of last known alive.

OS time will be estimated using the same Kaplan-Meier method and displayed graphically as described for PFS in Section 8.2.2.1. Median OS and 2-sided 95% CI will be provided. The OS rate at 6, 9, 12, 18, and 24 months will be estimated with corresponding two-sided 95% CIs.

Frequency (number and percentage) of participants with death events and censoring reasons will be presented by cohort along with the overall event and censor rates. The event and censoring reasons are as follows:

- Death;

- Alive (Ongoing and no death);

- Withdrawal of consent;
- Lost to follow-up.

The OS time or censoring time and the reasons for censoring will also be presented in a listing. The mITT Analysis will be used.

8.2.2.3. Time to Response (TTR)

In TTR analysis, TTR is defined, for participants with an objective response per IMWG criteria (i.e., subjects whose BOR are progressive disease, clinical relapse, stable disease, minimal response or deaths are excluded), as the time from the date of first dose to the first documentation of objective response that is subsequently confirmed. TTR will be calculated in days as follows:

TTR (days) = [date of first objective response – date of first dose + 1]

TTR will be summarized using simple descriptive statistics (mean, standard deviation, minimum, median, and maximum). **Censoring**: Subjects will be censored same as censoring for primary definition of progression free survival (PFS) used in the study. This will be calculated on all responding subjects.

8.2.2.4. Time to Complete Response (TTCR)

TTCR is defined, for participants with an objective response per IMWG criteria is CR or sCR, as the time from the date of first dose to the first documentation of sCR or CR that is subsequently confirmed. TTCR will be calculated in days as follows:

TTCR (days) = [date of first CR or sCR – date of first dose + 1]

TTCR will be summarized using simple descriptive statistics (mean, standard deviation, minimum, median, and maximum). **Censoring**: Subjects without response will be censored same as censoring for primary definition of progression free survival (PFS) used in the study. This will be calculated on all subjects with objective response of CR or sCR.

8.2.2.5. Time to VGPR or better (TTVGPR)

TTVGPR or better is defined, for participants with an objective response per IMWG criteria is VGPR, CR or sCR, as the time from the date of first dose to the first documentation of VFPR, CR or sCR that is subsequently confirmed. This will be calculated in days as follows:

TTVGPR (days) = [date of first VGPR, CR or sCR – date of first dose + 1]

TTVGPR or better will be summarized using simple descriptive statistics (mean, standard deviation, minimum, median, and maximum). **Censoring**: Subjects without response will be censored same as censoring for primary definition of progression free survival (PFS) used in

the study. This will be calculated on all subjects with objective response of VGPR, CR or sCR.

8.2.2.6. Duration of Response (DoR)

DOR is defined, for participants with an objective response per IMWG criteria, as the time from the first documentation of objective response that is subsequently confirmed, until PD per IMWG criteria, or death due to any cause, whichever occurs first. It will be calculated as follows:

DOR (months) = [date of event or censoring – first date of objective response + 1] / 30.4375

The censoring rules for DOR are as described for PFS in Section 8.2.2.1, except that participants will not be censored for inadequate baseline assessment or for no adequate post-baseline assessment, as only participants with an objective response are included in the analysis of DOR.

If at least 3 participants achieve an objective response and subsequently have an event, DOR will be estimated using the same Kaplan-Meier method as described for PFS in Section 8.2.2.1 and displayed graphically where appropriate. Otherwise, only listings will be provided.

The DOR rate at 3, 6, 9, 12 and 18 months (and in subsequent 6-month increments while there are participants still at risk) will be estimated with corresponding two-sided 95% CIs.

8.2.2.7. Duration of sCR or CR (DoCR)

DoCR is the time from first observation of sCR or CR to the time of disease progression, or death due to any cause. The censoring rules for DoCR are the same as those for PFS outlined in Section 8.2.2.1 . This will be calculated on responding subjects with confirmed responses of CR or sCR.

DoCR is defined, for participants with a sCR or CR per IMWG criteria, as the time from the first documentation of sCR or CR that is subsequently confirmed, until PD per IMWG criteria, or death due to any cause, whichever occurs first. It will be calculated as follows:

DoCR (months) = [date of event or censoring – first date of CR or sCR + 1] / 30.4375

The censoring rules for DoCR are as described for DOR in Section 8.2.2.4.

If at least 3 participants achieve a CR or sCR and subsequently have an event, DoCR will be estimated using the same Kaplan-Meier method as described for DOR in Section 8.2.2.4 and displayed graphically where appropriate. Otherwise, only listings may be provided.

The DoCR rate at 3, 6, 9, 12 and 18 months will be estimated with corresponding two-sided 95% CIs.

8.2.2.8. Overall Response Rate (ORR)

The ORR is defined as the percentage of subjects with BOR of sCR, CR, VGPR, or PR relative to the appropriate analysis set.

Criteria for IMWG Response as specified in Appendix 2 and 3. A response can be confirmed with a second response of same or better.

This is calculated from a sequence of objective status evaluations. The mITT analysis set and response evaluable analysis set will be used.

Table 6. Criteria for Best Response

sCR[#]	Stringent Complete Response: An objective status of Stringent Complete Response on at least two sequential disease assessments.
CR[#]	Complete Response: An objective status of Complete Response on at least two sequential disease assessments.
VGPR	Very Good Partial Response: An objective status of Very Good Partial Response on at least two sequential disease assessments.
PR	Partial Response: An objective status of Partial Response on at least two sequential disease assessments.
MR	Minimal response: An objective status of Minimal Response on at least two sequential disease assessments.
UsCR	Unconfirmed sCR: One objective status of Stringent Complete Response (based on evidence from serum and urine studies and, if drawn, bone marrow biopsy) but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and before new anti-cancer therapy.
UCR	Unconfirmed CR: One objective status of Complete Response (based on evidence from serum and urine studies and, if drawn, bone marrow biopsy) but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and before new anti-cancer therapy.
UVGPR	Unconfirmed VGPR: One objective status of Very Good Partial Response, but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and before new anti-cancer therapy.
UPR	Unconfirmed PR: One objective status of Partial Response, but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before

Table 6. Criteria for Best Response

	progression and before new anti-cancer therapy.
SD	No Change/Stable Disease: At least one objective status of Stable Disease but not qualifying as any of the above. If radiographic studies were performed there should be no known progressive or new bone lesions. Subjects who had a single response of sCR, CR, VGPR, PR, or MR but no SD response can also confirm SD.
Progressive Disease (PD)	First objective status recoded of Progression. Progression is defined per the IMWG response criteria for Progressive Disease. Clinical relapse will be equivalent to PD. Note that a progression is defined as: • 2 consecutive assessments of PD, • or 1 PD as last efficacy assessment followed by permanent treatment discontinuation, • or 1 PD following treatment discontinuation (EOT for both treatments in combined therapy - Part 1C and Part 1D). If the discontinuation is after PD but before the next response, then it is considered PD. If there are better responses before discontinuation, it is not considered PD to allow for possible pseudo progression from the treatment which is clinically possible and accepted.

CR and sCR: MRD tests should be initiated only at the time of suspected complete response. Confirmation with two consecutive assessments is not required.

8.2.2.9. Clinical Benefit Rate (CBR)

A subject with a BOR of sCR, CR (with or without MRD negativity) VGPR, PR, and MR is defined as having Clinical Benefit (CB). The CBR is defined as the percentage of subjects with CB according to the appropriate analysis set. Number and percentage of subjects having CB will be tabulated by treatment group.

Proportion of subjects having minimal residual disease among sCR and CR subjects will be summarized by dose cohorts. The mITT analysis set will be used.

8.2.2.10. Duration of Stable Disease (DoSD)

The DoSD is defined for patients with 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. It will be calculated as follows:

DoSD (months) = [date of event or censoring – first date of SD + 1] / 30.4375

The censoring rules for DoSD are as described for PFS in Section 8.2.2.1. This analysis will include only participants with confirmed stable disease or better. The DoSD rate at 3, 6, 9, 12 and 18 months will be estimated with corresponding two-sided 95% CIs.

For subjects with no adequate baseline assessment but with post-baseline assessments which can confirm SD, subjects will be censored to first dose date, then we will calculate DoSD= max ((date of event or censoring – first date of SD + 1) , 1). So DoSD will be 1 day instead of negative value.

8.2.2.11. Minimal Residual Disease (MRD)

MRD to be summarized as per Appendix 3 if data permits.

Minimal Residual Disease (MRD) (assessed by central lab) negativity rate is the proportion of participants with negative MRD per IMWG sequencing criteria by bone marrow aspirate (BMA) at any time after first dose.

MRD negativity rate is defined as the proportion of participants with negative MRD (assessed by central lab) per IMWG sequencing criteria at any time after first dose of study intervention. MRD negativity will be defined by two thresholds, 10^{-5} and 10^{-6}.

Point estimates of MRD negativity rate will be calculated along with the 2-sided 95% CIs using the Clopper-Pearson method[5].

MRD negativity rate will also be summarized among participants who achieved CR or sCR with 2-sided 95% CIs.

If data permits, MRD-negativity status at 1-year, 2-year and 3-year from the time of first documentation of MRD-negativity may be summarized by number and percentage among participants who achieved CR or sCR and MRD negativity.

8.2.2.12. Duration of Treatment

The duration of treatment is calculated as follows:

Duration of treatment (months) = (last nonzero dose date - first dose date + 1)/30.4375

Duration of treatment will be summarized with descriptive statistics (n, mean, median, mode, standard deviation and range), frequency of occurrence <2months, >=2months and <4months, >=4 months and <6months, >=6months and <8months, and >=8months. Duration of treatment may also be presented graphically.

8.2.3. Safety Analyses

Safety data will be summarized using Pfizer standard data summary procedures. Data will be summarized by cohort, defined by the initial dose. When the initial dose is determined to be the MTD, then the tables will also label the dose as the MTD. A breakdown of demographic

data will be provided for age, race, weight, body mass index, and height by cohort defined by initial dose.

On-treatment period is defined as the time from the first dose of study intervention through the minimum of (90 days (28 days for patients who completed the trial prior to approval of PA8 in June 2021) after last dose and start day of new anticancer therapy) – 1 day. Adverse events occurring on the same day as the first dose of study intervention and marked "After" will be considered to have occurred during the on-treatment period. For all AE analysis relative to dosing time or date, AEs occurring on the same day of dosing but marked "Before" will be attributed to previous dose, and those marked as "After" will be attributed to the dose.

The analysis sets to be used are the Safety Analysis set, DLT Evaluable Set will be used as applicable.

For some summary tables, the following clustered terms for cytopenia based on PT may be used:

- Thrombocytopenia (PT=Thrombocytopenia; Platelet count decreased),
- Anaemia (PT=Anaemia; Haemoglobin decreased, Red blood cell count decreased, Haematocrit decreased, Normochromic anaemia, Normocytic anaemia, Normochromic normocytic anaemia),
- Neutropenia (PT=Neutropenia; Neutrophil count decreased, Neutrophil percentage decreased, Cyclic neutropenia, Agranulocytosis, Granulocytopenia, Granulocyte count decreased), Leukopenia (PT=Leukopenia; White blood cell count decreased),
- Lymphopenia (PT=Lymphopenia; Lymphocyte count decreased, Lymphocyte percentage decreased, CD4 lymphocytes decreased, CD4 lymphocyte percentage decreased, CD8 lymphocytes decreased, CD8 lymphocyte percentage decreased),
- Hyperphosphataemia (PT=Blood phosphorus increased),
- Hypertension (PT=Blood pressure increased).

AE summarized as Peripheral Neuropathy includes MedDRA SMQ Peripheral neuropathy narrow and broad and SMQ Guillain-Barre syndrome narrow.

Hypogammaglobulinemia as an adverse even of clinical interest may be presented, using the following definition MedDRA PT terms: 'Blood immunoglobulin G decreased', 'Hypogammaglobulinaemia', 'Hypoglobulinaemia', 'Immunoglobulins decreased', 'Globulins decreased'.

AE summarized as Infection includes any event from SOC Infections and infestations.

8.2.3.1. Adverse Events

AEs will be graded by the investigator according to the CTCAE version 4.03 and coded using the MedDRA. 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 medication. The number and percentage of subjects who experienced any AE, serious 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. The Safety Analysis Set will be used.

8.2.3.2. Laboratory Tests Abnormalities

The number and percentage of subjects who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory test. The analyses will summarize laboratory tests in the entire study. Shift tables may be provided to examine the distribution of laboratory abnormalities. The Safety Analysis Set will be used. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal high/low or not done. Baseline is defined as the latest non-missing value from the pre-treatment period.

8.2.3.3. Study Conduct and Patient Disposition

An accounting of the study subjects will be tabulated. The subject evaluation groups will be listed. The Full Analysis Set will be used. Subject discontinuation from treatment and study will be tabulated and listed separately with their reason for discontinuation. The Safety Analysis Set will be used.

8.2.3.4. Baseline Characteristics

Baseline characteristics such as demographics, prior line of therapy, medical history, baseline Relapse or Refractory, baseline cytogenetic risk, IMWG Diagnosis Criteria, baseline bone marrow plasma cells, ECOG performance status will be tabulated and listed by dose. The Safety Analysis Set will be used.

8.2.3.4.1. Cytogenetic Risk

Cytogenetic risk will be calculated based on:

- If Karyotype if Blank: then cytogenetic risk is “Missing”.
- If Karyotype is Normal: Then cytogenetic risk is “Standard”
- If Karyotype is abnormal:
    - Look for the following in abnormalities or other:
        - Del 17p
        - T(4;14)
        - T(14;16)
        - Cytogenetic Del 13q
        - Cytogenetic Hypodiploidy
        - If collected, Plasma cell labeling index >3%

If any of these exist, then risk is “high” else “standard”.

8.2.3.5. Treatment Administration/Compliance

Listings and tables by dose level will be provided. Day 1 of a cycle is the date of first dose within that cycle. Each cycle is a 3-week period for Part 1, or 4-week period for Parts 1.1 1C, 1D, 1E, 2A, 2C, 2D, or 2E except cycle 0 for priming dose. The safety analysis set will be used.

The following will be summarized by subject for each dose level:

- Number of subjects per dose level;
- Median and range of number of cycles started per subject;
- Number (%) of subjects starting a cycle (1, 2, 3…);
- Number (%) of subjects with cycle delays;
- Number (%) of dose interruptions (include both known and unknown dates);
- Number (%) of subjects with dose reductions;
- Number (%) of each reason (AE vs. Other) for cycle delays, dose interruptions and dose reductions;
- Time on treatment (median, range).

The following will be summarized by cycle received for each dose level:

- Total number of cycles started;
- Number of cycles started per subject (median, range);

The following will be summarized for cumulative dose by dose level and cycle: Summary statistics (mean, median, standard deviation and range) of cumulative dose and percent of starting dose (compared to Day 1 dose of each cycle).

Listings by subject (ordered by dose level): start date and stop date of each dosing period within each cycle (including records with 0 mg), administered total daily dose for each period, any missed doses with unknown dates (Y/N), number of missed doses with unknown dates, reason for any dosing changes. Listings by subject and each cycle (ordered by dose level): cycle length, total planned dose, administered total dose, percentage of planned dose, dose delay (yes/no), dose reduction (yes/no), and dose interruption (yes/no).

8.2.3.6. Prior, Concomitant, and Further Therapies

Prior, concomitant, and further therapies (drug and non-drug treatments) will be coded by the World Health Organization (WHO) medical dictionary. Summary tables, listings of prior, concomitant, and further therapies will be provided separately.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation.

8.2.3.6.1. Prior Anti-Cancer Therapy

Number and percentage of participants with any prior regimen will be presented along with median and range of number of prior regimens. The number and percentage of participants in each of the following anticancer therapy categories will be tabulated:

- Participants with at least 1 type of prior anticancer treatment;
- Participants with at least 1 prior anticancer radiotherapy;
- Participants with prior IMiDs and type (e.g., lenalidomide, pomalidomide, or thalidomide, Iberdomide, CC-92480);
- Participants with prior PI and type (e.g., bortezomib, carfilzomib, ixazomib);
- Participants with prior anti-CD38 mAb and type (eg, daratumumab, isatuximab);
- Participants who are Triple-class refractory: refractory to at least 1 PI, and at least 1 IMiD, and at least 1 anti CD38.
- Participants who are Quad-class refractory: refractory to at least 2 PI, AND at least 2 IMiD;
- Participants who are Penta-class refractory: refractory to at least 2 PI, and at least 2 IMiD, and at least 1 anti CD38;
- Participants who received at least 2 PIs, 2 IMiDs and 1 anti-CD38;
- Participants with prior Selinexor;
- Participants with prior Elotuzumab;
- Participants with prior transplant and type (autologous or allogeneic);
- Refractory to last line of therapy;

- Type of prior BCMA-targeted therapy (ADC, CAR-T).

The prior anticancer drugs will be coded in the WHO Drug coding dictionary and will be summarized based on the number and percentage of participants by preferred term. A participant will be counted only once within a given preferred term, even if he or she received the same medication at different times unless specified.

Refractory is defined as having progression occurred after regimen during the regimen or discontinuation of the regimen due to progression.

8.2.3.7. Electrocardiograms (ECG)

Triplicate 12-lead ECGs will be performed per Schedule of Activities. The Day 1 triplicate ECG prior to treatment administration will be used as baseline; if it is missing, values from the ECG taken at screening will be used for baseline.

ECG assessments reported by the site will include PR, HR, QT, QRS, and QTcF. A mean score is calculated and reported for any replicate measurements having the same nominal visit. All summary statistics, analyses and figures will be based on the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates.

ECG summaries will include all ECG assessments from the on-treatment period. RR will be derived from HR. Fridericia's correction (QTcF) will be based on the values collected on the CRF. QTcF will be derived from QT and HR in case QTcF is missing using the following formula:

$$QTcF(msec) = QT(msec) / \sqrt[3]{RR(sec)}$$

All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

QTcF will be summarized by maximum on-treatment values using the following categories:

- <450 msec;
- ≥ 450 msec but ≤480 msec;
- >480 msec but ≤500 msec;
- >500 msec.

Unscheduled assessments will be utilized in addition to planned assessments. Shift tables will be provided for baseline QTcF value versus worst on-treatment value. Results of ECGS done as additional follow-up for prolonged PK $t_{1/2}$ and unscheduled ECG results will be listed but not summarized. Additionally, maximum increases from baseline (including

scheduled and unscheduled assessments) will be summarized based on the following categories:

- Change >60 msec;
- Change >30 msec but ≤60 msec;
- Change ≤30 msec.

Data listings will contain the means from a triplicate as well as the parameters from each of the 3 ECGs. Note that using the mean value may result in a participant having a measurement that is not represented by an actual ECG.

8.2.4. Other Safety Data – Screening and Other Special Purpose Data

Prior medication(s), non-drug treatment(s), medical history and physical examination will be listed in accordance with the sponsor reporting standards. Medical history will be mapped using the MedDRA thesaurus.

Cytokine Release Syndrome (CRS) and Immune Cell-Associated Neurotoxicity syndrome (ICANS) are the AEs of special interested in the study and will be presented in the form of summary tables and listings.

CRS will be graded according to the modified grading described by Lee *et al.* (2014) (Appendix 4) and the ASTCT consensus grading (Lee et al 2019). The ASTCT grading will be the primary CRS grading used for all analysis. The CRS grade as per the ASTCT (Lee et al. 2019) criteria captured in the CRS CRF page will be used for all summary tables containing CRS grades for SC cohorts. CRS grades as per Lee et al. 2014 captured in the AE CRF page will be used for all summary tables containing CRS grades for IV cohorts and listed for all cohorts.

Emphasis will be put on Cytokine Release Syndrome by analyzing all patient symptoms related to CRS, time to CRS onset, proportion of subjects treated with tocilizumab and time to CRS resolution.

Information on events of ICANS such as grade, symptoms and time to onset and duration will be summarized and listed.

Duration of Adverse Events may be presented for AEs of interest such as CRS and ICANs and is calculated as following:

Duration of AE = start data of the AE -stop date of the AE +1

Time to first onset of AE may be presented for AEs of interest such as CRS and ICANS and is computed as follows:

Date of onset of AE = date of first onset of CRS - first dose date +1.

8.2.5. PK Analyses

8.2.5.1. Pharmacokinetic Parameters

To assess the pharmacokinetics of PF-06863135, the PK parameters detailed in Section 6.4 will be listed and summarized for subjects in the PK analysis set (as defined in Section 5). Missing values will be handled as detailed in Section 7.1. Each PK parameter, if calculatable by data, will be summarized by dose, cycle, and day and will include the set of summary statistics as specified in the table below:

Parameter	Summary statistics
AUC_{τ}, C_{min}, C_{max}, CL, V_{ss}, and R_{ac}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum
T_{max}	N, median, minimum, maximum

To assess the relationship between the PK parameters and dose, dose normalized AUC_{τ} and C_{max} will be plotted against regimen, dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (by µg/kg or mg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented on the plot.

8.2.5.2. Pharmacokinetic Concentrations

To assess the PK profile of PF-06863135, PK concentrations will be listed; summarized (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean) by dose, cycle, day and nominal time; and plotted for subjects in the PK analysis set (as defined in Section 5), where missing and BLQ values will be handled as detailed in Section 7 above.

Presentations for PF-06863135 time-concentration data will include:

- A listing of all concentrations sorted by dose, subject ID, period and nominal time post-dose. The listing of concentrations will include the actual sample collection times, and the time of dosing. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by dose and nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations against nominal time post-dose by dose (based on the summary of concentrations by dose and time post-dose), with all doses presented on the same plot.

Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales.

For summary statistics and median plots by sampling time, the nominal PK sampling time will be used.

8.2.5.3. PD/Biomarker Endpoints

For baseline continuous endpoint data, descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided by treatment arm. Appropriate statistical methods, e.g., multivariate analysis, logistic regression, longitudinal or repeated measure analysis or Cox-regression analysis, may be used to investigate any possible relationship of biomarker levels with PF-06863135 anti-myeloma efficacy, either as a monotherapy or in combination therapy. Summary statistics will be tabulated by visit and treatment group.

8.2.5.4. Population PK and PK/PD Modeling

Pharmacokinetic and PD data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association/correlation between PF-06863135 exposure and biomarkers (e.g., soluble BCMA) or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

8.2.5.5. Immunogenicity Endpoints

For the immunogenicity data, the percentage of subjects with positive ADA of PF-06863135 and neutralizing antibodies (Nab) each will be summarized by dose level (Part 1) or by treatment arms. For subjects 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. Potential impact of immunogenicity on PK and clinical response including PD markers, safety/tolerability and efficacy of PF-06863135 will be explored, if data is warranted.

9. REFERENCES

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10. APPENDICES

Appendix 1. Abbreviations

Abbreviation	Term
ADA	Anti-drug Antibody
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALL	Acute Lymphoblastic Leukemia
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
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
AUC	Area Under the Concentration-Time Curve
AUC_{inf}	area under the concentration versus time curve to infinity
AUC_{last}, AUC_{τ}	concentration versus time curve
$AUC_{sd,\tau}$	area under the single dose concentration-time curve over dosing interval τ
$AUC_{ss,\tau}$	area under the single dose concentration-time curve over dosing interval τ
BBS	biospecimen banking system
BCMA	B-cell maturation antigen
BID	twice daily
BM	bone marrow
BOR	best overall response
BP	Blood Pressure
BUN	blood urea nitrogen
C	cycle
C1D1	Cycle 1 Day 1
CAR	chimeric antigen receptors
C_{av}	average concentration
CB	clinical benefit
CBC	Complete Blood Count
CBR	Clinical Benefit Response
CD	cluster of differentiation
CDC	Complement Mediated Cytotoxicity
C_{eff}	efficacious concentration

Abbreviation	Term
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
CL	Systemic Clearance
C_{max}	maximum (or peak) concentration
C_{min}	minimum concentration
CMV	cytomegalovirus
CNS	Central Nervous System
CR	Complete Response
CRAB	calcium elevation, renal failure, anemia, lytic bone lesions;
CrCl	creatinine clearance
CRF	Case Report Form
CRO	Contract Research Organization
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
CV	coefficient of variation
DILI	drug-induced liver injury
DLI	Donor Lymphocyte Infusion
DLT	Dose Limiting Toxicities
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	Electrocardiograms
echo	echocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	external data monitoring committee

Abbreviation	Term
EDP	Exposure During Pregnancy
EDV	end-diastolic volume
eg	for example
EI	Equivalence Interval
EOS	end of study
EOT	end of treatment
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
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal tract
GLP	Good Laboratory Practice
GM-CSF	granulocyte- macrophage colony stimulating factor
GnRH	gonadotropin-releasing hormone agonist
HbA1c	hemoglobin A1c
HBc	hepatitis B core
HBs	hepatitis B surface
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
ICH	International Conference on Harmonisation
ICU	intensive care unit
ID	Identification
ie	that is

Abbreviation	Term
IFNg	interferon gamma
Ig	immunoglobulin
IgGk	immunoglobulin G kappa
IHC	Immunohistochemistry
IL-	interleukin
iMiD	immunomodulatory drug
IMWG	international myeloma working group
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IP	Intraperitoneal
IP manual	Investigational Product manual
IRB	Institutional Review Board
IRC	internal review committee
IRR	infusion related reaction
ITT	intent to treat
IUD	Intrauterine Device
IV	Intravenous
K2EDTA	dipotassium edetic acid ethylenediaminetetraacetic acid
KD	equilibrium dissociation constant
LDH	lactate dehydrogenase
LFT	Liver Function Tests
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
MAS	macrophage activation syndrome
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
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
MMAE	Monomethyl Auristatin E
MOLP-8	a multiple myeloma cell line with t(11;14)(q13;q32) chromosomal abnormality and negative for CD28
M-Protein	myeloma protein

Abbreviation	Term
MR	minimal response
MRD	minimal residual disease
MRI	Magnetic Resonance Imaging
M-spike	monoclonal spike
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
MUGA	multigated acquisition scan
N/A	Not Applicable
NAb	neutralizing antibody
NCI	National Cancer Institute
NGF	next generation flow cytometry
NGS	next generation sequencing
NK	natural killer
NOAEL	no observed adverse effect level
NSAIDS	nonsteroidal anti-inflammatory drugs
NSG	NOD scid gamma
OBD	optimal biological dose
OPM-2	a type of multiple myeloma cell line
OR	objective response or overall response
ORR	Overall Response Rate
OS	overall survival
PCD	Primary Completion Date
PD	Progressive Disease
PD	Pharmacodynamic
PD-1	anti- programmed cell death protein-1
PD-L1	or anti- programmed death-ligand 1
PET	positron emission tomography
PFS	Progression Free Survival
PGx	pharmacogenomics
PI	principal investigator
PK	Pharmacokinetic
PO	by mouth
PP	posterior probability
PR	Partial Response
PR	Pulse Rate
PS	Performance Scale
pT	target probability
PT	Prothrombin Time
PTT	partial thromboplastin time
QD	every day
qPCR	quantitative polymerase chain reaction

Abbreviation	Term
QT	time between the start of the Q wave and the end of the T wave
QTcF	Fridericia QT Correction Formula
Rac	accumulation ratio
RCL	replication competent lentivirus
RD	response/remission duration
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
SBP	systolic blood pressure
scFv	single-chain variable fragment
sCR	stringent complete response
SCT	stem cell transplant
SD	Stable Disease
SIFE	serum immunofixation electrophoresis
sIL2Ra	soluble interleukin-2 receptor alpha
SOP	standard operating procedure
SPD	sum of the products of the maximal perpendicular diameters of measured lesions
SPEP	serum protein electrophoresis
SUV	standard uptake value
SWOG	Southwest oncology group
$t_{1/2}$	terminal elimination half-life
TALEN	transcription activator-like effector nucleases
TBili	total bilirubin
TBNK	T-, B-, and natural killer lymphocytes
TBR	tumor background ratio
TCR	T cell receptor
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
TNF	tumor necrosis factor
TNFa	tumor necrosis factor –alpha
TNFRSF17	tumor necrosis factor receptor superfamily Member 17
TRAC	T-cell receptor alpha constant
Tregs	T regulatory cells
$T_{ss,max}$	time to maximum concentration
TTR	time to response
UIFE	urine immunofixation electrophoresis
ULN	Upper Limit of Normal

Abbreviation	Term
UPEP	urine protein electrophoresis
UPM	Unit Probability Mass
US	United States
UVB	ultraviolet B
VGPR	very good partial response
V_{ss}	Volume of Distribution at Steady State
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. Subjects must have measurable disease at enrollment (study entry). Measurable disease is defined as:

Serum M-protein ≥0.5 g/dL;

Urine M-protein ≥200 mg/24 hrs;

Serum immunoglobulin FLC >10 mg/dL (>100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65).

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. Subjects will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; subjects 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 subjects, respectively, after counting ≥100 plasma cells)[2]
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]
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.
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. • If serum and urine M-protein are unmeasurable and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. • 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]	• 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 hrs;
	• In subjects without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL);
	• In subjects without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%);
	• 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;
	• ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease.

Clinical Relapse	Clinical relapse requires one or more of the following 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[2] 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 subjects 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 subjects 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. Subjects 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 subjects 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 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

Appendix 3. IMWG MINIMAL RESIDUAL DISEASE (MRD) Criteria

MRD tests should be initiated only at the time of suspected complete response. 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 10^5 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 10^5 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 MFC should follow NGF guidelines. The reference NGF method is an eight-colour 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-colour 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. Cytokine Release Symptoms Revised Grading System

Table 7: Lee et al 2014 CRS revised grading system

Toxicity Grade	Characteristics
1	Symptoms are not life threatening and require symptomatic treatment only, eg, Fever, nausea, fatigue, headache, myalgia, malaise
2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity
3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥40% or Hypotension requiring high-dose vasopressors or multiple vasopressors or Grade 3 organ toxicity (except transaminitis) or Grade 4 transaminitis
4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
5	Death

The original CRS grading system proposed by Lee et al in 20142 (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 criteria3 (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 may be modified as needed by the responsible Investigator according to the best practices at their institute.

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)

Detailed grading criteria is provided in Appendix 5 of the protocol.