Official Title of Study:

A Phase 1b/2a Multicenter, Open-label, Dose-escalation Study to Determine the Maximum Tolerated Dose, Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of CC-220 as Monotherapy and in Combination with Other Treatments in Subjects with Multiple Myeloma

NCT Number: NCT02773030

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A PHASE 1B/2A MULTICENTER, OPEN-LABEL, DOSE-ESCALATION STUDY TO DETERMINE THE MAXIMUM TOLERATED DOSE, ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND EFFICACY OF CC-220 AS MONOTHERAPY AND IN COMBINATION WITH OTHER TREATMENTS IN SUBJECTS WITH MULTIPLE MYELOMA

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Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

See appended electronic signature page	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
[redacted]	
Printed Name of Celgene Therapeutic Area Head and Title	
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.	

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

_____ _____ **Signature of Coordinating Principal Investigator** **dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.

PROTOCOL SUMMARY

Study Title

A Phase 1b/2a Multicenter, Open-label, Dose-escalation Study to Determine the Maximum Tolerated Dose, Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of CC-220 As Monotherapy and in Combination with Other Treatments in Subjects with Multiple Myeloma

Indication

Subjects with relapsed and refractory multiple myeloma (RRMM) and newly diagnosed multiple myeloma (NDMM) are eligible for the study, as further detailed in Table 1.

Table 1: Study Population

Part	Cohort	Eligibility
1 (dose escalation)	A: monotherapy (MonoT) B: CC-220 + DEX (DoubleT) E: CC-220 + daratumumab + DEX (CC-220Dd) G1: CC-220 + carfilzomib + DEX (CC-220Kd) G2: CC-220 + carfilzomib + DEX (CC-220Kd)	Received at least two prior therapies including lenalidomide or pomalidomide and a proteasome inhibitor. Documented PD during or within 60 days from the last dose of their last anti-myeloma therapy.
	F: CC-220 + bortezomib + DEX (CC-220Vd)	Received at least one prior therapy including lenalidomide or pomalidomide and a proteasome inhibitor. Documented PD during or within 60 days from the last dose of their last anti-myeloma therapy.
2 (dose expansion)	C: monotherapy (MonoT)	Received at least two prior therapies including lenalidomide or pomalidomide, a proteasome inhibitor, and a CD38 antibody. Documented PD during or within 60 days from the last dose of their last anti-myeloma therapy.

Table 1: Study Population (Continued)

Part	Cohort	Eligibility
2 (dose expansion)	D: CC-220 + DEX (DoubleT)	Received at least three prior therapies including lenalidomide, pomalidomide, a proteasome inhibitor, a glucocorticoid and a CD38 antibody. Refractory to an immunomodulatory agent, a proteasome inhibitor, a glucocorticoid, and a CD38 antibody. Refractory is defined as disease that is nonresponsive on therapy (failure to achieve minimal response or development of progressive disease while on therapy) or progresses within 60 days of last dose. Documented PD during or within 60 days from the last dose of their last anti-myeloma therapy.
	I: CC-220 + DEX (DoubleT) in post-BCMA RRMM	Received at least 3 prior therapies including lenalidomide or pomalidomide, a proteasome inhibitor, a CD38 antibody, and a **prior BCMA-targeted therapy**. Documented PD during or within 60 days from the last dose of their last anti-myeloma therapy. Subjects who had CAR T therapy as their last myeloma therapy must have documented disease progression.
	J1: CC-220 + bortezomib + DEX (CC-220Vd) for 8 cycles followed by CC-220 + DEX	Newly diagnosed multiple myeloma and not eligible for ASCT
	J2: CC-220 + bortezomib + DEX (CC-220Vd) for 4 to 6 cycles as induction followed by ASCT with or without maintenance as part of SOC	Newly diagnosed multiple myeloma and eligible for ASCT
	K: CC-220 + daratumumab + DEX (CC-220Dd)	Newly diagnosed multiple myeloma and not eligible for ASCT

Abbreviations: ASCT = autologous stem cell transplant; BCMA = B-cell maturation antigen; CAR T = Chimeric Antigen Receptor T-cell Therapy; DEX = dexamethasone; PD = progressive disease; NDMM = newly diagnosed multiple myeloma; RRMM = relapsed refractory multiple myeloma; SOC = standard of care.

Objectives

Primary

Part 1

- To determine the maximum tolerated doses (MTDs) and/or recommended Phase 2 doses (RP2Ds) of CC-220 as monotherapy (MonoT), in combination with dexamethasone (DEX) (DoubleT), in combination with DEX and daratumumab (DARA) (CC-220Dd), in combination with DEX and bortezomib (BTZ) (CC-220Vd) and in combination with DEX and carfilzomib (CFZ) (CC-220Kd) in subjects with RRMM.

Part 2

- To determine the efficacy of CC-220 in combination with DEX (DoubleT) in subjects with RRMM in Cohort D, as measured by overall response rate (ORR).

Secondary

- To evaluate the safety of CC-220 as MonoT, in combination with DEX (DoubleT), in combination with DEX and DARA (CC-220Dd), in combination with DEX and BTZ (CC-220Vd) and in combination with DEX and CFZ (CC-220Kd) in subjects with RRMM.
- To evaluate the preliminary efficacy and safety of CC-220 in combination with DEX and BTZ (CC-220Vd), and in combination with DEX and DARA (CC-220Dd) in subjects with NDMM, including subjects who are eligible for ASCT and subjects who are not eligible for ASCT.
- To evaluate additional efficacy parameters of CC-220 in combination with DEX including time-to-response (TTR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) in subjects with RRMM in Cohort D.
- To assess the preliminary efficacy of CC-220 as MonoT, in combination with DEX (DoubleT), in combination with DEX and DARA (CC-220Dd), in combination with DEX and BTZ (CC-220Vd), and in combination with DEX and CFZ (CC-220Kd) in subjects with RRMM in Part 1.
- To assess the preliminary efficacy and safety of CC-220 in combination with DEX in subjects with RRMM who have received prior B-cell maturation antigen (BCMA)-targeted therapy.
- To evaluate the pharmacokinetics (PK) of CC-220 in subjects with RRMM and NDMM.

Exploratory

- To explore genomic, molecular and immune biomarkers, including immune activation/exhaustion markers and cytokines, for mechanism of action of CC-220 and their correlation to clinical outcome measures and pharmacodynamics (Pd).
- To evaluate dose-related immune effects of CC-220.

- To evaluate the PK of metabolite M12 in subjects with RRMM.
- [redacted]
- To evaluate the safety for the combination of CC-220Dd when DARA is administered as subcutaneous (SC) injection.
- In Part 2 of the study,
  - [redacted]
  - [redacted]
  - To explore minimal residual disease (MRD) in subjects who achieve a very good partial response (VGPR) or better and its correlation to clinical outcome measures in subjects with RRMM and NDMM.
  - [redacted]

Study Design

This study is designed as a Phase 1b/2a study consisting of two parts: dose escalation (Part 1) for CC-220 MonoT, CC-220 in combination with DEX, CC-220 in combination with DEX and DARA, CC-220 in combination with DEX and BTZ and CC-220 in combination with DEX and CFZ; and the expansion of the RP2D (Part 2) for CC-220 MonoT and CC-220 in combination with DEX (DoubleT) for RRMM, and CC-220 in combination with DEX and BTZ, and CC-220 in combination with DEX and DARA for NDMM.

Part 1 (Dose-escalation)

Part 1 will consist of a dose-escalation phase with CC-220 given for 21 days of a 28-day cycle (14 days of a 21-day cycle for Cohort F) using a 3+3 design. There will be six cohorts in Part 1 of the study. Cohort A will enroll subjects treated with CC-220 (MonoT) to determine the MTD and/or the RP2D of MonoT, Cohort B will enroll subjects treated with CC-220 and DEX (DoubleT) to determine the MTD and/or the RP2D of DoubleT, Cohort E will enroll subjects treated with CC-220 in combination with intravenous (IV) DARA and DEX (CC-220Dd), Cohort F will enroll subjects treated with CC-220 in combination with BTZ and DEX (CC-220Vd), Cohort G1 will enroll subjects treated with CC-220 in combination with DEX and once weekly CFZ, and Cohort G2 may be opened to enroll subjects treated with CC-220 in combination with DEX and twice weekly CFZ to determine the MTD and/or RP2D of these triplet therapies. All subjects within the same dose-level cohort will be treated and observed for

at least 28 days (Cycle 1) after the first dose of CC-220 before initiation of the next dose-level cohort may begin, with the exception of subjects in Cohort F who will be treated and observed for 21 days (Cycle 1) after the first dose.

Once the MTD and/or RP2D is determined in Cohort E (CC-220Dd), 13 subjects will be enrolled at this dose level using SC DARA to evaluate the safety and tolerability with the SC formulation. The decision to evaluate any additional subjects with the SC formulation will be at the discretion of the Dose Escalation Committee (DEC), based on their review of the data.

Escalation to the next higher dose level will be determined by the DEC that includes an Independent Expert Reviewer (IER).

Cohorts A, B, E, G1 and G2 will have a 21 out of 28-day dosing regimen of CC-220 and Cohort F will have a 14 out of 21-day dosing regimen of CC-220. The treatment with investigational product (IP) will be continued until progressive disease (PD), unacceptable toxicity or the subject withdraws consent.

Subjects assigned to MonoT, Cohort A, who develop PD will have the option to receive DEX in addition to CC-220 after consultation with the Medical Monitor. The subject's dose of CC-220 will not be higher than the dose of CC-220 used in combination with DEX in Cohort B that has been determined to be safe. The site will be informed of the dose of CC-220 to be administered when DEX is added. Progressive disease must be confirmed in accordance with International Myeloma Working Group (IMWG) criteria.

For Cohorts A (if DEX is added after PD), B, E, and G1 the starting dose of DEX will be 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle for subjects who are ≤ 75 years of age. For subjects who are > 75 years of age, the starting dose of DEX is 20 mg on Days 1, 8, 15 and 22 of each 28-day cycle. Subjects who surpass the age of 75 years while on treatment may be switched to the 20 mg dose based on the Investigator's best judgement. For Cohort G2, the dose of DEX is 20 mg given on Days 1, 2, 8, 9, 15, 16, 22, 23 of each 28-day cycle. For Cohort F, the dose of DEX is 40 mg (or 20 mg if > 75 years of age) given on Days 1, 8, and 15 of each 21-day cycle. This treatment will continue until PD, unacceptable toxicity or the subject withdraws consent.

For Cohorts A and B, the starting dose level of CC-220, dose level 1, is 0.3 mg for both cohorts. A dose level -1, of 0.15 mg, may also be evaluated if the starting dose level of 0.3 mg for 21 days of a 28-day cycle is not tolerated (refer to Table 2).

The starting dose level of CC-220 in Cohorts E and F is detailed in Table 3.

The dose level assignments of CC-220 in Cohorts G1 and G2 are detailed in Table 4.

Approximately 34 subjects in Cohort A and 72 subjects in Cohort B will be treated and evaluated in Part 1 for MTD and/or RP2D. Approximately 85 additional subjects will be allocated to one of the four triplet regimen cohorts (Cohorts E, F, G1 and G2). The total number of subjects in Part 1 depends on the number of dose levels needed to establish the MTD and/or RP2D and may exceed these approximations.

The MTD may be the RP2D. The RP2D may also be determined by PK and biomarker data as well as the safety and preliminary efficacy data from Part 1, as applicable. The decision to determine the RP2D will be made in consultation with the DEC.

During the dose-escalation phase (Part 1), the decision to evaluate subsequent dose levels will be considered and documented by the DEC based on their review of clinical and laboratory safety data for all subjects in the cohorts. Additional dose levels up to 25% greater than the previous dose level declared tolerable by the DEC may be explored or dose levels expanded based on the DEC's evaluation and recommendation.

Part 2 (Expansion)

The initiation of Part 2 will begin when the RP2D is established in Part 1 in one of the following cohorts: Cohort A, Cohort B, Cohort E or Cohort F. The start of Part 2 does not require that all cohorts have determined the RP2D. Each cohort is independent. Part 2 cohorts may begin once the RP2D is determined for that cohort in Part 1. All expansion decisions will be determined by the DEC after review of all safety, PK, biomarker and preliminary efficacy data, as applicable. During Part 2, the DEC (including the IER) will continue to review the safety data and any other data deemed relevant so that subject safety is ensured.

Cohort C (MonoT Expansion)

- Once the RP2D is established for Cohort A (MonoT) by the DEC, the expansion cohort may be initiated (Part 2).
- Up to 24 subjects may be enrolled to further evaluate safety and assess preliminary efficacy.
- Subjects may start CC-220 at the RP2D based on safety, preliminary efficacy, PK and biomarker data from Part 1.

Following the 08 Nov 2019 DEC review of Cohort A, the 1 mg dose level was deemed tolerable. It was agreed that further investigation of CC-220 monotherapy was more appropriate in a newly diagnosed multiple myeloma maintenance setting. Therefore, Cohort C will not be opened.

Cohort D (DoubleT Expansion)

Once the RP2D is established for Cohort B (DoubleT) by the DEC, the expansion cohort may be initiated (Part 2). As of 18 Oct 2019, the DEC has recommended the 1.6 mg dose level as the RP2D for CC-220 plus DEX. A group sequential design (Jennison, 1999) will be used to evaluate the efficacy and safety of CC-220 (at the RP2D of 1.6 mg) plus DEX in Cohort D.

Stage 1

- In Stage 1, following the treatment of 40 subjects, an interim analysis will be performed to evaluate the preliminary efficacy of CC-220 plus DEX at the RP2D of 1.6 mg.

Stage 2

- If the results from Stage 1 do not cross the futility boundary (see Section 9.10), an additional 61 subjects may be treated to confirm the efficacy and safety of CC-220 plus DEX at the RP2D of 1.6 mg.

Cohort I (DoubleT Expansion in Post-BCMA RRMM)

- Once the RP2D is established for Cohort B (CC-220 plus DEX), this expansion cohort may be initiated. As of 18 Oct 2019, the DEC has recommended the 1.6 mg dose level as the RP2D for CC-220 plus DEX.
- Up to 40 subjects who have received prior BCMA-targeted therapy may be enrolled to evaluate the safety and preliminary efficacy of CC-220 plus DEX at the RP2D for this patient population. Minimum of 40% of the cohort will have prior BCMA-targeted CAR T therapy. The IRT will be used to monitor the inclusion of these subjects.

Cohort J1 (CC-220Vd in NDMM and not eligible for ASCT)

- Once the RP2D is established for Cohort F (CC-220Vd) by the DEC, this expansion cohort may be initiated. [redacted]
- Approximately 75 subjects may be enrolled to evaluate the safety and preliminary efficacy of up to 3 dose levels of CC-220 (1.0 mg, 1.3 mg, and 1.6 mg) in combination with BTZ and DEX in NDMM subjects who are not eligible for ASCT. Up to approximately 25 subjects per dose level may be enrolled. Additional subjects may be enrolled in any of the dose levels upon consultation with the DEC, based on review of the data.

Cohort J2 (CC-220Vd in NDMM eligible for ASCT)

- Once the RP2D is established for Cohort F (CC-220Vd) by the DEC, this expansion cohort may be initiated.
- Approximately 50 subjects may be enrolled to explore the safety and preliminary efficacy of CC-220 in combination with BTZ and DEX in NDMM subjects who are eligible for ASCT.

Cohort K (CC-220Dd in NDMM and not eligible for ASCT)

- Once the RP2D is established for Cohort E (CC-220Dd) by the DEC (IV DARA), this expansion cohort may be initiated. [redacted]
- Approximately 75 subjects may be enrolled to evaluate the safety and preliminary efficacy of up to 3 dose levels of CC-220 (1.0 mg, 1.3 mg, and 1.6 mg) in combination with SC DARA and DEX in NDMM subjects who are not eligible for ASCT. Up to approximately 25 subjects per dose level may be enrolled. Additional subjects may be enrolled in any of the dose levels upon consultation with the DEC, based on review of the data.

Any of the cohorts may be removed and/or terminated from the study based on emerging PK, Pd, efficacy or safety data, in consultation with the DEC.

Investigator response assessments will be used to determine the efficacy outcome throughout the study. An Independent Response Committee (IRC) may also be set up to review efficacy data from Part 2 RRMM Cohorts C, D, and/or I. The IRC will determine the tumor response to therapy based on the IMWG uniform Response Criteria as well as time of response (including PD) for each subject. The IRC will adjudicate efficacy data according to the IRC Charter.

The treatment with IP may be continued in all cohorts until disease progression, unacceptable toxicity or the subject withdraws consent except for Cohort J2. Subjects in Cohort J2 will receive CC-220Vd for up to 6 cycles or until PD, unacceptable toxicity or withdrawal of consent, whichever is earlier. Subjects will be allocated by Interactive Response Technology (IRT) in parallel to an appropriate cohort based on eligibility status and on cohort slot availability. Enrollment of NDMM subjects in Cohort J1 at the 1.6 mg dose level will start according to Protocol Amendment No. 9. Upon approval of Protocol Amendment No. 10, subjects will be allocated evenly into all open J1 and K dose level cohorts. Subjects will be allocated to each dose level cohort based on a fixed sequence via the IRT.

Subjects assigned to MonoT, Cohort C, who develop PD will have the option to receive DEX in addition to CC-220 after consultation with the Medical Monitor. The subject's dose of CC-220 will not be higher than the dose of CC-220 used in combination with DEX in Cohort B that has been determined to be safe. If the RP2D has been reached in Cohort B, that dose will be used in this situation. The site will be informed of the dose of CC-220 to be administered when DEX is added. Progressive disease must be confirmed in accordance with IMWG criteria. For Cohort D, Cohort I and for Cohort C (if DEX is added after PD), the starting dose of DEX will be 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle for subjects who are ≤ 75 years of age. For subjects who are > 75 years of age, the starting dose of DEX is 20 mg on Days 1, 8, 15 and 22 of each 28-day cycle. Subjects who surpass the age of 75 years while on treatment may be switched to the 20 mg dosage based on the Investigator's best judgement. This treatment will continue until PD, unacceptable toxicity or the subject withdraws consent.

All subjects who discontinue study treatment in Part 1 or Part 2 of the study for a reason other than PD or withdrawal of consent from the study will be followed for response assessment every 28 days (every 21 days for Cohort F) until PD or until a subsequent myeloma regimen has been started. Subjects in Cohort J1 and Cohort K will be followed every cycle for the first 2 years and thereafter, every 3 months until PD or until a subsequent myeloma regimen has been started. Subjects in Cohort J2, following induction and ASCT with or without maintenance, will be followed for response assessment during the Post-Treatment Response follow-up every 3 months until PD or until a subsequent anti-myeloma regimen has been started.

Table 2: Cohort and Dose Level Assignments for MonoT (Cohort A and C) and DoubleT (Cohort B, D and I)

Part	Dose-Level	Cohort A (MonoT)	Cohort B (DoubleT)
		CC-220[a] (28-d Cycle)	**CC-220[a] + DEX[b] (28-d Cycle)**
Part 1	-1	0.15 mg	0.15 mg +DEX
	Starting dose 1	0.3 mg	0.3 mg +DEX
	2	0.45 mg	0.45 mg +DEX

Table 2: Cohort and Dose Level Assignments for MonoT (Cohort A and C) and DoubleT (Cohort B, D and I) (Continued)

Part	Dose-Level	Cohort A (MonoT)	Cohort B (DoubleT)
		CC-220[a] (28-d Cycle)	**CC-220[a] + DEX[b] (28-d Cycle)**
	3	0.6 mg	0.6 mg +DEX
	4	0.75 mg	0.75 mg +DEX
	5	0.9 mg	0.9 mg +DEX
	6	1 mg	1 mg +DEX
	7 and subsequent	Up to 25% increase above the prior dose level[c]	Up to 25% increase above the prior dose level[c] + DEX
Part 2	**Dose-Level**	**Cohort C (MonoT) (28-d Cycle)**	**Cohorts D and I (DoubleT) (28-d Cycle)**
		CC-220[a]	**CC-220[a] + DEX[b]**
		MTD/RP2D	MTD/RP2D (1.6 mg) +DEX

Abbreviations: d = day; DEX=dexamethasone; DoubleT = combination treatment with 2 drugs; MonoT = monotherapy; MTD = maximum tolerated dose; PO = by mouth; RP2D = recommended Phase 2 dose.
[a] CC-220 dosing schedule: daily for 21 days of each 28-day cycle.
[b] DEX dosing: 40 mg (20 mg for subjects who are >75 years of age) PO on Days 1, 8, 15 and 22.
[c] Subsequent dose increases will be up to 25% higher than the prior dose level, as determined by the DEC. See Section 1.3.6.3.

Table 3: Cohort and Dose Level Assignments for Cohorts E, F, J1, J2 and K

	Dose Level	Cohort E (CC-220Dd) - 28-day Cycle			Cohort F (CC-220Vd) - 21-day Cycle		
		CC-220[a,c]	**Daratumumab (IV)[f] C1-2: Days 1, 8, 15, 22 C3-6: Days 1, 15 ≥ C7: Day 1**	**DEX Days 1, 8, 15 and 22**	**CC-220[a,d]**	**Bortezomib (SC) C1-8: Days 1, 4, 8, 11 ≥ C9: Days 1, 8**	**DEX Days 1, 8, 15**
Part 1	-1	0.9 mg	16 mg/kg	40 mg (≤ 75 years) 20 mg (> 75 years)	0.9 mg	1.3 mg/m^2	40 mg (≤ 75 years) 20 mg (> 75 years)
	Starting dose 1	1 mg	16 mg/kg		1 mg	1.3 mg/m^2	
	2	1.1 mg	16 mg/kg		1.1 mg	1.3 mg/m^2	
	3 and subsequent	Up to 25% increase above the prior dose level[b] + DARA + DEX			Up to 25% increase above the prior dose level[b] + BTZ + DEX		

Table 3: Cohort and Dose Level Assignments for Cohorts E, F, J1, J2 and K (Continued)

Part 2	Dose Level	Cohort K (CC-220Dd)[g]	Cohorts J1 and J2 (CC-220Vd)[e]
	-	1.0 mg, 1.3 mg and 1.6 mg of CC-220 + DARA + DEX	1.0 mg, 1.3 mg and 1.6 mg of CC-220 + BTZ + DEX

Abbreviations: BTZ = bortezomib; C = cycle; DARA = daratumumab; DEC = dose escalation committee; DEX = dexamethasone; IV = intravenous; RP2D = recommended Phase 2 dose; SC = subcutaneous

[a] The starting dose of CC-220 in Cohorts E and F will be one dose level below the maximum dose in Cohort B that has been determined to be safe by the DEC.

[b] Subsequent dose increases will be up to 25% higher than the prior dose level, as determined by the DEC. See Section 1.3.6.3.

[c] CC-220 dosing schedule: daily for 21 days of each 28-day cycle.

[d] CC-220 dosing schedule: daily for 14 days of each 21-day cycle.

[e] See Section 7.2.1.2 for details of treatment schedule in Cohorts J1 and J2.

[f] Once the MTD and/or RP2D is determined in Cohort E (CC-220Dd), an additional 13 subjects will be enrolled at this dose level using SC DARA. See Section 7.2.1.1 for details of treatment dose and schedule for SC DARA.

[g] See Section 7.2.1.2 for details of treatment schedule in Cohort K.

Table 4: Cohort and Dose Level Assignments for Cohorts G1 and G2

Dose Level	Cohort G1 (CC-220Kd) - 28-day cycle			Cohort G2 (CC-220Kd) - 28-day cycle		
	CC-220[a,b,c]	Carfilzomib (IV)[d] Days 1, 8, 15	Oral DEX Days 1, 8, 15, 22	CC-220[a,b,c]	Carfilzomib (IV)[d] Days 1, 2, 8, 9, 15, 16	Oral DEX Days 1, 2, 8, 9, 15, 16, 22, 23
-1	1 mg	20 mg/m^2 C1D1 56 mg/m^2 thereafter	40 mg (≤ 75 years) 20 mg (> 75 years)	1 mg	20 mg/m^2 C1D1 and C1D2 27 mg/m^2 thereafter	20 mg
Starting Dose 1	1.1 mg	20 mg/m^2 C1D1 56 mg/m^2 thereafter		1.1 mg	20 mg/m^2 C1D1 and C1D2 27 mg/m^2 thereafter	
2	1.1 mg[c]	20 mg/m^2 C1D1 70 mg/m^2 thereafter		1.1 mg[c]	20 mg/m^2 C1D1 and C1D2 56 mg/m^2 thereafter	
3 and subsequent	Up to 25% increase above prior dose[c]	20 mg/m^2 C1D1 56 OR 70 mg/m^2 thereafter[d]		Up to 25% increase above prior dose[c]	20 mg/m^2 C1D1 and C1D2 27 OR 56 mg/m^2 thereafter[d]	

Abbreviations: C = cycle; CFZ = carfilzomib; D = day; DEC = dose escalation committee; DEX = dexamethasone; IV = intravenous.

[a] The starting dose of CC-220 in triplet regimen cohorts will be one dose level below the maximum dose in Cohort B that has been determined to be safe by the DEC.
[b] CC-220 dosing schedule: daily for 21 days of each 28-day cycle.
[c] The CC-220 dose will be determined by the DEC. Subsequent dose increases will be up to 25% higher than the prior dose level, as determined by the DEC. See Section 1.3.6.3.
[d] Dosing regimen for CFZ will be determined by the DEC.
Different dosing regimens for CFZ may be evaluated, depending on DEC recommendation.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

Part 1 (dose escalation):

Eligible subjects must have a documented diagnosis of RRMM and must have documented disease progression on or within 60 days from the last dose of their last myeloma therapy.

- Subjects eligible for Cohorts A, B, E, G1, and G2 must have received at least two prior myeloma regimens including lenalidomide or pomalidomide and a proteasome inhibitor.
- Cohort F subjects must have received at least one prior regimen including lenalidomide or pomalidomide and a proteasome inhibitor.

Part 2 (dose expansion):

Dose expansion in RRMM

Eligible subjects must have a documented diagnosis of RRMM and must have documented disease progression on or within 60 days from the last dose of their last myeloma therapy. Subjects who had CAR T therapy as their last myeloma therapy must have documented disease progression.

- Subjects eligible for Cohort C must have received at least two prior myeloma regimens including lenalidomide or pomalidomide, a proteasome inhibitor, and a CD38 antibody.
- Subjects eligible for Cohort D must have received at least three prior myeloma regimens including lenalidomide, pomalidomide, a proteasome inhibitor, a glucocorticoid and a CD38 antibody. Subjects in Cohort D will also be required to be refractory to an immunomodulatory agent, a proteasome inhibitor, a glucocorticoid, and a CD38 antibody.
- Subjects eligible for Cohort I must have received at least three prior myeloma regimens including lenalidomide or pomalidomide, a proteasome inhibitor, a CD38 antibody, and prior BCMA-targeted therapy.

Dose expansion in NDMM

- Subjects eligible for Cohort J1 and Cohort K must have newly diagnosed multiple myeloma and are those for who ASCT is not planned for initial therapy or are not considered by the investigator as eligible for ASCT.

- Subjects eligible for Cohort J2 must have newly diagnosed multiple myeloma and are considered by the investigator as eligible for ASCT.

Length of Study

The study will consist of the Screening and Treatment phases for subjects in all dose-escalation cohorts (Part 1) as well as the expansion cohorts (Part 2). A Long-term Follow-up phase will be added for subjects in Part 2 RRMM expansion Cohorts C, D, and I. The Screening phase of this study may not exceed a 28-day window prior to the start of IP (Cycle 1 Day 1).

This is followed by the Treatment phase consisting of 28-day cycles for all cohorts except Cohorts F, J1 and J2 which consists of 21-day cycles. Treatment at each dose level and in each part of the study will continue until PD, unacceptable toxicity or the subject withdraws consent in all cohorts except for Cohorts J2. Subjects in Cohort J2 will receive CC-220Vd for up to 6 cycles or until PD, unacceptable toxicity or withdrawal of consent, whichever is earlier. There will be an End of Treatment (EOT) Visit to collect safety and efficacy assessments. For subjects in Cohort J2, the EOT Visit is considered either 3 months (±7 days) post ASCT (prior to any maintenance therapy, if applicable) or at any other moment for treatment discontinuation, whichever is earlier.

There will be a 28-day post-treatment visit to obtain safety assessments.

All subjects who discontinue study treatment in Part 1 or Part 2 of the study for a reason other than PD will enter the Post Treatment Response Follow Up phase and will be followed for response assessment every 28 days (21 days for Cohort F) until PD or until a subsequent myeloma regimen has been started (please refer to the Table of Events for the respective cohort). Additionally, subjects in Cohort J2, following induction, ASCT with or without maintenance, will be followed for response assessment during the Post-Treatment Response Follow Up visits every 3 months until PD or until a subsequent anti-myeloma regimen has been started whereby a Post-Treatment Response Follow Up Discontinuation visit will be performed.

All RRMM subjects (Cohorts C, D, and I) enrolled in Part 2 of the study will have long-term follow-up. Subjects will be contacted every 3 months for 5 years from the date of the last subject enrolled in the study (or longer if clinically indicated) to learn of the subject's death from any cause, to continue second primary malignancy (SPM) surveillance and to collect data on subsequent anti-myeloma therapies including date of progression.

The End of Trial is defined as either the date of the last long-term follow-up data collection, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

At the conclusion of the study, if the study intervention is not available as an approved treatment in the local country, participants who continue to demonstrate clinical benefit will be eligible to receive Sponsor-supplied study intervention. If the study treatment is not available as an approved and available treatment, study intervention will be provided via an extension of the study, or a rollover study requiring approval by the responsible Health Authority and ethics committee, or through another mechanism at the discretion of the Sponsor. The Sponsor reserves the right to terminate access to the supplied study intervention treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of CC-220 is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the

study objectives; c) the participant can obtain medication from a government-sponsored or other health program. In all cases, the Sponsor will follow local regulations.

Study Treatments

CC-220 will be provided as an investigational product by Celgene Corporation in formulated capsules.

Subjects enrolled in countries where DEX, IV DARA, SC DARA, BTZ, and/or CFZ are commercially available may obtain commercially available product through their local hospital pharmacy or licensed distributer (as applicable) and in accordance with local guidelines. Celgene will provide DEX, IV DARA, SC DARA, BTZ, and/or CFZ where supplies are not commercially available, or not readily available, or not provided by regulation.

Overview of Key Efficacy Assessments

- Myeloma paraprotein
- Serum immunoglobulins
- Serum free light chains
- Immunofixation
- Bone marrow aspirate (BMA)/bone marrow biopsy (BMB)
- Radiographic imaging assessments of lytic bone lesions
- Extramedullary plasmacytomas (EMPs) assessments
- MRD assessment for response of VGPR or better (Part 2)
- Eastern Cooperative Oncology Group (ECOG) Performance Status

Overview of Key Safety Assessments

- Adverse events (AEs) including AEs of special interest (AESIs) which would include second primary malignancies
- Complete physical examination including vital signs and venous thromboembolism (VTE) monitoring
- Clinical laboratory evaluations (hematology, serum chemistry, urinalysis)
- Renal function assessments
- Pancreatic function assessments (part of chemistry panel)
- Ophthalmologic assessment if clinically indicated
- 12-lead electrocardiograms
- Pregnancy testing/counseling
- Concomitant medications and procedures

Overview of Pharmacokinetic Assessments

Subjects in Part 1 and Part 2 will be required to participate in sparse PK sampling as a participant in the main study. An additional subset of subjects will be assigned to participate in the intensive PK sample collection. Both intensive and sparse PK samples will be collected to evaluate CC-220, and as appropriate, its R-enantiomer CC-17195 in plasma. The pharmacologically active metabolite, M12, will also be quantified in an exploratory manner. Please refer to Section 6.5 for further details.

Cohorts A and B

Sparse PK Sampling

Pharmacokinetic blood samples will be collected in all subjects at the following time points:

- Cycles 1-4, Days 8, 15, 22: one pre-dose sample per visit

Intensive PK Sampling

Participation in the intensive PK assessment will be selective. **In addition to the sparse PK sampling time points,** frequent collection of PK blood samples will be performed in approximately 2 subjects per dose level (a total of 8 subjects at minimum) at the following time points:

- Cycle 1, Day 15: 1, 2, 3, 4, 6, 8 hours and 24 hours after administration of CC-220.

At each timepoint, approximately 6 mL of blood will be collected.

Cohorts C and D

Sparse PK Sampling

Pharmacokinetic blood samples will be collected in all subjects at the following time points:

- Cycles 1-4, Day 15: one pre-dose sample per visit.

Intensive PK Sampling

In addition to the sparse PK sampling, frequent collection of PK blood samples will be performed in approximately 10 subjects enrolled. Samples will be collected at the following 3 time points:

- Cycle 1, Day 15: 1 timepoint at 2 h, 1 timepoint between 4-8 h, and 1 timepoint at 24 hours after administration of CC-220.

At each time point, approximately 3 mL of blood will be collected. The CC-220 concentration in plasma will be determined.

Cohorts E, F, G1, G2

Sparse PK Sampling

Pharmacokinetic blood samples will be collected in subjects at the following time points:

- Cycles 1-4, Days 8, 15: one pre-dose sample per visit.

Intensive PK Sampling

In addition to the sparse PK sampling, frequent collection of PK blood samples will be performed in approximately 1 subject per dose level of each cohort. Samples will be collected at the following 3 time points:

- Cycle 1, Day 8: 1 timepoint at 2 h, 1 timepoint between 4-8 h, and 1 timepoint at 24 hours after administration of CC-220.

At each timepoint, approximately 3 mL of blood will be collected.

Cohorts I and K

Sparse PK Sampling

Pharmacokinetic blood samples will be collected in all subjects at the following time points:

- Cycles 1-2, Day 15: 1 timepoint at pre-dose and 1 timepoint at 2 hours after administration of CC-220.

At each timepoint, approximately 3 mL of blood will be collected.

There is no intensive PK sampling in Cohorts I and K.

Cohorts J1 and J2

All subjects will participate in sparse PK as a participant in the main study. Only sparse PK samples will be collected to evaluate the concentrations of CC-220 in plasma. At each time point, approximately 3 mL of blood will be collected.

Sparse PK Sampling

Pharmacokinetic blood samples will be collected in subjects at the following time points:

- Cycles 1-2, Day 8: 1 timepoint at pre-dose and 1 timepoint at 2 hours after administration of CC-220.

There is no intensive sampling in Cohorts J1 and J2.

Overview of Biomarkers for Pharmacodynamic Assessments

The following assessments will be ***mandatory*** in the dose escalation (Part 1) and ***not collected*** in the expansion (Part 2).

- To evaluate the pharmacodynamic (Pd) effects of CC-220 on Aiolos and other Pd biomarkers (by protein expression) in peripheral blood cell components including mononuclear cells and secreted cytokines.

  Blood collection time points:

  – Cycle (C)1 Day(D) 1 – pre-dose, 3, 5 hours post dose

  – C1D12 – pre-dose, 3, 5 hours post dose. For Cohorts G1 and G2, this assessment will be performed on C1D15. Note, in all cohorts, the acceptable window for this assessment is C1D11 to C1D15.

- To explore TCR (T-cell receptor) clonality in peripheral blood.

  Blood collection time points:

  – C1D1– pre-dose
  – C2D15– pre-dose
  – C4D15– pre-dose
  – At IP discontinuation (EOT)

- To explore the Pd effects of CC-220 on T-cell counts in peripheral blood. This lymphocyte subset panel is obtained from existing hematology sampling; no additional sampling is required.

  Blood collection time points for all Cohorts **except** Cohorts F, G1 and G2:

  – Cycle 1 Days 1, 8, 12, 15, 22, 26– pre-dose
  – Cycles 2-4 Days 1, 8, 15, 22– pre-dose
  – Cycles 5+ Days 1, 15– pre-dose

  Blood collection timepoints for Cohort F:

  – Cycle 1 Days 1, 8, 12, 15– pre-dose when applicable
  – Cycles 2-4 Days 1, 8, 15– pre-dose when applicable
  – Cycles 5+ Days 1, 15 – pre-dose when applicable

  Blood collection timepoints for Cohorts G1 and G2:

  – Cycles 1-4 Days 1, 8, 15– pre-dose
  – Cycles 5+ Days 1, 15– pre-dose

- *For Cohorts B, G1, and G2, up to 3 subjects in each dose level at select United States (US) sites may be selected for the following assessment:* To evaluate the Pd effects of CC-220 on Aiolos and Ikaros in mononuclear cells with a novel exploratory assay. The IRT will be used to monitor inclusion of these participants.

  Blood collection time points:

  – C1D1 – pre-dose, 3, 6 hours post dose
  – C1D2 – pre-dose
  – C1D15 – pre-dose, 3 hours post dose

- *For Cohort F, up to 3 subjects in each dose level at select US sites may be selected for the following assessment:* To evaluate the Pd effects of CC-220 on Aiolos and Ikaros in mononuclear cells with a novel exploratory assay. The IRT will be used to monitor inclusion of these participants.

  Blood collection time points:

  – C1D1 – pre-dose, 3, 6 hours post dose
  – C1D2 – pre-dose

  - C1D11 – pre-dose, 3 hours post dose

The following assessments will be ***mandatory*** in dose escalation (Part 1) and ***mandatory*** in expansion (Part 2)

- To explore the pharmacodynamic (Pd) effects of CC-220 on T-Cell Activation in peripheral blood.

  Blood collection time points:

  - C1D1 – pre-dose, 3, 5 hours post dose
  - C1D12 – pre-dose, 3, 5 hours post dose. For Cohorts C, D, G1, G2, and K this assessment will be performed on C1D15. For Cohorts J1 and J2, this assessment will be performed on C1D11. Note, in all cohorts, the acceptable window for this assessment is C1D11 to C1D15.

- To explore Pd effects of CC-220 on immune cells in peripheral blood and association of baseline levels of these populations with response or resistance to CC-220

  Blood collection time points for Part 1 Cohorts A, B, E, F, G1, and G2:

  - C1D1 – pre-dose
  - C2D1 – pre-dose
  - C2D15 – pre-dose
  - C4D1 – pre-dose
  - C4D15 – pre-dose
  - C6D15– pre-dose
  - At IP discontinuation (EOT)

  Blood collection time points for Cohorts C, D, I and K:

  - C1D1 – pre-dose
  - C2D1 – pre-dose
  - C2D15 – pre-dose
  - C6D15– pre-dose
  - EOT

  Blood collection time points for Cohort J1:

  - C1D1 – pre-dose
  - C4D8– pre-dose
  - C8D8– pre-dose
  - EOT

Blood collection time points for Cohort J2:

- C1D1 – pre-dose
- C4D8 – pre-dose
- EOT

- To explore the pharmacogenomics of CC-220 response.

  Blood collection time points:

  - C1D1 – pre-dose

- To explore the association of CC-220 response or resistance to baseline levels and Pd changes in protein expression, gene expression, cytogenetics, copy number abnormalities and/or mutations in tumor cells and tumor microenvironment in the bone marrow

  Bone marrow aspirate (BMA)/ BMB collection time points (please refer to Table 18 for further details on BMA/BMB sample collection plan):

  - Screening BMA (and if possible, BMB)
  - C2D15 – 3-6 hours post dose BMA (and if possible, BMB). (C2D11 for Cohort F and Cohort J1)
  - Confirmatory BMA (and if possible, BMB) for complete response (CR) (by International Myeloma Working Group [IMWG] criteria, see Appendix B)
  - BMA (and if possible, BMB) taken at time of PD/treatment discontinuation or any time after PD and before the start of subsequent myeloma therapy
  - Optional: BMA and/or BMB taken at any time during the study period at request of investigator

The following will be ***mandatory*** in the expansion (Part 2) only.

- To explore the effects of CC-220 on MRD negativity in subjects achieving a response of VGPR or better until progression of disease (PD)

  BMA collection time points (please refer to Table 18 for details on BMA/BMB sample collection plan):

  - Screening
  - Confirmatory BMA (and, if possible, BMB) for complete response (CR)

- To evaluate the duration of MRD negativity and changes in MRD status in responding subjects, a BMA after achieving response of VGPR or better until disease progression. Please refer to Table 18 for further details on timepoints.

- *Only applicable for approximately 20 subjects enrolled in Cohort D at select US sites:* To evaluate the pharmacodynamic (Pd) effects of CC-220 on Aiolos and Ikaros in mononuclear cells with a novel exploratory assay. The IRT will be used to monitor inclusion of these participants.

  Blood collection time points:

  - C1D1 – pre-dose, 3, 6 hours post dose
  - C1D2 – pre-dose
  - C1D15 – pre-dose, 3 hours post dose
- *Only applicable for approximately 20 subjects enrolled in Cohort D at select US sites*: [redacted] The IRT will be used to monitor inclusion of these participants.

  Blood collection time points:

  - C1D1 – pre-dose
  - C2D1 – pre-dose
  - C2D15 – pre-dose
- *Only applicable for approximately 5 subjects enrolled in Cohort D at one pre-identified US site*: To evaluate time-matched concentration of CC-220 in peripheral blood and tumor microenvironment and assess the correlation between concentration, pharmacodynamic changes in tumor microenvironment, and outcome measures. The IRT will be used to monitor inclusion of these participants.

  BMA and blood collection timepoints:

  - Screening
  - C1D8 – 3-6 hours post dose
  - C2D15 – 3-6 hours post dose
- [redacted]

Other Assessments

- Beta 2 (β2)-microglobulin
- Cytogenetic testing by fluorescence in situ hybridization (FISH) at Screening
- [redacted]

Statistical Methods

The primary objective of Part 1 of the study is to determine the MTD and/or RP2D of CC-220 as monotherapy, in combination with DEX, and in combination with DEX and DARA, BTZ, or

CFZ in subjects with RRMM. Safety endpoints such as dose-limiting toxicity (DLT), treatment-emergent AEs, serious AEs (SAEs), and AEs of special interest (AESIs) will be summarized by cohort and dose level (described in Section 9.9). Preliminary efficacy of CC-220 as monotherapy, in combination with DEX, and in combination with DEX and DARA, BTZ, or CFZ will also be assessed with available data.

The expansion part of the study (Part 2) will be used to further evaluate the safety and efficacy of CC-220 as monotherapy and in combination with DEX in subjects with RRMM, and in combination with BTZ or DARA and DEX in subjects with NDMM.

In Cohort C, up to 24 subjects may be enrolled to further evaluate safety and assess preliminary efficacy.

The primary objective of Cohort D is to determine the efficacy of CC-220 plus DEX in subjects with RRMM, as measured by ORR, which is defined as the proportion of subjects with a partial response (PR) or better. The sample size is calculated based on a group sequential design (Jennison, 1999) for a one-sample binomial test with normal approximation. One interim analysis for futility at 40% information and one final analysis are planned. The null hypothesis is ORR $\leq$ 12% and the alternative hypothesis is ORR > 12%. Assuming a treatment benefit of ORR $\geq$ 24%, a sample size of 101 subjects would provide 90% power at a one-sided 0.025 alpha level. (Sample size calculation used EAST version 6.4.)

One interim analysis is planned at 40% information reached, ie, the interim analysis will be performed at approximately the first 40 treated subjects. The results of the interim analysis will be used for futility assessment only, for which a stopping boundary will be applied based on a beta spending function of gamma distribution with gamma = -2. The one-sided p-value to reject the alternative hypothesis (for futility) is $p \geq 0.656$, which is corresponding to $\leq$ 10% observed response rate at the time of interim analysis (assuming 40% information at interim analysis, may be adjusted according to actual percent of information available).

In Cohort I, up to 40 subjects will be enrolled to explore the safety profile and preliminary efficacy of CC-220 plus DEX in the post-BCMA treatment patient population. An ORR of 20% is considered as minimum clinically meaningful in this heavily pretreated patient population with prior BCMA-targeted therapy exposure. Bayesian continuous monitoring method will be applied to monitor the ORR. If the posterior probability of ORR less than or equal to 20% is greater than 0.8, then the cohort will be stopped for futility. Otherwise, enrollment will continue to up to 40 subjects to explore the safety profile and assess the preliminary efficacy CC-220 plus DEX in this patient population.

For Cohorts J1, J2 and K, the very good partial response or better ($\geq$ VGPR) rate is considered an important and clinically relevant efficacy parameter to explore the treatment effect for NDMM patient population (Durie, 2018; Facon, 2018). In the SWOG S0777 study, the $\geq$ VGPR rate in NDMM subjects not eligible for ASCT following 8 cycles of RVd (lenalidomide in combination with bortezomib and dexamethasone) is 57%. In the IFM2009 study, the $\geq$ VGPR rate in NDMM subjects eligible for ASCT following 4 cycles of RVd induction therapy is 57% (IFM 2009 and SWOG S0777 Clinical Study Reports; Data on File). In the MAIA study, the $\geq$ VGPR rate in NDMM subjects not eligible for transplant following DRd (daratumumab in combination with lenalidomide and dexamethasone) treatment is 81% at a median follow-up of 56.2 months (Facon, 2021). A sample size of approximately 50 subjects in Cohort J2 and up to approximately

75 subjects each for Cohorts J1 and K (with up to approximately 25 subjects in each of the three CC-220 dose levels) is considered clinically adequate to explore the preliminary efficacy, safety, and PK profile of CC-220Vd and CC-220Dd in this patient population. Summaries of subject disposition, demographic and baseline disease characteristics, treatment exposure, efficacy, safety, PK, and Pd will be provided. Categorical data will be summarized by frequency distributions (number and percent of subjects) and continuous data will be summarized using descriptive statistics (means, standard deviations, medians, minimums, and maximums). Severity of Treatment-emergent AEs (TEAEs) will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. The frequency of TEAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) Version 18 or higher by system organ class and preferred term. Selected laboratory analytes, vital signs, and 12-lead ECGs will be summarized. All data will also be presented in by-subject listings.

Investigator response assessments will be used to determine the response outcome throughout the study. An IRC may also be set up to review efficacy data from Part 2 RRMM Cohorts C, D, and/or I. The IRC will determine the tumor response to therapy based on the IMWG uniform Response Criteria as well as time of response (including PD) for each subject. The IRC will adjudicate efficacy data according to the IRC Charter.

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1. INTRODUCTION

1.1. Disease Background

Multiple myeloma (MM) is a B-cell neoplasm characterized by the malignant transformation of plasma cells and the accumulation of clonal plasma cells in the bone marrow (Kumar, 2018; Palumbo, 2011). The malignant proliferation of the plasma cell clone causes increasing levels of monoclonal protein (M-protein) in the serum and urine and may result in bone marrow failure, suppression of uninvolved immunoglobulin levels, and skeletal destruction. Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcemia, bone pain, and pathologic fractures (Munshi, 2012).

Despite a better understanding of the disease biology and the introduction of therapeutic options with new mechanisms of action, MM is not curable with current therapies. The overall 5-year relative survival rate was 52.2% in 2016 (Noone, 2018). Most subjects still experience disease relapse and require several lines of therapy, with the course of MM characterized by subsequently more aggressive disease and shorter periods of remission following sequential lines of treatment (Agarwal, 2017; Larocca, 2017; van de Velde, 2017; Moreau, 2017; Yong, 2016).

For patients with newly diagnosed multiple myeloma (NDMM), the choice of initial therapy is determined by the patient's age, fitness, and the presence of comorbidities (Kumar, 2018; Ludwig, 2014; Moreau, 2017; Palumbo, 2015). High-dose chemotherapy followed by autologous stem cell transplant (ASCT) has demonstrated superior outcomes compared with other treatment options and is the treatment of choice for patients with NDMM provided they are eligible, based on their age, comorbidities and functional status. The current optimal treatment paradigm for patients determined to be eligible for ASCT is initial induction therapy followed by treatment with high-dose chemotherapy and an ASCT, followed by maintenance treatment (with or without consolidation therapy). For those patients not considered eligible for ASCT, treatment with combination induction regimens including alkylators, proteasome inhibitors (PIs), immunomodulatory agents, steroids and novel agents are currently considered standard of care.

Even with optimal upfront therapy the vast majority of MM subjects progress/relapse and further treatment is needed. For these relapsed and refractory (RRMM) subjects, treatment options have also improved over time. With the introduction of newer classes of approved anti-myeloma agents, including monoclonal antibodies (eg, daratumumab and elotuzumab), advanced generation PIs (eg, carfilzomib, ixazomib), immunomodulatory compounds (eg, pomalidomide) and histone deacetylase inhibitors (eg, panobinostat), RRMM subjects can expect some degree of response (Botta, 2017; Dimopoulos, 2016a; Dimopoulos, 2016b; Lonial, 2015; Moreau, 2016; Palumbo, 2016; San Miguel, 2014; Stewart, 2015). Unfortunately, despite these advances in the treatment of MM, the vast majority of the subjects will ultimately relapse regardless of treatment choice. Additionally, with each relapse, tumors typically recur more aggressively, leading to decreased response duration and ultimately leading to refractory MM, which is associated with shortened survival times. Additional safe and effective therapies are needed to improve long-term survival for subjects with MM (Kumar, 2012).

1.2. Compound Background

1.2.1. CC-220

1.2.1.1. Mechanism of Action of CC-220

Recent research on the mechanism of action of lenalidomide (LEN), pomalidomide (POM), and thalidomide suggest that in tumor cells and T cells, these compounds bind cereblon, a component of an E3 ubiquitin ligase complex, to induce ubiquitination and degradation of the transcription factors Aiolos and Ikaros. Preclinical studies have shown that the loss of cereblon or a binding partner, such as deoxyribonucleic acid (DNA) damage-binding protein 1 (DDB1), decreases or eliminates the antitumor and immunomodulatory activity of lenalidomide and pomalidomide, respectively (Gandhi, 2014; Ito, 2010; Lopez-Girona, 2012; Zhu, 2011). CC-220, structurally similar to the "-domide" class of drugs (including thalidomide, lenalidomide, and pomalidomide) also binds directly to cereblon, but with 20-fold higher potency than lenalidomide or pomalidomide (Report 2610; Matyskiela, 2018). Upon engagement with cereblon, the thalidomide analogs induce ubiquitination and proteasomal degradation of Ikaros (encoded by the gene Ikaros family zinc finger 1 [IKZF1]) and Aiolos (encoded by the gene Ikaros family zinc finger 3 [IKZF3]) (Gandhi, 2014; Krönke, 2014; Lu, 2014). Ikaros and Aiolos are key transcription factors regulating immune cell development and homeostasis (John, 2011). Aiolos and Ikaros have also recently been shown to be involved in the survival and function of tumor cells of the B-cell lineage, including multiple myeloma cells (tumor cells derived from antibody-secreting plasma cells) (Lopez-Girona, 2012; Zhu, 2011), and activated B-cell-like diffuse large B-cell lymphoma (DLBCL) (tumor cells derived from the antibody-secreting plasmablasts) (Yang, 2012). In addition, Aiolos and Ikaros are also involved in regulating cytokine release from T cells, including interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-α) (Lopez-Girona, 2012).

Therefore, through more potent binding of cereblon and modulation of its function within the DDB1 and Cullin 4A (DDB1-CUL4A) ubiquitin ligase complex to induce degradation of Aiolos and Ikaros, CC-220 may be able to suppress the detrimental effects of malignant plasma cells and induce anti-tumor T-cell responses. Treatment of human whole blood with CC-220 has been shown to result in reduced expression of Aiolos and Ikaros proteins in lymphocytes, granulocytes, and monocytes (Aiolos) in vitro (Report 7637-007), with the effect in total lymphocytes, B cells, and T cells being time-and-concentration-dependent. Significant reductions in Aiolos and Ikaros proteins were observed as early as 1 hour after treatment initiation, with as little as 10 nM CC-220. Over time, Aiolos and Ikaros degradation continued to increase in lymphocytes, eventually exceeding 90% reduction at 18 hours in the presence of 1μM CC-220.

1.2.1.2. Nonclinical Experience

1.2.1.2.1. Antiproliferative Activity

1.2.1.2.1.1. Effects on Tritiated Thymidine Incorporation in Cultured Normal Cells

The effect of CC-220 on cell growth in primary normal human aortic smooth muscle cells (AoSMC) and normal human lung fibroblasts (NHLF) was assessed (Report 5827-34). The half

maximal inhibitory concentration (IC50) for inhibition of 3H-thymidine incorporation was > 10 μM in both cell types. Results indicated that CC-220 did not inhibit cell growth in normal primary human nonimmune cells (Report 5827-34).

CC-220 was also tested for its effects on anti-immunoglobulin M (IgM)-induced 3H-thymidine incorporation into normal CD19 + B cells. Incubation of CD19 + B cells with CC-220 was associated with an increase in 3H-thymidine incorporation in a 5-day assay. However, B-cell proliferation was quite low in these 5-day cultures and 3H-thymidine incorporation in the control cells decreased considerably over the 5-day assay period. The increase in thymidine incorporation in CD19 + B cells exposed to CC-220 on Day 5 reflected a protection of normal B cells from apoptosis. The results suggest that CC-220 promoted immunomodulatory effects and, under B cell stimulation conditions (anti-IgM), led to a protection of normal B cells from apoptosis.

1.2.1.2.1.2. Multiple Myeloma Cell Lines

The effect of CC-220 on myeloma cell proliferation was investigated using 16 human MM cell lines (HMCLs) representative of the genetic and phenotypic heterogeneity of MM (Report 201006C-V1). CC-220 had potent antiproliferative activity in 12 of the MM cell lines, with IC50 values ranging from < 0.1 nM in the Mm's multiple myeloma line to 320 nM in the XF 2 multiple myeloma cell line. Sensitivity of HMCLs to concentration-dependent growth inhibition by CC-220 was independent of the genetic background of the MM line. Four cell lines were not sensitive to growth inhibition by CC-220, including the JIM-3 and XF-7 lines.

In additional investigations, the antiproliferative activity of CC-220 in lenalidomide-sensitive and lenalidomide-refractory MM cell lines was also investigated (Report 2610). CC-220 inhibited cell growth in the 4 lenalidomide-refractory subclones (IC50 values ranging from 0.51 to 1.58 μM) after incubation with the cells for 5 days, although with lower potency than exhibited in the parent H929 MM cell line (IC50 = 0.01 μM) or the dimethyl sulfoxide (DMSO)-treated subclone (IC50 = 0.04 μM).

1.2.1.2.1.3. Natural Killer Cell Activity Against Diffuse Large B Cell Lymphoma Cell Lines

Natural killer (NK) cells play an important role in innate immunity. Activated NK cells lyse tumor cells and virus-infected cells. Interleukin-2 has been shown to activate NK cells, thereby contributing to the innate immune response against tumors and virally infected cells.

CC-220 enhanced NK cell interferon-gamma (IFN-γ) production in response to stimulation with IL-2 in the presence of immobilized immunoglobulin G (IgG) in a concentration-dependent manner (Report 5707-134). The concentration of CC-220 providing 50% of maximal production (EC50) of IFN-γ was 12 nM.

The potential of CC-220 to enhance a second human NK cell killing activity, antibody dependent cellular cytotoxicity (ADCC), was assessed using rituximab-coated cells from several different lymphoma cell lines. The level of cytotoxicity in the presence of 100 nM CC-220 was enhanced relative to rituximab alone in the DoHH2 follicular lymphoma cell line (double; 58% vs 26%), the Farage diffuse large B cell lymphoma (DLBCL) cell line (nearly quadruple; 44% vs 12%), the WSU-DLCL2 DLBCL cell line (55% vs 26%), the Riva DLBCL line (56% vs 24%), and the Raji Burkitt's lymphoma cell line (43% vs 31%).

1.2.1.2.1.4. B Cell Immunomodulation

The expression of transcription factors Aiolos and Ikaros in peripheral blood mononuclear cells (PBMC) in vitro was found to be sensitive to nanomolar concentrations of CC-220 (Report 7637-007). Reduction of Ikaros protein expression in human B cells, T cells, and total lymphocytes was time and concentration-dependent. Significant reductions in Aiolos and Ikaros proteins in lymphocytes were observed as early as 1 hour after treatment initiation, with as little as 10 nM CC-220. Over time, Aiolos and Ikaros degradation in lymphocytes continued to increase, eventually exceeding 90% reduction at 18 hours in the presence of 1 μM CC-220. Reduction of Ikaros protein also occurred in granulocytes and monocytes as well, and reduction of Aiolos production was observed in monocytes.

1.2.1.2.1.5. T Cell Immunomodulation

The T-cell immunomodulatory activity of CC-220 was evaluated in an anti-CD3-stimulated human T-cell assay that measured secreted levels of cytokines and chemokines released (Report 5802-148). In the presence of T-cell stimulatory antibody, concentrations of CC-220 as low as 1 nM enhanced production of the IL-2, IL-3, IL-5, IL-13, IFN-γ, granulocyte-macrophage colony stimulating factor, RANTES (regulated upon activation, normal T cell expressed and secreted), and TNF-α. Costimulation of T cells with CC-220 had the greatest impact on production of IL-2, which was enhanced 14- to 19-fold at concentrations of 10 nM to 10 μM CC 220.

For further information, refer to the CC-220 Investigator Brochure (IB).

1.2.1.3. Overview of Nonclinical Pharmacokinetics

A battery of in vitro and in vivo studies have been conducted to characterize the absorption, pharmacokinetics (PK), distribution, and metabolism of CC-220. Robust and reproducible bioanalytical methods for the quantitation of CC-220 levels were developed and used in PK and toxicokinetic studies.

Pharmacokinetics, oral bioavailability and tissue distribution (only rat) of CC-220 were evaluated in Sprague-Dawley rats, Cynomolgus monkeys as well as female rabbits. The systemic clearance of CC-220 was moderate both in rats and monkeys (approximately 1/2 to 1/5 hepatic blood flow). The volume of distribution was high in rats (approximately 5-fold of the body water volume) but moderate in monkeys (approximately 2-fold of the body water volume), suggesting good tissue distribution of CC-220. The terminal half-life ($t_{1/2}$) of CC-220 was approximately 2.8 to 6.8 hours in rats and approximately 1.5 hours in monkeys. Following a single or multiple oral dosing of CC-220 in rats, monkeys and female rabbits, the exposure of CC-17195 (R-enantiomer) was low CC-220 (≤ 11.4% of CC-220) suggesting low in vivo chiral inversion of CC-220 to its R-enantiomer. Following oral dosing to animals, CC-220 was rapidly absorbed and the median time to maximum plasma concentration of drug (Tmax) generally ranged from 0.5 to 2.0 hours post-dose. CC-220 exhibited ≥ 60% oral bioavailability in rats and 20% in monkeys.

Generally, following single or multiple oral doses of CC-220 to rats, systemic exposures were slightly higher (30% to 110%) in females than in males. However, in monkeys, no consistent sex differences in exposures were observed following multiple dosing. In rats and rabbits, the systemic exposure of CC-220 increased in an approximately dose proportional manner and no notable accumulation was observed. In monkeys, the systemic exposure of CC-220 increased in a greater than dose-proportional manner, and there was some accumulation observed

(accumulation ratio of 1.0 to 2.6). Following oral administration of racemate (CC-16915) to rats and monkeys, the systemic exposures of CC-17195 (R-enantiomer) were generally lower than CC-220 free base (S-enantiomer) suggesting higher clearance of R-enantiomer.

Following a single oral administration of [14C]CC-220 to rats, CC-220 derived radioactivity was widely distributed into tissues, with most tissue concentrations peaking between 0.5 to 2 hours, followed by rapid decrease to below quantifiable levels by 120 hours. CC-220 demonstrated a reversible melanin binding affinity to pigmented tissue in rats such as uveal tract. There was minimal distribution of radioactivity into brain of rats. Following oral administration of [14C]CC-220 to rats or monkeys, excretion of radioactivity was rapid and nearly complete (>90%). In rats and monkeys, the predominant route of elimination of radioactivity was in the feces. Majority of the absorbed drug was excreted via the bile as metabolites into feces and the excretion of intact drug was a minor component in monkeys and represented ≤19% of dose in rats.

Following multiple oral doses of CC-220 to female pregnant rabbits, the placental transfer of CC-220, determined as a ratio of fetal-to-maternal plasma concentrations, was very low (0.0227 to 0.0368) suggesting limited fetal exposure to CC-220.

Plasma protein binding of CC-220 was moderate in mouse, rat, monkey and human but high in female rabbit. No notable differences were observed in plasma protein binding over the concentration ranges tested, suggesting no saturation of plasma protein binding. Blood to plasma concentration ratios ranged from approximately 0.7 to 1.3, suggesting minimal preferential partitioning into blood cells.

In vitro, CC-220 was subjected to extensive biotransformations in hepatocytes of multiple species. In human and animal species, CC-220 was subjected to multiple oxidative metabolism, primarily on the morpholino ring, resulting in the formation of N-oxide (M1) and keto derivative (M12), as well as other morpholino ring transformation products. CC-220 also underwent non-enzymatic hydrolysis of the imide bonds in cell-free media, with approximately 20% hydrolysis formed in a 4-hour incubation. Qualitatively all metabolites formed in human hepatocytes were also formed in hepatocytes of rat or monkey, the two species used for preclinical safety testing. Oxidative metabolism in CC-220 was mediated by cytochrome (CYP) 3A4/5 isozymes.

In vivo, metabolism of CC-220 was evaluated following oral dose of [14C]CC-220 in rats and monkeys. Intact CC-220 was the predominant circulating component, representing >72% and 47% of plasma radioactivity in rats and monkeys respectively. The absorbed drug was excreted as metabolites of CC-220 and excretion of intact drug was minor. In vivo metabolism of CC-220 was consistent with in vitro profiles, and the primary metabolic pathway was oxidation of the morpholino functional group, hydrolysis of glutarimide ring of parent and oxidized metabolites as well as a combination of these pathways.

CC-220 did not show notable inhibition or induction of CYP enzymes. Therefore, CC-220 is unlikely to precipitate clinically relevant pharmacokinetic drug-drug interactions due to inhibition or induction of CYP enzymes when co-administered with CYP substrates. CC-220 is a substrate for both permeability glycoprotein (P-gp) and breast cancer resistance protein (BCRP). CC-220 is a weak inhibitor of P-gp (IC50 >50 μM) and a moderate inhibitor of BCRP (IC50 = 22.3 μM). CC-220 is projected to be administered at low doses. Hence, the gut or systemic concentrations of CC-220 are likely to be lower than the IC50; therefore, CC-220 is not

anticipated to cause any clinically relevant drug-drug interactions due to inhibition of these transporters.

1.2.1.4. Overview of Nonclinical Toxicology

To date, CC-220 toxicities have been evaluated in a series of repeat-dose toxicity studies (up to 6 months in Sprague-Dawley rats and up to 9 months in Cynomolgus monkeys), safety pharmacology and genetic toxicity studies in vitro and in vivo and a dose range finding embryofetal development (EFD) study in pregnant New Zealand White rabbits. The rat and Cynomolgus monkey were chosen as the standard rodent and nonrodent species for in vivo safety studies based on the comparative metabolic patterns in humans. In addition, monkeys following CC-220 treatment produced pharmacodynamic (Pd) effects comparable to those observed in healthy human volunteers.

In rats, no CC-220-related adverse effects were noted at the highest dose of 20 mg base/kg/day (no-observed-adverse-effect-level [NOAEL]) after 6 months of dosing. CC-220 mean systemic exposures of 16100 and 21900 ng•hr/mL for males and females, respectively.

In monkeys, multiple systemic effects of CC-220 observed were primarily due to its pharmacologic effects on the immune system. These changes were observed in blood and lymphatic organs (decreased peripheral blood B, T, and natural killer (NK) cells as well as monocytes, altered cellularity in the B and T cell areas, and increased/altered heterogeneous cell mixtures in lymphoid organs), gastrointestinal tract (unformed/watery stool leading to decreased body weight gain and increased magnitude of subacute/chronic inflammation in cecum/colon), eye (increased incidence of minimal mononuclear cell infiltrates in the uveal tract), and bone marrow (myeloid hyperplasia). The impact of CC-220 treatment on humoral responses (either enhancement or attenuation) to keyhole limpet hemocyanin (KLH) in monkeys was dependent on the timing of immunization in relation to the timing of CC-220 dosing. Additional CC-220-related effects in monkeys were observed in pancreas (degranulation/atrophy in acinar cells), testes/epididymides (bilateral hypospermatogenesis along with increased spermatogenic epithelial cell debris in epididymal lumen), liver (biliary epithelial hypertrophy/hyperplasia with mononuclear/mixed inflammatory cell infiltrates), lungs (increased alveolar macrophages and decreased goblet cell secretion in trachea), and salivary glands (decreased serous cell secretion ie, decreased acinar cell granules). Among all CC-220-related systemic effects in monkeys, only peripheral blood B-cell count was differentially affected by different dose schedules with the greatest decrease noted upon once daily (QD) dosing.

Overall, adverse effects of frequent unformed/watery stools and body weight loss requiring palliative care, marked decrease in peripheral blood B cells, significantly decreased cellularity in lymphoid organs and bilateral hypospermatogenesis were observed at 0.40 mg base/kg/day in the 9-month oral toxicity study in monkeys. Thus, the NOAEL in this study was 0.12 mg base/kg/day with a mean area under the curve over 24 hours (AUC24hr) of 77.6 ng•hr/mL.

The death of one monkey at 0.75 mg base/kg/day on Day 22 of the 1-month dose schedule study was associated with central nervous system (CNS)-related clinical signs and diffused astrogliosis. These CNS findings in a single animal were unlikely to be causally related to CC-220 based on the lack of CNS-related effects in monkeys receiving doses of up to 1, 0.75, and 0.4 mg base/kg/day for 1, 3, and 9 months, respectively.

CC-220 was not mutagenic in the Ames assay. CC-220 was positive in 1 of 3 experimental conditions in the in vitro clastogenicity assay; however, CC-220 was negative in the in vivo genetic toxicity studies in rats (micronucleus formation in bone marrow and DNA damage in liver [Comet assay]). These negative results from an in vivo study generated weight of evidence that was considered sufficient to demonstrate a lack of significant genotoxicity risk with CC-220 in humans.

In the CNS safety pharmacology study of rats, no CC-220-related effects on the CNS functions were noted at doses up to 50 mg base/kg, the highest dose evaluated (no-observed-effect-level [NOEL]). In an exploratory hERG (human ether à go related gene) study with CC-17220 (free base of CC-220) with concentrations up to 100 µM, the IC50 (the concentration of CC-220 required for 50% inhibition of the hERG ion channel currents) was determined to be 91.4 µM (41 µg/mL). In monkeys administered CC-220 up to 1 mg base/kg, the highest dose evaluated, no changes in cardiovascular functions and no adverse effects on respiratory functions were observed. Therefore, 1 mg base/kg/day is the NOEL for cardiovascular function and the no-observed-adverse-effect-level (NOAEL) for respiratory function in monkeys.

In a dose-range finding EFD toxicity study in pregnant rabbits, no CC-220-related maternal toxicity was noted at a dose range of 1 to 50 mg base/kg/day. CC-220 related developmental toxicities (decreased mean fetal body weight, increased incidences of small thymus and fused sternebrae) were observed primarily at 50 mg base/kg/day.

In conclusion, toxicology profile of CC-220 adequately supports the conduct of clinical trials in RRMM patients receiving CC-220 upon chronic treatment duration. Please refer to the IB for detailed descriptions of the findings from nonclinical PK and toxicology studies of CC-220.

1.2.1.5. Clinical Experience

Please refer to the IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies and adverse event (AE) profile of the investigational product (IP). Please refer to Appendix F.

1.2.2. Dexamethasone

Dexamethasone, a synthetic adrenal corticosteroid, has been used in North America and in the European Union (EU) for relapsed MM and has been widely used in combination with novel agents in several studies of relapsed/refractory and newly diagnosed MM (Richardson, 2005). The potential synergistic antiproliferative activities of immunomodulatory compounds (IMiDs) and dexamethasone (DEX) have been previously established in both in vitro and in vivo (Gandhi, 2010; Imnovid™ SmPC; Pomalyst® PI; Revlimid® PI; Revlimid™ SmPC; Thalidomide™ SmPC; Thalomid® PI).

1.3. Rationale

1.3.1. Immunomodulating Compounds in Multiple Myeloma

Thalidomide analogs, lenalidomide and pomalidomide are key components in the treatment of hematological malignancies through their actions on cereblon (Zhu, 2011). All three cereblon-binding compounds (thalidomide, lenalidomide and pomalidomide) are approved for use in the treatment of MM, and lenalidomide is approved for the treatment of mantle cell lymphoma and

myelodysplastic syndrome. These compounds are currently under investigation for a number of other hematologic malignancies.

The immunomodulatory effect of thalidomide, lenalidomide and pomalidomide, was soon recognized as a major determinant of their anti-MM activity (Davies, 2001). IMiDs are now incorporated into therapies for RRMM and newly-diagnosed MM (NDMM) due to a series of approvals based on their remarkable clinical activity (Benboubker, 2014; Richardson, 2014; Richardson, 2006b; San-Miguel, 2013).

Immunomodulating compounds (IMiDs®) may affect the immune system in several ways, such as inducing immune response, enhancing activity of immune cells, altering and modulating the induction of pro-and anti-inflammatory cytokines, and inhibiting inflammation. IMiDs are also antiangiogenic. Although their precise mechanism of action is currently under investigation, these agents offer promise for their anticancer and anti-inflammatory activities.

Refer to the approved drug labels for detailed information.

1.3.2. Daratumumab

Daratumumab (DARA) is a human $IgG1_k$ monoclonal antibody that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including multiple myeloma.

In the United States (US), Darzalex® injection for intravenous use (IV DARA) is approved for the treatment of adult patients with MM:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with RRMM who have received at least one prior therapy
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- in combination with carfilzomib and dexamethasone in patients who have received one to three prior lines of therapy
- in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

Darzalex Faspro™ (daratumumab and hyaluronidase-fihj; SC DARA), for SC use is approved in the US for the treatment of adult patients with MM:

- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for ASCT
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for ASCT and in patients with RRMM who have received at least one prior therapy
- in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for ASCT
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a PI
- as monotherapy, in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

In the European Union (EU), IV DARA is approved:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an immunomodulatory agent and who have demonstrated disease progression on the last therapy

Subcutaneous DARA is approved in the EU for the treatment of subjects with MM:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with NDMM who are ineligible for ASCT
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with NDMM who are eligible for ASCT
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy
- as monotherapy for the treatment of adult patients with RRMM, whose prior therapy included a PI and an immunomodulatory agent and who have demonstrated disease progression on the last therapy

Please refer to the current label for more information (Darzalex PI; Darzalex SmPC; Darzalex Faspro PI).

1.3.3. Bortezomib

Bortezomib is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. Bortezomib mediated proteasome inhibition affects cancer cells in a number of ways, including, altering regulatory proteins, which control cell cycle progression and nuclear factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumorigenesis, including cell growth and survival, angiogenesis, cell-cell interactions, and metastasis.

In the United States (US), bortezomib is authorized for the treatment of subjects with multiple myeloma (Velcade® PI). In the European Union (EU), bortezomib is authorized as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone in adult subjects who have received at least 1 prior therapy and who have already undergone or are unsuitable for stem cell transplantation. In the NDMM setting, bortezomib is authorized in combination with lenalidomide and dexamethasone (Revlimid SmPC), or melphalan and prednisone in subjects with previously untreated multiple myeloma who are not eligible for transplant, and in combination with dexamethasone or with thalidomide and dexamethasone as initial treatment for adult subjects with previously untreated MM who are eligible for transplant (Velcade SmPC).

1.3.4. Carfilzomib

Carfilzomib (CFZ) is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome, and displays little to no activity against other protease classes. Carfilzomib exhibits antiproliferative and proapoptotic activities in preclinical models in hematologic tumors. In animals, carfilzomib inhibits proteasome activity in blood and tissue and delayed tumor growth in models of multiple myeloma.

In the United States, carfilzomib is approved for use in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of subjects with relapsed or refractory multiple myeloma who have received one to three lines of therapy. It is also approved as a single agent for the treatment of subjects with relapsed or refractory multiple myeloma who have received at least one line of therapy, and more recently the Food and Drug Administration (FDA) approved a once-weekly dosing option of carfilzomib to use in combination with dexamethasone for subjects with RRMM (Kyprolis® PI).

In the EU, carfilzomib is approved for use in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of subjects with RRMM who have received at least one prior therapy (Kyprolis SmPC).

Please refer to the current CFZ label for more information (Kyprolis PI; Kyprolis SmPC).

1.3.5. CC-220 in Multiple Myeloma

CC-220 is an orally available novel cereblon-modulating agent that has multiple effects on cells of the immune system, including immune cell tumors, B cells and T cells, as well as nonimmune cell types such as fibroblasts and endothelial cells. CC-220 has immunomodulatory activity on both lymphoid and myeloid cells and demonstrate antifibrotic activity.

CC-220 shares a similar mechanism of action with lenalidomide and pomalidomide but has increased potency and unique pharmacokinetic properties. Based on these properties, CC-220 is expected to show improved efficacy and tolerability in the treatment of MM.

Please refer to the CC-220 IB for detailed information.

1.3.6. Rationale for Dose, Schedule and Regimen Selection

The primary objective in Part 1 of this study is to determine the maximum tolerated doses (MTDs) and/or recommended phase 2 dose (RP2D) of CC-220 as monotherapy (MonoT), in combination with DEX (DoubleT), and in combination with DEX and DARA, bortezomib (BTZ), or CFZ (in triplet regimen).

1.3.6.1. Dose of CC-220 in MonoT (Cohort A) and DoubleT (Cohort B)

The starting dose of 0.3 mg QD is supported by the Phase 1 data that showed 0.3 mg QD x 28-day dosing was well tolerated in healthy subjects and exhibited sustained effects on multiple Pd parameters.

Dose levels and dose schedule of CC-220 for evaluation in the CC-220-MM-001 study are based on data from two completed studies in healthy adults (CC-220-CP-001 and CC-220-CP-002) and preliminary safety data from the CC-220-SLE-001 study.

Study CC-220-CP-001 was a Phase 1 study to evaluate the safety, tolerability, PK, and Pd of a single oral dose of 0.03; 0.1; 0.3; 1; 2; 4; and 6 mg CC-220. CC-220 was well tolerated by healthy subjects when CC-220 was administered as single doses up to 6 mg.

Study CC-220-CP-002 was a Phase 1 study to evaluate the safety, tolerability, PK, and Pd of multiple oral doses of CC-220. Various multiple oral dose regimens of CC-220 were evaluated: 0.3 mg QD for 14 days; 1 mg QD for 28 days; 0.3 mg QD for 28 days; 1 mg QD for 7 days followed by a washout of 7 days and a further 7 days of treatment with 1 mg QD; 0.3 mg once every 3 days x 14 days for 5 total doses; and 1 mg once every 7 days x 28 days for 4 total doses.

During the CC-220-CP-002 study, three subjects experienced a dose-limiting toxicity of Grade 3 neutropenia after 3 weeks of continuous 1 mg QD dosing with CC-220 (after the Day 21 visit). The dosing of all subjects in that cohort was discontinued during study Week 4 and this dose (CC-220 1 mg QD, continuous) was established as a non-tolerated dose. Per discontinuation of dosing with CC-220, the decreased neutrophil counts in these subjects recovered to normal or to low but not clinically significant values by the Day 28 visit.

Please refer to the IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies and adverse events profile of CC-220.

1.3.6.2. Dose of CC-220 in Triplet Regimens (Cohorts E, F, G1 and G2)

As of 11 January 2019, 8 dose levels (0.3, 0.45, 0.6, 0.75, 0.9,1,1.1, and 1.2 mg) of CC-220 in combination with DEX (Cohort B) were explored. One out of six evaluable subjects in the 1.2 mg dose level experienced a DLT of Grade 4 sepsis. Based on the protocol dose escalation criteria, the Dose Escalation Committee (DEC) recommended to continue the per protocol dose escalation of CC-220 in combination with dexamethasone.

The starting dose of CC-220 in triplet regimen cohorts (Cohorts E, F, G1, and G2) will be one dose level below the maximum dose level of CC-220 that has been determined to be safe in Cohort B. Since there were no DLTs observed in the 1.1 mg dose level, the DEC has approved 1 mg (one dose level below 1.1 mg) CC-220 as the starting dose in combination with IV DARA and DEX for Cohort E and in combination with BTZ and DEX for Cohort F. The starting dose of CC-220 in combination with CFZ and DEX for Cohorts G1 and G2 will be 1.1 mg (one dose level below 1.2 mg).

1.3.6.3. Rationale for Dose Increments in Dose Escalation

CC-220 has been dosed up to 6 mg in a single ascending dose study (CC-220-CP-001) and 1 mg QD in a multiple ascending dose study (CC-220-CP-002) in healthy volunteers. The geometric mean Cmax and AUCs increased in a dose proportional manner from 0.3 mg to 6 mg and the geometric mean coefficient of variation (CV%) ranged from approximately 20%-40% after a single dose and at steady state. Population PK analysis on pooled healthy volunteer and RRMM data demonstrates that RRMM subjects treated with CC-220 display similar exposure and PK characteristics as healthy volunteers, with slight increases in variability (Refer to Figure 1, Table 5 and Table 6).

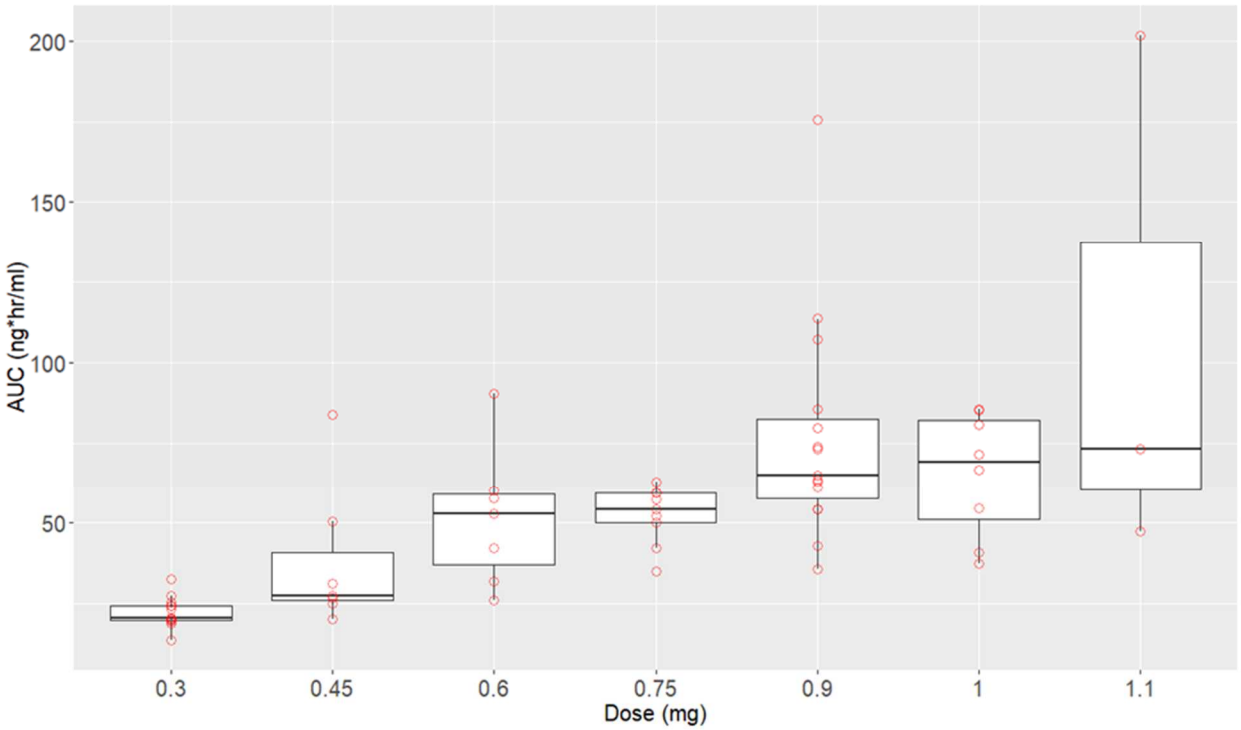
In the present study, at doses above 0.9 mg, dosing ascends in increments of 0.1 mg. Based on estimated PK parameters from this study's data, historical data variability, and the less than 10% increases in dose, clinically significant differences in exposure are not being achieved with 0.1 mg dose escalations.

In addition, preliminary data generated from the dose finding part of the present study thus far has reported a favorable safety profile of CC-220 as monotherapy and in combination with DEX in heavily pretreated subjects with RRMM who failed multiple prior therapies. As of 11 January 2019, a total 83 subjects have been treated with CC-220 at doses ranging from 0.3 to 1.2 mg, including 25 subjects in Cohort A (monotherapy) and 58 subjects in Cohort B (CC-220 + DEX). To date, the MTD/RP2D of CC-220 has not yet been reached at the dose levels studied in any cohort. Two DLTs, Grade 3 lower respiratory tract infection and Grade 4 neutropenia, were observed in Cohort A at the 0.75 and 0.9 mg dose levels, respectively. One DLT of Grade 4 sepsis was observed in Cohort B at the 1.2 mg dose level. Consequently, 3 additional subjects were enrolled into each cohort dose level per the protocol DLT/MTD definition criteria. No further DLTs were observed, thus dose escalation in both cohorts is ongoing.

In Cohort A (monotherapy), the most frequently occurring Grade 3/4 AEs were neutropenia (36%), infections (24%), anemia (20%), and thrombocytopenia (12%). In Cohort B (CC-220 + DEX), the most frequently occurring Grade 3/4 AEs included neutropenia (26%), anemia (23%), infections (19%), and thrombocytopenia (11%).

Therefore, based on the totality of the data, dose increases of up to 25% as determined by the DEC are implemented for subsequent dose level explorations.

Figure 1: Comparison of Estimated CC-220 PK Exposure (AUC0-τ) in RRMM Subjects (CC-220-MM-001)



Abbreviations: AUC0-τ = area under the concentration-time curve over the dosing interval; PK = pharmacokinetic; RRMM = relapsed/refractory multiple myeloma.
Box plot: The lower and upper edges of the box represent the 25th and the 75th percentiles, respectively. Whiskers indicate the maximum and minimum, respectively. The black line represents the median and the red circles represent the observed data. The red circles outside the whiskers represent the outliers.

Table 5: Estimated Median and Mean AUC0-τ (CV%) of CC-220 by Dose in RRMM Subjects (CC-220-MM-001)

Treatment	N	Median $AUC_{0-\tau}$ (ng*hr/ml)	Mean $AUC_{0-\tau}$ (ng*hr/ml) (CV%)
0.3 mg	13	20.64	22.4 (20.9)
0.45 mg	7	27.36	37.87 (59.2)
0.6 mg	7	52.80	51.63 (41.4)
0.75 mg	9	54.24	52.56 (17.1)
0.9 mg	15	64.80	76.51 (45.2)
1.0 mg	8	69.0	65.31 (29.3)
1.1 mg	3	73.20	107.4 (76.8)

Abbreviations: AUC0-τ = area under the concentration-time curve over the dosing interval; CV = coefficient of variation; N = number of subjects; RRMM = relapsed/refractory multiple myeloma.

Table 6: Observed CC-220 AUC0-τ (CV%) by Dose in Healthy Volunteers (CC-220-CP-002)

Treatment	N	Mean $AUC_{0-\tau}$ (ng*hr/ml) (CV%)
0.3 mg	6	14.78(29.0)
1 mg	5	71.78 (39.4)

Abbreviations: AUC0-τ = area under the concentration-time curve over the dosing interval; CV = coefficient of variation; N = number of subjects.

1.3.6.4. Rationale for Dose Levels in NDMM Cohorts J1 and K

The 1.0 mg, 1.3 mg and 1.6 mg dose levels of CC-220 are selected for further evaluation in combination with bortezomib and dexamethasone (Cohort J1) and in combination with daratumumab and dexamethasone (Cohort K) in NDMM subjects not eligible for transplant. Some key data from the CC-220-MM-001 study have been taken into consideration for the selection of these 3 dose levels to be further investigated in Part 2 of the study:

- [redacted]
- While CC-220 showed pharmacodynamic activity at all doses tested, activity in the immune compartment showed dose dependent trends in Cohort B (CC-220+dexamethasone) that appeared to be saturating between the 1.0 and 1.6 mg doses. However, in Cohort E (CC-220Dd) and Cohort F (CC-220Vd), pharmacodynamic activity in the immune compartment at the 1.0 mg dose appeared lower than the 1.3 or 1.6 mg dose, suggesting peak immune activity of CC-220 may require a higher dose in combination with either daratumumab or bortezomib.
- [redacted]
- The CC-220 exposure (ie, AUCss) increased in a dose-related manner with a moderate variability (approximately 46% [CV%]) over the tested dose range (0.3 mg to 1.6 mg) based on the popPK analysis. Given the extent of PK variabilities, the interval between the proposed doses (1.0 mg, 1.3 mg and 1.6 mg) will likely mitigate exposure overlaps and cover a wide range of exposures for dose optimization.

1.3.6.5. Schedule

A 21 out of 28-day treatment cycle for CC-220 was supported by data from a Celgene translational development study, "In Vitro Evaluation of Effect of CC-220 on Neutrophil

Maturation." This study reported that continuous dosing of CC-220 blocked neutrophil differentiation with no significant impact on proliferative capacity or viability of these cells. This effect could be only slightly mitigated by reducing CC-220 exposure to 5 out of 7 days per week to reflect a 2-day drug holiday in the clinic. Complete CC-220 removal for 5 days was necessary to fully restore normal maturation of neutrophils. This data suggests that a 21/28-day schedule is a more appropriate starting schedule for this Phase 1 study.

For Cohort E (CC-220 + DARA + DEX), a 21 out of 28-day treatment cycle for CC-220 will be kept in accordance with the approved label for Darzalex in RRMM (Darzalex PI; Darzalex SmPC; Darzalex Faspro PI).

For Cohort F (CC-220 + BTZ + DEX), a 14 out of 21-day treatment cycle for CC-220 will be implemented in accordance with the approved label for Velcade® in RRMM (Velcade PI; Velcade SmPC).

For Cohorts G1 and G2 (CC-220 + CFZ + DEX), a 21 out of 28-day treatment cycle for CC-220 will be implemented in accordance with the approved label for Kyprolis® in RRMM (Kyprolis PI; Kyprolis SmPC).

For Cohort I (CC-220 + DEX), a 21 out of 28-day treatment cycle for CC-220 will be implemented.

For Cohort J1 (CC-220 + BTZ + DEX), a 14 out of 21-day treatment cycle for CC-220 will be implemented according to the standard of care for Velcade for the first 8 cycles (Velcade PI; Velcade SmPC). Thereafter, after the discontinuation of bortezomib, a 21 out of 28-day treatment cycle for CC-220 + DEX will be implemented.

For Cohort J2 (CC-220 + BTZ + DEX), a 14 out of 21-day treatment cycle for CC-220 will be implemented according to the standard of care for Velcade (Velcade PI; Velcade SmPC).

For Cohort K (CC-220 + DARA + DEX), a 21 out of 28-day treatment cycle for CC-220 will be kept in accordance with the approved label for Darzalex and Darzalex Faspro (Darzalex Faspro PI; Darzalex SmPC).

1.3.6.6. Regimen

CC-220 Monotherapy (MonoT)

CC-220 has not previously been tested in vivo in MM; therefore, in order to gain data on single-agent safety and potential efficacy, a CC-220 monotherapy arm has been included.

Subjects assigned to MonoT, Cohort A (Part 1) or Cohort C (Part 2) who develop PD will have the option to receive DEX in addition to CC-220 after consultation with the Medical Monitor. The subject's dose of CC-220 will not be higher than the dose of CC-220 in combination with DEX tested in Cohort B (Part 1) that is considered safe or the same as the RP2D in Cohort D (Part 2). The site will be informed of the dose of CC-220 to be administered when DEX is added. Progressive disease must be confirmed in accordance with IMWG criteria. The starting dose of DEX will be 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle for subjects who are ≤ 75 years of age. For subjects who are > 75 years of age, the starting dose of DEX is 20 mg on Days 1, 8, 15 and 22 of each 28-day cycle. Subjects who surpass the age of 75 years while on treatment may be switched to the 20 mg dosage based on the Investigator's best judgement. This treatment will continue until PD, unacceptable toxicity or the subject withdraws consent.

CC-220 with Dexamethasone (DoubleT)

The potential synergistic antiproliferative activities of IMiDs and DEX have been previously established in both in vitro and in vivo (Gandhi, 2010; Imnovid SmPC; Pomalyst PI; Revlimid PI; Revlimid SmPC; Thalidomide SmPC; Thalomid PI).

CC-220 with Dexamethasone and Daratumumab, Bortezomib, or Carfilzomib

The potential synergistic activities of CC-220 with DEX and DARA, BTZ, or CFZ have been observed in preclinical data and are further detailed in Section 1.3.7 below.

1.3.7. Rationale for Choice of Combination Compounds

Please refer to Section 1.2.2, Section 1.3.2, Section 1.3.3, and Section 1.3.4 for information on the specific compounds.

CC-220 with Daratumumab and Dexamethasone

Daratumumab is a human $IgG1_k$ monoclonal antibody that targets CD38, a transmembrane receptor with enzymatic activity that is highly and consistently expressed on the surface of myeloma cells (Deaglio, 2007). Daratumumab induces directed myeloma cell killing through complement-dependent cytotoxicity, antibody-dependent cell cytotoxicity, and other potential mechanisms (Lokhorst, 2015). Clinical studies of daratumumab in combination with IMiD compounds have shown these combinations to be well tolerated with impressive efficacy in the relapsed myeloma setting (Dimopoulos, 2017b; Facon, 2017; Plesner, 2016) and more recently, in the newly diagnosed setting (Facon, 2021). Preclinical studies of CC-220 have shown remarkable immunomodulatory activity including enhanced IL-2 secretion and granzyme-b degranulation in stimulated peripheral blood mononuclear cells when compared to other IMiD compounds (Bjorklund, 2016). Furthermore, in co-culture systems using myeloma and immune cells, CC-220 has shown to significantly increase the antibody-dependent cellular cytotoxicity activity of daratumumab. Based on these preclinical data and the impressive clinical activity of daratumumab and IMiD compound combination therapy, the addition of daratumumab to CC-220 therapy could be a highly effective regimen in newly diagnosed and relapsed/refractory MM, and therefore, is chosen for further investigation.

CC-220 with Bortezomib and Dexamethasone

Preclinical data have shown synergistic antimyeloma activity between IMiD compounds and bortezomib (Katz, 2018). The tolerability and activity of combination therapy with IMiD compounds and bortezomib has also shown very promising results in clinical studies in both the front-line and relapsed/refractory MM setting (Richardson, 2018; Richardson, 2010; Richardson, 2011). CC-220, like IMiD compounds, has cereblon modulating activity that results in the proteasome dependent degradation of the transcription factors Aiolos and Ikaros. While the mechanism of action of CC-220 and BTZ may suggest antagonism, preclinical studies in myeloma cell lines have shown CC-220, like immunomodulatory compounds, has synergistic antiproliferative activity in combination with bortezomib (Amatangelo, 2018). Furthermore, CC-220 treatment has been shown to induce degradation of Aiolos and Ikaros in the presence of bortezomib and lead to deeper cell killing in combination with bortezomib than other combinations of IMiD compounds and bortezomib. Based on these preclinical data and the positive clinical activity of combination therapy with bortezomib and IMiD compounds, the

addition of bortezomib to CC-220 therapy could be a highly effective regimen in newly diagnosed and relapsed/refractory MM, and therefore, is chosen for further investigation.

CC-220 with Carfilzomib and Dexamethasone

Clinical and preclinical data support the synergistic activity with proteasome inhibitors and immunomodulatory compounds. CFZ is approved for the treatment of RRMM with lenalidomide and DEX based on the results of the ASPIRE trial (Siegel, 2018). In preclinical models CC-220 has been shown to induce degradation of Aiolos and Ikaros faster than other immunomodulatory compounds. The improved potency observed of CC-220 may confer greater efficacy than other immunomodulatory compounds in combination with more potent proteasome inhibitors such as CFZ. Improved outcomes with CFZ vs BTZ in RRMM suggests the addition of CFZ to CC-220 therapy could be highly effective in relapsed/refractory MM, and therefore, is chosen for further investigation (Dimopoulos, 2016b).

The objective of Cohorts G1 and G2 is to determine the MTD and/or RP2D of CC-220 in combination with DEX and CFZ, at the optimal dose and schedule of CFZ. In each cohort, different approved CFZ dosing schemes (weekly and twice weekly) will be evaluated by the DEC.

Cohort G1 will implement a weekly regimen of CFZ, based on the results of the A.R.R.O.W. study which compared CFZ with DEX once weekly at 70 mg/m² versus twice weekly at 27 mg/m² in patients with RRMM (Moreau, 2018). In the weekly regimen, CFZ was given as 70 mg/m² on Days 1, 8, 15, and 22 of a 28-day cycle. Accordingly, Cohort G1 dose level 1 will evaluate a starting CFZ dose of 56 mg/m^2 on Days 1, 8, 15, 22 and if deemed tolerable by the DEC, may be increased to 70 mg/m² in dose level 2. For subsequent dose levels, the DEC will determine the appropriate CFZ dose given once weekly in combination with DEX and with escalating doses of CC-220.

Cohort G2 may be opened to implement a twice weekly regimen of CFZ, which was implemented in the ENDEAVOR and ASPIRE trials (Dimopoulos, 2016b; Siegel, 2018). ENDEAVOR was a phase 3 trial comparing CFZ with DEX vs BTZ with DEX, using a CFZ regimen of 56 mg/m^2 given on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. The ASPIRE trial compared CFZ with LEN and DEX versus LEN and DEX using a twice weekly CFZ regimen given as 27 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Accordingly, in Cohort G2 dose level 1, CFZ will be given at 27 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. If tolerated, the next dose level will evaluate CFZ at a dose of 56 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. For subsequent dose levels, the DEC will determine the appropriate CFZ dose given twice weekly in combination with DEX and escalating doses of CC-220.

1.3.8. Rationale for Pharmacodynamics and Potential Predictive Biomarkers

Recent research on the mechanism of action of lenalidomide, pomalidomide and thalidomide suggest that in tumor cells and T cells, cereblon, a component of an E3 ubiquitin ligase complex, is a target for binding by these compounds. CC-220 also binds directly to cereblon, thus resulting in induced ubiquitination of the protein substrates Ikaros (encoded by the gene IKZF1) and Aiolos (encoded by the gene IKZF3) and degradation of these proteins. Preclinical studies have shown that the loss of cereblon or a binding partner, such as DDB1, decreases or eliminates the antitumor and immunomodulatory activity of lenalidomide and pomalidomide

respectively (Gandhi, 2014; Ito, 2010; Lopez-Girona, 2012; Zhu, 2011). A number of recent studies have reported correlation between baseline (pretreatment level of cereblon measured by gene expression or by immunohistochemical methods) to clinical outcomes in subjects treated with regimens containing lenalidomide, pomalidomide or thalidomide.

In addition, the measurement of cereblon (and other potential biomarkers, like Ikaros, Aiolos, and CD38) and its utility for determining response during treatment with CC-220 (as monotherapy, doublet, and triplet therapy) is an open scientific question. Thus, we would like to use validated assays for both gene and protein expression and measure baseline and on-treatment biomarker levels, to investigate any potential correlation to clinical outcomes. Additionally, we will evaluate tumor cytogenetics, gene mutations, and gene expression profiles of MM tumors in order to investigate correlations to response and possible identification of patient populations more likely to benefit from CC-220 based therapies.

In preclinical studies with lenalidomide and pomalidomide, immune-modulatory effects on T cells, natural killer (NK) cells, and monocytes have been observed (Gorgun, 2010; Gandhi, 2014). Clinical studies in RRMM patients treated with Pom/Dex show an increase in T cells and NK cells, along with a decrease in B cells during therapy (Sehgal, 2015). The effects of CC-220 treatment on immune cells in myeloma patients is uncertain. Thus, analysis of CC-220 modulation of immune cell populations, immune cell function and T-cell diversity will also be evaluated.

Results from biomarkers will be evaluated in association with parameters of clinical benefit to determine if biomarkers predictive of response or resistance to CC-220 may be identified. Statistical analysis will be conducted to determine any correlations with selected markers to efficacy and safety parameters including response rate, duration of response, and disease progression. In subjects where biomarkers are available during the Treatment phase, changes from the baseline will be examined. These data will be associated with the clinical parameters noted above to identify potential mechanisms of CC-220 activity. Prognostic markers that identify high-risk disease or identify/classify subtypes of disease will also be assessed. Trends between CC-220 exposure and indices of response such as relevant Pd biomarkers, efficacy endpoints and/or safety endpoints will be explored.

T-cell based therapies are a promising approach for treating MM that have shown success against leukemia and lymphoma (Maus, 2014). Chimeric antigen receptors (CARs) T-cells, are T-cells engineered to express fusion proteins with an antigen-recognition domain and a T-cell activating domain (Sadelain, 2013). Expression of CARs by T-cells redirects the specificity and function of these cells and induces their expansion upon repeated antigen exposure in the disease setting. Autologous CAR-T cell products with an antigen recognition domain targeting B-cell maturation antigen (BCMA), a protein expressed mostly by normal and malignant plasma cells, have recently shown great promise in treating high-risk myeloma patients who have run out of treatment options (Berdeja, 2017; Brudno, 2018). However, some patient's disease still progresses after receiving BCMA chimeric antigen receptor T-cell therapy (CAR T) therapy, despite continued BCMA expression by malignant plasma cells (Ali, 2016). Therefore, investigation of strategies to increase CAR-T cell therapy durability are actively ongoing.

Recent reports have highlighted that variations in individual patient's T-cell profile during CAR-T cell product apheresis and injection may be related to the efficacy and durability of CAR-T cell immunotherapy (Fraietta, 2018; Xu, 2014). We have observed that treatment with CC-220

affects T-cell profiles in patients, including increasing proportions of proliferating CD4+ and CD8+ T-cells, increasing proportion of effector memory T-cells and increasing proportion of activated T-cells. It is unknown if these changes in T-cells increase the quality of CAR-T product produced from MM patients. Therefore, the preclinical efficacy of research use only CAR-T products produced from subject's T-cells before and after treatment with CC-220 will be assessed to understand if CC-220 pretreatment improves the anti-MM efficacy of CAR-T products against MM cell lines.

1.3.9. Rationale for Cytogenetic Assessments

The prognosis of and treatment options for MM patients depend on a variety of factors. Strong prognostic factors for patients with MM include age/frailty, International Staging System and adverse-risk cytogenetics. Chromosomal abnormalities of t(4;14) or del 17p are known to be associated with shortened overall and progression-free survival (Fonseca, 2009). More recently, the IMWG (International Myeloma Working Group) have published a consensus recommendation on high-risk cytogenetic abnormalities including t(4;14), del 17p, t(11;14), t(14;20), gain 1q, del 1p, del 13q, and ploidy status (Sonneveld, 2016). While cytogenetic data may help identify high-risk/poor prognostic patients, identification of cytogenetic abnormalities may vary between different study groups and clinical sites due to differences in processing and analysis. These inconsistencies may impede robust analysis of cytogenetic data in studies where data is obtained from multiple sites. Standardized central lab processing and analysis of cytogenetic data will facilitate robust analysis of the clinical benefit of CC-220 in patients with cytogenetically defined high-risk disease where effective treatment options are limited.

1.3.10. Rationale for Minimal Residual Disease Assessments

Data from several studies of recently approved agents/regimens have demonstrated impressive clinical benefits with deep responses and long progression-free survival (PFS) and overall survival (OS) in both newly diagnosed multiple myeloma (NDMM) and RRMM. Identifying early readouts of clinical benefit for MM patients is now crucial for development of novel compounds. Initial minimal residual disease (MRD) data from a study of 52 RRMM patients showed that achievement of MRD-negative status prolonged time to progression (Paiva, 2015). Recently, two Phase 3 RRMM clinical trials provided the first randomized, controlled, prospective evaluation of MRD in this setting (Avet-Loiseau, 2016). Data from the POLLUX (Dimopoulos, 2016a) and CASTOR (Palumbo, 2016) trials indicated that the daratumumab, lenalidomide and dexamethasone (DRd) and daratumumab, bortezomib and dexamethasone (DVd) regimens resulted in significantly higher rates of MRD-negative status at 10-4, 10-5, and 10-6 thresholds as assessed by Adaptive's ClonoSEQ next generation sequencing assay (Adaptive Biotechnologies, Seattle, WA, United States) (Avet-Loiseau, 2016). Patients who achieved MRD-negative status at 10-5 had fewer PFS events compared to patients who were MRD positive. For patients who achieved ≥ complete response (CR), the rate of MRD-negative status was at least 3-fold higher across all sensitivity thresholds in the DRd/DVd versus lenalidomide and dexamethasone (Rd)/bortezomib and dexamethasone (Vd) control arms. These data in RRMM are consistent with earlier data in NDMM indicating clinical benefit with achievement of MRD-negative status. In addition, these data demonstrated that achievement of MRD-negative status predicts similar outcomes independent of treatment regimen received, which is consistent with earlier observations from smaller studies in NDMM (Avet-Loiseau,

2016; Landgren, 2016). These data suggest that MRD status may be an early readout associated with improved clinical outcomes. Additionally, MRD may serve as a tool for monitoring subjects as an early indicator of relapse. Therefore, the level of MRD will be evaluated in subjects receiving CC-220 and achieving a response of very good partial response (VGPR) or better.

1.3.11. Rationale for Cohort D Updated Design

As of 11 January 2019, 58 subjects received CC-220 plus DEX in doses ranging from 0.3 to 1.2 mg in Cohort B. The median age was 64.5 years (range 33–79), and median number of prior regimens was 5 (2–12). Prior therapies included autologous stem cell transplant (79%), LEN (100%), pomalidomide (POM) (69%), PIs (100%), and DARA (66%). Median duration of therapy was 12+ weeks (range 4–109). Grade 3–4 AEs were reported in 41 (72%) subjects. The most frequently occurring Grade 3/4 AEs included neutropenia (26%), anemia (23%), infections (19%), and thrombocytopenia (11%). Of the 51 efficacy-evaluable subjects, 16 achieved a PR or better (31%), 26 minimal response (MR) or better (51%), and 45 achieved stable disease or better (88%).

Data generated from the dose finding part of this study has reported preliminary favorable efficacy and safety of CC-220 plus DEX in heavily pretreated subjects with RRMM who failed multiple prior therapies. Once the RP2D is established for Cohort B and expansion is determined by the DEC, Part 2 may be initiated to further evaluate the efficacy and safety of CC-220 plus DEX in Cohort D. This part of the study will implement a group sequential design (refer to Section 3.1 for further details). As of 18 Oct 2019, the DEC has recommended the 1.6 mg dose level as the RP2D for CC-220 plus DEX.

1.3.12. Rationale for Cohort I

B-cell maturation antigen (BCMA), a member of the tumor necrosis factor receptor family, is exclusively expressed on the surface of plasmablasts, differentiated plasma cells, malignant plasma cells a subset of memory B cells, but is absent in early B cells, hematopoietic stem cells and other normal tissues (Laabi, 1994; Novak, 2004). BCMA binds to B-lymphocyte stimulator (BLyS), also known as B cell-activating factor (BAFF), and a proliferation-inducing ligand (APRIL), both critical proteins supporting the growth and survival of malignant plasma cells in MM (Tai, 2016). These data suggest BCMA may be a very promising target for the treatment of MM.

Currently, there are multiple BCMA-targeted treatment modalities being investigated to treat MM, including: antibody drug conjugates (ADC), bispecific T-cell engagers, CARTs, bispecific and bi/trispecific antibodies, as well as cancer vaccines (Cho, 2018). The development of novel agents targeting BCMA is ongoing and data from early clinical trials have demonstrated significant anti-myeloma activity in heavily pre-treated RRMM subjects. Notably, CAR Ts targeting BCMA have demonstrated encouraging results (Raje, 2019). In the 51 subjects who received bb2121 as of 17 Dec 2018 with a median of 5.8 months of follow-up, the objective response rate was 78.4% (95% confidence interval [CI]: 64.7, 88.7). Twenty subjects (39.2%) achieved a confirmed complete response or better. The median duration of response was 10.9 months (95% CI: 7.5, 13.7). The median progression-free survival was 10.2 months (95% CI: 5.9, 12). BCMA targeting bispecific T-cell engager (BiTE) immunotherapies have also shown promising results, in a phase I dose escalation study of AMG 420 there was a 70% response rate

(7/10) with 5 out of 7 responders achieving a sCR at 400 µg/d, the recommended dose for further investigation (Topp, 2019).

Despite encouraging results, BCMA-targeted therapy is not curative, and the vast majority of subjects will ultimately relapse, thus highlighting the need for effective novel therapies in the post-BCMA setting. Cohort I will enroll up to 40 subjects who have received prior BCMA-targeted therapy to explore the safety and preliminary efficacy of CC-220 plus DEX in this patient population. As CAR T therapy is anticipated to be a standard of care option in the future, Cohort I targets to enroll a minimum of 40% of subjects with prior BMCA-targeted CAR T therapy to ensure adequate representation of this population.

1.3.13. Rationale for NDMM Cohorts (J1, J2, and K)

For patients with NDMM, the choice of initial therapy is determined by the patient's age, fitness, and the presence of comorbidities (Kumar, 2018; Ludwig, 2014; Moreau, 2017; Palumbo, 2015). High-dose chemotherapy followed by ASCT has demonstrated superior outcomes compared with other treatment options and is the treatment of choice for patients with NDMM provided they are eligible, based on their age, comorbidities and functional status. The current optimal treatment paradigm for patients determined to be eligible for ASCT is initial induction therapy followed by treatment with high-dose chemotherapy and ASCT, followed by maintenance treatment (with or without consolidation therapy). For those patients not considered eligible for ASCT, treatment with combination induction regimens including alkylators, proteasome inhibitors, immunomodulatory agents, steroids and novel agents are currently considered standard of care.

Progress has been made in improving the overall survival in NDMM patients. The increase in survival has been driven by more effective combination induction regimens composed primarily of proteasome inhibitors, immunomodulatory agents and dexamethasone (Kumar, 2017; Moreau, 2017; Rajkumar, 2016).

SWOG S0777 was a Phase 3, multicenter, randomized, open-label, active-controlled efficacy and safety study of RVd (lenalidomide in combination with bortezomib and dexamethasone) versus Rd (lenalidomide in combination with dexamethasone) for initial treatment in subjects with NDMM without intent for immediate ASCT. Patients were randomly assigned to receive 6 months of primary therapy with either RVd (eight 3-week cycles) or Rd (six 4-week cycles), each followed by maintenance therapy with Rd until progression or unacceptable toxicity. The group treated with RVd showed a significantly longer PFS of 43 versus 30 months (hazard ratio [HR], 0.712; 95% CI, 0.56–0.906) and improved median overall survival (OS) of 75 versus 64 months (HR, 0.709; 95% CI, 0.524–0.959) (Durie, 2017). Based on the significant improvement in PFS and OS seen with RVd, this regimen was included in the NCCN clinical practice guidelines as a preferred option for the primary treatment of transplant-eligible and non–transplant-eligible patients with NDMM and in the European Society for Medical Oncology (ESMO) clinical guidelines as a major treatment regimen in front-line NDMM (Kumar, 2018; Moreau, 2017).

The MAIA trial randomly assigned 737 NDMM patients who were ineligible for ASCT to receive either daratumumab plus lenalidomide and dexamethasone (DRd) or lenalidomide and dexamethasone alone (Rd). Treatment was to continue until the occurrence of disease progression or unacceptable side effects. At a median follow-up of 56.2 months, the addition of daratumumab to lenalidomide and dexamethasone significantly decreased the risk of disease

progression or death (hazard ratio for PFS, 0.53; 95% CI, 0.43 to 0.66; P<0.0001). The percentage of patients with a complete response or better was 51% in the DRd group versus 30% in the Rd group (P<0.0001). A total of 31% of the patients in the DRd group, as compared with 10% of the patients in the Rd group had undetectable minimal residual disease at the 10^{-5} threshold (Facon, 2021). Based on the results from this trial, the DRd regimen is approved in the EU (Darzalex SmPC) and the US (Darzalex PI; Darzalex Faspro PI), and listed as a preferred regimen (category 1) as primary therapy for non-transplant candidates by the NCCN guidelines (NCCN Guidelines, 2021).

Despite a better understanding of the disease biology and the introduction of new and mechanistically different therapeutic options, MM is not curable with current therapies; thus, there is still a need to develop more efficacious and less toxic treatments for front line treatment (Willenbacher, 2018). As described in Section 1.3.7, preclinical studies in myeloma cell lines have shown CC-220, like immunomodulatory compounds, has synergistic antiproliferative activity in combination with bortezomib (Amatangelo, 2018). CC-220 treatment in combination with bortezomib induces deeper degradation of Aiolos and Ikaros and more robust cell killing than IMiD compounds in combination with bortezomib. Furthermore, in preclinical models CC-220 has been shown to induce degradation of Aiolos and Ikaros with faster kinetics than other IMiD compounds. As described in Section 1.3.7, CC-220 has also shown to significantly increase the antibody-dependent cellular cytotoxicity activity of daratumumab in co-culture systems using myeloma and immune cells.

Data generated from the CC-220-MM-001 study has reported favorable tolerability and promising clinical activity for CC-220Vd in subjects with RRMM. [redacted]

Similarly, data generated from the study has reported favorable tolerability and promising clinical activity for CC-220Dd in subjects with RRMM. [redacted]

Taken together, based on the preclinical synergy data, the positive clinical activity of combination therapy with bortezomib and IMiD compounds in the NDMM setting, and on the favorable tolerability and encouraging preliminary efficacy of CC-220 plus DEX, the addition of bortezomib to CC-220 therapy may represent a highly effective regimen in NDMM subjects who are eligible for ASCT and those who are not eligible for ASCT, and therefore, is chosen for further investigation. In addition, based on the preclinical data, the clinical activity of combination therapy of an IMiD with daratumumab in NDMM and on the favorable tolerability of daratumumab and CC-220 plus DEX, the addition of daratumumab to CC-220 therapy may represent a highly effective regimen in NDMM subjects who are not eligible for ASCT, and therefore, is chosen for further investigation.

1.3.14. Rationale for Addition of Subcutaneous Daratumumab

A new formulation of DARA for SC administration was developed to avoid the long infusion time and infusion reactions associated with IV administration of DARA. A recombinant human hyaluronidase PH20 (rHuPH20) was used to facilitate the SC administration of DARA in order to decrease the volume required for SC administration.

The safety and efficacy profile of SC DARA monotherapy was evaluated in COLUMBA, an open-label, randomized, non-inferiority Phase 3 study in subjects with RRMM. In this study, 263 subjects were randomized to receive SC DARA 1800 mg, coformulated with 30,000 units hyaluronidase administered subcutaneously, and 259 subjects were randomized to receive DARA 16 mg/kg administered intravenously; each administered weekly for Cycles 1 and 2, every two weeks for Cycles 3 through 6 and every 4 weeks from Cycle 7 onwards. SC DARA was shown to be non-inferior to IV DARA in terms of ORR, with both having similar safety profiles. In addition, SC DARA had a lower rate of injection-related reactions (IRRs) (Mateos, 2019).

The SC formulation of DARA in combination with standard MM treatment regimens was also investigated in the PLEIADES study, a multi-cohort, open-label, Phase 2 study. In this study, the safety and efficacy of SC DARA in combination with lenalidomide and DEX (DRd) in RRMM

subjects with > 1 prior line of therapy and in combination with bortezomib, melphalan, and prednisone (DVMP) in NDMM subjects who are ineligible for transplant were evaluated. The safety profiles in both cohorts were consistent with those observed with DARA IV. Rates of IRRs and injection site reactions were consistent with those observed with SC DARA monotherapy in the COLUMBA study. The PK of SC DARA in each regimen was consistent with historical data and the immunogenicity of DARA and hyaluronidase were comparable to previous reports (Chari, 2019).

As SC DARA is anticipated to be a standard of care option in the future, the combination of CC-220, SC DARA and DEX will be investigated in this study. Please refer to the current label for more information (Darzalex Faspro PI; Darzalex SmPC).

2. STUDY OBJECTIVES AND ENDPOINTS

Table 7: Study Objectives

Primary Objective
The primary objective in Part 1 of the study is to determine the maximum tolerated doses (MTDs) and/or recommended Phase 2 doses (RP2Ds) of CC-220 as monotherapy (MonoT), in combination with dexamethasone (DEX) (DoubleT), in combination with dexamethasone and daratumumab (CC-220Dd), in combination with DEX and bortezomib (CC-220Vd), and in combination with DEX and carfilzomib (CC-220Kd) in subjects with relapsed and refractory multiple myeloma (RRMM). The primary objective in Part 2 of the study is to determine the efficacy of CC-220 in combination with DEX (DoubleT) in subjects with RRMM in Cohort D, as measured by overall response rate (ORR).
Secondary Objective(s)
The secondary objectives are: – To evaluate the safety of CC-220 as MonoT, DoubleT, CC-220Dd, CC-220Vd, and CC-220Kd in subjects with RRMM. – To evaluate the preliminary efficacy and safety of CC-220Vd and CC-220Dd in subjects with NDMM, including subjects who are eligible for ASCT and subjects who are not eligible for ASCT. – To evaluate additional efficacy parameters of CC-220 in combination with DEX including time-to-response (TTR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) in subjects with RRMM in Cohort D. – To assess the preliminary efficacy of CC-220 as MonoT, DoubleT, CC-220Dd, CC-220Vd, and CC-220Kd in subjects with RRMM in Part 1. – To assess the preliminary efficacy and safety of CC-220 in combination with DEX in subjects with RRMM who have received prior B-cell maturation antigen (BCMA)-targeted therapy. – To evaluate the pharmacokinetics (PK) of CC-220 in subjects with RRMM and NDMM.

Table 7: Study Objectives (Continued)

Exploratory Objective(s)
The exploratory objectives are: – To explore genomic, molecular and immune biomarkers, including immune activation/exhaustion markers and cytokines, for mechanism of action of CC-220, their correlation to clinical outcome measures and pharmacodynamics. – To evaluate dose-related immune effects of CC-220. – To evaluate the PK of metabolite M12 in subjects with RRMM. – [redacted] – To evaluate the safety for the combination of CC-220Dd when DARA is administered as subcutaneous injection. • In Part 2 of the study, [redacted] – To explore minimal residual disease (MRD) in subjects who achieve a response of very good partial response (VGPR) or better and its correlation to clinical outcome measures in subjects with RRMM and NDMM. [redacted]

Table 8: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Recommended Dose and Regimen in Part 1	Establish the maximum tolerated doses (MTDs) and/or Recommended Phase 2 doses (RP2Ds) of CC-220 monotherapy, in combination with DEX, and in combination with DEX and daratumumab (CC-220Dd), in combination with DEX and bortezomib (CC-220Vd), and in combination with DEX and carfilzomib (CC-220Kd)	Part 1

Table 8: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Primary	Overall response rate (ORR) in Cohort D	Tumor response, including progressive disease (PD) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Kumar, 2016) in CC-220 in combination with DEX	From first subject first dose of IP until the last subject is no longer evaluable for response or has progressed
Secondary	Safety	Type, frequency, seriousness and severity of adverse events (AEs) (and AEs of special interest) and relationship of AEs to investigational product	From first subject first visit until 28 days after the last subject discontinues study treatment
	Very good partial response or better rate (VGPR)	Tumor response, including progressive disease (PD) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Kumar, 2016) for subjects who achieved VGPR or better	From first subject dose of IP until the last subject is no longer evaluable for response or has progressed
	Overall response rate (ORR)	Tumor response, including progressive disease (PD) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Kumar, 2016) for subjects who achieved partial response (PR) or better	From first subject dose of IP until the last subject is no longer evaluable for response or has progressed
	Time to response (TTR)	Time from enrollment to the first documentation of response (PR or greater)	From first subject dose of IP until the last subject is no longer evaluable for response or has progressed
	Duration of response (DOR)	Time from the first documentation of response (PR or greater) to the first documentation of PD	From first subject dose of IP until the last subject is no longer evaluable for response or has progressed
	Progression-free Survival (PFS)	Time from the first dose of investigational product (IP) to the first documentation of PD or death from any cause, whichever occurs first	From first subject first dose of IP until the last subject discontinues study

Table 8: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Overall Survival (OS) in Part 2 RRMM cohorts	Time from first dose of IP to death due to any cause	From first subject dose of IP until the last subject discontinues study
	Pharmacokinetic (PK) parameters	PK of CC-220, and as appropriate, its R-enantiomer CC-17195 in plasma, eg, AUC(TAU), Cmax, Tmax	During study treatment
Exploratory	Biomarkers	Evaluate the Pd effects of CC-220 on immune cell counts in peripheral blood	During study treatment
	Biomarkers	Evaluate modulation of immune responses (such as activation/exhaustion makers and cytokine secretion), gene expression, protein expression and T-cell receptor (TCR) clonality in immune cells by CC-220	During study treatment
	Biomarkers	Evaluate correlation of baseline and Pd changes in protein expression, gene expression, cytogenetics, copy number abnormalities and/or mutations in tumor cells and tumor microenvironment in the bone marrow to CC-220 response or resistance	During study treatment
	PK parameters	Evaluate the PK of metabolite M12 in plasma	During study treatment
	Biomarkers in Part 2	Evaluate minimal residual disease (MRD) negativity and duration in subjects who achieve a response of very good partial response (VGPR) or better and its association with clinical outcomes	From first subject dose of IP until the last subject is no longer evaluable for response or has progressed

[redacted]

Table 8: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
[redacted]			

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a multicenter, multicountry, open-label, Phase 1b/2a dose-escalation study to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of CC-220 when administered as monotherapy and in combination with other treatments. The study will consist of two parts: a dose-escalation portion (Part 1) and dose expansion (Part 2).

In Part 1 dose escalation, RRMM subjects may be enrolled into the following six cohorts: CC-220 monotherapy (MonoT, Cohort A), in combination with DEX (DoubleT, Cohort B), in combination with DEX and IV DARA (CC-220Dd, Cohort E), in combination with DEX and BTZ (CC-220Vd, Cohort F), and in combination with DEX and CFZ (CC-220Kd, Cohorts G1 and G2).

Once the MTD and/or RP2D is determined in Cohort E (CC-220Dd), 13 subjects will be enrolled at this dose level using SC DARA to evaluate the safety and tolerability with the SC formulation. The decision to evaluate any additional subjects with the SC formulation will be at the discretion of the DEC, based on their review of the data.

In Part 2 dose expansion, the following cohorts may be opened to evaluate efficacy and safety at the RP2D: (Cohort C: monotherapy, Cohort D: CC-220 in combination with DEX, Cohort I: CC-220 in combination with DEX in RRMM subjects with prior BCMA-targeted therapy, Cohort J1: CC-220Vd in NDMM subjects who are not eligible for ASCT, Cohort J2: CC-220Vd in NDMM subjects who are eligible for ASCT, Cohort K: CC-220Dd in NDMM subjects who are not eligible for ASCT). Cohorts J1 and K will evaluate up to 3 dose levels of CC-220 (1.0 mg, 1.3 mg, 1.6 mg). The decision to evaluate any additional subjects in any of the NDMM dose level cohorts will be made in consultation with the DEC, based on their review of the data.

A group sequential design (Jennison, 1999) will be used to evaluate the efficacy and safety of CC-220 (at the RP2D of 1.6 mg) in combination with DEX (Cohort D):

- ***Cohort D Stage 1***: Following the treatment of 40 subjects, an interim analysis will be performed to evaluate the preliminary efficacy of CC-220 plus DEX at the RP2D of 1.6 mg.
- ***Cohort D Stage 2***: If the results from Stage 1 do not cross the futility boundary (see Section 9.10), an additional 61 subjects may be treated to confirm the safety and efficacy of CC-220 plus DEX at the RP2D of 1.6 mg.

The dose and schedule of DEX for applicable cohorts is detailed in Section 7.2

The starting doses of CC-220 monotherapy in Cohort A and CC-220 in combination with DEX in Cohort B are detailed in Table 2; in combination with DEX and IV DARA in Cohort E and in combination with DEX and BTZ in Cohort F are detailed in Table 3; and in combination with DEX and CFZ in Cohorts G1 and G2 are detailed in Table 4.

Treatment will continue until progressive disease (PD), unacceptable toxicity or withdrawal of consent for all cohorts except for Cohort J2 where subjects will receive CC-220Vd for up to 6 cycles or until PD, unacceptable toxicity or withdrawal of consent, whichever is earlier.

All subjects who discontinue study treatment in Part 1 or Part 2 of the study for a reason other than PD or withdrawal of consent from the study will be followed for response assessment every 28 days (21 days for Cohort F: CC-220Vd) until PD or a subsequent myeloma regimen has been started. Subjects in Cohorts J1 and K will be followed every cycle for the first 2 years and thereafter, every 3 months until PD or until a subsequent myeloma regimen has been started. Subjects in Cohort J2, following induction and ASCT with or without maintenance, will be followed for response assessment during the Post-Treatment Response follow-up every 3 months until PD or until a subsequent anti-myeloma regimen has been started.

All RRMM subjects enrolled in Part 2 of the study (Cohorts C, D, and I) will have long-term follow-up. Subjects will be contacted every 3 months for 5 years from the date of the last subject enrolled in the study (or longer if clinically indicated) to learn of the subject's death from any cause, to continue second primary malignancy (SPM) surveillance, and to collect data on subsequent anti-myeloma therapies including date of progression.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

3.1.1. Dose Escalation (Part 1)

Subjects who meet all eligibility criteria and have completed all Screening procedures will be allocated in parallel to the appropriate treatment cohort, based on eligibility status and on cohort slot availability. Enrollment will be accomplished by a validated Interactive Response Technology (IRT). The 3+3 design will be utilized to determine the MTD and/or RP2D for CC-220 as monotherapy (Cohort A: MonoT), in combination with DEX (Cohort B: DoubleT), in combination with DEX and IV DARA (Cohort E: CC-220Dd), in combination with DEX and BTZ (Cohort F: CC-220Vd), and in combination with DEX and CFZ (Cohorts G1 and G2: CC-220Kd). Subjects in Cohorts A, B, E, G1 and G2 will have a 28–day treatment cycle and subjects in Cohort F will have a 21–day treatment cycle.

All subjects will be treated in each cohort (Cohorts A, B, E, G1 and G2) and observed for at least 28 days (21 days for Cohort F) after the first dose of CC-220 before the dose level is escalated in the next dose level.

The following dose-escalation rules will be applied in determining the MTD:

- Initially 3 subjects will be enrolled into each dose-level cohort (either Cohort A, Cohort B, Cohort E, Cohort F, Cohort G1, or Cohort G2).
  - If none of the 3 initial subjects in a dose-level cohort experience a dose-limiting toxicity (DLT) (see definition of DLT in Section 3.1.1.2) within the first cycle, then enrollment into the next 3-subject dose-level cohort at a higher dose level may be initiated.
  - If 2 or 3 of the 3 initial subjects in a dose-level cohort experience a DLT within the first cycle, then the MTD has been exceeded and no further dose escalation is needed.

  - If 1 of the 3 initial subjects in a dose-level cohort experiences a DLT within the first cycle, then an additional 3 subjects will be enrolled into the same dose-level cohort and dose level.
    - If 2 or more subjects in the expanded 6-subject dose-level cohort experience a DLT within the first cycle, then the MTD has been exceeded and no further dose escalation is needed.
    - If only 1 of the subjects in the expanded 6-subject dose-level cohort experiences a DLT within the first cycle, then the next higher dose-level cohort may be tested and enrollment of the next 3 subjects at the next higher dose-level cohort can be initiated.

- The MTD is defined as the previous dose level of the cohort where a DLT is observed in at least 2 subjects within the first cycle.
- Subjects within a dose-level cohort will be replaced if they are not evaluable for DLT during the first cycle due to missed doses for reasons other than DLT:
  - For Cohort A (MonoT) miss more than 4 doses of CC-220 within the first cycle (28 days)
  - For Cohort B (DoubleT) miss more than 4 doses of CC-220 and/or more than 2 doses of DEX within the first cycle (28 days)
  - For Cohort E (CC-220Dd) miss more than 4 doses of CC-220, more than 2 doses of DEX, and/or more than 1 dose of DARA within the first cycle (28 days)
  - For Cohort F (CC-220Vd) miss more than 4 doses of CC-220, more than 2 doses of DEX, and/or more than 1 dose of BTZ within the first cycle (21 days)
  - For Cohorts G1 and G2 (CC-220Kd) miss more than 4 doses of CC-220, more than 2 doses of DEX, and/or more than 1 dose of CFZ within the first cycle (28 days)
  - Discontinue IP for a reason unrelated to a DLT within the first cycle

Dose-limiting toxicity will be assessed to determine MTD during the first treatment cycle. Once the MTD and/or RP2D is determined for CC-220 in either Cohort A or Cohort B, subject enrollment may begin for Part 2 (expansion). The MTD may be the RP2D. The RP2D may also be determined by PK and biomarker data as well as the safety and preliminary efficacy data from Part 1, as applicable. The decision to determine the RP2D will be made in consultation with the DEC.

3.1.1.1. Dose Escalation Committee

Objectives:

In Part 1, the Dose Escalation Committee (DEC) members are responsible for dosing decisions. Dosing decisions may include escalations to the next-dose level, de-escalation to a lower dose; continuation, delay or termination of dosing, repetition of a dose-level cohort, or expansion of a dose-level cohort. At each time, at minimum all clinical and laboratory safety data for a given cohort will be reviewed.

The decision to either evaluate a higher dose level, declare MTD and/or RP2D is determined by the DEC. Additional dose levels up to 25% greater than the prior dose level deemed tolerable may be explored based on the DEC's evaluation and recommendation (refer to Section 1.3.6.3).

Members:

The DEC consists of Sponsor team members: Medical Monitor(s), Lead Safety Physician, Biostatistician, other functional area representatives as appropriate, Global Study Investigators, the IER and site Investigators and/or designees who have enrolled subjects in the given dose-level cohort will be on the DEC. Responsibilities of this committee are described in the Dose Escalation Committee and Independent Expert Reviewer Charter.

3.1.1.2. Dose-limiting Toxicity

The dose-limiting toxicity (DLT) population will be all subjects who missed no more than 4 scheduled doses of CC-220, and/or no more than 2 doses of DEX, and/or no more than 1 dose of IV DARA (Cohort E) and/or no more than 1 dose of BTZ (Cohort F) and/or no more than 1 dose of CFZ (Cohort G1 or Cohort G2) during Cycle 1 for reasons other than DLT. The DLT population will be used for analysis of the primary endpoint regarding the determination of the MTD. Subjects not evaluable for DLT will be replaced for purposes of adequately assessing DLT. Regardless of evaluability for DLT, all subjects receiving any dose of IP will remain in the safety database.

For the purpose of determining the MTD for this study, a DLT is defined as any of the following events occurring during the first 28 days (21 days for Cohort F) (Cycle 1) (*Note – Severity grades are defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.0).*

Hematologic DLTs

- Grade 4 neutropenia (absolute neutrophil count [ANC] <500/μL for >5 days)
- Grade 3 neutropenia (ANC < 1,000/μL) with fever ≥ 38.5°C of any duration
- Grade 4 thrombocytopenia (platelet count < 25,000/μL) or Grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion
- Any other grade 4 hematologic toxicity, other than anemia, that does not resolve to subject's pretreatment baseline level within 72 hours

Non-hematologic DLTs

- Any non-hematological toxicity ≥ Grade 3, except for alopecia and nausea controlled by medical management
- Any treatment interruption greater than 2 weeks due to an AE

While the rules for adjudicating DLTs in the context of dose escalation are specified above, an AE not listed above may be defined as a DLT after consultation with the DEC (Section 3.1.1.1).

3.1.2. Expansion (Part 2)

All expansion decisions will be determined by the DEC after review of all safety, PK, biomarker and preliminary efficacy data, as applicable.

Cohort C (MonoT)

Once a RP2D from the dose-escalation cohort in Part 1 is determined, up to an additional 24 subjects may be enrolled into the expansion Cohort C (MonoT).

Following the 08 Nov 2019 DEC review of Cohort A, the 1 mg dose level was deemed tolerable. It was agreed that further investigation of CC-220 monotherapy was more appropriate in a newly diagnosed MM maintenance setting. Therefore, Cohort C will not be opened.

Cohort D (DoubleT)

Once a RP2D from the dose-escalation cohort in Part 1 is determined, the expansion cohort may be initiated. As of 18 Oct 2019, the DEC has recommended the 1.6 mg dose level as the RP2D for CC-220 plus DEX. A group sequential design (Jennison, 1999) will be used to evaluate the efficacy and safety of CC-220 (at the RP2D of 1.6 mg) plus DEX in Cohort D.

Cohort D Stage 1

- In Stage 1, following the treatment of 40 subjects, an interim analysis will be performed to evaluate the preliminary efficacy of CC-220 plus DEX at the RP2D of 1.6 mg.

Cohort D Stage 2

- If the results from Stage 1 do not cross the futility boundary (see Section 9.10), an additional 61 subjects may be treated to confirm efficacy and safety of CC-220 plus DEX at the RP2D of 1.6 mg.

Cohort I (DoubleT Expansion in Post-BCMA RRMM)

- Once the RP2D is established for Cohort B (CC-220 plus DEX) and expansion is determined by the DEC, this expansion cohort may be initiated. As of 18 Oct 2019, the DEC has recommended the 1.6 mg dose level as the RP2D for CC-220 plus DEX.
- Up to 40 subjects who have received prior BCMA-targeted therapy may be enrolled to explore the safety and preliminary efficacy of CC-220 plus DEX at the RP2D for this patient population. A minimum of 40% of the cohort will have prior BCMA-targeted CAR T therapy. The IRT will be used to monitor the inclusion of these subjects.

Cohort J1 (CC-220Vd Expansion in NDMM)

- Once the RP2D is established for Cohort F (CC-220Vd) and expansion is determined by the DEC, this expansion cohort may be initiated. [redacted]

Approximately 75 subjects may be enrolled to explore the safety and preliminary efficacy of up to 3 dose levels of CC-220 (1.0 mg, 1.3 mg, and 1.6 mg) in combination with BTZ and DEX in NDMM subjects who are not eligible for ASCT. Up to approximately 25 subjects per dose level may be enrolled. Additional subjects may be enrolled in any of the dose levels upon consultation with the DEC, based on review of the data.

Cohort J2 (CC-220Vd Expansion in NDMM)

- Once the RP2D is established for Cohort F (CC-220Vd) and expansion is determined by the DEC, this expansion cohort may be initiated.

Approximately 50 subjects may be enrolled to explore the safety and preliminary efficacy of CC-220 in combination with BTZ and DEX in NDMM subjects who are eligible for ASCT.

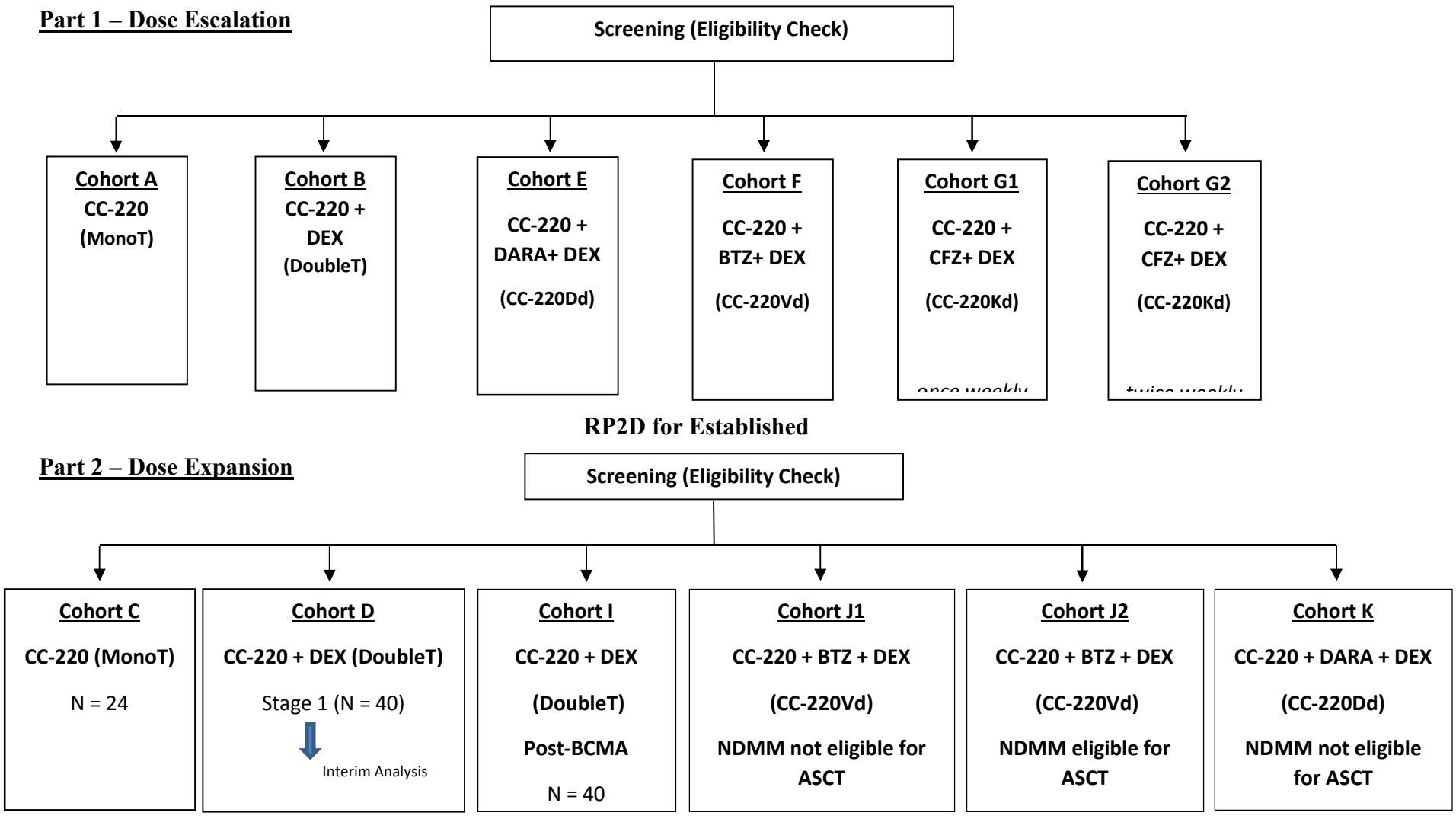
Cohort K (CC-220Dd in NDMM and not eligible for ASCT)

- Once the RP2D is established for Cohort E (CC-220Dd) by the DEC (IV DARA), this expansion cohort may be initiated. [redacted]
- Approximately 75 subjects may be enrolled to evaluate the safety and preliminary efficacy of up to 3 dose levels of CC-220 (1.0 mg, 1.3 mg, and 1.6 mg) in combination with SC DARA and DEX in NDMM subjects who are not eligible for ASCT. Approximately 25 subjects per dose level may be enrolled. Additional subjects may be enrolled in any of the dose levels upon consultation with the DEC, based on review of the data.

Any of the cohorts may be removed and/or terminated from the study based on emerging PK, Pd, efficacy or safety data, in consultation with the DEC.

During Part 2 of the study, the DEC (including the IER) will continue to review the safety data and any other data deemed relevant so that subject safety is ensured. This review, described in the Dose Escalation Committee Charter, is in addition to the review by the Safety Management Team of all CC-220 safety data and the ongoing review of study data by the clinical team. Further details are described in the charter.

Figure 2: Overall Study Design



ASCT = autologous stem cell transplant; BCMA = B-cell maturation antigen; BTZ = bortezomib; CC-220Dd = CC-220 + DARA + DEX; CC-220Vd = CC-220 + BTZ + DEX; CFZ = carfilzomib; DARA = daratumumab; DEX = dexamethasone; DoubleT = CC-220+DEX combination therapy; IRT = Interactive Response Technology; IV = intravenous; MonoT = monotherapy; NDMM= newly diagnosed multiple myeloma; RRMM = relapsed and refractory multiple myeloma; RP2D = recommended Phase 2 dose.

3.2. Study Duration for Subjects

The study will consist of the Screening and Treatment phases for the subjects in both Part 1 and Part 2 of the study. In Part 2, there is also a Long-term Follow-up phase for RRMM cohorts (Cohorts C, D, and I).

The Screening phase may not exceed a 28-day window prior to the start of IP (Cycle 1 Day 1).

Treatment at each dose level in Part 1 as well as treatment in Part 2 will continue until progressive disease (PD), unacceptable toxicity, or the subject withdraws consent for all cohorts except Cohort J2 where treatment will continue for up to 6 cycles or until PD, unacceptable toxicity or withdrawal of consent, whichever is earlier.

There will be an End of Treatment (EOT) Visit to collect safety and efficacy assessments. For subjects in Cohort J2, the EOT Visit is considered either 3 months (±7 days) post ASCT (prior to any maintenance therapy, if applicable) or at any other moment for treatment discontinuation.

Another visit will be conducted 28 days after the end of treatment to collect safety assessments.

All subjects who discontinue study treatment in Part 1 or Part 2 of the study for a reason other than PD or withdrawal of consent from the study will be followed for response assessment every 28 days (every 21 days for Cohort F) until PD or a subsequent myeloma regimen has been started. Subjects in Cohorts J1 and K will be followed every cycle for the first 2 years and thereafter, every 3 months until PD or until a subsequent myeloma regimen has been started. Subjects in Cohort J2, following induction, ASCT with or without maintenance, will be followed for response assessment during the Post-Treatment Response follow-up every 3 months until PD or until a subsequent anti-myeloma regimen has been started.

All RRMM subjects in Part 2 (Cohorts C, D, and I) will be contacted every 3 months for 5 years from the date of the last subject enrolled in the study to learn of the subject's death from any cause, to continue SPM surveillance, and to collect data on subsequent anti-myeloma therapies including date of progression.

3.3. End of Trial

The End of Trial is defined as either the date of the last Long-term Follow-up data collection, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

At the conclusion of the study, if the study intervention is not available as an approved treatment in the local country, participants who continue to demonstrate clinical benefit will be eligible to receive Sponsor-supplied study intervention. If the study treatment is not available as an approved and available treatment, study intervention will be provided via an extension of the study, or a rollover study requiring approval by the responsible Health Authority and ethics committee, or through another mechanism at the discretion of the Sponsor. The Sponsor reserves the right to terminate access to the supplied study intervention treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of CC-220 is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or other health program. In all cases, the Sponsor will follow local regulations.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 34 subjects in Cohort A and 72 subjects in Cohort B will be treated and evaluated in Part 1 for MTD and/or RP2D. Approximately 85 additional subjects will be allocated to one of the four triplet regimen cohorts (Cohorts E, F, G1 and G2). The actual number of subjects in dose escalation part (Part 1) will depend on the number of dose levels being tested (based on the occurrence of DLT) and may exceed these approximations. In Part 2, up to 341 subjects may be enrolled: up to 101 subjects may be enrolled in Cohort D, up to 40 subjects in Cohort I, approximately 75 subjects in Cohort J1, approximately 50 subjects in Cohort J2, and approximately 75 subjects in Cohort K.

Refer to Table 1 for a summary of each cohort's eligibility.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is ≥18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. All subjects in RRMM cohorts must have a documented diagnosis of MM and have measurable disease defined as:
    a. M-protein (serum and/or urine protein electrophoresis (sPEP or uPEP)): sPEP ≥0.5 g/dL or uPEP ≥ 200 mg/24 hours and/or
    b. Light chain MM without measurable disease in the serum or urine: serum immunoglobulin free light chain ≥ 10 mg/dL (100 mg/L) and abnormal serum immunoglobulin kappa lambda free light chain ratio
5. Subjects in Cohorts A, B, C, E, G1, and G2 must have received at least 2 prior myeloma regimens (note: induction with or without bone marrow transplant and with or without maintenance therapy is considered one regimen). Subjects in Cohort F must have received at least 1 prior myeloma regimen. Subjects in Cohorts D and I must have received at least 3 prior myeloma regimens.
6. All subjects in RRMM cohorts must have received prior treatment with at least 2 consecutive cycles of a lenalidomide or pomalidomide-containing regimen. Subjects in Cohort D must have received prior treatment with at least 2 consecutive cycles of a lenalidomide-containing regimen **and** at least 2 consecutive cycles of a pomalidomide-containing regimen.
7. All subjects in RRMM cohorts must have received prior treatment with at least 2 consecutive cycles of a proteasome inhibitor or a proteasome inhibitor-containing regimen.

8. For Part 2 RRMM cohorts (Cohorts C, D, and I), all subjects must have received prior treatment with at least 2 consecutive cycles of a CD38 antibody or a CD38 antibody-containing regimen.
9. All subjects in RRMM cohorts must have documented disease progression on or within 60 days from the last dose of their **last** myeloma therapy. Subjects who had CAR T therapy as their last myeloma therapy must have documented disease progression.
10. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2.
11. A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months) and must:
    a. Have two negative pregnancy tests as verified by the Investigator prior to starting study treatment. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence* from heterosexual contact.
    b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with two forms of contraception: one highly effective, and one additional effective (barrier) measure of contraception without interruption 28 days prior to starting investigational product, during the study treatment (including dose interruptions), and for at least 28 days after the last dose of CC-220, 90 days after the last dose of DARA (for Cohorts E and K), 7 months after last dose of BTZ (for Cohorts F, J1 and J2), or 6 months after the last dose of CFZ (for Cohorts G1 and G2), whichever is longer. Contraception requirements are detailed in Appendix D.
12. Male subjects must:
    a. Practice true abstinence* (which must be reviewed on a monthly basis and source documented) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 90 days following the last dose of study treatment, 4 months after the last dose of BTZ (for Cohort F, J1 and J2), or 3 months after the last dose of CFZ (for Cohorts G1 and G2), whichever is longer, even if he has undergone a successful vasectomy.

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.]

13. Males must agree to refrain from donating sperm while on study treatment, during dose interruptions and for at least 90 days following last dose of study treatment.
14. All subjects must agree to refrain from donating blood while on study treatment, during dose interruptions and for at least 28 days following the last dose of study treatment.

15. All male and female subjects must follow all requirements defined in the Pregnancy Prevention Program (v5.1). See Appendix D for CC-220 Pregnancy Prevention Plan for Subjects in Clinical Trials.
16. Subjects in Cohort D must have received prior treatment with at least 2 consecutive cycles of a glucocorticoid-containing regimen.
17. Subjects in Cohort D must be refractory to an immunomodulatory agent, a proteasome inhibitor, a glucocorticoid and a CD38 antibody. Refractory is defined as disease that is nonresponsive on therapy (failure to achieve minimal response or development of progressive disease while on therapy) or progresses within 60 days of last dose.
18. Subjects in Cohort I must have received prior treatment with a BCMA targeted therapy.

Additional Inclusion Criteria for Part 2 Cohorts J1 and J2 (CC-220 + BTZ + DEX in NDMM), and K (CC-220 + DARA + DEX in NDMM):

19. Subject must have documented diagnosis with previously untreated symptomatic MM as defined by the criteria below (Rajkumar, 2016):
    - MM diagnostic criteria:
      - Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma*
      - And any one or more of the following myeloma defining events:
        - one or more of the following myeloma-related organ dysfunction (at least one of the following):
          - [C] Calcium elevation (serum calcium > 0.25 mmol/L [> 1 mg/dL] higher than the upper limit of laboratory normal or > 2.75 mmol/L [> 11 mg/dL])
          - [R] Renal insufficiency (serum creatinine > 2 mg/dl [> 177 μmol/L] or creatinine clearance < 40 ml/min)
          - [A] Anemia (hemoglobin < 10 g/dl or > 2 g/dL below the lower limit of laboratory normal)
          - [B] Bone lesions (lytic or osteopenic) one or more bone lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)/CT
        - one or more of the following biomarkers of malignancy:
          - Clonal bone marrow plasma cell percentage* ≥ 60%
          - Abnormal serum free light-chain (FLC) ratio ≥ 100 (involved kappa) or < 0.01 (involved lambda) and involved FLC level must be ≥ 100 mg/L

* Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

- >1 focal lesion detected by magnetic resonance imaging (MRI) (at least 5 mm in size)

AND have measurable disease, as assessed by central laboratory, defined by any of the following:

- Immunoglobulin (Ig)G myeloma: serum M-protein level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24 hours; or
- IgA, IgM, IgD, or IgE multiple myeloma: serum M-protein level ≥ 0.5 g/dL or urine M-protein level ≥ 200 mg/24 hours; or
- Light chain multiple myeloma without measurable disease in serum or urine: serum FLC ≥ 100 mg/L and abnormal kappa lambda (κ/λ) ratio

20. Subjects in Cohorts J1 and K are those for who ASCT is not planned for initial therapy or are not considered by the investigator as eligible for high-dose chemotherapy and autologous stem cell transplantation due to:
    - Age ≥65 years, OR
    - In subjects <65 years: presence of important comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with autologous stem cell transplantation.
21. Subjects in Cohort J2 are considered by the investigator as eligible for high-dose chemotherapy and autologous stem cell transplantation according to the institution's criteria based on age, medical history, cardiac and pulmonary status, overall health and condition, co-morbid condition(s), physical examination, and laboratory data.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
3. Subject has any condition that confounds the ability to interpret data from the study
4. Subject has nonsecretory multiple myeloma
5. Subjects with Plasma Cell leukemia or amyloidosis
6. Any of the following laboratory abnormalities
    - Absolute neutrophil count (ANC) < 1,000/μL
    - Platelet count < 75,000/μL for Part 1. For Part 2; platelet count < 75,000/μL for subjects in whom < 50% of bone marrow nucleated cells are plasma cells; otherwise platelet count < 50,000/μL (transfusions are not permitted to achieve minimum platelet counts)
    - Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L)

- Serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST) or serum glutamic pyruvic transaminase (SGPT)/alanine aminotransferase (ALT) ≥ 2.0 x upper limit of normal (ULN)
- Serum total bilirubin and alkaline phosphatase >1.5 x ULN
- Subjects with serious renal impairment (creatinine clearance [CrCl] < 30 mL/min) or requiring dialysis would be excluded.

7. Subjects with peripheral neuropathy ≥ Grade 2
8. Subjects with gastrointestinal disease that may significantly alter the absorption of CC-220
9. Subjects with a prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years with the exception of the following noninvasive malignancies:
   - Basal cell carcinoma of the skin
   - Squamous cell carcinoma of the skin
   - Carcinoma in situ of the cervix
   - Carcinoma in situ of the breast
   - Incidental histological findings of prostate cancer such as T1a or T1b using the Tumor/Node/Metastasis (TNM) classification of malignant tumors or prostate cancer that is curative
10. Subject has a history of anaphylaxis or hypersensitivity to thalidomide, lenalidomide, pomalidomide, DEX, daratumumab (for Cohorts E and K), bortezomib (for Cohorts F, J1 and J2), or carfilzomib (for Cohorts G1 and G2). Subject has known or suspected hypersensitivity to the excipients contained in the formulation of CC-220, DEX, daratumumab (for Cohorts E and K), bortezomib (for Cohorts F, J1, and J2), or carfilzomib (for Cohorts G1 and G2).
11. Contraindications to the other treatment regimens, as per local prescribing information
12. Subject has received any of the following within the last 14 days of initiating IP:
    - Plasmapheresis
    - Major surgery (as defined by the Investigator)
    - Radiation therapy other than local therapy for MM associated bone lesions
    - Use of any systemic myeloma drug therapy
13. Subject has been treated with an investigational agent (ie, an agent not commercially available) within 28 days or 5 half-lives (whichever is longer) of initiating IP. Not applicable for subjects who had CAR T as last prior regimen.
14. Subject has any one of the following:
    - Clinically significant abnormal electrocardiogram (ECG) finding at Screening.

- Congestive heart failure (New York Heart Association Class III or IV)
- Myocardial infarction within 12 months prior to starting IP
- Unstable or poorly controlled angina pectoris, including the Prinzmetal variant of angina pectoris

15. Subject has current or prior use of immunosuppressive medication within 14 days prior to the first dose of IP. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical or local steroid injections (eg, intra-articular injection)
    - Systemic corticosteroids at physiologic doses that do not exceed 10 mg/day of prednisone or equivalent
    - Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication)
16. Subject has taken a strong inhibitor or inducer of CYP3A4/5 including grapefruit, St. John's Wort or related products within two weeks prior to dosing and during the course of study
17. Subject known to test positive for human immunodeficiency virus (HIV), chronic or active hepatitis B, or active hepatitis A or C
18. Subject is unable or unwilling to undergo protocol required thromboembolism prophylaxis
19. Subject is a female who is pregnant, nursing or breastfeeding, or who intends to become pregnant during the participation in the study

Additional Exclusion Criteria for Cohorts E and K (CC-220 + DARA + DEX):

20. Subject has known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) 50% of predicted normal. Note that forced expiratory testing (FEV1) is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is < 50% of predicted normal
21. Subject has received previous allogeneic stem cell transplant; or received autologous stem cell transplantation within 12 weeks prior to enrollment
22. Subject has known moderate or severe persistent asthma, or currently has uncontrolled asthma of any classification

Additional Exclusion Criteria for Cohorts F, J1 and J2 (CC-220 + BTZ + DEX):

23. Subject has acute diffuse infiltrative pulmonary and pericardial disease

Additional Exclusion Criteria for Cohorts G1 and G2 (CC-220 + CFZ + DEX):

24. Left ventricular ejection fraction (LVEF) < 45% as determined by echocardiogram (ECHO) or multigated acquisition (MUGA) scan and/or an ECG with corrected QT interval (QTc) of > 470 milliseconds at Screening
25. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to enrollment

26. Subject has symptomatic ischemia, pericardial disease, history of severe coronary artery disease, sick sinus syndrome, uncontrolled arrhythmias, Grade 3 conduction system abnormalities not mitigated by a pacemaker, hypertrophic cardiomyopathy, or restrictive cardiomyopathy
27. Subject has mild hepatic impairment defined as elevated bilirubin > 1.0 but < 1.5 x ULN or normal bilirubin with any elevation of AST

Additional Exclusion Criteria for Part 2 Cohorts C (MonoT) and D (DoubleT):

28. Previous history of treatment with any gene therapy-based therapeutic for cancer or investigational cellular therapy for cancer or BCMA targeted therapy

Additional Exclusion Criteria for Part 2 Cohorts J1 and J2 (CC-220 + BTZ + DEX in NDMM), and K (CC-220 + DARA + DEX in NDMM):

29. Previous treatment with anti-myeloma therapy, including treatment for smoldering myeloma (does not include radiotherapy, bisphosphonates, or a single short course of steroid [ie, less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days; such a short course of steroid treatment must not have been given within 14 days of initiating study treatment]).

5. TABLE OF EVENTS

Table 9: Table of Events for Part 1 Cohorts A (monotherapy) and B (CC-220+DEX): 28-day Cycle

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)				≥ Cycle 5 (±2 days for all visits)				
	-28 to -1	D1	D8	D12	D15	D22	D26	D1	D8	D15	D22	D1	D15	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
STUDY ENTRY AND GENERAL ASSESSMENTS																
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
IRT registration	X	X	-	-	-	-	-	-	-	-	-	-	-	X		
Prior cancer history	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Medical history	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Prior disease history	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Prior disease therapies	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
SAFETY ASSESSMENTS																
Prior/concomitant medication evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication														
Prior/concomitant procedures evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication														
AE (AESI) evaluation	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication														
SPM surveillance	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication														
Physical examination (includes VTE monitoring and ophthalmologic exam if clinically indicated)[a, c]	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	-

Table 9: Table of Events for Part 1 Cohorts A (monotherapy) and B (CC-220+DEX): 28-day Cycle (Continued)

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)				≥ Cycle 5 (±2 days for all visits)		EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D8	D12	D15	D22	D26	D1	D8	D15	D22	D1	D15			
Vital signs (includes weight)	X	X	X	X	X	X	-	X	X	X	X	X	-	X	X	-
ECG [b]	X	X	X	And during treatment if clinically indicated										X	-	-
Hematology [c, i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X
Chemistry [c]	X	X	X	-	X	X	-	X	X	X	X	X	-	X	-	X
Renal function (CrCL)	X	X	X	-	X	X	-	X	X	X	X	X	-	X	-	-
Urinalysis	X	Repeated only if clinically indicated												X	-	-
Pregnancy test for FCBP with regular or no menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 28 days											X	X	-
Pregnancy test for FCBP with irregular menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 14 days											X	14 and 28 days after last dose	-
Pregnancy counseling for all subjects [k]	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	-
Hepatitis B (HBV) serology local testing [o]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EFFICACY AND OTHER ASSESSMENTS																
ECOG performance status [c]	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X
Assessment of response (IMWG Uniform Response Criteria) [d, l]	-	-	-	-	-	-	-	X	-	-	-	X	-	X	-	X
Serum and urine protein electrophoresis	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X
Serum and urine immunofixation [e]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum free light chain assay	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X

Table 9: Table of Events for Part 1 Cohorts A (monotherapy) and B (CC-220+DEX): 28-day Cycle (Continued)

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)				≥ Cycle 5 (±2 days for all visits)		EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D8	D12	D15	D22	D26	D1	D8	D15	D22	D1	D15			
Quantitative serum immunoglobulin	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X
β-2 microglobulin	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EMP clinical assessment	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically)	X	-	-	-	-	-	-	Day 1 starting at C3, then every 3 cycles thereafter						X	-	X[p]
Skeletal Survey/CT Scan/MRI (Bone lesion)	X	- Repeated during treatment if clinically indicated to confirm response or PD													-	X[m]
Bone marrow aspirate and/or biopsy sampling [f]	X	- Screening: BMA and, if possible, BMB for local % plasma cells and central cytogenetics and other biomarkers -C2D15: BMA and if possible BMB at 3-6 hours post dose, for biomarkers - BMA and, if possible, BMB at CR confirmation and at PD/treatment discontinuation - Optional BMA and/or BMB taken at any time point during treatment at request of investigator and prior to subsequent myeloma therapy													-	X[n]
Whole blood sample for biomarkers [g]	-	X		X	-	-	-	C2 and C4	-	C2 and C4	-	-	C6	X	-	-
Additional whole blood sample for biomarkers for selected subjects in Cohort B at select US sites (notified via IRT) [h]	-	D1 and D2	-	-	X	-	-	-	-	-	-	-	-	-	-	-
Whole blood samples for PK [j]	-	-	X	-	X	X	-	-	X	X	X	-	-	-	-	-
COHORT A																
Oral CC-220	-	Days 1-21/28-day cycle												-	-	-

Table 9: Table of Events for Part 1 Cohorts A (monotherapy) and B (CC-220+DEX): 28-day Cycle (Continued)

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)				≥ Cycle 5 (±2 days for all visits)				
	-28 to -1	D1	D8	D12	D15	D22	D26	D1	D8	D15	D22	D1	D15	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
COHORT B																
Oral CC-220	-	Days 1-21/28-day cycle												-	-	-
Oral DEX	-	Days 1, 8, 15, 22/28-day cycle												-	-	-
VTE prophylaxis	-	C1D1 to EOT												-	-	-
IP (CC-220, DEX, as applicable) accountability/compliance	-	X	X	-	X	X	-	X	X	X	X	X	-	X	-	-

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BMA = bone marrow aspirate; BMB = bone marrow biopsy; C = Cycle; CR = complete response; CrCL = creatinine clearance; CT = computed tomography; D = Day; D/C = discontinuation; DEX = dexamethasone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytomas; EOT = End of Treatment; FCBP = female of child-bearing potential; FU = follow-up; IMWG = International Myeloma Working Group; IRT = Interactive Response Technology; IP = investigational product; MRI = magnetic resonance imaging; PD = progressive disease; Pd = pharmacodynamics; PK = pharmacokinetics; SPM = second primary malignancy; sPEP = serum protein electrophoresis; Tx = treatment; uPEP = urine protein electrophoresis; VTE = venous thromboembolism.

[a] Height will be included in the physical examination and only measured at Screening.

[b] ECG will be taken at time of median Tmax approximately 3-4 hours post first dose on C1D1, C1D8, and at EOT. Also, the ECG will be repeated during treatment if clinically indicated.

[c] On C1D1, safety laboratory assessments must be performed locally, in addition to central laboratory collection, to confirm that the subject continues to meet the required safety laboratory values prior to initiating IP. However, if Screening assessments were performed within 72 hours of C1D1, safety laboratory (hematology and chemistry), physical examinations, and ECOG do not need to be repeated at C1D1.

[d] Refer to Appendix B for IMWG criteria.

[e] After C1D1, assessment to be taken only if myeloma paraprotein is not detected or too few to quantify in sPEP and uPEP assessments.

[f] Refer to Table 18 for details on BMA and BMB collection plan.

[g] Whole blood sample for biomarkers for all subjects: Samples drawn for Pd effects of CC-220 on Aiolos and other Pd biomarkers by protein expression on C1D1 and C1D12. Samples drawn for t-cell receptor clonality on C1D1, C2D15, C4D15 and EOT. Samples drawn for Pd effects of CC-220 on T-Cell activation on C1D1 and C1D12. Samples for Pd effects of CC-220 on immune cells in peripheral blood and association of baseline levels of these populations with response or resistance to CC-220 on C1D1, C2D1, C2D15, C4D1, C4D15, C6D15, and EOT. Samples for pharmacogenomics on C1D1. See Section 6.6.

[h] For Cohort B, up to 3 subjects in each dose level at selected US sites may be selected for the following assessment (notified via IRT): To evaluate the pharmacodynamic (Pd) effects of CC-220 on Aiolos and Ikaros in mononuclear cells with a novel exploratory assay. Samples taken on C1D1, C1D2 and C1D15.

[i] Hematology sample collection contains a lymphocyte panel to support biomarker assessment of Pd effects on T-cell counts, as detailed in Section 6.6.

[j] Intensive PK samples will be drawn from selected subjects on C1D15 in addition to the samples drawn for sparse PK on all subjects.

[k] See Appendix D.

[l] See Section 6.3.4.
[m] Skeletal survey will be performed during Post Treatment Response Follow up phase if clinically indicated to confirm response or PD
[n] For subjects who enter Post Treatment Response follow up, BMA (and, if possible, BMB) will be collected at confirmed PD instead of treatment discontinuation.
[o] All subjects will be tested for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (antiHBs), and hepatitis B core antibody (antiHBc) locally during screening.
[p] During Post-Tx Response FU, EMP radiological assessment is required every 3 months for those with a history of or clinical indication of EMPs only assessable radiographically.

Table 10: Table of Events for Part 1 Cohort E (CC-220Dd): 28-day Cycle

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)				≥ Cycle 5 (±2 days for all visits)		EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D8	D12	D15	D22	D26	D1	D8	D15	D22	D1	D15			
STUDY ENTRY AND GENERAL ASSESSMENTS																
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
IRT registration	X	X	-	-	-	-	-	-	-	-	-	-	-	X		
Prior cancer history	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Medical history	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Prior disease history	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Prior disease therapies	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
SAFETY ASSESSMENTS																
Prior/concomitant medication evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication														
Prior/concomitant procedures evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication														
AE (AESI) evaluation	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication														
SPM surveillance	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication														
Physical examination (includes VTE monitoring and ophthalmologic exam if clinically indicated)[a, c]	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	-
Vital signs (includes weight)[r]	X	X	X	X	X	X	-	X	X	X	X	X	-	X	X	-

Table 10: Table of Events for Part 1 Cohort E (CC-220Dd): 28-day Cycle (Continued)

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)				≥ Cycle 5 (±2 days for all visits)		EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D8	D12	D15	D22	D26	D1	D8	D15	D22	D1	D15			
ECG [b]	X	X	X	And during treatment if clinically indicated										X	-	-
Hematology [c, h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X
Chemistry [c]	X	X	X	-	X	X	-	X	X	X	X	X	-	X	-	X
Renal function (CrCL)	X	X	X	-	X	X	-	X	X	X	X	X	-	X	-	-
Urinalysis	X	Repeated only if clinically indicated												X	-	-
Pregnancy test for FCBP with regular or no menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 28 days											X	X	-
Pregnancy test for FCBP with irregular menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 14 days											X	14 and 28 days after last dose	-
Pregnancy counseling for all subjects [j]	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	-
Hepatitis B (HBV) serology local testing [n]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HBV DNA local [o]	X	If indicated, every 12 weeks during treatment, at the EOT Visit, and every 12 weeks for up to 6 months after the last dose of DARA														
EFFICACY AND OTHER ASSESSMENTS																
ECOG performance status [c]	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X
Assessment of response (IMWG Uniform Response Criteria) [d, k]	-	-	-	-	-	-	-	X	-	-	-	X	-	X	-	X
Serum and urine protein electrophoresis	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X
Serum and urine immunofixation [e]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum free light chain assay	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X

Table 10: Table of Events for Part 1 Cohort E (CC-220Dd): 28-day Cycle (Continued)

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)				≥ Cycle 5 (±2 days for all visits)		EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D8	D12	D15	D22	D26	D1	D8	D15	D22	D1	D15			
Quantitative serum immunoglobulin	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X
β-2 microglobulin	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EMP clinical assessment	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically)	X	-	-	-	-	-	-	Day 1 starting at C3, then every 3 cycles thereafter						X	-	X[p]
Skeletal Survey/CT Scan/MRI (Bone lesion)	X	- Repeated during treatment if clinically indicated to confirm response or PD													-	X[l]
Bone marrow aspirate and/or biopsy sampling [f]	X	- Screening: BMA and, if possible, BMB for local % plasma cells and central cytogenetics and other biomarkers -C2D15: BMA and if possible BMB at 3-6 hours post dose, for biomarkers - BMA and, if possible, BMB at CR confirmation and at PD/treatment discontinuation - Optional BMA and/or BMB taken at any time point during treatment at request of investigator and prior to subsequent myeloma therapy													-	X[m]
Whole blood sample for biomarkers [g]	-	X		X	-	-	-	C2 and C4	-	C2 and C4	-	-	C6	X	-	-
Whole blood samples for PK [i]	-	-	X	-	X	-	-	-	X	X	-	-	-	-	-	-
COHORT E																
Oral CC-220	-	Days 1-21/28-day cycle												-	-	-
Oral DEX	-	Days 1, 8, 15, 22/28-day cycle												-	-	-
IV DARA or SC DARA (as assigned)[q, s]	-	C1-2: Days 1, 8, 15, 22; C3-6: Days 1, 15; ≥ C7: Day 1/28-day cycle												-	-	-

Table 10: Table of Events for Part 1 Cohort E (CC-220Dd): 28-day Cycle (Continued)

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)				≥ Cycle 5 (±2 days for all visits)				
	-28 to -1	D1	D8	D12	D15	D22	D26	D1	D8	D15	D22	D1	D15	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
VTE prophylaxis	-	C1D1 to EOT												-	-	-
IP (CC-220, DARA, DEX, as applicable) accountability/compliance	-	X	X	-	X	X	-	X	X	X	X	X	-	X	-	-

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BMA = bone marrow aspirate; BMB = bone marrow biopsy; C = Cycle; CR = complete response; CrCL = creatinine clearance; CT = computed tomography; D = Day; DARA = daratumumab; D/C = discontinuation; DEX = dexamethasone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytomas; EOT = End of Treatment; FCBP = female of child-bearing potential; FU = follow-up; IMWG = International Myeloma Working Group; IP = investigational product; IRT = Interactive Response Technology; IV = intravenous; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetics; Pd = pharmacodynamics; SPM = second primary malignancy; sPEP = serum protein electrophoresis; Tx = treatment; uPEP = urine protein electrophoresis; VTE = venous thromboembolism.

[a] Height will be included in the physical examination and only measured at Screening.

[b] ECG will be taken at time of median Tmax approximately 3-4 hours post first dose on C1D1, C1D8, and at EOT. Also, the ECG will be repeated during treatment if clinically indicated.

[c] On C1D1, safety laboratory assessments must be performed locally, in addition to central laboratory collection, to confirm that the subject continues to meet the required safety laboratory values prior to initiating IP. However, if Screening assessments were performed within 72 hours of C1D1, safety laboratory (hematology and chemistry), physical examinations, and ECOG do not need to be repeated at C1D1.

[d] Refer to Appendix B for IMWG criteria.

[e] After C1D1, assessment to be taken only if myeloma paraprotein is not detected or too few to quantify in sPEP and uPEP assessments.

[f] Refer to Table 18 for details on BMA and BMB collection plan.

[g] Whole blood sample for biomarkers for all subjects: Samples drawn for Pd effects of CC-220 on Aiolos and other Pd biomarkers by protein expression on C1D1 and C1D12. Samples drawn for t-cell receptor clonality on C1D1, C2D15, C4D15 and EOT. Samples drawn for Pd effects of CC-220 on T-Cell activation on C1D1 and C1D12. Samples for Pd effects of CC-220 on immune cells in peripheral blood and association of baseline levels of these populations with response or resistance to CC-220 on C1D1, C2D1, C2D15, C4D1, C4D15, C6D15, and EOT. Samples for pharmacogenomics on C1D1. See Section 6.6.

[h] Hematology sample collection contains a lymphocyte panel to support biomarker assessment of Pd effects on T-cell counts, as detailed in Section 6.6.

[i] Intensive PK samples will be drawn from selected subjects on C1D8 in addition to the samples drawn for sparse PK on all subjects.

[j] See Appendix D.

[k] See Section 6.3.4.

[l] Skeletal survey will be performed during Post Treatment Response Follow up phase if clinically indicated to confirm response or PD.

[m] For subjects who enter Post Treatment Response follow up, BMA (and, if possible, BMB) will be collected at confirmed PD instead of treatment discontinuation.

[n] All subjects will be tested for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (antiHBs), and hepatitis B core antibody (antiHBc) locally during screening.

[o] For subjects with serologic evidence of resolved HBV infection (ie, positive antiHBs or positive antiHBc) at Screening, HBV DNA testing by polymerase chain reaction (PCR) must be performed locally at screening, every 12 weeks during treatment, at the End of Treatment Visit, and every 12 weeks for up to 6 months after the last dose of DARA.

Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR

[p] During Post-Tx Response FU, EMP radiological assessment is required every 3 months for those with a history of or clinical indication of EMPs only assessable radiographically.

[q] Once the MTD and/or RP2D is determined in Cohort E (CC-220Dd), an additional 13 subjects will be enrolled at this dose level using SC DARA. See Section 7.2.1.1 for details of treatment schedule for SC DARA.

[r] For SC DARA, vital signs are to be measured at the following time points on C1D1: immediately before SC DARA administration; at the end of SC DARA administration (+ 10 minutes); 30 minutes (± 10 minutes) and 1 hour (± 10 minutes) after the end of SC DARA administration.

[s] For SC DARA administration, all subjects will be observed for at least 6 hours after the end of the SC injection during C1D1 and, if deemed necessary by the Investigator, after subsequent injections.

Table 11: Table of Events for Part 1 Cohort F (CC-220Vd): 21-day Cycle

EVENTS	Screening	Treatment																				Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)					Cycle 5-8 (±2 days for all visits)					≥ Cycle 9 (±2 days for all visits)				28 days after EOT (± 3 d)	Every 21 days and at D/C visit (± 2 d)
	-28 to -1	D1	D4	D8	D11	D12	D15	D1	D4	D8	D11	D15	D1	D4	D8	D11	D15	D1	D8	D15	EOT		
STUDY ENTRY AND GENERAL ASSESSMENTS																							
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
IRT registration	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X		
Prior cancer history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Medical history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Prior disease history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Prior disease therapies	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
SAFETY ASSESSMENTS																							
Prior/concomitant medication evaluation	X (≤28 days from Screening)	Continuous, until 28 days after last dose of study medication																					
Prior/concomitant procedures evaluation	X (≤28 days from Screening)	Continuous, until 28 days after last dose of study medication																					
AE (AESI) evaluation	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication																					
SPM surveillance	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication																					
Physical examination (includes VTE monitoring and ophthalmologic exam if clinically indicated) [a,c]	X	X	-	-	-	-	-	X	-	-	-	-	X	-	-	-	-	X	-	-	X	-	-
Vital signs (includes weight)	X	X	-	X	-	X	X	X	-	X	-	X	X	-	-	-	-	X	-	-	X	X	-

Table 11: Table of Events for Part 1 Cohort F (CC-220Vd): 21-day Cycle (Continued)

EVENTS	Screening	Treatment																				Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)					Cycle 5-8 (±2 days for all visits)					≥ Cycle 9 (±2 days for all visits)				28 days after EOT (± 3 d)	Every 21 days and at D/C visit (± 2 d)
	-28 to -1	D1	D4	D8	D11	D12	D15	D1	D4	D8	D11	D15	D1	D4	D8	D11	D15	D1	D8	D15	EOT		
ECG [b]	X	X	-	X	And during treatment if clinically indicated																X	-	-
Hematology [c, k]	X	X	-	X	-	X	X	X	-	X	-	X	X	-	-	-	X	X	-	X	X	-	X
Chemistry [c]	X	X	-	X	-	-	X	X	-	X	-	X	X	-	-	-	-	X	-	-	X	-	X
Renal function (CrCL)	X	X	-	X	-	-	X	X	-	X	-	X	X	-	-	-	-	X	-	-	X	-	-
Urinalysis	X	Repeated only if clinically indicated																			X	-	-
Pregnancy test for FCBP with regular or no menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 21 days after first dose, then every 21 days																		X	X	-
Pregnancy test for FCBP with irregular menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 21 days after first dose, then every 14 days																		X	14 and 28 days after last dose	-
Pregnancy counseling for all subjects [i]	X	X	-	-	-	-	-	X	-	-	-	-	X	-	-	-	-	X	-	-	X	-	-
Hepatitis B (HBV) serology local testing [p]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EFFICACY AND OTHER ASSESSMENTS																							
ECOG performance status [c]	X	X	-	-	-	-	-	X	-	-	-	-	X	-	-	-	-	X	-	-	X	-	X
Assessment of response (IMWG Uniform Response Criteria) [d, j]	-	-	-	-	-	-	-	X	-	-	-	-	X	-	-	-	-	X	-	-	X	-	X
Serum and urine protein electrophoresis	X	X	-	-	-	-	-	X	-	-	-	-	X	-	-	-	-	X	-	-	X	-	X
Serum and urine immunofixation [e]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum free light chain assay	X	X	-	-	-	-	-	X	-	-	-	-	X	-	-	-	-	X	-	-	X	-	X
Quantitative serum immunoglobulin	X	X	-	-	-	-	-	X	-	-	-	-	X	-	-	-	-	X	-	-	X	-	X

Table 11: Table of Events for Part 1 Cohort F (CC-220Vd): 21-day Cycle (Continued)

EVENTS	Screening	Treatment																				Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)					Cycle 5-8 (±2 days for all visits)					≥ Cycle 9 (±2 days for all visits)					
	-28 to -1	D1	D4	D8	D11	D12	D15	D1	D4	D8	D11	D15	D1	D4	D8	D11	D15	D1	D8	D15	EOT	28 days after EOT (± 3 d)	Every 21 days and at D/C visit (± 2 d)
β-2 microglobulin	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EMP clinical assessment	X	X	-	-	-	-	-	X	-	-	-	-	X	-	-	-	-	X	-	-	X	-	X
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically)	X	-	-	-	-	-	-	Day 1 starting at C3, then every 3 cycles thereafter													X	-	X[q]
Skeletal Survey/CT Scan/MRI (Bone lesion)	X	Repeated during treatment if clinically indicated to confirm response or PD																				-	X[o]
Bone marrow aspirate and/or biopsy sampling	X	- Screening: BMA and, if possible, BMB for local % plasma cells and central cytogenetics and other biomarkers -C2D11: BMA and if possible BMB at 3-6 hours post dose, for biomarkers - BMA and, if possible, BMB at CR confirmation and at PD/treatment discontinuation - Optional BMA and/or BMB taken at any time point during treatment at request of investigator and prior to subsequent myeloma therapy																				-	X[n]
Whole blood sample for biomarkers for all subjects [g, h]	-	X	-	-	-	X	-	C2 and C4	-	-	-	C2 and C4	-	-	-	-	C6	-	-	-	X	-	-
Additional whole blood sample for biomarkers for selected subjects at select US sites (notified via IRT) [l]	-	D1 and D2	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Whole blood samples for PK [m]	-	-	-	X	-	-	X	-	-	X	-	X	-	-	-	-	-	-	-	-	-	-	-
COHORT F																							
Oral CC-220	-	Days 1-14/21-day cycle																			-	-	-
Oral DEX	-	Days 1, 8, 15/21-day cycle																			-	-	-

EVENTS	Screening	Treatment																			Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)					Cycle 5-8 (±2 days for all visits)					≥ Cycle 9 (±2 days for all visits)				
	-28 to -1	D1	D4	D8	D11	D12	D15	D1	D4	D8	D11	D15	D1	D4	D8	D11	D15	D1	D8	D15	EOT	28 days after EOT (± 3 d)	Every 21 days and at D/C visit (± 2 d)
SC BTZ	-	C1-8: Days 1, 4, 8, 11; ≥ C9: Days 1, 8/21-day cycle																			-	-	-

Table 11: Table of Events for Part 1 Cohort F (CC-220Vd): 21-day Cycle (Continued)

EVENTS	Screening	Treatment																			Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)					Cycle 5-8 (±2 days for all visits)					≥ Cycle 9 (±2 days for all visits)				
	-28 to -1	D1	D4	D8	D11	D12	D15	D1	D4	D8	D11	D15	D1	D4	D8	D11	D15	D1	D8	D15	EOT	28 days after EOT (± 3 d)	Every 21 days and at D/C visit (± 2 d)
VTE prophylaxis	-	C1D1 to EOT																			-	-	-
IP (CC-220, DEX, BTZ, as applicable) accountability/compliance	-	X	-	X	-	-	X	X	-	X	-	X	X	-	-	-	-	X	-	-	X	-	-

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BMA = bone marrow aspirate; BMB = bone marrow biopsy; BTZ = bortezomib; C = Cycle; CR = complete response; CrCL = creatinine clearance; CT = computed tomography; DEX = dexamethasone; D = Day; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytomas; EOT = End of Treatment; FCBP = female of child-bearing potential; FU = follow-up; IMWG = International Myeloma Working Group; IP = investigational product; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; Pd = pharmacodynamics; PD = progressive disease; PK = pharmacokinetics; sPEP = serum protein electrophoresis; SPM = second primary malignancy; SC = subcutaneous; Tx = treatment; uPEP = urine protein electrophoresis; VTE = venous thromboembolism.

[a] Height will be included in the Physical examination and only measured at Screening.

[b] ECG will be taken at time of median Tmax approximately 3-4 hours post first dose on C1D1, C1D8, and at EOT. Also, the ECG will be repeated during treatment if clinically indicated.

[c] On C1D1, safety laboratory assessments must be performed locally, in addition to central laboratory collection, to confirm that the subject continues to meet the required safety laboratory values prior to initiating IP. However, if Screening assessments were performed within 72 hours of C1D1, safety laboratory (hematology and chemistry), physical examinations, and ECOG do not need to be repeated at C1D1.

[d] Refer to Appendix B for IMWG criteria.

[e] After C1D1, assessment to be taken only if myeloma paraprotein is not detected or too few to quantify in sPEP and uPEP assessments.

[f] Screening and C2D11 Bone marrow sampling for biomarkers.

[g] Whole blood sample for biomarkers for all subjects: Samples drawn for Pd effects on CC-220 on Aiolos and other Pd biomarkers by protein expression on C1D1 and C1D12. Samples drawn for t-cell receptor clonality on C1D1, C2D15, C4D15 and EOT. See Section 6.6.

[h] Additional biomarker sampling for all subjects: Samples drawn for Pd effects of CC-220 on T-cell Activation on C1D1 and C1D12. Samples drawn for Pd effects of CC-220 on immune cells in peripheral blood on C1D1, C2D1, C2D15, C4D1, C4D15, C6D15, and EOT. Sample drawn for pharmacogenomics of CC-220 on C1D1. See Section 6.6.
[i] See Appendix D.
[j] See Section 6.3.4.
[k] Hematology sample collection contains a lymphocyte panel to support biomarker assessment of Pd effects on T-cell counts, as detailed in Section 6.6.
[l] For Cohort F, up to 3 subjects in each dose level at selected US sites may be selected for the following assessment (notified via IRT): To evaluate the pharmacodynamic (Pd) effects of CC-220 on Aiolos and Ikaros in mononuclear cells with a novel exploratory assay (C1D1, C1D2, C1D11).
[m] Intensive PK samples will be drawn from selected subjects C1D8 in addition to the samples drawn for sparse PK on all subjects.
[n] For subjects who enter Post Treatment Response follow up, BMA (and, if possible, BMB) will be collected at confirmed PD instead of treatment discontinuation.
[o] Skeletal survey will be performed during Post Treatment Response Follow up phase if clinically indicated to confirm response or PD.
[p] All subjects will be tested for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (antiHBs), and hepatitis B core antibody (antiHBc) locally during screening.
[q] During Post-Tx Response FU, EMP radiological assessment is required every 3 months for those with a history of or clinical indication of EMPs only assessable radiographically.

Table 12: Table of Events for Part 1 Cohort G1 (CC-220Kd once weekly): 28-day Cycle

EVENTS	Screening	Treatment										Safety Follow-up	Post-Tx Response FU
		Cycle 1			Cycle 2 –4 (±2 days for all visits)			≥ Cycle 5 (±2 days for all visits)					
	-28 to -1	D1	D8	D15	D1	D8	D15	D1	D8	D15	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
STUDY ENTRY AND GENERAL ASSESSMENTS													
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-		
IRT registration	X	X	-	-	-	-	-	-	-	-	X		
Prior cancer history	X	-	-	-	-	-	-	-	-	-	-		
Medical history	X	-	-	-	-	-	-	-	-	-	-		
Demographics	X	-	-	-	-	-	-	-	-	-	-		
Prior disease history	X	-	-	-	-	-	-	-	-	-	-		
Prior disease therapies	X	-	-	-	-	-	-	-	-	-	-		
SAFETY ASSESSMENTS													
Prior/concomitant medication evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication											
Prior/concomitant procedures evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication											
AE (AESI) evaluation	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication											
SPM surveillance	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication											
Physical examination (includes VTE monitoring and ophthalmologic exam if clinically indicated)[a, c]	X	X	-	-	X	-	-	X	-	-	X	-	-
Vital signs (includes weight)	X	X	X	X	X	X	X	X	X	X	X	X	-
ECG [b]	X	X	X	And during treatment if clinically indicated							X	-	-

Table 12: Table of Events for Part 1 Cohort G1 (CC-220Kd once weekly): 28-day Cycle (Continued)

EVENTS	Screening	Treatment										Safety Follow-up	Post-Tx Response FU
		Cycle 1			Cycle 2 –4 (±2 days for all visits)			≥ Cycle 5 (±2 days for all visits)			EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D8	D15	D1	D8	D15	D1	D8	D15			
ECHO/MUGA	X	-	-	-	-	-	-	-	-	-	-	-	-
Hematology [c,o]	X	X	X	X	X	X	X	X	-	X	X	-	X
Chemistry [c]	X	X	X	X	X	X	X	X	-	-	X	-	X
Renal function (CrCL)	X	X	X	X	X	X	X	X	-	-	X	-	-
Urinalysis	X	Repeat only if clinically indicated									X	-	-
Pregnancy test for FCBP with regular or no menstrual cycles	X	X	10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 28 days								X	X	-
Pregnancy test for FCBP with irregular menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 14 days								X	14 and 28 days after last dose	-
Pregnancy counseling for all subjects [j]	X	X	-	-	X	-	-	X	-	-	X	-	-
Hepatitis B (HBV) serology local testing [p]	X	-	-	-	-	-	-	-	-	-	-	-	-
EFFICACY AND OTHER ASSESSMENTS													
ECOG performance status [c]	X	X	-	-	X	-	-	X	-	-	X	-	X
Assessment of response (IMWG Uniform Response Criteria) [d, k]	-	-	-	-	X	-	-	X	-	-	X	-	X
Serum and urine protein electrophoresis	X	X	-	-	X	-	-	X	-	-	X	-	X
Serum and urine immunofixation [e]	X	-	-	-	-	-	-	-	-	-	-	-	-
Serum free light chain assay	X	X	-	-	X	-	-	X	-	-	X	-	X

Table 12: Table of Events for Part 1 Cohort G1 (CC-220Kd once weekly): 28-day Cycle (Continued)

EVENTS	Screening	Treatment										Safety Follow-up	Post-Tx Response FU
		Cycle 1			Cycle 2 –4 (±2 days for all visits)			≥ Cycle 5 (±2 days for all visits)			EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D8	D15	D1	D8	D15	D1	D8	D15			
Quantitative serum immunoglobulin	X	X	-	-	X	-	-	X	-	-	X	-	X
β-2 microglobulin	X	-	-	-	-	-	-	-	-	-	-	-	-
EMP clinical assessment	X	X	-	-	X	-	-	X	-	-	X	-	X
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically)	X	-	-	-	Day 1 starting at C3, then every 3 cycles thereafter						X	-	X[q]
Skeletal Survey/CT Scan/MRI (Bone lesion)	X	Repeated during treatment if clinically indicated to confirm response or PD										-	X[l]
Bone marrow aspirate and/or biopsy sampling [f]	X	- Screening: BMA and, if possible, BMB for local % plasma cells and central cytogenetics and other biomarkers -C2D15: BMA and if possible BMB at 3-6 hours post dose, for biomarkers - BMA and, if possible, BMB at CR confirmation and at PD/treatment discontinuation - Optional BMA and/or BMB taken at any time point during treatment at request of investigator and prior to subsequent myeloma therapy										-	X[m]
Whole blood sample for biomarkers [g]	-	X	-	X	C2 and C4	-	C2 and C4	-	-	C6	X	-	-
Additional whole blood sample for biomarkers for selected subjects at select US sites (notified via IRT) [h]	-	D1 and D2	-	X	-	-	-	-	-	-	-	-	-
Whole blood samples for PK [i]	-	-	X	X	-	X	X	-	-	-	-	-	-

Table 12: Table of Events for Part 1 Cohort G1 (CC-220Kd once weekly): 28-day Cycle (Continued)

EVENTS	Screening	Treatment										Safety Follow-up	Post-Tx Response FU
		Cycle 1			Cycle 2 –4 (±2 days for all visits)			≥ Cycle 5 (±2 days for all visits)			EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D8	D15	D1	D8	D15	D1	D8	D15			
COHORT G1													
Oral CC-220	-	Days 1-21/28-day cycle									-	-	-
Oral DEX	-	Days 1, 8, 15, 22/28-day cycle									-	-	-
IV CFZ	-	Days 1, 8, 15/28-day cycle									-	-	-
Oral and IV hydration [n]	-	X	As indicated								-	-	-
VTE prophylaxis	-	C1D1 to EOT									-	-	-
IP (CC-220, DEX, CFZ as applicable) accountability/compliance	-	X	X	X	X	X	X	X	X	X	X	-	-

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BMA = bone marrow aspirate; BMB = bone marrow biopsy; C = Cycle; CFZ = carfilzomib; CR = complete response; CrCL = creatinine clearance; CT = computed tomography; D = Day; D/C = discontinuation; DEX = dexamethasone; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytomas; EOT = End of Treatment; FCBP = female of child-bearing potential; FU = follow-up; HBV = Hepatitis B virus; IMWG = International Myeloma Working Group; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetics; IP = investigational product; IV = intravenous; MUGA = multiple gated acquisition scan; Pd = pharmacodynamics; SPM = second primary malignancy; sPEP = serum protein electrophoresis; Tx = treatment; uPEP = urine protein electrophoresis; VTE = venous thromboembolism.

[a] Height will be included in the physical examination and only measured at Screening.

[b] ECG will be taken at time of median Tmax approximately 3-4 hours post first dose on C1D1, C1D8, and at EOT. Also, the ECG will be repeated during treatment if clinically indicated.

[c] On C1D1, safety laboratory assessments must be performed locally, in addition to central laboratory collection, to confirm that the subject continues to meet the required safety laboratory values prior to initiating IP. However, if Screening assessments were performed within 72 hours of C1D1, safety laboratory (hematology and chemistry), physical examinations, and ECOG do not need to be repeated at C1D1.

[d] Refer to Appendix B for IMWG criteria.

[e] After C1D1, assessment to be taken only if myeloma paraprotein is not detected or too few to quantify in sPEP and uPEP assessments.

[f] Refer to Table 18 for details on BMA/BMB collection plan.

[g] Whole blood sample for biomarkers for all subjects: Samples drawn for Pd effects of CC-220 on Aiolos and other Pd biomarkers by protein expression on C1D1 and C1D15. Samples drawn for t-cell receptor clonality on C1D1, C2D15, C4D15 and EOT. Samples for Pd effects of CC-220 on immune cells in peripheral blood and association of baseline levels of these populations with response or resistance to CC-220 on C1D1, C2D1, C2D15, C4D1, C4D15, C6D15, and EOT. Samples drawn for Pd effects of CC-220 on T-Cell activation on C1D1 and C1D15. Samples for pharmacogenomics on C1D1. See Section 6.6.

[h] In Cohort G1, up to 3 subjects in each dose level at select US sites may be selected for the following assessment (notified via IRT): To evaluate the pharmacodynamic (Pd) effects of CC-220 on Aiolos and Ikaros in mononuclear cells with a novel exploratory assay on C1D1, C1D2, C1D15. See Section 6.6.

[i] Intensive PK samples will be drawn from selected subjects (notified via IRT) on C1D8 in addition to the samples drawn for sparse PK on all subjects. See Section 6.5.
[j] See Appendix D.
[k] See Section 6.3.4.
[l] Skeletal survey will be performed during Post Treatment Response Follow up phase if clinically indicated to confirm response or PD.
[m] For subjects who enter Post Treatment Response Follow up, BMA (and, if possible, BMB) will be collected at confirmed PD instead of treatment discontinuation.
[n] Oral hydration should start 48 hours prior to C1D1. IV hydration before dosing (recommended) and after (if needed) during Cycle 1. Continue oral and/or IV hydration in subsequent cycles if necessary.
[o] Hematology sample collection containing a lymphocyte panel to support biomarker assessment. See Section 6.6.
[p] All subjects will be tested for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (antiHBs), and hepatitis B core antibody (antiHBc) locally during screening.
[q] During Post-Tx Response FU, EMP radiological assessment is required every 3 months for those with a history of or clinical indication of EMPs only assessable radiographically.

Table 13: Table of Events for Part 1 Cohort G2 (CC-220Kd twice weekly): 28-day Cycle

EVENTS	Screening	Treatment																			Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)						≥ Cycle 5 (±2 days for all visits)						EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D2	D8	D9	D15	D16	D1	D2	D8	D9	D15	D16	D1	D2	D8	D9	D15	D16			
STUDY ENTRY AND GENERAL ASSESSMENTS																						
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
IRT registration	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X		
Prior cancer history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Medical history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Prior disease history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Prior disease therapies	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
SAFETY ASSESSMENTS																						
Prior/concomitant medication evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication																				
Prior/concomitant procedures evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication																				
AE (AESI) evaluation	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication																				
SPM surveillance	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication																				
Physical examination (includes VTE monitoring and ophthalmologic exam if clinically indicated)[a, c]	X	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-
Vital signs (includes weight)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
ECG [b]	X	X	-	X	And during treatment if clinically indicated															X	-	-

Table 13: Table of Events for Part 1 Cohort G2 (CC-220Kd twice weekly): 28-day Cycle (Continued)

EVENTS	Screening	Treatment																			Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)						≥ Cycle 5 (±2 days for all visits)						EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D2	D8	D9	D15	D16	D1	D2	D8	D9	D15	D16	D1	D2	D8	D9	D15	D16			
ECHO/MUGA	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology [c, o]	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	-	-	X	-	X	-	X
Chemistry [c]	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	-	-	-	-	X	-	X
Renal function (CrCL)	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	-	-	-	-	X	-	-
Urinalysis	X	Repeat only if clinically indicated																		X	-	-
Pregnancy test for FCBP with regular or no menstrual cycles	X	X	10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 28 days																	X	X	-
Pregnancy test for FCBP with irregular menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 14 days																	X	14 and 28 days after last dose	-
Pregnancy counseling for all subjects [j]	X	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-
Hepatitis B (HBV) serology local testing [p]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EFFICACY AND OTHER ASSESSMENTS																						
ECOG performance status [c]	X	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	X
Assessment of response (IMWG Uniform Response Criteria) [d, k]	-	-	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	X
Serum and urine protein electrophoresis	X	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	X
Serum and urine immunofixation [e]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum free light chain assay	X	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	X
Quantitative serum immunoglobulin	X	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	X
β-2 microglobulin	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 13: Table of Events for Part 1 Cohort G2 (CC-220Kd twice weekly): 28-day Cycle (Continued)

EVENTS	Screening	Treatment																		Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)						≥ Cycle 5 (±2 days for all visits)							
	-28 to -1	D1	D2	D8	D9	D15	D16	D1	D2	D8	D9	D15	D16	D1	D2	D8	D9	D15	D16	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
EMP clinical assessment	X	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	X
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically)	X	-	-	-	-	-	-	Day 1 starting at C3, then every 3 cycles thereafter												X	-	X[q]
Skeletal Survey/CT Scan/MRI (Bone lesion)	X	Repeated during treatment if clinically indicated to confirm response or PD																			-	X[l]
Bone marrow aspirate and/or biopsy sampling [f]	X	- Screening: BMA and, if possible, BMB for local % plasma cells and central cytogenetics and other biomarkers -C2D15: BMA and if possible BMB at 3-6 hours post dose, for biomarkers - BMA and, if possible, BMB at CR confirmation and at PD/treatment discontinuation - Optional BMA and/or BMB taken at any time point during treatment at request of investigator and prior to subsequent myeloma therapy																			-	X[m]
Whole blood sample for biomarkers [g]	-	X	-	-	-	X	-	C2 and C4	-	-	-	C2 and C4	-	-	-	-	-	C6	-	X	-	-
Additional whole blood sample for biomarkers for selected subjects at select US sites (notified via IRT) [h]	-	X	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Whole blood samples for PK [i]	-	-	-	X	-	X	-	-	-	X	-	X	-	-	-	-	-	-	-	-	-	-

Table 13: Table of Events for Part 1 Cohort G2 (CC-220Kd twice weekly): 28-day Cycle (Continued)

EVENTS	Screening	Treatment																			Safety Follow-up	Post-Tx Response FU
		Cycle 1						Cycle 2 –4 (±2 days for all visits)						≥ Cycle 5 (±2 days for all visits)						EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D2	D8	D9	D15	D16	D1	D2	D8	D9	D15	D16	D1	D2	D8	D9	D15	D16			
COHORT G2																						
Oral CC-220	-	Days 1-21/28-day cycle																		-	-	-
Oral DEX	-	Days 1, 2, 8, 9, 15, 16, 22, 23/28-day cycle																		-	-	-
IV CFZ	-	Days 1, 2, 8, 9, 15, 16/28-day cycle																		-	-	-
Oral and IV hydration [n]	-	X	As indicated																	-	-	-
VTE prophylaxis	-	C1D1 to EOT																		-	-	-
IP (CC-220, DEX, CFZ as applicable) accountability/compliance	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	-

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BMA = bone marrow aspirate; BMB = bone marrow biopsy; C = Cycle; CFZ = carfilzomib; CR = complete response; CrCL = creatinine clearance; CT = computed tomography; D = Day; D/C = discontinuation; DEX = dexamethasone; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytomas; EOT = End of Treatment; FCBP = female of child-bearing potential; FU = follow-up; HBV = Hepatitis B virus; IMWG = International Myeloma Working Group; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetics; IP = investigational product; IV = intravenous; MUGA = multiple gated acquisition scan; Pd = pharmacodynamics; SPM = second primary malignancy; sPEP = serum protein electrophoresis; Tx = treatment; uPEP = urine protein electrophoresis; VTE = venous Thromboembolism.

[a] Height will be included in the physical examination and only measured at Screening.

[b] ECG will be taken at time of median Tmax approximately 3-4 hours post first dose on C1D1, C1D8, and at EOT. Also, the ECG will be repeated during treatment if clinically indicated.

[c] On C1D1, safety laboratory assessments must be performed locally, in addition to central laboratory collection, to confirm that the subject continues to meet the required safety laboratory values prior to initiating IP. However, if Screening assessments were performed within 72 hours of C1D1, safety laboratory (hematology and chemistry), physical examinations, and ECOG do not need to be repeated at C1D1.

[d] Refer to Appendix B for IMWG criteria.

[e] After C1D1, assessment to be taken only if myeloma paraprotein is not detected or too few to quantify in sPEP and uPEP assessments.

[f] Refer to Table 18 for details on BMA/BMB collection plan.

[g] Whole sample for biomarkers for all subjects: Samples drawn for Pd effects of CC-220 on Aiolos and other Pd biomarkers by protein expression on C1D1 and C1D15. Samples drawn for t-cell receptor clonality on C1D1, C2D15, C4D15 and EOT. Samples for Pd effects of CC-220 on immune cells in peripheral blood and association of baseline levels of these populations with response or resistance to CC-220 on C1D1, C2D1, C2D15, C4D1, C4D15, C6D15, and EOT. Samples drawn for Pd effects of CC-220 on T-Cell activation on C1D1 and C1D15. Samples for pharmacogenomics on C1D1. See Section 6.6.

[h] For Cohort G2, up to 3 subjects in each dose level at select US sites may be selected for the following assessment (notified via IRT): To evaluate the pharmacodynamic (Pd) effects of CC-220 on Aiolos and Ikaros in mononuclear cells with a novel exploratory assay on C1D1, C1D2, C1D15. See Section 6.6.

[i] Intensive PK samples will be drawn from selected subjects (notified via IRT) on C1D8 in addition to the samples drawn for sparse PK on all subjects. See Section 6.5.

[j] See Appendix D.

[k] See Section 6.3.4.
[l] Skeletal survey will be performed during Post Treatment Response Follow up phase if clinically indicated to confirm response or PD.
[m] For subjects who enter Post Treatment Response Follow up, BMA (and, if possible, BMB) will be collected at confirmed PD instead of treatment discontinuation.
[n] Oral hydration should start 48 hours prior to C1D1. IV hydration before dosing (recommended) and after (if needed) during Cycle 1. Continue oral and/or IV hydration in subsequent cycles if necessary. See Section 7.2.4.
[o] Hematology sample collection containing a lymphocyte panel to support biomarker assessment. See Section 6.6.
[p] All subjects will be tested for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (antiHBs), and hepatitis B core antibody (antiHBc) locally during screening.
[q] During Post-Tx Response FU, EMP radiological assessment is required every 3 months for those with a history of or clinical indication of EMPs only assessable radiographically.

Table 14: Table of Events for Part 2 Cohorts C (monotherapy), D, and I (CC-220+DEX): 28-day Cycle

EVENTS	Screening	Treatment							Safety Follow-up	Post-Tx Response FU	Long Term FU
		Cycle 1			Cycle 2-4 (±2 days for all visits)		≥ Cycle 5 (±2 days for all visits)	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)	Every 3 months for 5 years
	-28 to -1	D1	D8	D15	D1	D15	D1				
STUDY ENTRY AND GENERAL ASSESSMENTS											
Informed consent	X	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-			
IRT registration	X	X	-	-	-	-	-	X			
Prior cancer history	X	-	-	-	-	-	-	-			
Medical history[p]	X	-	-	-	-	-	-	-			
Demographics	X	-	-	-	-	-	-	-			
Prior disease history	X	-	-	-	-	-	-	-			
Prior disease therapies	X	-	-	-	-	-	-	-			
SAFETY ASSESSMENTS											
Prior/concomitant medication evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication									-
Prior/concomitant procedures evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication									-
AE (AESI) evaluation	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication									-
SPM surveillance	X	Continuous starting after informed consent signature, until the end of the 5-year Long-term Follow-up phase									
Physical examination (includes VTE monitoring and ophthalmologic exam if clinically indicated) [a, c]	X	X	-	-	X	-	X	X	-	-	-
Vital signs (includes weight)	X	X	X	X	X	X	X	X	X	-	-

Table 14: Table of Events for Part 2 Cohorts C (monotherapy), D, and I (CC-220+DEX): 28-day Cycle (Continued)

EVENTS	Screening	Treatment							Safety Follow-up	Post-Tx Response FU	Long Term FU
		Cycle 1			Cycle 2-4 (±2 days for all visits)		≥ Cycle 5 (±2 days for all visits)				
	-28 to -1	D1	D8	D15	D1	D15	D1	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)	Every 3 months for 5 years
ECG [b]	X	X	X	And during treatment if clinically indicated				X	-	-	-
Hematology [c]	X	X	X	X	X	X	X	X	-	X	-
Chemistry [c]	X	X	X	X	X	X	X	X	-	X	-
Renal function (CrCl)	X	X	X	X	X	X	X	X	-	-	-
Urinalysis	X	Repeated only if clinically indicated						X	-	-	-
Pregnancy test for FCBP with regular or no menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 28 days					X	X	-	-
Pregnancy test for FCBP with irregular menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 14 days					X	14 and 28 days after last dose	-	-
Pregnancy counseling for all subjects [i]	X	X	-	-	X	-	X	X	-	-	-
EFFICACY AND OTHER ASSESSMENTS											
ECOG performance status [c]	X	X	-	-	X	-	X	X	-	X	-
Assessment of response (IMWG Uniform Response Criteria) [d, j]	-	-	-	-	X	-	X	X	-	X	-
Serum and urine protein electrophoresis	X	X	-	-	X	-	X	X	-	X	-
Serum and urine immunofixation [e]	X	-	-	-	-	-	-	-	-	-	-
Serum free light chain assay	X	X	X	X	X	-	X	X	-	X	-
Quantitative serum immunoglobulin	X	X	-	-	X	-	X	X	-	X	-
β-2 microglobulin	X	-	-	-	-	-	-	-	-	-	-

Table 14: Table of Events for Part 2 Cohorts C (monotherapy), D, and I (CC-220+DEX): 28-day Cycle (Continued)

EVENTS	Screening	Treatment							Safety Follow-up	Post-Tx Response FU	Long Term FU
		Cycle 1			Cycle 2-4 (±2 days for all visits)		≥ Cycle 5 (±2 days for all visits)				
	-28 to -1	D1	D8	D15	D1	D15	D1	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)	Every 3 months for 5 years
EMP clinical assessment	X	X	-	-	X	-	X	X	-	X	-
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically)	X	-	-	-	Day 1 starting at C3, then every 3 cycles thereafter			X	-	X [q]	-
Skeletal Survey/CT Scan/MRI (Bone lesion)	X	Repeated during treatment if clinically indicated to confirm response or PD							-	X [n]	-
Bone marrow aspirate and/or biopsy sampling [k]	X	- Screening: BMA and if possible BMB for local % plasma cells and central cytogenetics and other biomarkers -C2D15: BMA and if possible BMB at 3-6 hours post dose, for biomarkers - BMA and if possible BMB at CR confirmation and at PD/treatment discontinuation - BMA at 6, 12, 18, 24 months from C1D1 and yearly thereafter after achieving a response of VGPR or better until disease progression for MRD - Optional BMA and/or BMB taken at any time point during treatment at request of investigator and prior to subsequent myeloma therapy							-	X [m]	-
[redacted]											
Whole blood sample for biomarkers for all subjects [g]	-	X	-	X	C2	C2	C6D15	X	-	-	-
Additional whole blood sample for biomarkers for selected subjects at select US sites in Cohort D (notified via IRT) [l]	-	D1 and D2	-	X	C2	C2	-	-	-	-	-
Additional whole blood sample and BMA for 5 selected subjects in Cohort D at one pre-identified US site [o]	X	-	X	-	-	C2	-	-	-	-	-

Table 14: Table of Events for Part 2 Cohorts C (monotherapy), D, and I (CC-220+DEX): 28-day Cycle (Continued)

EVENTS	Screening	Treatment							Safety Follow-up	Post-Tx Response FU	Long Term FU
		Cycle 1			Cycle 2-4 (±2 days for all visits)		≥ Cycle 5 (±2 days for all visits)				
	-28 to -1	D1	D8	D15	D1	D15	D1	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)	Every 3 months for 5 years
[redacted]											
Whole blood samples for PK for Cohorts C and D [h]	-	-	-	X	-	X	-	-	-	-	-
Whole blood samples for PK for Cohort I[h]	-	-	-	X	-	C2	-	-	-	-	-
Survival	-	-	-	-	-	-	-	-	-	-	X
Subsequent myeloma therapies including date of progression	-	-	-	-	-	-	-	-	-	-	X
COHORT C											
Oral CC-220	-	Days 1-21/28-day cycle						-	-	-	-
COHORT D and I											
Oral CC-220	-	Days 1-21/28-day cycle						-	-	-	-
Oral DEX	-	Days 1, 8, 15, 22/28-day cycle						-	-	-	-
VTE prophylaxis	-	C1D1 to EOT						-	-	-	-
IP (CC-220, DEX as applicable) accountability/compliance	-	X	X	X	X	X	X	X	-	-	-

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BMA = bone marrow aspirate; BMB = bone marrow biopsy; [redacted] C = Cycle; CR = complete response; CrCL = creatinine clearance; CT = computed tomography; D = Day; D/C = discontinuation; DEX = dexamethasone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytomas; EOT = End of Treatment; FCBP = female of child-bearing potential; FU = follow-up; IMWG = International Myeloma Working Group; IRT = Interactive Response Technology; IP = investigational product; MRD = minimal residual disease; MRI = magnetic resonance imaging; PD = progressive disease; Pd = pharmacodynamics; PK = pharmacokinetics; SPM = second primary malignancy; sPEP = serum protein electrophoresis; Tx = treatment; uPEP = urine protein electrophoresis; VGPR = very good partial response; VTE = venous thromboembolism.

[a] Height will be included in the Physical examination and only measured at Screening.

[b] ECG will be taken at time of median Tmax approximately 3-4 hours post first dose on C1D1, C1D8, and at EOT. Also, the ECG will be repeated during treatment if clinically indicated.
[c] On C1D1, safety laboratory assessments must be performed locally, in addition to central laboratory collection, to confirm that the subject continues to meet the required safety laboratory values prior to initiating IP. However, if Screening assessments were performed within 72 hours of C1D1, safety laboratory (hematology and chemistry), physical examinations, and ECOG do not need to be repeated at C1D1.
[d] Refer to Appendix B for IMWG criteria.
[e] After C1D1, assessment to be taken only if myeloma paraprotein is not detected or too few to quantify in sPEP and uPEP assessments.

[redacted]

[g] Whole blood sample for biomarkers for all subjects: samples drawn for Pd effects of CC-220 on T-Cell Activation on C1D1, C1D15. Samples for Pd effects of CC-220 on immune cells in peripheral blood and association of baseline levels of these populations with response or resistance to CC-220 on C1D1, C2D1, C2D15, C6D15, EOT. Samples for pharmacogenomics on C1D1. See Section 6.6.
[h] Intensive PK samples will be drawn from selected subjects on C1D15 (for Cohorts C and D) in addition to the samples drawn for sparse PK on all subjects. For Cohort I, no intensive PK samples will be drawn from subjects.
[i] See Appendix D.
[j] See Section 6.3.4.
[k] Refer to Table 18 for details on BMA and BMB collection plan.
[l] Additional whole blood sample for biomarkers for select subjects at select US sites in Cohort D (notified via IRT if subject will be participating in one or more): Samples collected on C1D1, C2D1, C2D15 [redacted]. Samples collected on C1D1, C1D2, and C1D15 to evaluate Pd effect on CC-220 on Aiolos and Ikaros with novel assay. See Section 6.6.
[m] For subjects who enter Post Treatment Response follow up, BMA (and, if possible, BMB) will be collected at confirmed PD instead of EOT.
[n] Skeletal survey will be performed during Post Treatment Response Follow up phase if clinically indicated to confirm response or PD.
[o] Cohort D subjects from one selected US site: samples collected on screening, C1D8, C2D15 to evaluate time-matched concentration of CC-220 in peripheral blood and tumor microenvironment and assess the correlation between concentration, pharmacodynamic changes in tumor microenvironment, and outcome measures. See Section 6.6.
[p] For subjects in Cohort D, this will include data on subject's prior CAR T cell candidacy.
[q] During Post-Tx Response FU, EMP radiological assessment is required every 3 months for those with a history of or clinical indication of EMPs only assessable radiographically.

Table 15: Table of Events for Part 2 Cohort J1 (CC-220Vd in NDMM and not eligible for ASCT)

EVENTS	Screening	Treatment											Safety Follow-up	Post-Tx Response FU[m]
		Cycle 1(21-day cycle) ±2 days for all visits				Cycles 2 –8 (21-day cycle) ±2 days for all visits				Cycles 9-29 (28-day cycle) ±2 days for all visits	≥ Cycle 30 (28-day cycle) ±7 days for all visits		28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D4	D8	D11	D1	D4	D8	D11	D1	D1	EOT		
STUDY ENTRY AND GENERAL ASSESSMENTS														
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-		
IRT registration	X	X	-	-	-	-	-	-	-	-	-	X		
Prior cancer history	X	-	-	-	-	-	-	-	-	-	-	-		
Medical history	X	-	-	-	-	-	-	-	-	-	-	-		
Demographics	X	-	-	-	-	-	-	-	-	-	-	-		
Prior disease history	X	-	-	-	-	-	-	-	-	-	-	-		
Prior disease therapies	X	-	-	-	-	-	-	-	-	-	-	-		
SAFETY ASSESSMENTS														
Prior/concomitant medication evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication												
Prior/concomitant procedures evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication												
AE (AESI) evaluation	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication												
SPM surveillance	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication												
Physical examination (includes VTE monitoring and ophthalmologic exam if clinically indicated)[a, c]	X	X	-	-	-	X	-	-	-	X	X	X	-	-
Vital signs (includes weight)	X	X	X	X	X	X	X	X	X	X	X	X	X	-

Table 15: Table of Events for Part 2 Cohort J1 (CC-220Vd in NDMM and not eligible for ASCT) (Continued)

EVENTS	Screening	Treatment										Safety Follow-up	Post-Tx Response FU[m]
		Cycle 1(21-day cycle) ±2 days for all visits				Cycles 2 –8 (21-day cycle) ±2 days for all visits				Cycles 9-29 (28-day cycle) ±2 days for all visits	≥ Cycle 30 (28-day cycle) ±7 days for all visits			
	-28 to -1	D1	D4	D8	D11	D1	D4	D8	D11	D1	D1	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
ECG [b]	X	X	-	X	And during treatment if clinically indicated							X	-	-
Hematology [c]	X	X	-	X	-	X	-	X	-	X	X	X	-	-
Chemistry [c]	X	X	-	X	-	X	-	X	-	X	X	X	-	-
Renal function (CrCL)	X	X	-	X	-	X	-	X	-	X	X	X	-	-
Urinalysis	X	Repeated only if clinically indicated										X	-	-
Pregnancy test for FCBP with regular or no menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 21 days after first dose, then every 21 days from cycle 1 to 8, then every 28 days thereafter									X	X	-
Pregnancy test for FCBP with irregular menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 21 days after first dose, then every 14 days									X	14 & 28 days after last dose	-
Pregnancy counseling for all subjects [h]	X	X	-	-	-	X	-	-	-	X	X	X	-	-
EFFICACY AND OTHER ASSESSMENTS														
ECOG performance status [c]	X	X	D1 of Cycle 3, 6, 9, 12 for year 1; every 6th cycle thereafter									X	-	X
Assessment of response (IMWG Uniform Response Criteria) [d, i]	-	-	-	-	-	X	-	-	-	X	C30 & every 3 cycles thereafter	X	-	X
Serum and urine protein electrophoresis	X	X	-	-	-	X	-	-	-	X	C30 & every 3 cycles thereafter	X	-	X
Serum and urine immunofixation [e]	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum free light chain assay	X	X	-	-	X	X	-	-	-	X	C30 & every 3 cycles thereafter	X	-	X
Quantitative serum immunoglobulin	X	X	-	-	-	X	-	-	-	X	C30 & every 3 cycles thereafter	X	-	X

Table 15: Table of Events for Part 2 Cohort J1 (CC-220Vd in NDMM and not eligible for ASCT) (Continued)

EVENTS	Screening	Treatment											Safety Follow-up	Post-Tx Response FU[m]
		Cycle 1 ±2 days for all visits				Cycles 2 –8 (21-day cycle) ±2 days for all visits				Cycles 9-29 (28-day cycle) ±2 days for all visits	≥ Cycle 30 (28-day cycle) ±7 days for all visits		28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
	-28 to -1	D1	D4	D8	D11	D1	D4	D8	D11	D1	D1	EOT		
β-2 microglobulin	X	-	-	-	-	-	-	-	-	-	-	-	-	-
EMP clinical assessment	X	X	-	-	-	X	-	-	-	X	X	X	-	X
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically)	X	-	-	-	-	Day 1 starting at C3, then every 3 cycles thereafter if clinically indicated						X	-	X[l]
Skeletal Survey/CT Scan/MRI (Bone lesion)	X(within 60 days prior to first dose is acceptable)	Repeated during treatment if clinically indicated to confirm response or PD											-	X[k]
Bone marrow aspirate and/or biopsy sampling [f]	X	- Screening: BMA and, if possible, BMB for local % plasma cells and central cytogenetics and other biomarkers - C2D11: BMA and if possible BMB at 3-6 hours post dose, for biomarkers - BMA and, if possible, BMB at CR confirmation and at PD/treatment discontinuation - BMA at C7D1 and 12, 18, 24 months from C1D1 and yearly thereafter after achieving a response of VGPR or better until disease progression for MRD - Optional BMA and/or BMB taken at any time point during treatment at request of investigator and prior to subsequent myeloma therapy											-	X[j]
Whole blood sample for biomarkers [g]	-	X	-	-	X	-	-	C4 and C8	-	-	-	X	-	-
Whole blood samples for PK	-	-	-	X	-	-	-	C2	-	-	-	-	-	-
COHORT J1														
Oral CC-220	-	Cycles 1 – 8: Days 1-14/21-day cycle Cycle ≥ 9: Days 1-21/28-day cycle										-	-	-

Table 15: Table of Events for Part 2 Cohort J1 (CC-220Vd in NDMM and not eligible for ASCT) (Continued)

EVENTS	Screening	Treatment											Safety Follow-up	Post-Tx Response FU[m]
		Cycle 1 ±2 days for all visits				Cycles 2 –8 (21-day cycle) ±2 days for all visits				Cycles 9-29 (28-day cycle) ±2 days for all visits	≥ Cycle 30 (28-day cycle) ±7 days for all visits			
	-28 to -1	D1	D4	D8	D11	D1	D4	D8	D11	D1	D1	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
Oral DEX	-	Cycles 1 – 8: Days 1, 2, 4, 5, 8, 9, 11,12/21-day cycle Cycle ≥ 9: Days 1, 8, 15, 22/28-day cycle										-	-	-
SC BTZ	-	Cycles 1 - 8: Days 1, 4, 8, 11/21-day cycle										-	-	-
VTE prophylaxis	-	C1D1 to EOT										-	-	-
IP (CC-220, DEX, BTZ, as applicable) accountability/compliance	-	X	-	X	-	X	-	X	-	X	X	X	-	-

Abbreviations: AE = adverse event; AESI = adverse events of special interest; ASCT = autologous stem cell transplant; BMA = bone marrow aspirate; BMB = bone marrow biopsy; BTZ = bortezomib; C = Cycle; CR = complete response; CrCL = creatinine clearance; CT = computed tomography; DEX = dexamethasone; D = Day; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytomas; EOT = End of Treatment; FCBP = female of child-bearing potential; FU = follow-up; IMWG = International Myeloma Working Group; IP = investigational product; IRT = Interactive Response Technology; MRD = minimal residual disease; MRI = magnetic resonance imaging; NDMM = newly diagnosed multiple myeloma; Pd = pharmacodynamics; PD = progressive disease; PK = pharmacokinetics; sPEP = serum protein electrophoresis; SPM = second primary malignancy; SC = subcutaneous; Tx = treatment; uPEP = urine protein electrophoresis; VGPR = very good partial response; VTE = venous thromboembolism.

[a] Height will be included in the Physical examination and only measured at Screening.

[b] ECG will be taken at time of median Tmax approximately 3-4 hours post first dose on C1D1, C1D8, and at EOT. Also, the ECG will be repeated during treatment if clinically indicated.

[c] On C1D1, safety laboratory assessments must be performed locally, in addition to central laboratory collection, to confirm that the subject continues to meet the required safety laboratory values prior to initiating IP. However, if Screening assessments were performed within 72 hours of C1D1, safety laboratory (hematology and chemistry), physical examinations, and ECOG do not need to be repeated at C1D1.

[d] Refer to Appendix B for IMWG criteria.

[e] From C1D1, assessment to be taken only if myeloma paraprotein is not detected or too few to quantify in sPEP and uPEP assessments.

[f] Screening and C2D11 Bone marrow sampling for biomarkers.

[g] Whole blood sample for biomarkers for all subjects: Samples drawn for Pd effects of CC-220 on T-cell Activation on C1D1 and C1D11. Samples drawn for Pd effects of CC-220 on immune cells in peripheral blood on C1D1, C4D8, C8D8, and EOT. Sample drawn for pharmacogenomics of CC-220 on C1D1. See Section 6.6.

[h] See Appendix D.

[i] See Section 6.3.4.

[j] For subjects who enter Post Treatment Response follow up, BMA (and, if possible, BMB) will be collected at confirmed PD instead of treatment discontinuation.

[k] Skeletal survey will be performed during Post Treatment Response Follow up phase if clinically indicated to confirm response or PD.

[l] During Post-Tx Response FU, EMP radiological assessment is required every 3 months for those with a history of or clinical indication of EMPs only assessable radiographically.

[m] All subjects who discontinue study treatment for a reason other than PD or withdrawal of consent from the study will enter the Post Treatment Response Follow Up phase and will be followed for response assessment every 28 days until PD or until subsequent myeloma regimen has been started.

Table 16: Table of Events: Part 2 Cohort J2 (CC-220Vd in NDMM and Eligible for ASCT): 21-day Cycle

Events	Screening Period	Treatment Period					Follow-up Period		
		Cycles 1-6 Induction (±2 days)		Post-induction/Pre-ASCT [b]	Post-ASCT/Pre-maintenance (monthly up to 3 months post-ASCT) [c]	EOT [d]	28 days after EOT [e]	Post-Tx Response FU every 3 months [f]	Post-Tx Response FU D/C
	-28 to -1	D1	D4, D8, D11	(±7 days)	(±7 days)	(≤ 7 days from Tx D/C)	(±3 d)	(±7 d)	(±3 d)
STUDY ENTRY AND GENERAL ASSESSMENTS									
Informed consent	X	-	-	-	-	-	-	-	-
Inclusion/Exclusion criteria	X	-	-	-	-	-	-	-	-
IRT registration	X	X	-	-	-	X	-	-	-
Prior cancer history	X	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-
Prior disease history	X	-	-	-	-	-	-	-	-
Prior disease therapies	X	-	-	-	-	-	-	-	-
SAFETY ASSESSMENTS									
Prior/concomitant medication and procedures evaluation	X (≤ 28 days from Screening)	Continuous until 28 days after the last dose of induction treatment					-	-	-
AE (AESI) evaluation [g]	Continuous, starting after informed consent signature, until 28 days after the last dose of induction treatment						-	-	-
SPM surveillance	Continuous, starting after informed consent signature, until 28 days after the last dose of induction treatment						-	-	-
Physical examination (includes VTE monitoring and ophthalmologic exam if clinically indicated) [a]	X	X	-	X	X	X	-	-	-
Vital signs (including weight)	X	X	X	X	X	X	X	-	-
Height	X	-	-	-	-	-	-	-	-

Table 16: Table of Events: Part 2 Cohort J2 (CC-220Vd in NDMM and Eligible for ASCT): 21-day Cycle (Continued)

Events	Screening Period	Treatment Period					Follow-up Period		
		Cycles 1-6 Induction (±2 days)		Post-induction/Pre-ASCT [b]	Post-ASCT/Pre-maintenance (monthly up to 3 months post-ASCT) [c]	EOT [d]	28 days after EOT [e]	Post-Tx Response FU every 3 months [f]	Post-Tx Response FU D/C
	-28 to -1	D1	D4, D8, D11	(±7 days)	(±7 days)	≤ 7 days from Tx D/C	(±3 d)	(±7 d)	(±3 d)
ECG	X	C1D1	C1D8	If clinically indicated		X	-	-	-
Hematology [a]	X	X	X	X	X	X	X	-	-
Chemistry [a]	X	X	X	X	X	X	X	-	-
Renal function (CrCl) [h]	X	X	X	X	X	X	X	-	-
Urinalysis	X	If clinically indicated				X	-	-	-
Pregnancy test for FCBP with regular or no menstrual cycles	-10 to -14 days and -24 hours prior to first dose, weekly for the first cycle (C1D8, C1D15), then Day 1 of every cycle thereafter (starting with C2D1), at treatment discontinuation and 28 days following the last dose of CC-220							-	-
Pregnancy test for FCBP with irregular menstrual cycles	-10 to -14 days and -24 hours prior to first dose, weekly for the first cycle (C1D8, C1D15), then every 14 days thereafter (starting with C2D1), at treatment discontinuation and 14 and 28 days following the last dose of CC-220							-	-
Pregnancy counseling [i]	X	X	-	X	-	X	-	-	-
EFFICACY and OTHER ASSESSMENTS									
ECOG Performance status [a]	X	X	-	X	X	X	-	X	X
Assessment of response (IMWG Uniform Response Criteria) [j]	-	C2 onwards	-	X	X	X	-	X [k]	X [k]
Serum and urine protein electrophoresis	X	X	-	X	X	X	-	X [k]	X [k]
Serum and urine immunofixation [q]	X	-	-	-	-	-	-	-	-
Serum free light chains assay	X	X	C1D11	X	X	X	-	X [k]	X [k]
Quantitative serum immunoglobulin	X	X	-	X	X	X	-	X [k]	X [k]

Table 16: Table of Events: Part 2 Cohort J2 (CC-220Vd in NDMM and Eligible for ASCT): 21-day Cycle (Continued)

Events	Screening Period	Treatment Period					Follow-up Period		
		Cycles 1-6 Induction (±2 days)		Post-induction/Pre-ASCT [b]	Post-ASCT/Pre-maintenance (monthly up to 3 months post-ASCT) [c]	EOT [d]	28 days after EOT [e]	Post-Tx Response FU every 3 months [f]	Post-Tx Response FU D/C
	-28 to -1	D1	D4, D8, D11	(±7 days)	(±7 days)	≤ 7 days from Tx D/C	(±3 d)	(±7 d)	(±3 d)
β-2 microglobulin	X	-	-	-	-	-	-	-	-
EMP clinical assessment	X	X	-	X	X	X	-	X [k]	X [k]
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically) [l]	X	C4	-	X	3 months after ASCT	X	-	If clinically indicated as per Institutional SOC and to confirm PD [k]	
Skeletal Survey/CT Scan/MRI (Bone lesion)[m]	X (within 60 days prior to first dose is acceptable)	Repeated during treatment if clinically indicated to confirm PD					-	If indicated to confirm PD	
Bone marrow aspirate and/or biopsy sampling [n]	- Screening: BMA and, if possible, BMB for local % plasma cells, central cytogenetics and other central biomarkers - BMA and, if possible, BMB at CR confirmation and at PD/treatment discontinuation -BMA for MRD at C4D1 of induction or end of induction, whichever comes first after achieving VGPR and 100 days post ASCT if achieved VGPR or better -Optional BMA and/or BMB taken at any time point during treatment at request of investigator and prior to subsequent myeloma therapy						-	If indicated as per Institutional SOC	
Whole blood sample for biomarkers all subjects [o]	-	C1D1	C1D11, C4D8	-	-	X	-	-	-
Whole blood sample for PK	-	-	C1D8, C2D8	-	-	-	-	-	-

Table 16: Table of Events: Part 2 Cohort J2 (CC-220Vd in NDMM and Eligible for ASCT): 21-day Cycle (Continued)

Events	Screening Period	Treatment Period					Follow-up Period		
		Cycles 1-6 Induction (±2 days)		Post-induction/Pre-ASCT [b]	Post-ASCT/Pre-maintenance (monthly up to 3 months post-ASCT) [c]	EOT [d] ≤ 7 days from Tx D/C	28 days after EOT [e]	Post-Tx Response FU every 3 months [f]	Post-Tx Response FU D/C
	-28 to -1	D1	D4, D8, D11	(±7 days)	(±7 days)		(±3 d)	(±7 d)	(±3 d)
STUDY TREATMENT (CC-220, BTZ, DEX)									
Oral CC-220	-	Days 1-14/21-day cycle		-	-	-	-	-	-
Oral DEX	-	Days 1, 2, 4, 5, 8, 9, 11, 12/21-day cycle		-	-	-	-	-	-
Subcutaneous BTZ [p]	-	X	X	-	-	-	-	-	-
VTE prophylaxis	-	C1D1 to EOT		-	-	-	-	-	-
IP (CC-220, BTZ, DEX) accountability/compliance	-	X	X	-	-	X[r]	-	-	-

Abbreviations: AE = adverse event; ASCT = autologous stem cell transplant; BMA = bone marrow aspirate; BMB = bone marrow biopsy; BTZ = bortezomib; C = cycle; CR = complete response; CrCl = creatinine clearance; CT = computed tomography; D = day; D/C = discontinuation; DEX = dexamethasone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytoma; EOT = end of treatment; FCBP = female of childbearing potential; FU = follow-up; IMWG = International Myeloma Working Group; IRT Interactive Response Technology; MRD = minimal residual disease; MRI = magnetic resonance imaging; NDMM = newly diagnosed multiple myeloma; PD = progressive disease; Pd = pharmacodynamic; PK = pharmacokinetics; SAE = serious adverse event; SOC = standard of care; sPEP = serum protein electrophoresis; SPM =second primary malignancy; Tx D/C = treatment discontinuation; uPEP = urine protein electrophoresis; VGPR = very good partial response; VTE = venous thromboembolism.

[a] On C1D1, safety laboratory assessments must be performed locally, in addition to central laboratory collection, to confirm that the subject continues to meet the required safety laboratory values prior to initiating IP. However, if Screening assessments were performed within 72 hours of C1D1, safety laboratory (hematology and chemistry), physical examinations, and ECOG do not need to be repeated at C1D1.

[b] The post-induction/pre-ASCT visit should be performed at a minimum of 4 weeks after completion of the last induction cycle.

[c] The post-ASCT/pre-maintenance visits should be done monthly from the date of ASCT and the last visit performed 3 months ± 7 days after the ASCT.

[d] The EOT visit should be performed for all subjects at 3 months ±7 days post ASCT (prior to any maintenance therapy), or at moment of induction treatment discontinuation.

[e] The 28-day safety follow-up visit after EOT is only required for subjects who do not continue with an ASCT.

[f] The Post-Tx Response FU visits will be done every 3 months following EOT. Only efficacy and response assessments will be performed during these visits. Subjects will continue to be followed in the Post-Tx Response FU phase until PD or until a subsequent anti-myeloma regimen has been started.

[g] All SAEs made known to the Investigator at any time after 28 days after the last dose of induction treatment, that are suspected of being related to induction treatment will be recorded.

[h] Estimation of renal function will be assessed using the 24-hour urine creatinine clearance, or CrCl calculated based on the Cockcroft-Gault formula or the CrCL directly calculated from the 24-hour urine collection method.

[i] Pregnancy counseling at the post-induction/pre-ASCT is only required for subjects who continue with an ASCT. Subjects who do not continue with an ASCT will perform pregnancy counseling at the EOT Visit.
[j] Per IMWG Uniform Response Criteria all response categories and progressive disease require 2 consecutive assessments.
[k] Efficacy assessments during the Post-Tx Response FU will be done locally as per the Institutional SOC.
[l] EMPs assessable radiographically by CT or MRI.
[m] Skeletal survey is done locally and can be performed by X-ray, CT or MRI provided the same modality will be used for future assessments.
[n] The 100 day post-ASCT BMA for MRD in subjects that have achieved VGPR or better may be performed +/- 1 week.
[o] Biomarker sampling for all subjects: Samples drawn for Pd effects of CC-220 on T-cell Activation on C1D1 and C1D11. Samples drawn for Pd effects of CC-220 on immune cells in peripheral blood on C1D1, C4D8 and EOT (end of induction). Sample drawn for pharmacogenomics of CC-220 on C1D1. See Section 6.6.
[p] BTZ doses should be given at least 72 hours apart.
[q] From C1D1, assessment to be taken only if myeloma paraprotein is not detected or too few to quantify in sPEP and uPEP assessments.
[r] IP accountability/compliance to be performed at the end of induction.

Table 17: Table of Events for Part 2 Cohort K (CC-220Dd): 28-day Cycle

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU[p]
		Cycle 1 (±2 days for all visits)				Cycle 2 (±2 days for all visits)				Cycle 3-6 (±2 days for all visits)		≥ Cycle 7 (±2 days for all visits)	≥ Cycle 26 (±7 days for all visits)			
	-28 to -1	D1	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1	D1	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
STUDY ENTRY AND GENERAL ASSESSMENTS																
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
IRT registration	X	X	-	-	-	-	-	-	-	-	-	-	-	X		
Prior cancer history	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Medical history	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Prior disease history	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
Prior disease therapies	X	-	-	-	-	-	-	-	-	-	-	-	-	-		
SAFETY ASSESSMENTS																
Prior/concomitant medication evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication														
Prior/concomitant procedures evaluation	X (≤ 28 days from Screening)	Continuous, until 28 days after last dose of study medication														
AE (AESI) evaluation	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication														
SPM surveillance	X	Continuous starting after informed consent signature, until 28 days after last dose of study medication														
Physical examination (includes VTE monitoring and ophthalmologic exam if clinically indicated)[a, c]	X	X	-	-	-	X	-	-	-	X	-	X	X	X	-	-

Table 17: Table of Events for Part 2 Cohort K (CC-220Dd): 28-day Cycle (Continued)

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU[p]
		Cycle 1 (±2 days for all visits)				Cycle 2 (±2 days for all visits)				Cycle 3-6 (±2 days for all visits)		≥ Cycle 7 (±2 days for all visits)	≥ Cycle 26 (±7 days for all visits)			
	-28 to -1	D1	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1	D1	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
Vital signs (includes weight) [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
ECG [b]	X	X	-	And during treatment if clinically indicated										X	-	-
Hematology [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Chemistry [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Renal function (CrCL)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Urinalysis	X	Repeated only if clinically indicated												X	-	-
Pregnancy test for FCBP with regular or no menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 28 days											X	X	-
Pregnancy test for FCBP with irregular menstrual cycles	X	X	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 14 days											X	14 and 28 days after last dose	-
Pregnancy counseling for all subjects[g]	X	X	-	-	-	X	-	-	-	X	-	X	X	X	-	-
Hepatitis B (HBV) serology local testing [k]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HBV DNA local [l]	X	If indicated, every 12 weeks during treatment, at the EOT Visit, and every 12 weeks for up to 6 months after the last dose of DARA														
EFFICACY AND OTHER ASSESSMENTS																
ECOG performance status [c]	X	X	-	-	-	-	-	-	-	D1 of Cycle 3, 6, 9, 12 for year 1; every 6th cycle thereafter				X	-	X

Table 17: Table of Events for Part 2 Cohort K (CC-220Dd): 28-day Cycle (Continued)

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU[p]
		Cycle 1 (±2 days for all visits)				Cycle 2 (±2 days for all visits)				Cycle 3-6 (±2 days for all visits)		≥ Cycle 7 (±2 days for all visits)	≥ Cycle 26 (±7 days for all visits)			
	-28 to -1	D1	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1	D1	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
Assessment of response (IMWG Uniform Response Criteria) [d, h]	-	-	-	-	-	X	-	-	-	X	-	X	C26 & every 3 cycles thereafter	X	-	X
Serum and urine protein electrophoresis	X	X	-	-	-	X	-	-	-	X	-	X	C26 & every 3 cycles thereafter	X	-	X
Serum and urine immunofixation [e]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum free light chain assay	X	X	-	X	-	X	-	-	-	X	-	X	C26 & every 3 cycles thereafter	X	-	X
Quantitative serum immunoglobulin	X	X	-	-	-	X	-	-	-	X	-	X	C26 & every 3 cycles thereafter	X	-	X
β-2 microglobulin	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EMP clinical assessment	X	X	-	-	-	X	-	-	-	X	-	X	X	X	-	X
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically)	X	-	-	-	-	-	-	-	-	Day 1 starting at C3, then every 3 cycles thereafter				X	-	X[m]

Table 17: Table of Events for Part 2 Cohort K (CC-220Dd): 28-day Cycle (Continued)

EVENTS	Screening	Treatment													Safety Follow-up	Post-Tx Response FU[p]
		Cycle 1 (±2 days for all visits)				Cycle 2 (±2 days for all visits)				Cycle 3-6 (±2 days for all visits)		≥ Cycle 7 (±2 days for all visits)	≥ Cycle 26 (±7 days for all visits)			
	-28 to -1	D1	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1	D1	EOT	28 days after EOT (± 3 d)	Every 28 days and at D/C visit (± 2 d)
Skeletal Survey/CT Scan/MRI (Bone lesion)	X(within 60 days prior to first dose is acceptable)	Repeated during treatment if clinically indicated to confirm response or PD													-	X[i]
Bone marrow aspirate and/or biopsy sampling [f]	X	- Screening: BMA and, if possible, BMB for local % plasma cells and central cytogenetics and other biomarkers -C2D15: BMA and if possible BMB at 3-6 hours post dose, for biomarkers - BMA and, if possible, BMB at CR confirmation and at PD/treatment discontinuation BMA at 6, 12, 18, 24 months from C1D1 and yearly thereafter after achieving a response of VGPR or better until disease progression for MRD - Optional BMA and/or BMB taken at any time point during treatment at request of investigator and prior to subsequent myeloma therapy													-	X[j]
Whole blood sample for biomarkers	-	X		X	-	X	-	X	-	-	C6	-	-	X	-	-
Whole blood samples for PK	-	-	-	X	-	-	-	X	-	-	-	-	-	-	-	-
COHORT K																
Oral CC-220	-	Days 1-21/28-day cycle												-	-	-
Oral DEX	-	Days 1, 8, 15, 22/28-day cycle												-	-	-
SC DARA[o]	-	C1-2: Days 1, 8, 15, 22; C3-6: Days 1, 15; ≥ C7: Day 1/28-day cycle												-	-	-
VTE prophylaxis	-	C1D1 to EOT												-	-	-
IP (CC-220, DARA, DEX, as applicable) accountability/compliance	-	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BMA = bone marrow aspirate; BMB = bone marrow biopsy; C = Cycle; CR = complete response; CrCL = creatinine clearance; CT = computed tomography; D = Day; DARA = daratumumab; D/C = discontinuation; DEX = dexamethasone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytomas; EOT = End of Treatment; FCBP = female of child-bearing potential; FU = follow-up; HBV = hepatitis B virus; IMWG = International Myeloma Working Group; IP = investigational product; IRT = Interactive Response Technology; MRD = minimal residual disease; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetics; SC = subcutaneous; sPEP = serum protein electrophoresis; SPM = second primary malignancy; Tmax = time to maximum plasma concentration; Tx = treatment; uPEP = urine protein electrophoresis; VGPR = very good partial response; VTE = venous thromboembolism.

[a] Height will be included in the physical examination and only measured at Screening.

[b] ECG will be taken at time of median Tmax approximately 3-4 hours post first dose on C1D1, and at EOT. Also, the ECG will be repeated during treatment if clinically indicated.

[c] On C1D1, safety laboratory assessments must be performed locally, in addition to central laboratory collection, to confirm that the subject continues to meet the required safety laboratory values prior to initiating IP. However, if Screening assessments were performed within 72 hours of C1D1, safety laboratory (hematology and chemistry), physical examinations, and ECOG do not need to be repeated at C1D1.

[d] Refer to Appendix B for IMWG criteria.

[e] From C1D1, assessment to be taken only if myeloma paraprotein is not detected or too few to quantify in sPEP and uPEP assessments.

[f] Refer to Table 18 for details on BMA and BMB collection plan.

[g] See Appendix D.

[h] See Section 6.3.4.

[i] Skeletal survey will be performed during Post Treatment Response Follow up phase if clinically indicated to confirm response or PD.

[j] For subjects who enter Post Treatment Response follow up, BMA (and, if possible, BMB) will be collected at confirmed PD instead of treatment discontinuation.

[k] All subjects will be tested for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (antiHBs), and hepatitis B core antibody (antiHBc) locally during screening.

[l] For subjects with serologic evidence of resolved HBV infection (ie, positive antiHBs or positive antiHBc) at Screening, HBV DNA testing by polymerase chain reaction (PCR) must be performed locally at screening, every 12 weeks during treatment, at the End of Treatment Visit, and every 12 weeks for up to 6 months after the last dose of DARA. Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR

[m] During Post-Tx Response FU, EMP radiological assessment is required every 3 months for those with a history of or clinical indication of EMPs only assessable radiographically.

[n] For SC DARA, vital signs are to be measured at the following time points on C1D1: immediately before SC DARA administration; at the end of SC DARA administration (+ 10 minutes); 30 minutes (± 10 minutes) and 1 hour (± 10 minutes) after the end of SC DARA administration.

[o] For SC DARA administration, all subjects will be observed for at least 6 hours after the end of the SC injection during C1D1 and, if deemed necessary by the Investigator, after subsequent injections.

[p] All subjects who discontinue study treatment for a reason other than PD or withdrawal of consent from the study will enter the Post Treatment Response Follow Up phase and will be followed for response assessment every 28 days until PD or until subsequent myeloma regimen has been started.

6. PROCEDURES

Any questions regarding the protocol should be directed to the Celgene Medical Monitor or designee.

6.1. Screening Period

Screening evaluations will be performed centrally for all subjects to determine study eligibility. These evaluations must be completed within 28 days of first dosing unless noted otherwise below. The Celgene Medical Monitor or designee must be contacted if there is a discrepancy between central safety laboratory results and local safety laboratory results. Upon review of the local laboratory results, the Celgene Medical Monitor or designee may deem the subject eligible for the study if all other eligibility criteria are satisfied.

Any questions regarding subject eligibility should be directed to the Celgene Medical Monitor or designee. Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Tests that may result in dose interruption and/or reduction should also be performed locally to allow for treatment-related decisions during subject visits. All results from local laboratories used in treatment decisions or AE reporting must be entered as an unscheduled visit into the electronic case report form (eCRF). Screening laboratory values must demonstrate subject eligibility, but may be repeated within the Screening window, if necessary. Platelet transfusions or granulocyte colony-stimulating factor (GCSF) should not be administered during Screening to enable eligible laboratory values.

The following will be performed at Screening as specified in the Table of Events, after informed consent has been obtained:

- Interactive Response Technology (IRT) registration
- Demographics (initials, age, sex, race, and if allowed by local regulations, ethnicity, initials and date of birth will be collected in the eCRF and/or IRT systems)
- Prior disease history (if available, the date of initial diagnosis, staging at time of diagnosis, cytogenetics at diagnosis to be collected)
- Prior disease therapies: includes surgery, radiation, systemic or any other therapy for MM
- Complete medical history (all relevant medical conditions diagnosed/ occurring prior to Screening should also be included)
- Prior and concomitant procedures evaluation (including all procedures occurring ≤ 28 days before Screening)
- Prior and concomitant medication evaluation (including those taken ≤ 28 days before Screening, except for those taken for MM).
- Physical examination including height (at Screening only), and assessment for potential venous thromboembolism events (VTEs) (must be source documented only)

- Vital signs (including weight, blood pressure, temperature, and heart rate)
- ECOG performance status
- 12-lead electrocardiogram (ECG)
- Efficacy assessment/ tumor evaluation (see Section 6.3).
- Hematology panel including lymphocyte panel and complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count (with differential), and platelet count. These assessments will be performed at a central laboratory; however, laboratory tests performed locally that are used for eligibility in cases of discrepancy between central safety laboratory results and local safety laboratory results or that result in dose interruption and/or reduction must be recorded in the eCRF.
- Chemistry panel including sodium, potassium, calcium, corrected serum calcium, chloride, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), lactate dehydrogenase (LDH), magnesium, bicarbonate, lipase, gamma glutamyl transferase (GGT), uric acid, triglycerides, cholesterol, amylase, and phosphate. These assessments will be performed at a central laboratory; however, laboratory tests performed locally that are used for eligibility in cases of discrepancy between central safety laboratory results and local safety laboratory results or that result in dose interruption and/or reduction must be recorded in the eCRF.
- Estimation of renal function will be assessed using the 24-hour urine creatinine clearance, or CrCL calculated based on the Cockcroft-Gault formula or the CrCL directly calculated from the 24-hour urine collection method. Cockcroft-Gault formula: CrCL (mL/min) = (140-age) (weight [kg])/(72 (serum creatinine [mg/dL])); for females, the formula is multiplied by 0.85.
- Urinalysis (a urine dipstick may be used)
- Pregnancy test is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test (with a sensitivity of at least 25 mIU/mL) must be performed at Screening within 10 to 14 days prior to the start of CC-220. The second pregnancy test must be performed within 24 hours prior to the start of CC-220. A urine (or serum) pregnancy test will be performed to assess subject eligibility within 24 hours prior to the first administration of IP (CC-220 monotherapy or CC-220 plus DEX combination therapy).
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted and documented in the source notes (see Appendix D). For Cohort J2, pregnancy counseling at the post-induction/pre-ASCT is only required for subjects who continue with an ASCT. Subjects who do not continue with an ASCT will perform pregnancy counseling at the EOT Visit.

- Bone marrow aspirate/biopsy for cytogenetics (fluorescence in situ hybridization [FISH]), percent plasma cells, and biomarkers and in Part 2 of the study including a sample for MRD assessment.
- Adverse event assessment, including SPM surveillance, begins when the subject signs the informed consent form
- Local hepatitis panel: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (antiHBs), hepatitis B core antibody (antiHBc) and if applicable hepatitis B virus (HBV) DNA testing by PCR. Refer to the Table of Events for further details (Table 9, Table 10, Table 11, Table 12, Table 13, and Table 17as applicable).
- ECHO/MUGA for Cohorts G1 and G2. Refer to Table 12 and Table 13.

6.2. Treatment Period

The subject will begin treatment upon confirmation of eligibility. The subject must start treatment within 28 days of signing the informed consent form (ICF) and will be allocated by IRT to an appropriate cohort, depending on his/her eligibility and on the cohort slot availability. After Cycle 1, for all subsequent visits, an administrative window of ± 2 days is permitted. On Cycle 1 Day 1 (C1D1), safety laboratory assessments must be drawn for the central lab and performed locally to confirm that the subject continues to meet the required safety laboratory values prior to initiating IP. However, if Screening assessments were performed within 72 hours of C1D1, safety laboratory for the central lab and physical examinations need not be repeated at C1D1.

Treatment cycles are 28 days in duration for all cohorts with the exception of Cohorts F, J1(first 8 cycles) and J2 (CC-220Vd), which are 21 days in duration. Further details can be found in Section 7.2.

The following evaluations will be performed at the frequency specified in the Table of Events (Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15, Table 16, and Table 17 as applicable). The evaluations should be performed unless otherwise specified.

- IRT Registration (C1D1)
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Adverse event (including AEs of special interest [AESI] and SPM surveillance) evaluation (continuously). Note in Cohort J2, all SAEs made known to the Investigator at any time after 28 days after the last dose of induction treatment, that are suspected of being related to induction treatment will be recorded.
- Physical examination including assessment for ECOG performance status, potential VTEs (source documented only)
- Vital signs including weight
- Hematology panel
- Chemistry panel (including renal function [CrCl])

- 12-lead ECGs
- Efficacy assessment (see Section 6.3)
- Response assessment in accordance with IMWG criteria (Day 1 of each cycle starting with Cycle 2). Subjects in Cohorts J1and K will be followed every cycle for the first 2 years and thereafter, every 3 months until PD or until a subsequent myeloma regimen has been started. Subjects in Cohort J2, following induction, ASCT with or without maintenance, will be followed for response assessment during the Post-Treatment Response follow-up every 3 months until PD or until a subsequent anti-myeloma regimen has been started.
- Urine (or serum) pregnancy test for FCBP (prior to dosing on Day 1 of every cycle). For cycle 1, pregnancy testing will occur weekly, then at Day 1 for each subsequent cycle. For FCBP with irregular menstrual cycles, pregnancy testing will be weekly for cycle 1, and biweekly for each subsequent cycle.
- Counseling about pregnancy precautions and the potential risks of fetal exposure for subjects receiving CC-220 (see Appendix D)
- Continuous thromboembolism prophylaxis treatment
- Bone marrow aspirate/biopsy and blood sampling for biomarkers (see Section 6.3.1), percent plasma cells and in **Part 2 of the study**, MRD assessment (see Table 18 for details)
- Blood sampling for biomarker assessments (see Section 6.6)
- Blood sampling for PK assessments (see Section 6.5)
- Blood sampling for immunogenicity assessments (see Section 6.6)
- IP (CC-220, DEX, BTZ, DARA, and CFZ as applicable) accountability/compliance
- Urinalysis if clinically indicated
- Ophthalmological examination if clinically indicated
- For Cohorts E and K subjects, HBV DNA by PCR (local testing) every 12 weeks if indicated and applicable (see Table 10 and Table 17)
- [redacted]

6.2.1. End of Treatment Visit

An end of treatment (EOT) evaluation will be performed for subjects who are withdrawn from treatment for any reason within 7 days after the decision to permanently discontinue treatment has been made. For subjects in Cohort J2 who will not undergo an ASCT for whatever reason, an EOT Visit should be performed. For those subjects in Cohort J2 who undergo an ASCT, the EOT Visit should be performed three months (± 7 days) after the transplant.

The following evaluations will be performed as specified in the Schedule of Events (Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15, Table 16 and Table 17 as applicable):

- IRT registration
- Physical examination including ECOG performance status and VTE monitoring (source documented only)
- Vital signs including weight
- Concomitant medications evaluation (monitored for 28 days after the last dose of CC-220)
- Concomitant procedures evaluation (monitored for 28 days after the last dose of CC-220)
- Adverse event (including AESIs and SPM) evaluation (monitored through 28 days after the last dose of IP)
- Counseling about pregnancy precautions and the potential risks of fetal exposure for subjects who received CC-220 (see Appendix D)
- Response assessment in accordance with IMWG criteria
- 12-lead ECG
- Urinalysis
- Hematology panel
- Chemistry panel (including CrCL)
- BMA/BMB if treatment discontinuation is due to PD for biomarkers (see Section 6.3.1) and percent plasma cells
- Whole blood sample collection for biomarkers
- Urine or serum pregnancy test for FCBP
- Ophthalmological examination if clinically indicated
- IP accountability/compliance
- Efficacy assessment will be performed according to the schedule defined in the Schedule of Events (Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15, Table 16 and Table 17 as applicable), and does not need to be performed specifically for the EOT visit except as specified in Section 6.3.
- For Cohorts E and K subjects, HBV DNA by PCR (local testing) at EOT and every 12 weeks for up to 6 months after the last dose of DARA, if indicated/applicable (see Table 10, and Table 17)
- [redacted]

6.2.2. 28-Day Post Treatment Visit

The following assessments will be performed at this visit 28 days after the EOT visit (+/- 3 days):

- Urine or serum pregnancy test for FCBP. Additionally, for FCBP with irregular menstrual cycles, a urine or serum pregnancy test will be performed 14 days after treatment discontinuation.
- Follow up on any ongoing AEs at time of IP discontinuation
- Vital signs and weight

6.2.3. Post Treatment Response Assessment

Subjects who discontinue study treatment in Part 1 or Part 2 of the study for a reason other than PD or withdrawal of consent from the study will be followed for response assessment every 28 days (or 21 days for Cohort F subjects) until PD or a subsequent myeloma regimen has been started. Concomitant medications, concomitant procedures and adverse event (including AESIs and SPM) evaluations will continue to be collected for subjects who enter this follow up phase. Additionally, subjects in Cohort J2, following induction, ASCT with or without maintenance, will be followed for response assessment every 3 months until PD or until a subsequent anti-myeloma regimen has been started. For Cohort J2, these efficacy assessments every 3 months will be done locally. Subjects are expected to have a visit at the time of discontinuation from the Post Treatment Response Assessment follow-up period.

6.2.4. Long-term Follow-up

Part 2 RRMM subjects (Cohorts C, D, and I) will have long-term follow-up. Subjects will be contacted every 3 months to collect data on survival, SPM status, and subsequent anti-myeloma therapies including date of progression for at least 5 years after the date of the last subject enrolled into the study. Cause of death is to be recorded on the eCRF.

6.3. Efficacy Assessment

All laboratory assessments for efficacy will be performed centrally.

If Screening assessments are performed within 72 hours of C1D1, efficacy laboratory assessments need not be repeated at C1D1.

- Serum protein electrophoresis (sPEP) and urine protein electrophoresis (uPEP) tests (performed on 24-hour urine collection) are required at Screening, on Day 1 of each cycle, at the EOT Visit, and at the Post-Treatment Response Follow Up visits (for subjects who enter this phase).
  - For Cohort J1 and K: at Screening, on Day 1 from Cycle 1 to Cycle 30 (Cohort J1), on Day 1 from Cycle 1 to Cycle 26 (Cohort K) (ie, first ~ 2 years) and thereafter, every 3 months (done locally) until PD or until a subsequent myeloma regimen has been started.

  - For Cohort J2: at Screening, on Day 1 from Cycle 1 to 6, pre-ASCT, monthly post-ASCT, at the EOT Visit and then every 3 months (done locally) during the Post-Treatment Response Follow Up visits.

- Serum and urine immunofixation tests are required at Screening and will be triggered to be performed whenever M-protein is undetectable or too few to quantify in both sPEP and uPEP assays.
  - For Cohorts J1 and K: at Screening, on Day 1 from Cycle 1 to Cycle 30 (Cohort J1), on Day 1 from Cycle 1 to Cycle 26 (Cohort K) (ie, first 2 years) and thereafter, every 3 months (done locally) until PD or until a subsequent myeloma regimen has been started.
  - For Cohort J2: at Screening, on Day 1 from Cycle 1 to 6, pre-ASCT, monthly post-ASCT, at the EOT Visit and then every 3 months (done locally) during the Post-Treatment Response Follow Up visits.
- Quantitative serum immunoglobulin assessment includes IgG, immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin E (IgE) and immunoglobulin D (IgD). Immunoglobulin E or IgD will only be drawn on Day 1 of each cycle, at the EOT Visit, and during the Post-Treatment Response Follow Up visits (for subjects who enter this phase) for subjects who demonstrate MM subtype IgE and IgD at Screening.
  - For Cohorts J1 and K: at Screening, on Day 1 from Cycle 1 to Cycle 30 (Cohort J1), on Day 1 from Cycle 1 to Cycle 26 (Cohort K) (ie, first ~ 2 years) and thereafter, every 3 months (done locally) until PD or until a subsequent myeloma regimen has been started.
  - Cohort J2: at Screening, on Day 1 from Cycle 1 to 6, pre-ASCT, monthly post-ASCT, at the EOT Visit and then every 3 months (done locally) during the Post-Treatment Response Follow Up visits.
- Serum free light chain assay is required at Screening, on Day 1 of each cycle, at the EOT Visit, and at the Post-Treatment Response Follow Up Visits (for subjects who enter this phase). For Part 2 subjects, an additional serum free light chain assay is required on Day 8, and Day 15 of Cycle 1 for RRMM Cohorts C, D and I.
  - For Cohort J1: at Screening, on C1D11, on Day 1 from Cycle 1 to Cycle 30 (ie first ~ 2 years) and thereafter, every 3 months (done locally) until PD or until a subsequent myeloma regimen has been started.
  - Cohort J2: at Screening, on C1D11, on Day 1 from Cycle 1 to 6, pre-ASCT, monthly post-ASCT, at the EOT Visit and then every 3 months (done locally) during the Post-Treatment Response Follow Up visits.
  - For Cohort K: at Screening, on C1D15, on Day 1 from Cycle 1 to Cycle 26 (ie first ~ 2 years) and thereafter, every 3 months (done locally) until PD or until a subsequent myeloma regimen has been started.
- Assessment of clinically assessable extramedullary plasmacytomas (EMPs) at Screening, Day 1 of each cycle and at the EOT Visit

- Assessment of radiographically assessable EMPs at Screening, Day 1 of every 3rd cycle after Screening and at the EOT Visit
- β-2 microglobulin at Screening only.

Daratumumab detection on serum immunofixation has been demonstrated in subjects treated with DARA and may interfere with the traditional IMWG criteria of negative serum immunofixation for CR or stringent complete response (sCR). To mitigate this interference, a reflex assay that utilizes anti-idiotype antibody to bind DARA and confirm its interference on serum immunofixation will be performed. For subjects in Cohorts E with VGPR, and a negative endogenous M-protein by sPEP, reflex serum immunofixation testing will be performed centrally to confirm the presence of DARA on serum immunofixation.

6.3.1. Bone Marrow Aspirate and/or Biopsy

A BMA and, if possible, BMB is **mandatory** at the following time points:

- At Screening, BMA and, if possible, BMB for percent plasma cells, cytogenetics (FISH), biomarkers assessments **and in Part 2 of the study** minimal residual disease (MRD) testing.
- During treatment:
  - *Only applicable for approximately 5 Cohort D subjects at one pre-identified US site:* a C1D8 BMA may be taken for PK/Pd assessments.
  - BMA and, if possible, BMB at C2D15 for biomarker assessments (C2D11 for Cohorts F and J1 subjects)
  - BMA and, if possible, BMB at the time of confirmed first complete response (CR) for biomarker assessments and percent plasma cells (by IMWG criteria, see Appendix B) and **in Part 2 of the study**, MRD assessment on BMA.
  - **In Part 2 of the** study, BMA for MRD assessment:
    - For Cohorts C, D, I, and K: At 6, 12, 18, 24 months from C1D1 and yearly thereafter after achieving a response of VGPR or better until disease progression
    - For Cohort J1: At C7D1 and 12, 18, 24 months from C1D1 and yearly thereafter after achieving a response of VGPR or better until disease progression
    - For Cohort J2: At C4D1 of induction or end of induction, whichever comes first, and 100 days post-transplant after achieving VGPR or better
  - BMA and, if possible, BMB at time of confirmed PD/treatment discontinuation for biomarker assessments and percent plasma cells. Collection of this sample may be up to the time preceding the start of subsequent myeloma treatment after IP discontinuation.

A BMA and/or BMB is **optional** at the following time points

- BMA and/or BMB taken at any time during the study at the request of investigator will have samples processed for biomarker assessments and percent plasma cells and in **Part 2 of the study**, MRD assessments if the subject has a response of VGPR or better and has not progressed.

The analysis of BMA/BMB for percentage of plasma cells will be performed locally. The bone marrow (BM) samples for cytogenetics (FISH), biomarkers will be submitted to a central laboratory. Bone marrow aspirate samples for MRD assessment collected at Screening will be submitted to a central laboratory and samples collected at VGPR, CR or any time during this response will be submitted to both a central laboratory (for next-generation sequencing analysis of MRD) and a specialized laboratory (for next-generation flow cytometry analysis of MRD).

The BMA and/or BMB collection sample plan is further outlined in Table 18 below.

Table 18: Bone Marrow Aspirate and/or Biopsy Sample Collection Plan

Study Phase	Type	Visit	Sample	Assessments[b]
Part 1	Mandatory	Screening	BMA (and, if possible, BMB)	Percent plasma cells Cytogenetics (FISH) Biomarkers assessments
	Mandatory	C2D15 (C2D11 for Cohort F)	BMA (and, if possible, BMB)	Biomarker assessments
	Mandatory	At CR confirmation	BMA (and, if possible, BMB)	Percent plasma cells (by IMWG criteria) Biomarker assessments
	Optional	During study: any time requested by investigator (prior to start of subsequent myeloma therapy)	BMA and/or BMB	Percent plasma cells Biomarker assessments
	Mandatory	Treatment discontinuation/time of confirmed PD [a]	BMA (and, if possible, BMB)	Percent plasma cells Biomarker assessments

Table 18: Bone Marrow Aspirate and/or Biopsy Sample Collection Plan (Continued)

Study Phase	Type	Visit	Sample	Assessments[b]
Part 2	Mandatory	Screening	BMA (and, if possible, BMB)	Percent plasma cells Cytogenetics (FISH) Biomarkers assessments MRD
	Mandatory (only applicable for one pre-identified US site)[c]	C1D8	BMA	Pharmacokinetic/pharmacodynamic assessments
	Mandatory for C, D, I, J1 and K (not required for J2)	C2D15 for C, D, I and K C2D11 for Cohort J1	BMA (and, if possible, BMB)	Biomarker assessments
	Mandatory	At CR confirmation	BMA (and, if possible, BMB)	Percent plasma cells (by IMWG criteria) Biomarker assessments MRD on BMA
	Mandatory for Cohorts C, D, I, and K	During treatment: at 6, 12, 18 and 24 months from C1D1 and yearly thereafter after achieving a response of VGPR or better until disease progression	BMA	MRD
	Mandatory for Cohort J1	During treatment: at C7D1 and 12, 18 and 24 months from C1D1 and yearly thereafter after achieving a response of VGPR or better until disease progression	BMA	MRD
	Mandatory for Cohort J2	C4D1 of induction or end of induction, whichever comes first, after achieving VGPR or better	BMA	MRD
	Mandatory for Cohort J2	100 days post ASCT if achieved VGPR or better +/- 7 days	BMA	MRD

Table 18: Bone Marrow Aspirate and/or Biopsy Sample Collection Plan (Continued)

Study Phase	Type	Visit	Sample	Assessments[b]
Part 2	Optional	During study: any time requested by investigator (prior to start of subsequent myeloma therapy)	BMA and/or BMB	Percent plasma cells Biomarker assessments MRD (if VGPR or better)
	Mandatory	Treatment discontinuation/time of confirmed PD[a]	BMA (and, if possible, BMB)	Percent plasma cells Biomarker assessments

Abbreviations: ASCT = autologous stem cell transplant; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CR = complete response; FISH = fluorescence in situ hybridization; IMWG = International Myeloma Working Group; MRD = minimal residual disease; PD = progressive disease; US = United States; VGPR= very good partial response.

[a] Collection of this sample may be up to the time preceding the start of subsequent myeloma treatment after treatment discontinuation. For subjects who enter Post-Treatment Response Follow up, the collection of this sample will be at the time of confirmed PD, not at treatment discontinuation.

[b] All biomarker assessments will be submitted to a central laboratory with the exception of percent plasma cells for all subjects in Part 1 and Part 2 and cytogenetics for a subset of subjects in Part 1, which will be performed at the local laboratory. MRD assessments by next-generation flow cytometry will be submitted to a specialized laboratory.

[c] Assessment only applicable for approximately 5 subjects enrolled in Cohort D at one pre-identified US site.

6.3.2. Bone Lesion Assessment

Bone lesion assessment by x-ray (skeletal survey), CT Scan or MRI will be performed at Screening and when clinically indicated. Bone lesion assessments will also be performed when clinically indicated for subjects who enter the Post-Treatment Response Follow up Phase. The same method (x-ray, CT Scan or MRI) should be used throughout the study. All films will be analysed locally by the site Investigator/Radiologist. If a bone lesion assessment by x-ray, CT Scan or MRI was performed within 60 days prior to C1D1, it may be used for the Screening assessment.

If assessment is done by x-ray, the following are the minimum plain radiological films required for the skeletal (bone) survey:

- Lateral skull
- Anterior/posterior (AP) and lateral cervical spine
- AP and lateral thoracic spine
- AP and lateral lumbar spine
- AP chest
- AP pelvis
- AP upper extremities, shoulder to elbow
- AP lower extremities, hip to knee

Other radiological films may be necessary to view symptomatic areas of known pre-existing lesions in skeletal regions not included in the films above.

6.3.3. Extramedullary Plasmacytoma Assessments

Clinical assessment for EMPs will be performed at Screening, on Day 1 of every cycle, at the EOT Visit, and at the Post-Treatment Response Follow Up visits if applicable. In addition, for Cohort J2, EMP assessments will be done pre-ASCT, monthly post-ASCT, at the EOT Visit and then every 3 months during the Post-Treatment Response Follow-up visits.

For EMPs that are only assessable radiographically (by x-ray and/or conventional [spiral] CT/magnetic resonance imaging [MRI] scan), scans are required at Screening, at Cycle 3 Day 1, every 3 cycles thereafter (Cycle 6 Day 1, Cycle 9 Day 1, etc.) during treatment and at the EOT Visit and when clinically indicated to confirm a response or PD. EMP assessments will also be performed for subjects who enter the Post-Treatment Response Follow up Phase. For Cohort J2, EMP assessments will be done at Cycle 4 Day 1, pre-ASCT, post-ASCT (3 months after ASCT), at the EOT Visit, during the Post-Treatment Response Follow up visits if clinically indicated. The radiographic modality used at Screening (eg, x-ray) will be repeated at each assessment time point throughout the study. All scans will be reviewed locally.

6.3.4. Assessment of Response

Starting from Cycle 2, response will be assessed by the Investigator using the International Myeloma Working Group (IMWG) Uniform Response Criteria (Kumar, 2016) (see Appendix B) at every cycle starting at Cycle 2 on Day 1, and at the EOT Visit. Additionally, subjects who discontinue study treatment for a reason other than PD or withdrawal from the study will be followed every 28 days (or 21 days for Cohort F) for response assessment until PD or the start of a subsequent myeloma regimen. Accordingly, IMWG response will continue to be assessed at the Safety Follow Up visit and the Post-Treatment Response Follow Up visits for these subjects, as applicable. Subjects in Cohort J2, following induction, response assessment will be done pre-ASCT, monthly post-ASCT, at the EOT Visit, every 3 months during the Post-Treatment Response Follow-up and at the Post-Treatment Response Discontinuation Visit.

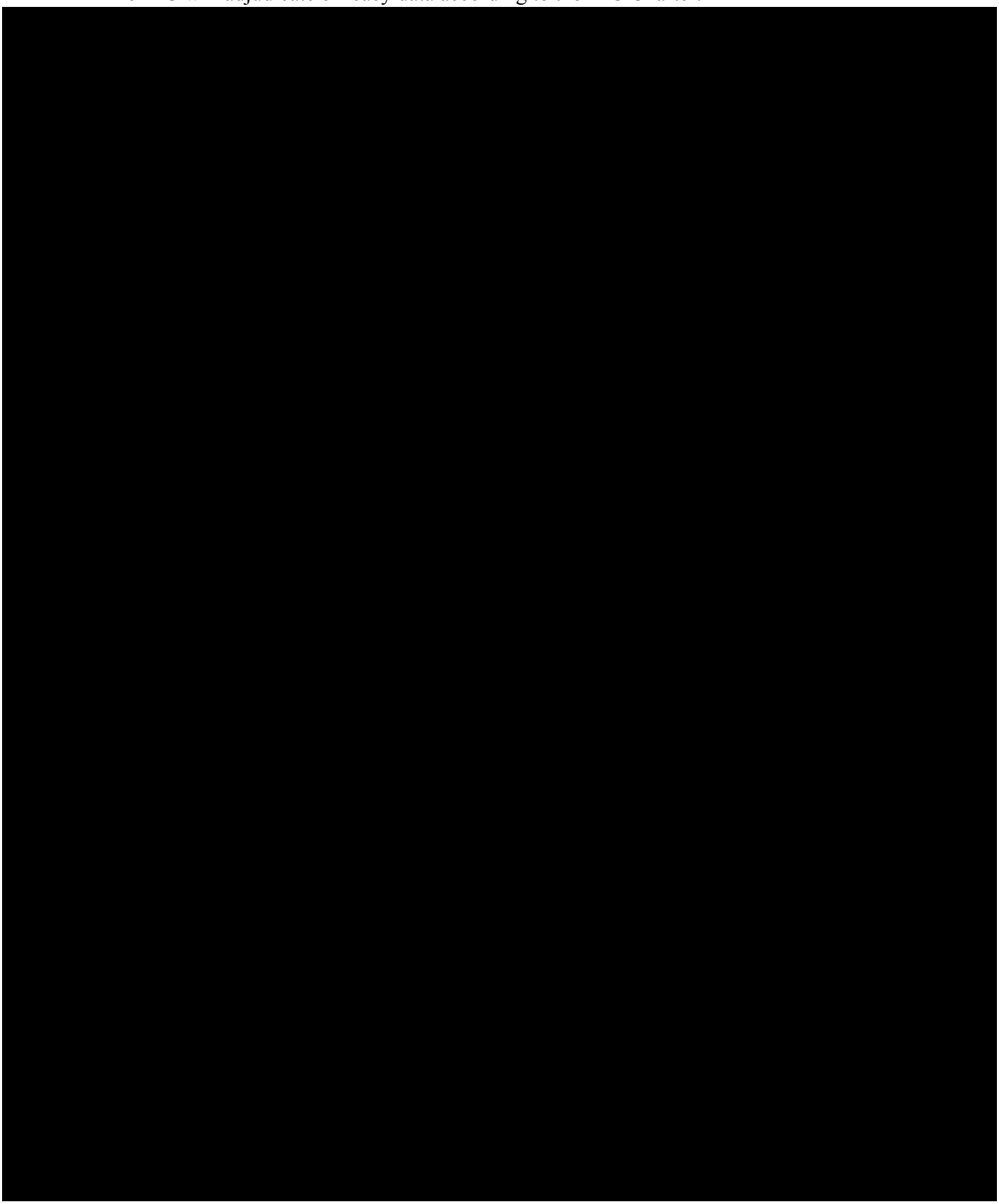
Response must be based on the central laboratory data to ensure consistency across investigative sites. For Cohorts J1 and K, central laboratory will be used for response assessment from Cycle 1 to Cycle 30 (Cohort J1), or from Cycle 1 to Cycle 26 (Cohort K) (ie, first ~2 years) and thereafter, local laboratory will be used for response assessment every 3 months until PD or until a subsequent myeloma regimen has been started. For Cohort J2, local laboratory will be used for response assessment every 3 months during the Post-Treatment Response Follow Up visits.

NOTE: IMWG Uniform Response Criteria requires 2 consecutive assessments for all response categories and progressive disease except for radiographic or bone marrow assessments.

6.3.5. Independent Response Committee (IRC) Assessment

Investigator response assessments will be used to determine the efficacy outcome throughout the study. An Independent Response Committee (IRC) may also be set up to review efficacy data from Part 2 RRMM Cohorts C, D, and/or I. The IRC will determine the tumor response to therapy based on the IMWG uniform Response Criteria as well as time of response (including PD) for each subject.

The IRC will adjudicate efficacy data according to the IRC Charter.



6.5. Pharmacokinetics

Cohorts A and B

All subjects will participate in sparse PK as a participant in the main study. Both intensive and sparse PK samples will be collected to evaluate CC-220, and as appropriate, its R-enantiomer CC-17195 in plasma. The pharmacologically active metabolite, M12, will also be quantified in an exploratory manner. At each timepoint, approximately 6 mL of blood will be collected.

Sparse PK Sampling

All subjects will have sparse PK samples collected.

Pharmacokinetic blood samples will be collected in subjects at the following time points:

- Cycles 1-4, Days 8, 15, 22: one pre-dose sample per visit.

Intensive PK Sampling

A subset of subjects will be selected to participate in the intensive PK assessment**. In addition to the sparse PK sampling**, frequent collection of PK blood samples will be performed in approximately 2 subjects per dose level (a total of 8 subjects at the minimum). Samples will be collected at the following time points:

- Cycle 1, Day 15: 1, 2, 3, 4, 6, 8 hours and 24 hours after administration of CC-220.
- The IRT will be used to monitor inclusion of a minimum of 2 intensive PK participants per dose group.

Cohorts C and D

All subjects will participate in sparse PK as a participant in the main study. Both intensive and sparse PK samples will be collected to evaluate the concentrations of CC-220 in plasma. At each time point, approximately 3 mL of blood will be collected.

Sparse PK Sampling

All subjects will have sparse PK samples collected.

Pharmacokinetic blood samples will be collected in subjects at the following time points:

- Cycles 1-4, Day 15: one pre-dose sample per visit.

Intensive PK Sampling

In addition to the sparse PK sampling, frequent collection of PK blood samples will be performed in approximately 10 subjects enrolled. Samples will be collected at the following 3 time points:

- Cycle 1, Day 15: 1 timepoint at 2 h, 1 timepoint between 4-8 h, and 1 timepoint at 24 hours after administration of CC-220.
- The IRT will be used to monitor inclusion of a minimum of 10 intensive PK participants

Cohorts E, F, G1, and G2

All subjects will participate in sparse PK as a participant in the main study. Both intensive and sparse PK samples will be collected to evaluate CC-220 in plasma. At each time point, approximately 3 mL of blood will be collected.

Sparse PK Sampling

All subjects will have sparse PK samples collected.

Pharmacokinetic blood samples will be collected in subjects at the following time points:

- Cycles 1-4, Days 8, 15: one pre-dose sample per visit.

Intensive PK Sampling

A subset of subjects will be selected to participate in the intensive PK assessment**. In addition to the sparse PK sampling**, frequent collection of PK blood samples will be performed in approximately 1 subject per dose level of each cohort. Samples will be collected at the following 3 time points:

- Cycle 1, Day 8: 1 timepoint at 2 h, 1 timepoint between 4-8 h, and 1 timepoint at 24 hours after administration of CC-220.
- The IRT will be used to monitor inclusion of the minimum required intensive PK participants per dose group.

Cohorts I and K

All subjects will participate in sparse PK as a participant in the main study. Only sparse PK samples will be collected to evaluate the concentrations of CC-220 in plasma. At each time point, approximately 3 mL of blood will be collected.

Sparse PK Sampling

All subjects will have sparse PK samples collected.

Pharmacokinetic blood samples will be collected in subjects at the following time points:

- Cycles 1-2, Day 15: 1 timepoint at pre-dose and 1 timepoint at 2 hours after administration of CC-220.

There is no intensive sampling in Cohorts I and K.

Cohorts J1 and J2

All subjects will participate in sparse PK as a participant in the main study. Only sparse PK samples will be collected to evaluate the concentrations of CC-220 in plasma. At each time point, approximately 3 mL of blood will be collected.

Sparse PK Sampling

Pharmacokinetic blood samples will be collected in subjects at the following time points:

- Cycles 1-2, Day 8: 1 timepoint at pre-dose and 1 timepoint at 2 hours after administration of CC-220.

There is no intensive sampling in Cohorts J1 and J2.

Pharmacokinetic samples should be collected within the following collection windows:

- -30 to -5 minutes for the pre-dose sample
- ± 10 minutes for the samples collected at time points of 1 to 4 hours
- ± 20 minutes for the samples collected at the time point of between 6 and 8 hours
- ± 5 hours for the sample collected at the time point of 24 hours (this sample must be collected prior to the second dose)

The CC-220 concentration in plasma will be determined. Specific details regarding the collection, processing, storage, and shipment of PK samples will be provided in a separate document.

On all PK visits, subjects must bring their CC-220 to the study center and CC-220 must be administered to subjects at the study center after the collection of the pre-dose PK blood sample. Subjects will be asked to report the date and time of their last CC-220 dose (prior to the current study visit day) to the study staff during their visit at the study center. Dosing and sample collection information including CC-220 dose level, dosing date, dosing time (24-hour clock), and actual PK blood sampling time (24-hour clock) should be accurately documented on the appropriate eCRF pages.

6.6. Biomarkers, Pharmacodynamics and Pharmacogenomics

The changes of each biomarker will be determined by comparing the levels of biomarkers in pre-treatment and post-treatment samples and, where possible, correlate these with PK findings and tumor response over time.

If Celgene determines, during the conduct of the study, that a Pd measurement is not reliable or informative, the sites will be notified, via an administrative letter, that this Pd sample should no longer be collected.

Full details of all statistical analyses and modeling for these outcomes will be described in the statistical analysis plan and final study report.

The following will be ***mandatory*** in dose escalation (Part 1) and ***not collected*** in expansion (Part 2)

- To evaluate the pharmacodynamic (Pd) effects of CC-220 on Aiolos and other Pd biomarkers (by protein expression) in peripheral blood cell components including mononuclear cells and secreted cytokines.

  Blood collection time points:

  – C1D1 – pre-dose, 3, 5 hours post dose

  – C1D12 – pre-dose, 3, 5 hours post dose. For Cohorts G1 and G2, this assessment will be performed on C1D15. Note, in all cohorts, the acceptable window for this assessment is C1D11 to C1D15.

- To explore TCR (T-cell receptor) clonality in peripheral blood.

  Blood collection time points:

  – C1D1– pre-dose
  – C2D15– pre-dose
  – C4D15– pre-dose
  – IP discontinuation (EOT)

- To explore Pd effects of CC-220 on T-cell counts in peripheral blood. This lymphocyte subset panel is obtained from existing hematology sampling; no additional sampling is required.

  Blood collection time points for all Cohorts **except** Cohorts F, G1 and G2:

  – Cycles 1 Days 1, 8, 12, 15, 22, 26– pre-dose
  – Cycles 2-4 Days 1, 8, 15, 22– pre-dose
  – Cycles 5+ Days 1, 15– pre-dose

  Blood collection timepoints for Cohort **F**:

  – Cycles 1 Days 1, 8, 12, 15– pre-dose when applicable
  – Cycles 2-4 Days 1, 8, 15– pre-dose when applicable
  – Cycles 5+ Days 1, 15– pre-dose when applicable

  Blood collection timepoints for Cohorts **G1 and G2**:

  – Cycles 1-4 Days 1, 8, 15– pre-dose
  – Cycles 5+ Days 1, 15– pre-dose

- *For Cohorts B, G1, and G2, up to 3 subjects in each dose level at select US sites may be selected for the following assessment:* To evaluate the pharmacodynamic (Pd) effects of CC-220 on Aiolos and Ikaros in mononuclear cells with a novel exploratory assay. The IRT will be used to monitor inclusion of these participants.

  Blood collection time points:

  – C1D1 – pre-dose, 3, 6 hours post dose
  – C1D2 – pre-dose
  – C1D15 – pre-dose, 3 hours post dose

- *For Cohort F, up to 3 subjects in each dose level at select US sites may be selected for the following assessment:* To evaluate the pharmacodynamic (Pd) effects of CC-220 on Aiolos and Ikaros in mononuclear cells with a novel exploratory assay. The IRT will be used to monitor inclusion of these participants.

  Blood collection time points:

  – C1D1 – pre-dose, 3, 6 hours post dose

– C1D2 – pre-dose

– C1D11 – pre-dose, 3 hours post dose

The following will be ***mandatory*** in dose escalation (Part 1) and ***mandatory*** in expansion (Part 2)

- To explore the pharmacodynamic (Pd) effects of CC-220 on T-Cell Activation in peripheral blood

  Blood collection time points:

  – C1D1 – pre-dose, 3, 5 hours post dose

  – C1D12 – pre-dose, 3, 5 hours post dose. For Cohorts C, D, G1, G2 and K this assessment will be performed on C1D15. For Cohorts J1 and J2, this assessment will be performed on C1D11. Note, in all cohorts, the acceptable window for this assessment is C1D11 to C1D15.

- To explore the Pd effects of CC-220 on immune cell populations in peripheral blood and association of baseline levels of these populations with response or resistance to CC-220

  Blood collection time points for Cohorts A, B, E, F, G1, and G2:

  – C1D1 – pre-dose

  – C2D1 – pre-dose

  – C2D15 – pre-dose

  – C4D1 – pre-dose

  – C4D15 – pre-dose

  – C6D15– pre-dose

  – At IP discontinuation (EOT)

  Blood collection time points for Cohorts C, D, I and K:

  – C1D1 – pre-dose

  – C2D1 – pre-dose

  – C2D15 – pre-dose

  – C6D15– pre-dose

  – EOT

  Blood collection time points for Cohort J1:

  – C1D1 – pre-dose

  – C4D8– pre-dose

  – C8D8– pre-dose

  – EOT

Blood collection time points for Cohort J2:

- C1D1 – pre-dose
- C4D8 – pre-dose
- EOT

- To explore pharmacogenomics of CC-220 response

  Blood collection time point:

  - C1D1 – pre-dose

- To explore the association of CC-220 response or resistance to baseline levels and Pd changes in protein expression, gene expression, cytogenetics, copy number abnormalities and/or mutations in tumor cells and tumor microenvironment in the bone marrow

  BMA/BMB collection time points (Please refer to Table 18 for details on BMA/BMB sample collection plan):

  - Screening BMA (and, if possible, BMB)
  - C2D15 – 3-6 hours post dose BMA (and, if possible, BMB). (C2D11 for Cohort F and Cohort J1)
  - Confirmatory BMA (and, if possible, BMB) for complete response (CR)
  - *Optional* BMA and/or BMB taken at any time requested by investigator during the study period
  - BMA (and, if possible, BMB) taken at the time of PD/treatment discontinuation or any time after PD and before the start of subsequent myeloma therapy

The following will be ***mandatory*** in expansion (Part 2) only.

- To explore the effects of CC-220 on minimal residual disease (MRD) negativity in subjects achieving a response of VGPR or better and who have not progressed.

  BMA collection time points (Please refer to Table 18 for details on BMA/BMB sample collection plan):

  - Screening
  - Confirmatory BMA (and, if possible, BMB) for complete response (CR)

- To evaluate the duration of MRD negativity and changes in MRD status in responding subjects, a BMA after achieving response of VGPR or better until disease progression. Please refer to Table 18 for details on timepoints.

- *Only applicable for approximately 20 subjects enrolled in Cohort D at select US sites:* To evaluate the pharmacodynamic (Pd) effects of CC-220 on Aiolos and Ikaros

in mononuclear cells with a novel exploratory assay. The IRT will be used to monitor inclusion of these participants.

Blood collection time points:

- C1D1 – pre-dose, 3, 6 hours post dose
- C1D2 – pre-dose
- C1D15 – pre-dose, 3 hours post dose

- *Only applicable for approximately 20 subjects enrolled in Cohort D at select US sites*: [redacted] The IRT will be used to monitor inclusion of these participants.

  Blood collection time points:

  - C1D1 – pre-dose
  - C2D1 – pre-dose
  - C2D15 – pre-dose

- *Only applicable for approximately 5 subjects enrolled in Cohort D at one pre-identified US site*: To evaluate time-matched concentration of CC-220 in peripheral blood and tumor microenvironment and assess the correlation between concentration, pharmacodynamic changes in tumor microenvironment, and outcome measures. The IRT will be used to monitor inclusion of these participants.

  BMA and blood collection timepoints:

  - Screening
  - C1D8 – 3-6 hours post dose
  - C2D15 – 3-6 hours post dose

- [redacted]

Full details of all statistical analyses for biomarkers will be described in a separate biomarker study report.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

CC-220

- CC-220 has a chemical name of 2,6-piperidinedione, 3-[1,3-dihydro-4-[[4-(4-morpholinylmethyl)phenyl]methoxy]-1-oxo-2H-isoindol-2-yl]-, (3S)-, hydrochloride (1:1). It has a molecular weight of 485.96.

  CC-220 will be supplied by Celgene Corporation in formulated capsules and will be labeled appropriately as investigational material.

Dexamethasone

- Subjects enrolled in countries where DEX is commercially available may obtain commercially available product through their local hospital pharmacy or licensed distributer.
- Celgene will provide DEX for countries where supplies are not commercially available, or not readily available, or not provided per regulation.
- Please refer to local prescribing information for more details on available formulations, preparation, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of dexamethasone (see current version of prescribing information). The DEX dosing schedule and dose adjustments to be followed for this study are described in Section 7.3.2.

Intravenous (IV) Daratumumab

- Subjects enrolled in countries where IV DARA is commercially available may obtain commercially available product through their local hospital pharmacy or licensed distributer.
- Celgene will provide IV DARA for countries where supplies are not commercially available, or not readily available, or not provided per regulation.
- Please refer to local prescribing information for more details on available formulations, preparation, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of IV DARA (see current version of prescribing information). The IV DARA dosing schedule and dose adjustments to be followed for this study are described in Section 7.3.3 and the Protocol Summary Table 3.

Subcutaneous (SC) Daratumumab

- Subjects enrolled in countries where SC DARA is commercially available may obtain commercially available product through their local hospital pharmacy or licensed distributer.
- Celgene will provide SC DARA for countries where supplies are not commercially available, or not readily available, or not provided per regulation.

- Please refer to local prescribing information for more details on available formulations, preparation, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of SC DARA (see current version of prescribing information). The SC DARA dosing schedule and dose adjustments to be followed for this study are described in Section 7.3.3 and the Protocol Summary Table 3.

Bortezomib

- Subjects enrolled in countries where BTZ is commercially available may obtain commercially available product through their local hospital pharmacy or licensed distributer.
- Celgene will provide BTZ for countries where supplies are not commercially available, or not readily available, or not provided per regulation.
- Please refer to local prescribing information for more details on available formulations, preparation, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of bortezomib (see current version of prescribing information). The bortezomib dosing schedule and dose adjustments to be followed for this study are described in Section 7.3.4 and the Protocol Summary Table 3.

Carfilzomib

- Subjects enrolled in countries where CFZ is commercially available may obtain commercially available product through their local hospital pharmacy or licensed distributer.
- Celgene will provide CFZ for countries where supplies are not commercially available, or not readily available, or not provided per regulation.
- Please refer to local prescribing information for more details on available formulations, preparation, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of carfilzomib (see current version of prescribing information). The carfilzomib dosing schedule and dose adjustments to be followed for this study are described in Section 7.3.5 and Protocol Summary Table 4.

7.2. Treatment Administration and Schedule

The first day of IP dosing (CC-220) is considered Day 1 of a cycle for all cohorts, including triplet regimen cohorts. Capsules of CC-220 will be taken by mouth (PO) with or without food.

7.2.1. Treatment Schedule

7.2.1.1. Part 1 (Dose Escalation)

Cohort A (MonoT)

Subjects who have been allocated to Cohort A will receive CC-220 monotherapy (MonoT).

- Oral CC-220 at dose specified by cohort dose level from Day 1-21 of each 28-day cycle.
- Subjects who have confirmed PD (by IMWG criteria) on MonoT may have DEX added to CC-220. The subject's dose of CC-220 will not be higher than the dose of CC-220 used in combination with DEX in Cohort B that has been determined to be safe. The site will be informed of the dose of CC-220 to which DEX will be added.

Cohort B (DoubleT)

Subjects who have been allocated to Cohort B will receive CC-220 in combination with DEX (DoubleT)

- Oral CC-220 at dose specified by cohort dose level from Day 1-21 of each 28-day cycle
- For subjects ≤ 75 years old, oral DEX 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle. For subjects >75 years old, DEX will be administered at 20 mg on Days 1, 8, 15, and 22 of each 28-day cycle. Subjects who surpass the age of 75 years while on treatment may be switched to the 20 mg dosage based on the investigator's best judgement.

Cohort E (CC-220Dd)

Subjects who have been allocated to Cohort E will receive CC-220 in combination with DARA and DEX

- Oral CC-220 at dose specified by cohort dose level from Day 1-21 of each 28-day cycle
- Intravenous (IV) DARA administered at a dose of 16 mg/kg for:
  - Cycles 1 and 2 on Days 1, 8,15, 22 of each 28-day cycle
  - Cycles 3 to 6 on Days 1, 15 of each 28-day cycle
  - Cycles ≥ 7 on Day 1 of each 28-day cycle
- For subjects ≤ 75 years old, oral DEX 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle. For subjects >75 years old, DEX will be administered at 20 mg on Days 1, 8, 15, and 22 of each 28-day cycle. Subjects who surpass the age of 75 years while on treatment may be switched to the 20 mg dose based on the investigator's judgement.

Once the MTD and/or RP2D is determined in Cohort E (CC-220Dd), subjects will be enrolled at this dose level using SC DARA.

- Oral CC-220 at the MTD/RP2D from Days 1-21 of each 28-day cycle
- SC DARA administered at a dose of 1800 mg over 3 to 5 minutes for:
  - Cycles 1 and 2 on Days 1, 8, 15 and 22 of a 28-day cycle
  - Cycles 3 to 6 on Days 1 and 15 of a 28-day cycle
  - Cycles ≥ 7 on Day 1 of a 28-day cycle

- For subjects ≤ 75 years old, oral DEX 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle. For subjects >75 years old, DEX will be administered at 20 mg on Days 1, 8, 15, and 22 of each 28-day cycle. Subjects who surpass the age of 75 years while on treatment may be switched to the 20 mg dose based on the investigator's judgement.

Cohort F (CC-220Vd)

Subjects who have been allocated to Cohort F will receive CC-220 in combination with BTZ and DEX

- Oral CC-220 at dose specified by cohort dose level from Day 1-14 of each 21-day cycle
- Subcutaneous (SC) BTZ administered at a starting dose of 1.3 mg/m^2:
  - Cycles 1 to 8 on Days 1, 4, 8, 11 of each 21-day cycle
  - Cycles ≥ 9 on Days 1, 8 of each 21-day cycle

  Bortezomib doses must be at least 72 hours apart.
- For subjects ≤ 75 years old, oral DEX 40 mg on Days 1, 8, and 15 of each 21-day cycle. For subjects >75 years old, DEX will be administered at 20 mg on Days 1, 8, and 15 of each 21-day cycle. Subjects who surpass the age of 75 years while on treatment may be switched to the 20-mg dose based on the investigator's judgement.

Cohort G1 (CC-220Kd)

Subjects who have been allocated to Cohort G1 will receive CC-220 in combination with once weekly CFZ and DEX

- Oral CC-220 at dose specified by cohort dose level from Day 1-21 of each 28-day cycle
- Intravenous (IV) CFZ administered at a starting dose of 20 mg/m^2 on C1D1; and at a dose specified by cohort dose level thereafter (refer to Table 4):
  - Days 1, 8, 15 of each 28-day cycle
- Oral DEX on Days 1, 8, 15, and 22 of each 28-day cycle
  - For subjects ≤ 75 years old, the DEX dose will be 40 mg. For subjects > 75 years old, the DEX dose will be 20 mg.
  - Administer DEX 30 minutes to 4 hours before CFZ.

Cohort G2 (CC-220Kd)

Subjects who have been allocated to Cohort G2 will receive CC-220 in combination with twice weekly CFZ and DEX

- Oral CC-220 at dose specified by cohort dose level from Day 1-21 of each 28-day cycle
- Intravenous (IV) CFZ administered at a starting dose of 20 mg/m^2 on C1D1; and at a dose level specified by cohort dose level thereafter (refer to Table 4):

- Days 1, 2, 8, 9, 15, 16 of each 28-day cycle

- Oral DEX on Days 1, 2, 8, 9, 15, 16, 22, 23 of each 28-day cycle
  - The DEX dose will be 20 mg.
  - Administer DEX 30 minutes to 4 hours before CFZ

7.2.1.2. Part 2 (Expansion)

Cohort C (MonoT)

Subjects who have been allocated to Cohort C will receive CC-220 monotherapy (MonoT).

- Oral CC-220 at RP2D from Day 1-21 of each 28-day cycle
- Subjects who have confirmed PD (by IMWG criteria) on MonoT may have DEX added to their current dose of CC-220. The subject's dose of CC-220 will not be higher than the dose used in Cohort B that has been determined to be safe. If MTD has been reached in Cohort B, the RP2D of CC-220 will be used when DEX is added.

Cohort D (DoubleT)

Subjects who have been allocated to Cohort D will receive CC-220 in combination with DEX

- Oral CC-220 at RP2D from Day 1-21 of each 28-day cycle
- Oral DEX 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle. For subjects > 75 years old, DEX will be administered at 20 mg on Days 1, 8, 15, and 22 of each 28-day cycle. Subjects who surpass the age of 75 years while on treatment may be switched to the 20 mg dosage based on the Investigator's best judgement.

Cohort I (DoubleT in prior BCMA Targeted Therapy)

Subjects who have been enrolled to Cohort I will receive CC-220 in combination with DEX

- Oral CC-220 at RP2D from Day 1-21 of each 28-day cycle
- Oral DEX 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle. For subjects > 75 years old, DEX will be administered at 20 mg on Days 1, 8, 15, and 22 of each 28-day cycle. Subjects who surpass the age of 75 years while on treatment may be switched to the 20 mg dosage based on the Investigator's best judgement.

Cohort J1 (CC-220Vd in NDMM)

Subjects who have been enrolled to Cohort J1 will receive CC-220 in combination with BTZ and DEX.

- Oral CC-220 at 1.0 mg, 1.3 mg or 1.6 mg as follows:
  - Cycles 1 to 8 on Days 1-14 of each 21-day cycle
  - Cycles $\geq$ 9 on Days 1-21 of each 28-day cycle
- Subcutaneous (SC) BTZ administered at a starting dose of 1.3 mg/m^2:
  - Cycles 1 to 8 on Days 1, 4, 8, 11 of each 21-day cycle. Bortezomib doses must be at least 72 hours apart

- Oral DEX administered as follows:
  - Cycles 1 to 8, 20 mg (≤ 75 years old) or 10 mg (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of each 21-day cycle
  - Cycles ≥ 9, 40 mg (≤ 75 years old) or 20 mg (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle

Cohort J2 (CC-220Vd in NDMM)

Subjects who have been enrolled to Cohort J2 will receive CC-220 in combination with BTZ and DEX as induction treatment for up to 6 cycles.

- Oral CC-220 at RP2D from Day 1-14 of each 21-day cycle
- Subcutaneous (SC) BTZ administered at a starting dose of 1.3 mg/m^2:
  - Cycles 1 to 6 on Days 1, 4, 8, 11 of each 21-day cycle. Bortezomib doses must be at least 72 hours apart.
- Oral DEX dosed at 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) for:
  - Cycles 1 to 6 on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle
- Mobilization of hematopoietic stem cells as per Institutional's standard practice and subsequent apheresis
- After 4 to 6 cycles of induction, subjects may undergo ASCT as per Institutional's standard of practice
- Maintenance regimen or observation as per Institutional's standard practice until PD or a subsequent anti-myeloma regimen has been started

Cohort K (CC-220Dd)

Subjects who have been allocated to Cohort K will receive CC-220 in combination with DARA and DEX

- Oral CC-220 at 1.0 mg, 1.3 mg or 1.6 mg from Days 1-21 of each 28-day cycle
- SC DARA administered at a dose of 1800 mg over 3 to 5 minutes for:
  - Cycles 1 and 2 on Days 1, 8, 15 and 22 of a 28-day cycle
  - Cycles 3 to 6 on Days 1 and 15 of a 28-day cycle
  - Cycles ≥ 7 on Day 1 of a 28-day cycle
- For subjects ≤ 75 years old, oral DEX 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle. For subjects >75 years old, DEX will be administered at 20 mg on Days 1, 8, 15, and 22 of each 28-day cycle. Subjects who surpass the age of 75 years while on treatment may be switched to the 20 mg dose based on the investigator's judgement.

7.2.2. Dexamethasone

Refer to the full prescribing information and labeling for DEX contained in the respective current prescribing information, SmPC, or equivalent document for the specific region/country.

7.2.3. Daratumumab

Refer to the full prescribing information and labeling for DARA contained in the respective current PI, SmPC, or equivalent document for the specific region/country. It should be noted that DARA interferes with blood group compatibility testing and cross matching for up to 6 months after the last DARA administration (due to drug-mediated positive indirect antiglobulin test).

Guidance on pre- and post-administration medications for injection reaction prophylaxis in relation to DARA dosing is given in Table 19 and can be used in conjunction with the site's standard of care for DARA administrations. Investigators should refer to the current DARA PI or SmPC for guidelines on the management of infusion or injection-related reactions (Darzalex PI; Darzalex Faspro PI; Darzalex SmPC).

Table 19: Daratumumab Pre- and Post-administration Medications

Time point	Medication	Subjects NOT Receiving DEX As Part Of Study Regimen	Subjects Receiving DEX As Part Of Study Regimen
Pre-administration (~1 hr prior to every DARA administration)	oral montelukast (if approved and available)	per Investigator discretion prior to first administration	per Investigator discretion prior to first administration
	IV corticosteroid	methylprednisolone 100 mg or equivalent dose of an intermediate-acting or long-acting corticosteroid (refer to Table 20 for conversion table). Following the second administration, the dose of corticosteroid may be reduced (methylprednisolone 60 mg intravenously)	not applicable[a]
	oral antipyretics	acetaminophen 650 to 1000 mg[b]	acetaminophen 650 to 1000 mg
	oral or IV antihistamine	diphenhydramine 25 to 50 mg or equivalent[b]	diphenhydramine 25 to 50 mg or equivalent
Post-administration medication (1st and 2nd day after every DARA administration)	oral corticosteroid[c]	20 mg methylprednisolone or equivalent dose of a corticosteroid in accordance with local standards	Not applicable[a, d]

DARA = daratumumab; DEX = dexamethasone; IV = intravenous.
[a] Not applicable since dexamethasone is already given as part of the study treatment, see Section 7.2.1.

[b] If necessary, oral pre-administration medications may be administered at the subject's home on the day of administration, provided they are given within 3 hours prior to the administration.
[c] For subjects with a history of obstructive pulmonary disorder, consider prescribing post-administration medications such as short and long-acting bronchodilators, and inhaled corticosteroids. Following the first four administrations, if the subject experiences no major infusion or injection reactions, these additional inhaled post-administration medications may be discontinued.
[d] For subjects receiving dexamethasone ≤ 20 mg/week (> 75 years or with DEX dose reduced) and given as pre-administration medication, may receive low-dose methylprednisolone (≤ 20 mg) orally (or equivalent in accordance with local standards) for the prevention of delayed infusion or injection-related reactions, as clinically indicated.

Table 20: Conversion Table for Glucocorticoid Dose

Medication	Oral or Intravenous Dose (mg)
Dexamethasone	0.75
Hydrocortisone	20
Methylprednisolone	4
Prednisolone	5
Prednisone	5

7.2.3.1. Subcutaneous Daratumumab

Subcutaneous DARA will be provided as a fixed-dose of 1800 mg DARA and 30,000 units hyaluronidase per 15 mL (120 mg and 2000 units/mL).

Daratumumab (1800 mg) will be administered via SC injection by manual push over 3 to 5 minutes in the abdominal subcutaneous tissues in left/right locations, alternating between individual doses. All subjects will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the Investigator, after subsequent injections. Reasons for continued observation on subsequent DARA injections may include but are not limited to the following: subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 < 80% at screening or developed FEV1 < 80% during the study without any medical history), subjects with IRRs with first injection of study drug, or subjects with a decreased condition on day of dosing compared to the prior dosing day.

For further details regarding storage, preparation and administration, please refer to the current approved prescribing information and labeling.

7.2.3.1.1. Management of Injection-site and Injection-related Reactions

7.2.3.1.1.1. Injection-related Reactions

If an IRR develops, then DARA administration should be temporarily interrupted. Subjects who experience AEs during DARA administration must be treated for their symptoms. Subjects should be treated with acetaminophen (paracetamol), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may

require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, DARA should be discontinued.

7.2.3.1.1.2. Injection-related Reactions of Grade 1 or Grade 2

If the Investigator assesses a Grade 1 or 2 IRR AE to be related to administration of study drug, then the DARA administration should be paused. When the subject's condition is stable, DARA administration may be restarted at the Investigator's discretion.

If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be permanently discontinued from DARA treatment.

7.2.3.1.1.3. Injection-related Reactions of Grade 3 or Higher

For IRR AEs (other than laryngeal edema or bronchospasm) that are Grade 3, the DARA administration must be stopped, and the subject must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the DARA administration may be restarted at the Investigator’s discretion.

If the intensity of the AE returns to Grade 3 after restart of the DARA administration, then the subject must be permanently discontinued from DARA treatment.

For IRR AEs that are Grade 4, the DARA administration must be stopped and the subject permanently discontinued from DARA treatment.

7.2.3.1.1.4. Recurrent Injection-related Reactions

If a Grade 3 IRR (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent DARA administration, the subject must be permanently discontinued from all DARA treatments.

7.2.4. Carfilzomib

Refer to the full prescribing information and labeling for CFZ contained in the respective current PI, SmPC, or equivalent document for the specific region/country.

Guidance on pre-infusion and post-infusion medications for infusion reaction prophylaxis in relation to CFZ dosing is provided and can be used in conjunction with the site’s standard of care for CFZ infusions:

- At least 48 hours before C1D1, oral hydration to be given as follows: 30 mL/kg/day (approximately 6 to 8 cups of liquid per day) continuing up to the time of treatment. Oral hydration may be continued in Cycle 2 and beyond as per Investigator’s discretion.
- Intravenous hydration with 250 to 500 mL of normal saline or other appropriate IV fluid to be given immediately prior to CFZ during Cycle 1 and at the Investigator’s discretion in Cycle 2 and onwards.
- Carfilzomib to be given as an IV infusion over approximately 30 minutes. Subjects to remain at the site under observation for at least 1 hour following each dose of CFZ in

Cycle 1. Post dose IV hydration (between 250 to 500 mL normal saline or other appropriate IV fluid) as needed may be given. It is recommended to use no more than 750 mL IV fluids as a combination of pre- and post-dose hydration. Subjects to be monitored periodically during this period for evidence of fluid overload.

7.3. Dose Reduction and Interruption

Dosing interruptions and reductions are permitted throughout the study. Subjects will be evaluated for adverse events at each visit with the NCI CTCAE (version 4.0) used as a guide for the grading of severity. Dosing is to be modified in subjects who experience a DLT as described in Section 3.1.1.2.

In the event of any CC-220 dose reduction for a subject, the site staff must contact the IRT to record the new dose level and obtain the new IP assignment.

Dose delays for CC-220 of more than 28 days for any reason should be discussed with the Medical Monitor.

Cohorts B, D, and I (DoubleT)

- If CC-220 dosing is withheld, then DEX dosing must also be withheld.
- If CC-220 is permanently discontinued, then the subject must be permanently discontinued from all study medications.
- If DEX is withheld or permanently discontinued, CC-220 may be continued

Cohorts E and K (CC-220Dd)

- If DARA dosing is withheld or permanently discontinued, then CC-220 and DEX dosing may still be continued
- If CC-220 dosing is withheld during a cycle, then DARA and DEX dosing may still be continued at the discretion of the treating physician.
- If CC-220 dosing is permanently discontinued, then the subject must be permanently discontinued from all study medications.
- If DEX dosing is withheld or permanently discontinued, then CC-220 and DARA dosing may still be continued.
- If DARA and DEX dosing is withheld or permanently discontinued, then CC-220 dosing may still be continued.
- If CC-220 and DEX dosing is withheld during a cycle, then DARA dosing may still be continued.
- If CC-220 and DEX dosing is permanently discontinued, then the subject must be permanently discontinued from all study medications.
- If CC-220 and DARA dosing is withheld, then DEX must also be withheld.

Cohorts F, J1, and J2 (CC-220Vd)

- If BTZ dosing is withheld or permanently discontinued, then CC-220 and DEX dosing may still be continued
- If CC-220 dosing is withheld during a cycle, then BTZ and DEX dosing may still be continued at the discretion of the treating physician.
- If CC-220 dosing is permanently discontinued, then the subject must be permanently discontinued from all study medications.
- If DEX dosing is withheld or permanently discontinued, then CC-220 and BTZ dosing may still be continued.
- If BTZ and DEX dosing is withheld or permanently discontinued, then CC-220 dosing may still be continued.
- If CC-220 and DEX dosing is withheld during a cycle, then BTZ dosing may still be continued.
- If CC-220 and DEX dosing is permanently discontinued, then the subject must be permanently discontinued from all study medications.
- If CC-220 and BTZ dosing is withheld, then DEX must also be withheld.

Cohorts G1 and G2 (CC-220Kd)

- If CFZ dosing is withheld or permanently discontinued, then CC-220 and DEX dosing may still be continued
- If CC-220 dosing is withheld during a cycle, then CFZ and DEX dosing may still be continued at the discretion of the treating physician.
- If CC-220 dosing is permanently discontinued, then the subject must be permanently discontinued from all study medications.
- If DEX dosing is withheld or permanently discontinued, then CC-220 and CFZ dosing may still be continued.
- If CFZ and DEX dosing is withheld or permanently discontinued, then CC-220 dosing may still be continued.
- If CC-220 and DEX dosing is withheld during a cycle, then CFZ dosing may still be continued.
- If CC-220 and DEX dosing is permanently discontinued, then the subject must be permanently discontinued from all study medications.
- If CC-220 and CFZ dosing is withheld, then DEX must also be withheld.

7.3.1. Dose Modification Instructions for CC-220

Instructions for CC-220 dose interruptions and reductions are provided in Table 21 and Table 22, which outlines the dose reduction steps for CC-220.

Table 21: Dose Modification Instructions for CC-220

Toxicity	Dose Modification
Hematologic Toxicity	
Neutropenia Grade 4 neutropenia (ANC < 500/μL) or Febrile neutropenia (fever ≥ 38.5°C and ANC < 1,000/μL)	Stop the dose for the remainder of the CC-220 treatment cycle If the subject was not receiving GCSF therapy for given cycle (not permitted during Cycle 1 for Cohorts A and B only), initiate GCSF therapy On Day 1 of the next cycle, the dose of CC-220 may be maintained if neutropenia was the only CC-220-related toxicity requiring a dose modification and GCSF treatments are continued. ANC must return to ≥1,000/μL to resume dosing.
Grade 4 thrombocytopenia (platelet count <25,000/μL) or Grade 3 thrombocytopenia with bleeding or any requirement for a platelet transfusion	Stop the dose for the remainder of the CC-220 treatment cycle Decrease by one dose level when restarting treatment when platelet count returns to ≥50,000/μL
Non-Hematologic Toxicity	
Rash = Grade 3	Withhold dose of CC-220 for remainder of cycle. Decrease by one dose level CC-220 when treatment is restarted (rash must be resolved or improved to ≤Grade 1 before dose resumption).
Rash = Grade 4 or Blistering	Permanently discontinue IP.
Thrombosis/embolism ≥Grade 3	Stop the dose of CC-220 for remainder of cycle Anticoagulation therapy should be adapted based on the clinical and investigational results. Decrease by one dose level of CC-220 when restarting treatment
Peripheral neuropathy = Grade 3	Stop the dose of CC-220 for remainder of cycle Decrease CC-220 by one dose level when restarting treatment (neuropathy must resolve to ≤Grade 1)
Peripheral neuropathy = Grade 4	Discontinue the subject from IP
Non-Hematologic Toxicity	
Other ≥ Grade 3 CC-220-related adverse events[a, b]	Withhold dose for remainder of cycle. Decrease by one dose level when dosing resumed at next cycle (adverse event must be resolved or improved to ≤Grade 2 before restarting dosing).

ANC = absolute neutrophil count; GCSF = granulocyte colony-stimulating factor; IP = investigational product.
[a] For Grade 3 or 4 AEs that are not considered to be related to CC-220, the Investigator should consult with the Celgene Medical Monitor for dose interruptions and reductions.
[b] Not applicable to Second Primary Malignancies (SPMs) where dosing modification is at the discretion of the Investigator and in consideration of any SPM-related procedures/therapy.

To initiate a new cycle of CC-220, the absolute neutrophil count must be ≥ 1,000 μL/mL with or without granulocyte colony-stimulating factor (G-CSF) (not permitted during Cycle 1 for Cohort

A and B only), the platelet count must be ≥ 50,000/μL, and non-hematologic AEs must be resolved or improved as outlined in Table 21.

If recovery from toxicities is prolonged and CC-220 dose withholding is beyond 14 days, then the dose of CC-220 should be decreased by one dose level when dosing is resumed in the new cycle.

Dose delays of more than 28 days for any reason should be discussed with the Medical Monitor.

Dose level reductions will follow the dose levels in Part 1. No dose re-escalation is permitted for CC-220.

Table 22: Dose Level Reduction (DLR) for CC-220

Starting Dose Level	**Part 1**		
	DLR-1	**DLR-2**	**DLR-3**
0.3 mg	0.15 mg	--	--
0.45 mg	0.3 mg	0.15 mg	--
0.6 mg	0.45 mg	0.3 mg	0.15 mg
0.75 mg	0.6 mg	0.45 mg	0.3 mg
0.9 mg	0.75 mg	0.6 mg	0.45 mg
1 mg	0.9 mg	0.75 mg	0.6 mg
Subsequent dose levels	Reductions will be made in one dose level decreases		
	Part 2		
1.6 mg	1.3 mg	1.0 mg	0.75 mg
1.3 mg	1.0 mg	0.75 mg	-
1.0 mg	0.75 mg	-	-

Treatment with CC-220 should be discontinued if the subject is unable to tolerate 0.15 mg dose. Treatment with CC-220 may continue if DEX is discontinued. The Celgene Medical Monitor should be contacted in cases where subjects require more than 3 dose level reductions.

7.3.2. Dose Modification Instructions for Dexamethasone

Table 23 details instructions for DEX dose interruptions and reductions and Table 24 outlines the dose reduction steps for DEX; however, dose withholding/resumption decision is at the treating physician's discretion per the full prescribing information and labeling in the respective current US prescribing information, EU SmPC, or equivalent document for the specific region/country.

Table 23: Dose Modification for Dexamethasone-related Toxicities

Toxicity	Dexamethasone Dose Reduction
Dyspepsia = Grade 1-2	Maintain dose and treat with histamine blockers (H2) or equivalent. Decrease by one dose level if symptoms persist.
Dyspepsia ≥ Grade 3	Withhold dose until symptoms are controlled. Add H2 blocker or equivalent and decrease one dose level when dosing is resumed.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Withhold dose until symptoms resolve. When dosing is resumed, decrease dose by one dose level.
Muscle weakness (steroid myopathy) ≥ Grade 2	Withhold dose until muscle weakness ≤ Grade 1. When dosing is resumed, decrease dose by one dose level.
Hyperglycemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycemic agents as needed.
Acute pancreatitis	Discontinue dexamethasone from treatment regimen.
Other ≥ Grade 3 dexamethasone-related adverse events	Stop dexamethasone dosing until the adverse event resolves to ≤ Grade 2. Decrease by one dose level when dosing is resumed.

If recovery from toxicities is prolonged and DEX dosing withholding is beyond 14 days, then the dose of DEX will be decreased by one dose level when dosing is resumed in the new cycle.

Table 24: Dose Level Reduction for Dexamethasone

Starting Dose Level	40 mg	20 mg	10 mg
Dose Level Reduction -1	20 mg	12 mg	6 mg
Dose Level Reduction -2	10 mg	8 mg	4 mg

Dexamethasone should be discontinued if the subject is unable to tolerate 10 mg if ≤ 75 years old or 8 mg if > 75 years old unless subject's starting dose level is 10 mg. Dexamethasone is to be discontinued if CC-220 is discontinued.

No dose re-escalation of DEX is permitted.

7.3.3. Dose Modification Instructions for Daratumumab

For dose modification instructions for DARA, refer to the full prescribing information.

The criteria for a dose delay are:

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia;
- Grade 3 or higher thrombocytopenia with bleeding;
- Grade 3 or 4 febrile neutropenia;
- Grade 3 or 4 neutropenia with infection;
- Grade 3 or 4 non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment,

- Grade 3 diarrhea that responds to antidiarrheal treatment,
- Grade 3 fatigue or asthenia that lasts for < 7 days after the last administration of DARA.

DARA treatment should be resumed when the toxicity has resolved to ≤ Grade 2, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered. If DARA administration does not commence within the pre-specified window (Table 10, and Table 17) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated. Primary antiviral prophylaxis is permitted as per local standard of care.

Table 25: Daratumumab-related Toxicity Management

Cycles	Dosing Frequency	Missed Dose	Dosing Resumption
1 and 2	Weekly (Days 1, 8, 15, 22)	> 3 days	Next planned weekly dosing date
3 to 6	Biweekly (Days 1, 15)	> 7 days	Next planned biweekly dosing date
≥7	Every 4 weeks (Day 1)	> 14 days	Next planned every 4-week dosing date

Any dose held for more than 28 days due to toxicity may result in permanent discontinuation of DARA unless continuation is approved by the medical monitor. Dose delays of more than 28 days for any reason should be discussed with the Medical Monitor.

7.3.3.1. Daratumumab Interruption or Missed Doses

Dose delay of 3 days or more from the planned date of administration for any reason other than toxicities suspected to be related to DARA should be brought to the attention of the Medical Monitor at the earliest possible time.

The Celgene Medical Monitor should be informed of any subjects missing ≥ 3 consecutive planned doses of DARA for reasons other than toxicity. In Cycle 1, for subjects being evaluated for DLTs in Cohort E (IV DARA), subject cannot miss any more than 1 dose of DARA for reasons other than drug-related AE to be considered DLT evaluable.

7.3.4. Dose Modification Instructions for Bortezomib

Table 26 details instructions for BTZ dose interruptions and reductions and Table 27 outlines the dose reduction levels for BTZ; however, dose modification decisions for BTZ will be at the treating physician's discretion per the full prescribing information and labeling in the respective current US Prescribing Information, EU SmPC, or equivalent document for the specific region/country.

Table 26: Bortezomib Dose Modification

Toxicity	Bortezomib Dose Modification
≥ Grade 3 non-hematological toxicity (excluding neuropathy)	Withhold bortezomib until the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at reduced bortezomib dosing by 1 dose level
Grade 4 hematological toxicity	Withhold bortezomib until the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at reduced bortezomib dosing by 1 dose level
Grade 1 neuropathy without pain or loss of function	No action
Grade 1 neuropathy with pain or Grade 2 neuropathy	Reduce bortezomib dosing by one level
Grade 2 neuropathy with pain or Grade 3 neuropathy	Withhold bortezomib until toxicity resolves, bortezomib therapy may be reinitiated at a reduced dose level of 0.7 mg/m^2 and change treatment schedule to once per week (Days 1 and 8 of a 21-day cycle)
Grade 4 neuropathy	Permanently discontinue study treatment

Table 27: Dose Level Reductions for Bortezomib

Starting Dose Level	Bortezomib Dose Level[a] (Cycle 1-8: Days 1, 4, 8, 11 of a 21-day cycle Cycle ≥ 9: Days 1, 8 of a 21-day cycle)
Starting Dose	1.3 mg/m^2
Dose Level -1 (25% reduction from starting dose)	1 mg/m^2
Dose Level -2 (25% reduction from dose level -1)	0.7 mg/m^2

[a] Cycle ≥ 9 only applicable for Cohort F.

The minimum permitted dose level for bortezomib is 0.7 mg/m^2. No dose re-escalation is permitted for bortezomib.

7.3.5. Dose Modification Instructions for Carfilzomib

Table 28 details instructions for CFZ dose interruptions and reductions.

Table 29 outlines the dose reduction levels for CFZ; however, dose modification decisions for CFZ will be at the treating physician's discretion per the full prescribing information and labeling in the respective current PI, SmPC, or equivalent document for the specific region/country.

Table 28: Carfilzomib Dose Modifications

Toxicity	Carfilzomib Dose Modification
Hematologic Toxicity	
Neutropenia Grade 4 Neutropenia (ANC < 500/μL)	Withhold the carfilzomib dose. Continue at the same dose level if the ANC recovers to ≥ 500/μL. For subsequent ANC levels < 500/μL, follow the same as above and consider reducing the dose by 1 dose level when restarting carfilzomib.
Febrile neutropenia (Fever > 38.5°C or 2 consecutive readings > 38°C for 2 hours and ANC < 500/μL)	Withhold the carfilzomib dose. Continue at the same dose level if the ANC recovers to baseline and the fever resolves.
Thrombocytopenia If platelet count < 10,000/μL or evidence of bleeding with thrombocytopenia	Withhold the carfilzomib dose. Continue at same dose level if platelets recover to ≥ 10,000/μL and/or bleeding is controlled. For subsequent platelet levels < 10,000/μL, withhold dose and consider reducing dose by 1 dose level when restarting carfilzomib.
Non-Hematologic Toxicity	
Renal Toxicity Serum creatinine ≥ 2x baseline or CrCl < 15 mL/min or CrCl ≤ 50% of baseline or need for hemodialysis	Withhold the carfilzomib dose and continue monitoring renal function (serum creatinine or creatinine clearance). If attributable to carfilzomib, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction. If not attributable to carfilzomib, dosing may be resumed at the discretion of the investigator. For subjects on hemodialysis receiving carfilzomib, the dose is to be administered after the hemodialysis procedure.

Table 28: Carfilzomib Dose Modifications (Continued)

Toxicity	Carfilzomib Dose Modification
Hepatic Dysfunction and Related Investigations Mild to moderate liver dysfunction defined as 2 consecutive values, at least 28 days apart, of: 1) total bilirubin (> 33% direct) > 1x ULN to < 3x ULN OR 2) an elevation of AST and/or ALT with normal bilirubin	25% dose reduction. Dose may be re-escalated if liver function tests return to normal and drug-induced hepatotoxicity is excluded.
Grade 3 elevation in ALT and/or AST (> 5xULN)	Hold carfilzomib until resolution to baseline. Monitor any abnormality weekly. Resume carfilzomib with a 25% dose reduction if drug-induced hepatotoxicity is excluded.
Grade 3 elevation in total bilirubin	Hold carfilzomib until resolution to baseline. Monitor total bilirubin and direct bilirubin weekly. Upon resolution of total bilirubin to normal, resume carfilzomib dosing with a 25% dose reduction if drug induced hepatotoxicity is excluded.
Drug-induced hepatotoxicity (attributable to carfilzomib)	Discontinue carfilzomib
Any other drug-related non-hematologic toxicity ≥ Grade 3	Withhold the carfilzomib dose until resolved or returned to baseline. Consider restarting at 1 dose level reduction. **Please refer to full prescribing information and labeling in the respective current PI, SmPC, or equivalent document for the specific region/country.**

Abbreviations: ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; PI = prescribing information; SmPC = summary of product characteristics; ULN = upper limit of normal.

For any dose held for more than 28 days due to toxicity, subjects may be required to permanently discontinue CFZ unless continuation is approved by the medical monitor. Dose delays of more than 28 days for any reason should be discussed with the Medical Monitor.

Table 29: Dose Level Reductions for Carfilzomib

Starting Dose Level	Carfilzomib Dose Level	Carfilzomib Dose Level	Carfilzomib Dose Level
Starting Dose	70 mg/m^2	56 mg/m^2	27 mg/m^2
Dose Level -1	56 mg/m^2	45 mg/m^2	20 mg/m^2

Table 29: Dose Level Reductions for Carfilzomib (Continued)

Starting Dose Level	Carfilzomib Dose Level	Carfilzomib Dose Level	Carfilzomib Dose Level
Dose Level -2	45 mg/m^2	36 mg/m^2	15 mg/m^2 [a]
Dose Level -3	36 mg/m^2 [a]	27 mg/m^2 [a]	-

Note: infusion times remain unchanged during dose reduction(s).
[a] If toxicity persists, carfilzomib therapy should be discontinued.

7.4. Overdose

Overdose, as defined for this protocol, refers to CC-220 (oral), DEX (oral), DARA (IV and SC), BTZ (SC), and CFZ (IV) dosing.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of CC-220, DEX, DARA, BTZ, or CFZ assigned to a given subject, regardless of any associated adverse events or sequelae.

- For CC-220 and DEX (oral), any amount over the protocol-specified dose
- For DARA (IV and SC) and CFZ (IV), 10% over the protocol-specified dose
- For BTZ (SC), 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as any amount more frequent than the protocol-required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the electronic case report form (eCRF). See Section 10.1 for the immediate reporting of adverse events associated with overdose.

7.4.1. CC-220 Overdose

There is no information available about the appropriate dose of CC-220 in humans nor is there any available information regarding overdose. There is no experience in the management of human CC-220 overdose. In the event of overdose, subjects should be managed by symptomatic and supportive care. Please refer to the IB for full information.

7.5. Method of Treatment Assignment

Subjects will be allocated via IRT to an appropriate cohort based on eligibility status and on cohort availability. Slots will be assigned for Part 1 cohorts. Sites will have up to 2 weeks to identify a subject, obtain informed consent and begin the screening process. If no subject is identified within 2 weeks from the time of slot assignment, the site must contact the Medical Monitor or designee, or the slot may be reassigned.

The Celgene Medical Monitor or designee will review specific eligibility criteria for all screened subjects prior to allocation via IRT.

An IRT system will be used to track subject assignments to the cohorts and dose levels as well as subjects who are assigned to participate in the intensive PK and/or Pd sample collection.

Once MTD and/or RP2D has been reached in Cohort A, Cohort B, Cohort E, or Cohort F in Part 1, IRT allocations may continue to the expansion phases of the study in that cohort even if the MTD and/or RP2D has not yet been achieved in the other cohorts of Part 1.

Enrollment of NDMM subjects in Cohort J1 at the 1.6 mg dose level will start according to Protocol Amendment No. 9. Upon approval of Protocol Amendment No. 10, subjects will be allocated evenly into all open J1 and K dose level cohorts. Subjects will be allocated to each dose level based on a fixed sequence via the IRT.

7.6. Packaging and Labeling

The label(s) for Celgene-supplied IP may include but is not limited to Sponsor name, address and telephone number, the protocol number, name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the approved drug label as applicable per local regulations.

7.7. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.8. Investigational Product Compliance

Accurate recording of all IP administration (CC-220, DEX, DARA, BTZ, and CFZ) will be made in the appropriate section of the subject's eCRF and source documents. The Investigator or designee is responsible for accounting for all study-specific treatment either administered or in their custody during the course of the study.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from IPs or disease progression. Antibiotics (including those for prophylactic use) may be administered at the discretion of the Investigator. Other supportive care, including but not limited to analgesics, antihistamines, and/or antiemetic medications, may be administered at the discretion of the Investigator.

All concomitant treatments, including blood and blood products, used from 28 days prior to first dose of IP until 28 days after the last dose of IP must be reported on the eCRF.

Subjects must check with study personnel before initiating the use of prescribed or over-the-counter medications during the study. Medication doses and treatment regimens should remain generally stable throughout the course of the study.

In the event a subject requires a surgical or invasive procedure during the course of the study, the Celgene Medical Monitor or designee must be contacted to discuss whether or not the subject is eligible to continue.

For information regarding other drugs that may interact with CC-220 and DEX and affect its metabolism, pharmacokinetics, or excretion, please see the IB and/or local prescribing information.

8.1. Permitted Concomitant Medications and Procedures

Subjects with myeloma-associated bone disease may receive bisphosphonate therapy prior to study entry. The use of bisphosphonates is permitted throughout the study.

Platelet/RBC transfusions and hematopoietic growth factors are also permitted during the study. Granulocyte colony-stimulating factor (GCSF) and similar hematopoietic growth factors are encouraged to prevent neutropenia and to support neutrophil recovery. However, prophylactic use of platelet transfusions or GCSF to prevent a potential DLT during Cycle 1 should be avoided in Cohorts A and B unless deemed medically necessary by the treating physician for subject safety. Use of GCSF is permitted during Cycle 1 for Cohorts E, F, G and Part 2 subjects per local standard of care and Investigator discretion.

8.2. Prohibited Concomitant Medications and Procedures

The following medications are considered exclusionary during the study. The Celgene Medical Monitor or designee must be notified if a subject receives any of these medications during the study.

a. The prophylactic use of hematopoietic growth factors or platelet transfusions to prevent a potential DLT during Cycle 1 should be avoided in Cohorts A and B unless deemed medically necessary by the treating physician for subject safety; however, it is permitted at the Investigator's discretion after a subject completes the first cycle or within the first cycle if a hematological DLT has already been declared for that subject. Use of GCSF is permitted during Cycle 1 for Cohorts E, F, G and Part 2 subjects per site standard of care and Investigator discretion. Subjects who fail absolute neutrophil count or platelet eligibility criteria at Screening should not be retested for the study after being treated with GCSF or platelet transfusion(s).

b. Any anticancer therapy including investigational therapy
c. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment.
d. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent. Use of immunosuppressive medications for the management of CC-220-related AEs or in subjects with contrast allergies is acceptable. Use of corticosteroids for DARA pre-administration and post-administration is acceptable. In addition, use of inhaled, topical, intranasal corticosteroids or local steroid injection (eg, intra-articular injection) is permitted. Temporary use of corticosteroids for concurrent illnesses (eg, food allergies, CT scan contrast hypersensitivity, pneumonia, etc.) are acceptable upon discussion and agreement with the Medical Monitor.
e. Medications that are strong inhibitors or inducers of CYP3A4/5 are prohibited. Of note, any antibiotics/antifungals listed as strong inhibitors or inducers of CYP3A4/5 should be avoided and replaced by alternate treatment. In general, azole antifungals such as itraconazole as well as antibiotics clarithromycin and rifampin should be avoided. Also, grapefruit, St. John's Wort, and related products are prohibited while participating in this study. Please refer to Table 30 for a list of medications that are strong inhibitors or inducers of CYP3A4/5. Please note this list is not exhaustive. If there are any questions regarding whether a medication is a strong CYP3A4/5 inhibitor or inducer, please contact the Celgene Medical Monitor or designee.

For subjects receiving CC-220Vd, caution should be exercised when bortezomib is combined with CYP3A4 and CYP2C19 substrates.

Table 30: Medications that are CYP3A4/5 Strong Inhibitors and Inducers

Drug Class	Generic Name
CYP3A4/5 Strong Inhibitors	
Human Immunodeficiency Virus (HIV) Protease Inhibitor	Atazanavir
	Indinavir
	Darunavir
	Lopinavir
	Saquinavir
	Nelfinavir
	Ritonavir and ritonavir containing coformulations
Antihepaciviral (NS 3/4A) Protease Inhibitor	Boceprevir
	Telaprevir
	Ombitasvir-paritaprevir- ritonavir
	Ombitasvir-paritaprevir- ritonavir plus dasabuvir
CYP450 Inhibitor	Cobicistat and cobicistat containing coformulations

Table 30: Medications that are CYP3A4/5 Strong Inhibitors and Inducers (Continued)

Drug Class	Generic Name
Azole Antifungal	Itraconazole
	Ketoconazole
	Posaconazole
	Voriconazole
Macrolide antibiotic	Telithromycin
	Clarithromycin
Antiprogestin	Mifepristone
Serotonin Reuptake Inhibitor	Nefazodone
Phosphatidylinositol 3-kinase inhibitor	Idelalisib
CYP3A4/5 Strong Inducers	
Anticonvulsant	Carbamazepine
	Fosphenytoin
	Phenytoin
	Phenobarbital
	Primidone
Antineoplastic/Antiandrogen	Enzalutamide
	Apalutamide
Antineoplastic agent	Mitotane
Cystic fibrosis agent	Lumacaftor
Antitubercular	Rifampin (rifampicin)
Herbal	St. John's wort

8.3. Required Concomitant Medications and Procedures

- **Thromboembolism prophylaxis** consisting of low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anticoagulant will be given to all subjects as part of the study.
- **Antiviral prophylaxis**: Subjects in Cohort E (CC-220Dd), Cohort F (CC-220Vd), Cohorts G1 and G2 (CC-220Kd), J1(CC-220Vd) and J2 (CC-220Vd), and Cohort K (CC-220Dd) must initiate antiviral prophylaxis to prevent herpes virus infection. Subjects in Cohorts E and K (CC-220Dd) must start therapy within 1 week of starting DARA and continue for 3 months following last dose of DARA.

- **Infusion or injection reaction prophylaxis:** Guidance on pre-administration and post-administration medications for infusion or injection reaction prophylaxis in relation to DARA dosing is detailed in Table 19.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 1b/2a, multicenter, open-label, dose-escalation study to determine the MTD and or RP2D, assess the safety, tolerability, PK and efficacy of CC-220 as monotherapy and in combination with other treatments in subjects with MM.

All analyses will be done by cohort and dose level, as necessary and applicable. No statistical test will be performed to compare different dose levels or cohorts. For subjects who are treated with CC-220 in combination with DEX following confirmed PD in the monotherapy cohort, efficacy and safety information during the combination treatment period will be summarized separately. Details on the statistical analyses will be given in the statistical analysis plan (SAP).

9.2. Study Population Definitions

The following analysis populations will be used:

Full Analysis Population: includes all subjects enrolled into this study regardless of whether or not they receive study treatment.

Safety Population: includes all enrolled subjects who take at least one dose of study treatment. All safety analyses will be based on this population.

DLT Evaluable Population: includes all subjects from the Safety Population who meet the minimum exposure criterion and have sufficient safety evaluations or experience a DLT during the first treatment cycle.

Efficacy Evaluable Population: includes all enrolled subjects who take at least one dose of study treatment and have measurable disease at baseline and at least one post-baseline response assessment.

Patient Reported Outcome (PRO) Evaluable Population: includes all subjects who complete their baseline PRO questionnaires and have at least one post-baseline measurement in the safety population. All analyses of PRO data will be based on the PRO Evaluable population.

Pharmacokinetic Population: includes all subjects who receive at least one dose of study treatment and have measurable plasma concentration data. All analysis of PK data will be based on the PK population and subjects will be analyzed according to treatment group.

9.3. Sample Size and Power Considerations

In the MTD and/or RP2D determination part of the study (Part 1), a 3+3 design will be used to determine the MTD and/or RP2D level for CC-220 cohort (MonoT), CC-220 + DEX cohort (DoubleT), CC-220 + DARA + DEX (CC-220Dd), CC-220 + BTZ + DEX (CC-220Vd), and CC-220 + CFZ + DEX (CC-220Kd). Approximately 34 subjects will be enrolled for Cohort A and approximately 72 subjects will be enrolled for Cohort B. Approximately 85 additional subjects will be allocated to one of the four triplet regimen cohorts. Additional subjects may be enrolled into a dose-level cohort, as determined by the DEC. The actual number of subjects will depend on the number of dose levels being tested and may exceed these approximations.

In Part 2 of the study, for Cohort C, a sample size of 24 at the MTD and/or RP2D level based on clinical consideration may be enrolled to obtain the preliminary efficacy information of the treatment. If the observed response rate is 20% at the final analysis, the two-sided 95% confidence intervals will be 20%±16%.

The primary objective of Cohort D is to determine the efficacy of CC-220 plus DEX (Cohort D) in subjects with RRMM, as measured by ORR, which is defined as the proportion of subjects with a partial response (PR) or better. The sample size is calculated based on a group sequential design (Jennison, 1999) for a one-sample binomial test with normal approximation. One interim analysis for futility at 40% information and one final analysis are planned. The null hypothesis is ORR ≤ 12% and the alternative hypothesis is ORR > 12%. Assuming a treatment benefit of ORR ≥ 24%, a sample size of 101 subjects would provide 90% power at a one-sided 0.025 alpha level (Sample size calculation used EAST version 6.4).

In Cohort I, up to 40 subjects will be enrolled to explore the safety profile and preliminary efficacy of CC-220 + DEX in the post BCMA treatment patient population. An objective response rate (ORR) of 20% is considered as minimum clinically meaningful in this heavily pretreated patient population with prior BCMA-targeted therapy exposure. Bayesian continuous monitoring method will be applied to monitor the objective response rate (ORR).

For Cohorts J1, J2, and K the very good partial response or better (≥ VGPR) rate is considered an important and clinically relevant efficacy parameter to explore the treatment effect for NDMM patient population (Durie, 2018; Facon, 2018). In the SWOG S0777 study, the ≥ VGPR rate in NDMM subjects not eligible for ASCT following 8 cycles of RVd is 57%. In the IFM2009 study, the ≥ VGPR rate in NDMM subjects eligible for ASCT following 4 cycles of RVd induction therapy is 57% (IFM 2009 and SWOG S0777 Clinical Study Reports; Data on File). In the MAIA study, the ≥ VGPR rate in NDMM subjects not eligible for transplant following DRd (daratumumab in combination with lenalidomide and dexamethasone) treatment is 81% at a median follow-up of 56.2 months (Facon, 2021). A sample size of approximately 50 subjects in Cohort J2 and approximately 75 subjects each for Cohorts J1 and K (with up to approximately 25 subjects in each of the three CC-220 dose levels) is considered clinically adequate to explore the preliminary efficacy, safety, and PK profile of CC-220Vd and CC-220Dd in this patient population.

9.4. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent by cohort and dose level and follow-up phases.

Protocol deviations will be summarized using frequency tabulations by dose cohort and deviation.

9.5. Background and Demographic Characteristics

Age, height, weight, and other continuous baseline disease characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be provided using frequency tabulations.

9.6. Medical History

Medical history data will be summarized using frequency tabulations by the Medical Dictionary for Regulatory Activities (MedDRA) Version 18 or higher by system organ class and preferred term.

9.7. Concomitant Medications and Procedures

All concomitant medications and procedures documented during the study will be summarized using frequency tabulations. The Anatomical Therapeutic Chemical coding scheme of the World Health Organization will be used to group medications into relevant categories for these tabulations.

9.8. Efficacy Analysis

All efficacy analyses will be summarized using the Safety population. Supportive efficacy analyses will also be performed using the Efficacy Evaluable (EE) Population.

An IRC may also be set up to review efficacy data from Part 2 Cohorts C, D, and/or I. The IRC will determine the tumor response to therapy based on the IMWG uniform Response Criteria as well as time of response (including PD) for each subject. The IRC will adjudicate efficacy data according to the IRC Charter.

9.8.1. Overall Response Rate (ORR)

The overall response rate (ORR) is defined as the proportion of subjects with best response of PR or better during the trial without administration of myeloma therapy other than study treatment. The ORR with 95% confidence interval (CI) together with the proportions in each response category based on the IMWG Uniform Response Criteria (ie, Stringent Complete Response [sCR], Complete Response [CR], Very Good Partial Response [VGPR], Partial Response [PR], Minimal Response [MR], Stable Disease [SD], and Progressive Disease [PD]) will be examined. Efficacy Evaluable Population will also be used for sensitivity response analysis (see Appendix B).

For Part 2 Cohort D, the ORR will be analyzed based on a one-sample binomial test. The null hypothesis ORR $\leq$ 12% will be tested by a one-sided binominal test (normal approximation) with a type I error of 0.025 (one-sided).

9.8.2. Very Good Partial Response or Better Rate

The very good partial response or better ($\geq$ VGPR) rate is defined as the proportion of subjects with best response of VGPR or better during the trial without administration of myeloma therapy other than study treatment. The $\geq$ VGPR rate with 95% confidence interval (CI) together with the proportions in each response category based on the IMWG Uniform Response Criteria will be presented for NDMM cohorts (Cohorts J1, J2 and K).

9.8.3. Time to Response (TTR)

Time to response is defined as the time from the first dose date of study treatment to the first date of documented response (PR or better). Time to response will be summarized for responders using descriptive statistics by cohort and dose level.

9.8.4. Response Duration (DoR)

Duration of response is defined as time from the earliest date of documented response (PR or better) to the earliest date of disease progression per IMWG Uniform Response Criteria or death, whichever occurred first. Subjects who do not have progression of disease or death will be censored on the last adequate response assessment date. Duration of response for responders will be summarized using Kaplan-Meier estimates by cohort and dose level as appropriate.

9.8.5. Progression-free Survival (PFS)

Progression-free Survival is defined as time from the first dose date of study treatment to first documentation of PD, or death due to any cause, whichever occurs first. Subjects who do not have a PFS event will be censored on the last adequate response assessment date. PFS will be summarized using Kaplan-Meier estimates by cohort and dose level as appropriate.

9.8.6. Overall Survival (OS)

Overall survival is defined as time from first dose of study treatment to time of death due to any cause. Subjects who are still alive will be censored at the date last known alive or the data cut-off date (if applicable), whichever is earlier. OS will be summarized using Kaplan-Meier estimates by cohort and dose level as appropriate.

9.9. Safety Analysis

All safety analyses will be conducted using the Safety population. All analyses will be presented by cohort and dose level. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18 or higher. The intensity of AEs will be graded according to the NCI CTCAE Version 4.0.

Treatment-emergent AEs are defined as any AE occurring or worsening on or after the first dose of study treatment and up to 28 days after the date of last dose of the study treatment (CC-220, DEX, DARA, BTZ, or CFZ as applicable). If a subject experienced the same AE multiple times, then the event was counted only once and by the greatest severity. Treatment-emergent AEs, (TEAEs) leading to permanent study treatment discontinuation, TEAEs leading to dose reduction/interruption, TEAEs related to study treatment, serious adverse events (SAEs) and TEAEs leading to death will be summarized by system organ class, and preferred term for each cohort and dose level. A summary of TEAEs with NCI CTCAE Grade 3 or higher, as well as the most frequent preferred terms, will be provided. A summary of TEAEs by dosing cycle based on onset date will also be provided. If a subject experiences the same preferred term multiple times, then the event will be counted only once and by greatest severity. All death and reasons for death will be summarized. Death within 28 days after the last dose of study treatment will be summarized separately. A summary of DLTs by dose cohort will also be provided.

Clinical laboratory values will be graded according to NCI CTC version 4.0 for applicable tests. Shift from baseline to the worst grade observed during the treatment for selected laboratory results will be provided.

For vital signs, summary statistics (N, Mean, Standard Deviation, Median, Minimum, and Maximum) of observed values and change from baseline will be presented.

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with 'Normal', 'Abnormal, not clinically significant' and 'Abnormal, clinically significant' readings. Shift from baseline to worst during the treatment in the overall ECG interpretation will be displayed in cross–tabulations.

Graphical displays will be provided where useful to assist in the interpretation of results.

9.10. Interim Analysis

One interim analysis for Cohort D is planned at 40% information reached, ie, the interim analysis will be performed at approximately the first 40 treated subjects. The results of the interim analysis will be used for futility assessment only, for which a stopping boundary will be applied based on a beta spending function of gamma distribution with gamma = -2. The one-sided p-value to reject the alternative hypothesis (for futility) is $p \geq 0.656$, which is corresponding to ≤ 10% observed response rate at the time of interim analysis (assuming 40% information at interim analysis, may be adjusted according to actual percent of information available).

Bayesian continuous monitoring method will be applied to monitor the ORR for futility of Cohort I after enrollment of 21 subjects. Assume a relatively weak prior of Beta (0.2, 0.8) for ORR, which will allow the accruing data to dominate the posterior distribution of ORR, if the posterior probability of ORR is less than or equal to 20% and is greater than 0.8, then this cohort will be stopped for futility. Otherwise, treatment will continue, and enrollment will continue to up to 40 subjects to explore the safety profile and assess the preliminary efficacy for this patient population. The following stopping rule will be applied, accounting for subjects already enrolled in the study.

Table 31: Stopping Rules for Cohort I

Number of Subjects	Number of Responses to Stop for Futility
1-20	No futility stopping
21	<= 2
22-27	<= 3
28-33	<= 4
34-39	<=5

9.11. Other Topics

9.11.1. Pharmacokinetic Analysis

Pharmacokinetic measures are incorporated into the study to assess the extent of systemic exposure, and to explore the relationship between CC-220 and clinical response, provided data is sufficient. Blood samples for PK will be collected at selected visits from all subjects. PK parameters area under the plasma concentration-time curve from time zero to tau, where tau is the dosing interval (AUC[TAU]), maximum plasma concentration of drug (Cmax), time to Cmax (Tmax), apparent total plasma clearance (CLT/F), concentration at the end of a dosing interval (Ctau), trough observed plasma concentration (Ctrough), Enantiomer ratio (ER_Cmax,

ER_AUC) and metabolite ratio to parent (MR_Cmax, MR_AUC) will be estimated from CC-220, CC17195 and M12 versus time data using noncompartmental analysis, as appropriate. Descriptive statistics will be provided for CC-220, CC17195 and M12 concentrations and PK parameters, and the results will be presented in tabular and graphic form as appropriate.

9.11.2. Exploratory Analysis

Exploratory analysis will be performed based on the exploratory objectives of the study.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE, should be reported on the overdose eCRF. (See Section 7.4 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-220, DARA, BTZ, CFZ or DEX overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to CC-220, DARA, BTZ, CFZ or DEX, as applicable. AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;

- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the IP (CC-220, DARA, BTZ, CFZ DEX, as applicable), action taken regarding the IP, and outcome.

10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of the IP (CC-220, DARA, BTZ, CFZ, DEX to be assessed separately) and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to CC-220, DARA, BTZ, CFZ, or DEX administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of CC-220, DARA, BTZ, CFZ or DEX caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between CC-220, DARA, BTZ, CFZ, or DEX and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with CC-220, DARA, BTZ, CFZ or DEX as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of CC-220, DARA, BTZ, CFZ or DEX, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, reduction/ interruption of IP (CC-220, DARA, BTZ, CFZ or DEX) dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or female partner of a male subject are immediately reportable events.

In the event of a pregnancy occurring in a female subject of child bearing potential or female partner of the male subject, Celgene Drug Safety will follow up with the clinical investigator each trimester of the pregnancy and for 1 year following the birth of the infant (if applicable).

Please reference the informed consent (permission) forms for data collection regarding the pregnancy of a female subject participating in a Celgene sponsored study, the pregnancy of a female partner of a male subject participating in a Celgene sponsored study and the pregnancy of a nonsubject pregnant female. In all scenarios, data collection will occur each trimester of the pregnancy and for 1 year after the birth of the infant (if applicable).

The exposure of any nonsubject pregnant female (eg, caregiver, pharmacist, study coordinator or monitor) to CC-220 is also an immediately reportable event.

Females of childbearing potential are instructed to practice two forms of reliable contraception. One must be a highly effective method and one additional effective (barrier) method without interruption, 28 days prior to starting IP, throughout the entire duration of treatment, during dose interruptions and for at least 28 days after the last dose of CC-220 or 90 days after the last dose of DARA (for Cohorts E and K), or 7 months after the last dose of BTZ (for Cohorts F, J1, and J2), or 6 months after the last dose of CFZ (for Cohorts G1 and G2), whichever is longer. See Appendix D for the CC-220 Pregnancy Prevention Plan.

10.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of CC-220 or within 90 days after last dose of DARA, or within 7 months after the last dose of BTZ, or within 6 months after the last dose of CFZ, whichever occurs later, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

In the event of a pregnancy occurring in a female subject of childbearing potential, Celgene will follow up with the clinical investigator each trimester of the pregnancy and for 1 year following the birth of the infant (if applicable). Any follow-up information or outcome information must be reported to Celgene Drug Safety immediately.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious

criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

The event must also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form. In the event, of a pregnancy occurring in a female partner of the male subject, Celgene will follow up with the clinical investigator each trimester of the pregnancy and for 1 year following the birth of the infant (if applicable). Any follow-up information or outcome information must be reported to Celgene Drug Safety immediately.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to the IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-220 based on the IB.

In the US, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other IPs (DEX, DARA, BTZ and/or CFZ as applicable) based on the SmPC.

Events of disease progression for the disease under study (including deaths due to disease progression for indications that are considered to be fatal) will be assessed as expected adverse events and will not be reported as expedited safety reports to regulatory authorities.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 14.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

10.7. Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding the safety profile of the Investigational Product, CC-220, and may require close

monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand their association with the use of this investigational product.

Further information on potential risks (eg, presenting symptoms) can be found in the current version of the IB including guidelines for their evaluation and treatment.

10.7.1. Second Primary Malignancies (SPMs)

Second primary malignancies (SPMs) will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment cohort the subject is in. This includes any second primary malignancy, regardless of causal relationship to IP occurring at any time for the duration of the study, from the time of signing the ICF until the end of the 5-year Long-term Follow-up phase. Events of second primary malignancy are to be reported using the SAE report form and must be considered "Important Medical Events" if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF (ie, AE and SPM eCRF) and subject's source documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as an SAE (eg, any confirmatory histology or cytology results, X- rays, CT scans, etc.).

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Progressive Disease
- Adverse Event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the eCRF)

The reason for discontinuation of treatment should be recorded in the eCRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the eCRF)

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Investigational product can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has

been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

At the conclusion of the study, if the study intervention is not available as an approved treatment in the local country, participants who continue to demonstrate clinical benefit will be eligible to receive Sponsor-supplied study intervention. If the study treatment is not available as an approved and available treatment, study intervention will be provided via an extension of the study, or a rollover study requiring approval by the responsible Health Authority and ethics committee, or through another mechanism at the discretion of the Sponsor. The Sponsor reserves the right to terminate access to the supplied study intervention treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of CC-220 is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or other health program. In all cases, the Sponsor will follow local regulations. In addition, the

Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of eCRFs or CD-ROM.

14.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

15.3. Product Quality Complaint

Issues that call into question IMP safety, purity, potency, quality and identity (eg, evidence of suspected tampering of product) must be reported as soon as possible to your study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all Sponsor supplied investigational medicinal product (IMP), non-investigational medicinal product (NIMP) or auxiliary medicinal product (AxMP) suspected to have occurred before the product was transferred to the responsibility of the investigational site (eg, during manufacturing, packaging and labeling, storage, and/or distribution).

This includes suspected quality issues of components co-packaged with the drug, labelling, and IMP device/drug combination products, and medical devices.

In the event of a suspected product quality issue, the immediate action to be taken by site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps). When reporting, provide as much product information as possible. Suspected IMP quality issues will be investigated and a response will be provided back to the investigational site.

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

17. REFERENCES

[redacted]

Agarwal A, Chow E, Bhutani M, Voorhees PM, Friend R, Usmani SZ. Practical considerations in managing relapsed multiple myeloma. Clin Lymphoma Myeloma Leuk. 2017;17(2):69-77.

Ali SA, Shi V, Maric I, Wang M, Stroncek DF, Rose JJ, et al. T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. Blood. 2016 Sep 29;128(13):1688-700.

Amatangelo M, Bjorklund CC, Kang J, Polonskaia A, Viswanatha S, Thakurta A. Iberdomide (CC-220) has Synergistic Anti-Multiple Myeloma Activity in Combination with both Bortezomib and Dexamethasone, or in combination with Daratumumab in vitro. Blood. 2018;132(Suppl 1):1935.

Avet-Loiseau H, Casneuf T, Chiu C, Laubach J, Lee J, Moreau P, et al. Evaluation of Minimal Residual Disease (MRD) in Relapsed/Refractory Multiple Myeloma (RRMM) Patients Treated with Daratumumab in Combination with Lenalidomide Plus Dexamethasone or Bortezomib Plus Dexamethasone. Blood. 2016; 128(22):246.

Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014 Sep 4;371(10):906-17.

Berdeja J, Lin Y, Raje N, Munshi N, Siegel D, Liedtke M, et al. Durable Clinical Responses in Heavily Pretreated Patients with Relapsed/Refractory Multiple Myeloma: Updated Results from a Multicenter Study of bb2121 Anti-Bcma CAR T Cell Therapy. Blood. 2017; 130 (Suppl 1): 740.

Bjorklund C, Kang J, Lu L, Amatangelo M, Chiu H, Hagner P, et al. CC-122 Is a Cereblon Modulating Agent That Is Active in Lenalidomide-Resistant and Lenalidomide/Dexamethasone-Double-Resistant Multiple Myeloma Pre-Clinical Models. Blood. 2016;128(Suppl 1):1592.

Botta C, Ciliberto D, Rossi M, Staropoli N, Cucè M, Galeano T, et al. Network meta-analysis of randomized trials in multiple myeloma: efficacy and safety in relapsed/refractory patients. Blood Advances. 2017 Feb 28;1(7):455-66.

Brudno JN, Maric I, Hartman SD, Rose JJ, Wang M, Lam N, et al. T Cells Genetically Modified to Express an Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor Cause Remissions of Poor-Prognosis Relapsed Multiple Myeloma. J Clin Oncol. 2018 Aug 1;36(22):2267-80.

Chari A, San-Miguel J, McCarthy H, Suzuki K, Hungria VT, Sureda AS, et al. Subcutaneous Daratumumab Plus Standard Treatment Regimens in Patients with Multiple Myeloma across Lines of Therapy: Pleiades Study Update. Blood. 2019; 134 (Supplement_1): 3152.

Cho SF, Anderson KC, Tai YT. Targeting B Cell Maturation Antigen (BCMA) in Multiple Myeloma: Potential Uses of BCMA-Based Immunotherapy. Front Immunol. 2018 Aug 10;9:1821.

Cowan J, Allen C, Barac A, Basaleem H, Bensenor I, Curado Maria P, et al. Global Burden of Multiple Myeloma: A Systematic Analysis for the Global Burden of Disease Study 2016. JAMA Oncol. 2018 Sep 1;4(9):1221-7.

Darzalex. [Package Insert]. Horsham, PA: Janssen Biotech. Available from: https://www.janssenmd.com/pdf/darzalex/darzalex_pi.pdf.

Darzalex. [Summary of Product Characteristics]. Available from: https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf

Darzalex FASPRO. [Package Insert]. Horsham, PA: Janssen Biotech. Available from: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf.

Darzalex FASPRO. [Summary of Product Characteristics]. Available from: https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf

Davies FE, Raje N, Hideshima T, Lentzsch S, Young G, Tai YT, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. Blood. 2001 Jul 1;98(1):210-6.

Deaglio S, Vaisitti T, Billington R, Bergui L, Omede P, Genazzani AA, et al. CD38/CD19: a lipid raft-dependent signaling complex in human B cells. Blood. 2007 Jun 15;109(12):5390-8.

Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hajek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncology. 2016b Jan;17(1):27-38.

Dimopoulos M, White D, Benboubker L, Cook G, Leiba M, Morton J, et al. Daratumumab, Lenalidomide, and Dexamethasone (DRd) Versus Lenalidomide and Dexamethasone (Rd) in Relapsed or Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Analysis of Pollux. Blood. 2017;130(Suppl 1):739.

Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016a Oct 6;375(14):1319-31.

Durie BG, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017 Feb 4;389(10068):519-27.

Durie BGM, Hoering A, Sexton R, Munner AH, Epstein J, Rajkumar SV, et al. Longer Term Follow-up of the Randomized Phase III Trial SWOG S0777: Bortezomib, Lenalidomide and Dexamethasone Vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant (ASCT). American Society of Hematology; December 1-4, 2018; San Diego, CA. Abstract 1992.

Engelhardt M, Terpos E, Kleber M, Gay F, Wasch R, Morgan G, et al. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. Haematologica. 2014 Feb;99(2):232-42.

Facon T, Lonial S, Weiss B, Suvannasankha A, Fay JW, Arnulf B, et al. Daratumumab in Combination with Pomalidomide and Dexamethasone for Relapsed and/or Refractory Multiple Myeloma (RRMM) Patients with >/=2 Prior Lines of Therapy: Updated Analysis of MMY1001. Blood. 2017;130(Suppl 1):1824.

Facon T, Dimopoulos MA, Dispenzieri A, Catalano JV, Belch A, Cavo, M, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood. 2018;131(3):301-310.

Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2021; 22: 1582-96.

Fonseca R, Bergsagel P L, Drach J, Shaughnessy J, Gutierrez N, Stewart A K, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia. 2009 Dec;23(12):2210-21.

Fraietta J, Lacey S, Orlando E, Pruteanu-Malinici I, Gohil M, Lundh S, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. Nature Medicine. 2018 May;24(5):563-71.

Gorgun G, Calabrese E, Soydan E, Hideshima T, Perrone G, Bandi M, et al. Immunomodulatory effects of lenalidomide and pomalidomide on interaction of tumor and bone marrow accessory cells in multiple myeloma. Blood. 2010 Oct 28;116(17):3227-37.

Gandhi AK, Kang J, Capone L, Parton A, Wu L, Zhang LH, et al. Dexamethasone synergizes with lenalidomide to inhibit multiple myeloma tumor growth, but reduces lenalidomide-induced immunomodulation of T and NK cell function. Curr Cancer Drug Targets. 2010 Mar;10(2):155-67.

Gandhi AK, Kang J, Havens CG, Conklin T, Ning Y, Wu L, et al. Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4CRBN. Br J Haematol. 2014 Mar;164(6):811-21.

[redacted]

Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, et al. SEER Cancer Statistics Review (CSR), 1975-2013, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/archive/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.

Imnovid. [Summary of Product Characteristics]. Uxbridge, United Kingdom: Celgene Europe Ltd. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002682/WC500147717.pdf.

Ito T, Ando H, Suzuki T, Ogura T, Hotta K, Imamura Y, et al. Identification of a Primary Target of Thalidomide Teratogenicity. Science. 2010 Mar 12;327(5971):1345-50.

Jennison C, Turnbull BW. Group Sequential Methods with Applications to Clinical Trials. 1st ed. Boca Raton, FL: CRC Chapman & Hall; c1999.

John LB, Ward AC. The Ikaros gene family: transcriptional regulators of hematopoiesis and immunity. Mol Immunol. 2011 May;48(9-10):1272-8.

Katz M, Bjorklund CC, Thakurta A, Serbina N. Mechanistic insights of pomalidomide activity in combination with bortezomib and dexamethasone in multiple myeloma and immune cells. Blood. 2018;132(suppl 1):1934.

Krönke J, Udeshi ND, Narla A, Grauman P, Hurst SN, McConkey M, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. Science. 2014 Jan 17;343(6168):301-5.

Kumar S, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study. Leukemia. 2012 Jan;26(1):149-57.

Kumar SK, Rajkumar V, Kyle RA, van Duin M, Sonneveld P, Mateos MV, et al. Multiple myeloma. Nat Rev Dis Primers. 2017 Jul 20;3:17046.

Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Castillo J, et al. NCCN Guidelines Insights: Multiple Myeloma, Version 3.2018. J Natl Compr Canc Ne. 2018 Jan;16(1):11-20.

Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016 Aug;17(8):e328-e46.

Kyprolis. [Package Insert]. Thousand Oaks, California, United States: Amgen. Available from: https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/kyprolis/kyprolis_pi.pdf.

Kyprolis. [Summary of Product Characteristics]. Breda, Netherlands: Amgen Europe BV. Available from: https://www.ema.europa.eu/en/documents/product-information/kyprolis-epar-product-information_en.pdf.

Laabi Y, Gras M-P, Brouet J-C, Berger R, Larsen C-J, Tsapis A, et al. The BCMA gene, preferentially expressed during B lymphoid maturation, is bidirectionally transcribed. Nucleic Acids Research. 1994 Apr 11;22(7):1147–54.

Larocca A, Mina R, Gay F, Bringhen S, Boccadors M. Emerging drugs and combinations to treat multiple myeloma. Oncotarget 2017;8(36):60656-72.

Landgren O, Devlin S, Boulad M, Mailankody S. Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis. Bone Marrow Transplantation. 2016 Dec;51(12):1565-8.

Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med. 2015 Sep 24;373(13):1207-19.

Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med. 2015 Aug 13;373(7):621-31.

Lonial S, van de Donk N, Popat R, Zonder JA, Minnema MC, Larsen J, et al. First clinical (phase 1b/2a) study of iberdomide (CC-220; IBER), a CELMoD, in combination with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). J Clin Oncol. 2019;37(Suppl 15):8006.

Lopez-Girona A, Mendy D, Ito T, Miller K, Gandhi A K, Kang J, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. Leukemia. 2012 Nov;26(11):2326-35.

Lu G, Middleton RE, Sun H, Naniong M, Ott CJ, Mitsiades CS, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. Science. 2014 Jan 17;343(6168):305-9.

Ludwig H, Miguel JS, Dimopoulos MA, Palumbo A, Sanz GR, Powles R, et al. International Myeloma Working Group recommendations for global myeloma care. Leukemia. 2014 May;28(5):981-92.

Matyskiela ME, Zhang W, Man HW, Muller G, Khambatta G, Baculi F, et al. A Cereblon Modulator (CC-220) With Improved Degradation of Ikaros and Aiolos. J Med Chem. 2018; Jan 25;61(2):535-542.

Mateos MV, Nahi H, Legiec W, Grosicki S, Vorobyev V, Spicka I, et al. Efficacy and safety of the randomized, open-label, non-inferiority, phase 3 study of subcutaneous (SC) versus intravenous (IV) daratumumab (DARA) administration in patients (pts) with relapsed or refractory multiple myeloma (RRMM): COLUMBA. J Clin Oncol. 2019; 37(Suppl 15):8005.

Maus MV, Grupp SA, Porter DL, June CH. Antibody-modified T cells: CARs take the front seat for hematologic malignancies. Blood. 2014 Apr 24;123(17):2625-35.

Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016 Apr 28;374(17):1621-34.

Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(Suppl 4):iv52-61.

Moreau P, Mateos MV, Berenson JR, Weisel K, Lazzaro A, Song K, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. Lancet Oncology. 2018 Jul;19(7):953-64.

Munshi NC, Longo DL, Anderson KC. Plasma cell disorders In: Oncology and Hematology 2012; Chapter 111: p. 936-944.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Multiple myeloma; Version 4.2021; 2021. Available from: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.

Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.

Novak AJ, Darce JR, Arendt BK, Harder B, Henderson K, Kindsvogel W, et al. Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a mechanism for growth and survival. Blood. 2004 Jan 15;103(2):689-94.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55.

Paiva B, van Dongen JJM, Orfao A. New criteria for response assessment: role of minimal residual disease in multiple myeloma. Blood. 2015 May 14;125(20):3059-68.

Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011 Mar 17;364(11):1046-60.

Palumbo A, Bringhen S, Mateos MV, Larocca A, Facon T, Kumar SK, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Wording Group report. Blood. 2015 Mar 26;125(13):2068-74.

Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Aug 25;375(8):754-66.

Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. J Clin Oncol. 2014 Feb 14;32(6):587-600.

Plesner T, Arkenau HT, Gimsing P, Krejcik J, Lemech C, Minnema MC, et al. Phase 1/2 study of daratumumab, lenalidomide, and dexamethasone for relapsed multiple myeloma. Blood. 2016 Oct 06;128(14):1821-8.

Pomalyst. [Package Insert]. Summit, NJ: Celgene Corporation. Available from: http://www.pomalyst.com/wp-content/uploads/2013/08/prescribing_information.pdf.

Pulte D, Gondos A, Brenner H. Improvement in survival of older adults with multiple myeloma: results of an updated period analysis of SEER data. Oncologist. 2011;16(11):1600-3.

Raje N, Hege K, Kochenderfer JN. Anti-BCMA CAR T-Cell Therapy in Multiple Myeloma. N Engl J Med. 2019 Jul 18;381:e6.

Rajkumar SV. Multiple myeloma: 2011 update on diagnosis, risk-stratification, and management. Am J Hematology. 2011 Jan;86(1):57-65.

Rajkumar SV, Kumar S. Multiple Myeloma: Diagnosis and Treatment. Mayo Clin Proc. 2016 Jan;91(1):101-119.

Revlimid. [Package Insert]. Summit, NJ: Celgene Corporation. Available from: http://www.revlimid.com/.

Revlimid ™. [Summary of Product Characteristics]. Uxbridge, United Kingdom: Celgene Europe Ltd. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000717/WC500056018.pdf.

Richardson, Siegel, Vij. Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014 Mar 20;123(12):1826-1832.

Richardson P, Oriol Rocafiguera A, Beksac M, Marina Liberati A, Galli M, Schjesvold F, et al. Pomalidomide (POM), bortezomib, and low-dose dexamethasone (PVd) vs bortezomib and low-dose dexamethasone (Vd) in lenalidomide (LEN)-exposed patients (pts) with relapsed or refractory multiple myeloma (RRMM): Phase 3 OPTIMISMM trial. J Clin Oncol. 2018 May 20;36(Suppl):8001.

Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003 Jun 26;348(26):2609-17.

Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin DH, et al. Extended follow-up of a phase II trial in relapsed, refractory multiple myeloma: final time-to-event results from the SUMMIT trial. Cancer. 2006 Mar 15;106(6):1316-9.

Richardson PG, Blood E, Mitsiades CS, Jagannath S, Zeldenrust SR, Alsina M, et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. Blood. 2006 Nov 15;108(10):3458-64.

Richardson PG, Jagannath S, Jakubowiak AJ, Lonial S, Raje N, Alsina M, et al. Phase II trial of lenalidomide bortezomib and dexamethasone in patients (pts) with relapsed and relapsed/refractory multiple myeloma (MM): Updated efficacy and safety data after >2 years of follow-up. Blood. 2010;116(Suppl 1):3049.

Richardson PG, Siegel DS, Vij R, Hofmeister CC, Jagannath S, Chen C, et al. Randomized open label phase 1/2 study of pomalidomide (POM) alone or in combination with low-dose dexamethasone (LoDex) in patients (Pts) with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide (LEN) and bortezomib (BORT): Phase 2 results. Blood. 2011;118(Suppl 1):634.

Richardson PG, Sonneveld P, Schuster M, Irwin D, Stadtmauer E, Facon T, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. Blood. 2007 Nov 15;110(10):3557-60.

Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005 Jun 16;352(24):2487-98.

Sadelain M, Brentjens R, Rivière I. The basic principles of chimeric antigen receptor design. Cancer Discovery. 2013 Apr;3(4):388-98.

San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014 Oct;15(11):1195-206.

San-Miguel JF, Weisel KC, Moreau P, Lacy M, Song KW, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): randomised, open label, phase 3 trial. Lancet Oncology. 2013 Oct;14(11):1055-66.

Sehgal K, Das R, Zhang L, Verma R, Deng Y, Kocoglu M, et al. Clinical and pharmacodynamic analysis of pomalidomide dosing strategies in myeloma: impact of immune activation and cereblon targets. Blood. 2015 Jun 25;125(26):4042-51.

Siegel DS, Dimopoulos MA, Ludwig H, Facon T, Goldschmidt H, Jakubowiak A, et al. Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma. J Clin Oncol. 2018 Mar 10;36(8):728-34.

Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016 Jun 16;127(24):2955-62.

Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015 Jan 8;372(2):142-52.

Tai YT, Acharya C, An G, Moschetta M, Zhong MY, Feng X, et al. APRIL and BCMA promote human multiple myeloma and immunosuppression in the bone marrow microenvironment. Blood. 2016 Jun 23;127(25):3225-36.

Thalidomide. [Summary of Product Characteristics]. Uxbridge, United Kingdom: Celgene Europe Ltd. Available from: https://www.ema.europa.eu/en/documents/product-information/thalidomide-celgene-epar-product-information_en.pdf.

Thalomid. [Package Insert]. Summit, NJ: Celgene Corporation. Available from: http://www.celgene.com/content/uploads/thalomid-pi.pdf.

Topp MS, Duell J, Zugmaier G, Attal M, Moreau P, Langer C, et al. Evaluation of AMG 420, an anti-BCMA bispecific T-cell engager (BiTE) immunotherapy, in R/R multiple myeloma (MM) patients: Updated results of a first-in-human (FIH) phase I dose escalation study. J Clin Oncol. 2019 May 26;37(Suppl 15):8007.

Van de Velde H, Londhe A, Ataman O, Johns HL, Hill S, Landers E, et al. Association between complete response and outcomes in transplant-eligible myeloma patients in the era of novel agents. Eur J Haematol. 2017;98(3):269-79.

Velcade. [Package Insert]. Cambridge, MA: Millennium Pharmaceuticals. Available from: http://www.velcade.com/files/PDFs/VELCADE_PRESCRIBING_INFORMATION.pdf. Accessed on 02/16/2018.

Velcade. [Summary of Product Characteristics]. Beerse, Belgium: Janssen-Cilag International NV. Available from: https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_en.pdf.

Willenbacher E, Balog A, Willenbacher W. Short overview on the current standard of treatment in newly diagnosed multiple myeloma. Memo. 2018 Mar;11(1):59-64.

Xu Y, Zhang M, Ramos CA, Durett A, Liu E, Dakhova O, et al. Closely related T-memory stem cells correlate with in vivo expansion of CAR.CD19-T cells and are preserved by IL-7 and IL-15. Blood. 2014 Jun 12;123(24):3750-9.

Yang Y, Shaffer AL, Emre NC, Ceribelli M, Zhang M, Wright G, et al. Exploiting synthetic lethality for the therapy of ABC diffuse large B cell lymphoma. Cancer Cell. 2012 Jun 12;21(6):723-37.

Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol. 2016;175(2):252-64.

Zhu YX, Braggio E, Shi CX, Bruins LA, Schmidt JE, Van Wier S, et al. Cereblon Expression Is Required for the Anti-Myeloma Activity of Lenalidomide and Pomalidomide. Blood. 2011 Nov 3;118(18):4771-9.

18. APPENDICES

Appendix A: Table of Abbreviations

Table 32: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADC	Antibody drug conjugate
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
antiHBs	Hepatitis B surface antibody
antiHBc	Hepatitis B core antibody
AP	Anterior/posterior
AST	Aspartate aminotransferase
ASCT	Autologous stem cell transplant
AUC	Area under the curve
AxMP	Auxiliary medicinal product
β-hCG	Serum beta human chorionic gonadotropin
BAFF	B-cell-activating factor
BCMA	B-cell maturation antigen
BiTE	bispecific T-cell engager
BLyS	B lymphocyte stimulator
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BTZ	Bortezomib
C	Cycle
CAR T	Chimeric Antigen Receptor T-cell Therapy
CC-220Dd	CC-220 + daratumumab + dexamethasone
CC-220Vd	CC-220 + bortezomib + dexamethasone
CC-220Kd	CC-220 + carfilzomib + dexamethasone
CFZ	Carfilzomib
CI	Confidence interval
CLT/F	Apparent total plasma clearance

Table 32: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
Cmax	Maximum plasma concentration of drug
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CrCl	Creatinine clearance
CT	Computed tomography
Ctau	Concentration at the end of a dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough observed plasma concentration
CYP	Cytochrome
D	Day
DARA	Daratumumab
DDB1	Deoxyribonucleic acid damage binding protein 1
DLBCL	Diffuse large B cell lymphoma
DEC	Dose Escalation Committee
DEX	Dexamethasone
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoubleT	Combination treatment with 2 drugs
DRd	Daratumumab, lenalidomide, and dexamethasone
DVd	Daratumumab, bortezomib, and dexamethasone
DVMP	Daratumumab, bortezomib, melphalan, and prednisone
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEA	European Economic Area
EFD	Embryofetal development
EMP	Extramedullary plasmacytoma

Table 32: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
EOT	End of treatment
ER_AUC	Enantiomer ratio of AUC
ER_Cmax	Enantiomer ratio of Cmax
ESMO	European Society for Medical Oncology
EU	European Union
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FISH	Fluorescence in situ hybridization
FLC	Free light chain
GCP	Good Clinical Practice
GCSF	Granulocyte colony stimulating factor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hERG	Human ether à go go related gene
HMCL	Human multiple myeloma cell lines
HR	Hazard ratio
IB	Investigator Brochure
IC50	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IER	Independent Expert Reviewer
IFN-γ	Interferon-gamma
IgA	Immunoglobulin A
IgD	Immunoglobulin D
IgE	Immunoglobulin E
IgG	Immunoglobulin G

Table 32: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
IgM	Immunoglobulin M
IL-2	Interleukin-1
IKZF1	Ikaros family zinc finger 1
IKZF3	Ikaros family zinc finger 3
IMiD®	Immunomodulatory compounds
IMP	Investigational medicinal product
IMWG	International Myeloma Working Group
IP	Investigational product
IRB	Institutional Review Board
IRC	Independent Response Committee
IRR	Infusion or injection-related reactions
IRT	Interactive Response Technology
IV	Intravenous
LEN	Lenalidomide
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MonoT	monotherapy
MR	Minimal response
MR_AUC	Metabolite ratio of AUC to parent
MR_Cmax	Metabolite ratio of Cmax to parent
MRD	Minimal residual disease
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDMM	Newly diagnosed multiple myeloma
NF-kB	Nuclear factor-kappa B
NGS	Next generation sequencing
NIMP	Non-investigational medicinal product
NK	Natural killer

Table 32: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
NOAEL	No-observed-adverse-effect-level
NOEL	No-observed-effect-level
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
Pd	Pharmacodynamic
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
[redacted]	[redacted]
P-gp	Permeability glycoprotein
PI	Package insert/prescribing information
PI	Proteasome inhibitor
PK	Pharmacokinetics
POM	Pomalidomide
PQC	Product quality complaint
PR	Partial response
PRO	Patient Reported Outcome
QD	Once daily
RBC	Red blood cell count
RP2D	Recommended Phase 2 dose
RRMM	Relapsed and refractory multiple myeloma
RVd	Lenalidomide in combination with bortezomib and dexamethasone
SAE	Serious adverse event
SAP	Statistical analysis plan
sCR	Stringent complete response
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure

Table 32: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
sPEP	Serum protein electrophoresis
SPM	Second primary malignancy
SC	Subcutaneous
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal-phase elimination half-life
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma concentration of drug
TNF-α	Tumor necrosis factor-alpha
[redacted]	[redacted]
ULN	Upper limit of normal
uPEP	Urine protein electrophoresis
US	United States
VGPR	Very good partial response
VTE	Venous thromboembolism

Appendix B: International Myeloma Working Group Uniform Response Criteria 2016

Table 33: International Myeloma Working Group Uniform Response Criteria

Response Category	Response Criteria*
MRD response Criteria (requires a complete response)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) 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	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 plus MRD-negative	MRD negativity as defined by NGF or 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¶
Standard IMWG response criteria	
Stringent Complete Response (sCR)	Complete response (CR) as defined below, *plus* Normal serum free light chain (FLC) ratio** *and* Absence of clonal plasma cells by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete Response (CR)	Negative immunofixation of serum and urine *and* Disappearance of any soft tissue plasmacytomas *and* < 5% plasma cells in bone marrow aspirates In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above.
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis *or* 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours In patients in whom the only measurable disease is by serum FLC levels: VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

Table 33: International Myeloma Working Group Uniform Response Criteria (Continued)

Response Category	Response Criteria*
Partial Response (PR)	≥ 50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours If the serum and urine M-protein are not measurable, 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 the serum free light chain assay is also unmeasurable, a ≥ 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 measured by sum of the products (SPD) §§ of the maximal perpendicular diameters of soft tissue plasmacytomas is also required
Stable Disease (SD)	Not meeting criteria for CR, VGPR, MR, PR, or progressive disease (PD)
Progressive disease (PD) ¶¶ ‖‖	**Requires only one of the following:** Increase of 25% from lowest response value in any of the following: • Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or* • Urine M-component (absolute increase must be ≥ 200 mg/24 h), *and/or* Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be ≥ 10 mg/dL) Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute increase must be ≥ 10%) Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD§§ 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

Table 33: International Myeloma Working Group Uniform Response Criteria (Continued)

Response Category	Response Criteria*
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. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; 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§§ of the measurable lesion; Hypercalcaemia (> 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
Relapse from complete response (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥ 5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)
Relapse from MRD negative (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥ 5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia)
Minimal Response (MR)	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50%-89% In addition to the above criteria, if present at baseline, ≥50% reduction in the size (SPD) §§ of soft tissue plasmacytomas is also required

Refer to IMWG criteria for specific details (Kumar, 2016).
For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4–5 mL to avoid haemodilution. IMWG = International Myeloma Working Group. MRD = minimal residual disease. NGF = next-generation flow. NGS = next-generation sequencing. FLC = free light chain. M-protein = myeloma protein. SPD = sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features = calcium elevation, renal

failure, anaemia, lytic bone lesions. FCM = flow cytometry. SUVmax = maximum standardised uptake value. MFC = multiparameter flow cytometry. ^{18}F-FDG PET = ^{18}F-fluorodeoxyglucose PET. ASCT = autologous stem cell transplantation.

* All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

† Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

‡ 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 eight-colour technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-colour method is most efficient using a lyophilised mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

§ DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequenta).

¶ Criteria used by Zamagni and colleagues, and expert panel (IMPetUs; Italian Myeloma criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUVmax=2·5 within osteolytic CT areas >1 cm in size, or SUVmax=1·5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS. ||Derived from international uniform response criteria for multiple myeloma. Minor response definition and clarifications derived from Rajkumar and colleagues. When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0·26 to 1·65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

** All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

†† 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.

‡‡ Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody. §§Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD.

¶¶ Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

|||| In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

Appendix C: ECOG Performance Status

Table 34: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source (Oken, 1982).
Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

Appendix D: CC-220 Pregnancy Prevention Plan for Subjects in Clinical Trials

1. CC-220 PREGNANCY PREVENTION PLAN FOR SUBJECTS IN CLINICAL TRIALS

1.1. The Pregnancy Prevention Plan (PPP) (v5.1) applies to all subjects receiving CC-220 within a clinical trial. The following PPP documents are included:

- The CC-220 Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 2) provides the following information:
- Potential risks to the fetus associated with CC-220 exposure
- Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
- Requirements for counseling of all subjects receiving CC-220 about pregnancy precautions and the potential risks of fetal exposure to CC-220
- Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving CC-220 in the study
- Pregnancy testing requirements for subjects receiving CC-220 who are FCBP

1.2. The CC-220 Education and Counseling Guidance Document for each gender (female and male; Section 1 and Section 2 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of CC-220. A copy of this document must be maintained in the subject's records for each dispense.

1.3. The CC-220 Information Sheet (Section 3) will be given to each subject receiving CC 220. The subject must read this document prior to starting CC-220 and each time the subject receives a new supply of CC-220.

2. CC-220 RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

2.1. Risks Associated with Pregnancy

CC-220 was found to cause birth defects in experimental animals (rat and rabbit). CC-220 is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If CC-220 is taken during pregnancy, it may cause birth defects or death to an unborn baby. Therefore, a pregnancy prevention program must be followed.

2.2. Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

2.3. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

2.4. Counseling

2.4.1. Females of Childbearing Potential

For a FCBP, CC-220 is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of CC-220):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting CC-220, throughout the entire duration of CC-220, during dose interruptions and for at least 28 days after the last dose of CC-220
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence CC-220 as soon as it is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 2.6) and in the Informed Consent
- She acknowledges she understands the hazards CC-220 can cause to an unborn fetus and the necessary precautions associated with the use of CC-220.
- The Investigator must ensure that a FCBP:
- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

2.4.2. Females Not of Childbearing Potential

For a FNCBP, CC-220 is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of CC-220):

- She acknowledges she understands the hazards CC-220 can cause to an unborn fetus and the necessary precautions associated with the use of CC-220.

2.4.3. Males

In a 9-month toxicity study in monkeys given CC-220 at doses higher than the highest dose planned for this study, male monkeys had a decrease in the amount of sperm producing cells. It is not known at this time if this finding can be reversed or at what time after the start of CC-220 treatment this decrease will occur. It is not known if there might be a similar effect in men taking CC-220 and how this will affect their ability to father children. There were no observable effects in male sex organs in monkeys that received more than the highest dose given to humans. There were no effects of CC-220 in the sex organs of female monkeys.

Therefore, male subjects taking CC-220 must meet the following conditions (ie, they must be counseled concerning the following risks and requirements prior to the start of CC-220):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.
- Understand that the effects on fertility are currently unknown, therefore all family planning options and/or alternatives should be thoroughly discussed with the study doctor prior to receiving CC-220.

2.5. Contraception

2.5.1. Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal or post ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting CC-220; 2) while taking CC-220; 3) during dose interruptions; and 4) for at least 28 days after the last dose of CC-220.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

Examples of highly effective methods:

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [eg, desogestrel])
- Tubal ligation
- Partner’s vasectomy

Examples of additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

2.5.2. Male Subjects

Subjects must either:

1. practice complete abstinence (true abstinence), which is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal or post-ovulation methods) and withdrawal are not acceptable methods of contraception, or
2. agree to use a condom during sexual contact with a pregnant female or a FCBP while taking CC-220, including during dose interruptions, and for at least 90 days following the last dose of CC-220, even if he has undergone a successful vasectomy.

2.6. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting CC-220. The first pregnancy test must be performed within 10 to 14 days prior to the start of CC-220 and the second pregnancy test must be performed within 24 hours prior to the start of CC-220. The subject may not receive CC-220 until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking CC-220, at study discontinuation, and at Day 28 following the last dose of CC-220.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking CC 220, at study discontinuation, and at Days 14 and 28 following the last dose of CC-220.

2.7. Pregnancy Precautions for CC-220 Use

2.7.1. Before Starting CC-220

2.7.1.1. Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting CC-220. The first pregnancy test must be performed within 10 to 14 days prior to the start of CC-220 and the second pregnancy test must be performed within 24 hours prior to the start of CC-220. The subject may not receive CC-220 until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting CC-220.

2.7.1.2. Male Subjects

Subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar,

ovulation, symptothermal or post ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking CC-220, during dose interruptions and for at least 90 days following the last dose of CC-220, even if he has undergone a successful vasectomy.

2.7.2. During and After Study Participation

2.7.2.1. Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking CC-220, at study discontinuation, and at Day 28 following the last dose of CC-220.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking CC-220, at study discontinuation, and at Days 14 and 28 following the last dose of CC-220.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, CC-220 must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. CC-220 must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking CC-220 and for at least 28 days after the last dose of CC-220.

2.7.2.2. Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal or post ovulation methods] and withdrawal are not acceptable methods of contraception) or use a condom during sexual contact with a pregnant female or a FCBP while receiving CC-220, during dose interruptions and for at least 90 days following the last dose of CC-220, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving CC-220, during dose interruptions or for at least 90 days following the last dose of CC-220.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking CC-220, the Investigator must be notified immediately.

2.7.3. Additional Precautions

- Subjects should be instructed to never give CC-220 to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving CC-220, during dose interruptions and for at least 28 days following the last dose of CC-220.
- No more than a 28 day CC-220 supply may be dispensed to a subject.

1. CC-220 EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of CC-220.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- NOT FCBP

Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:

- Potential risk of fetal exposure to CC-220: CC-220 was found to cause birth defects in experimental animals (rat and rabbit). A teratogenic potential of CC-220 in humans cannot be ruled out. If CC-220 is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking CC-220. Females of childbearing potential must agree not to become pregnant while taking CC-220.
- That the required pregnancy tests performed are negative.
- The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal or post ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving CC-220, while receiving CC-220, during dose interruptions and for at least 28 days after the last dose of CC-220).

One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:

o Intrauterine device (IUD)

o Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [eg, desogestrel])

o Tubal ligation

o Partner's vasectomy

- Examples of additional effective methods:

o Male condom

o Diaphragm

o Cervical Cap

• The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

• Pregnancy tests before, during administration of CC-220 and at the last dose of CC 220, even if the subject agrees not to have reproductive heterosexual contact.

• Frequency of pregnancy tests to be done:

- Two pregnancy tests will be performed prior to receiving CC-220, one within 10 to 14 days, and a second within 24 hours of the start of CC-220.

- Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking CC-220 if menstrual cycles are regular.

- Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking CC-220 if menstrual cycles are irregular.

- If the subject missed a period or has unusual menstrual bleeding.

- When the subject is discontinued from the study and at Day 28 after CC-220 discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of CC-220.

• The subject confirmed that she will stop taking CC-220 immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

• The subject confirmed that she has not and will not breastfeed a baby while taking CC-220 and for at least 28 days after the last dose of CC-220.

• The subject has not and will never share CC-220 with anyone else.

• The subject has not and will not donate blood while taking CC-220, during dose interruptions and for at least 28 days after the last dose of CC-220.

- The subject has not and will not break, chew, or open CC-220 capsules at any point.
- The subject confirmed that she will return unused CC-220 capsules to the study doctor.

2. I have provided the CC-220 Information Sheet to the subject.

Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:

- Potential risk of fetal exposure to CC-220: CC-220 was found to cause birth defects in experimental animals (rat and rabbit). A teratogenic potential of CC-220 in humans cannot be ruled out. If CC-220 is taken during pregnancy, it may cause birth defects or death to any unborn baby.
- The subject has not and will never share CC-220 with anyone else.
- The subject has not and will not donate blood while taking CC-220, during dose interruptions and for at least 28 days after the last dose of CC-220.
- The subject has not and will not break, chew, or open CC-220 capsules at any point.
- The subject confirmed that she will return unused CC-220 capsules to the study doctor.

2. I have provided the CC-220 Information Sheet to the subject.

Do Not Dispense CC-220 if:

- The subject is pregnant.
- No pregnancy tests were conducted for a FCBP.
- The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving CC-220, while receiving CC-220 and during dose interruptions.
- The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

2. CC-220 EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of CC-220.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:

- Potential risk of fetal exposure to CC-220: CC-220 was found to cause birth defects in experimental animals (rat and rabbit). A teratogenic potential of CC-220 in humans cannot be ruled out. If CC-220 is taken during pregnancy, it may cause birth defects or death to any unborn baby.
- The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal or post ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking CC-220, during dose interruptions and for at least 90 days after the last dose of CC-220.
- The subject confirmed that he has not impregnated his female partner while in the study.
- The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking CC-220 confirmed that she will call her healthcare provider immediately if she becomes pregnant.
- The subject has not and will never share CC-220 with anyone else.
- The subject confirmed that he has not donated and will not donate semen or sperm while taking CC-220 or during dose interruptions and that he will not donate semen or sperm for at least 90 days after the last dose of CC-220.
- The subject has not and will not donate blood while taking CC-220, during dose interruptions and for at least 28 days after the last dose of CC-220.
- The subject has not and will not break, chew, or open CC-220 capsules at any point.
- The subject confirmed that he will return unused CC-220 capsules to the study doctor.

2. I have provided the CC-220 Information Sheet to the subject.

Do Not Dispense CC-220 if:

- The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____ (dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

3. CC-220 INFORMATION SHEET

For subjects enrolled in clinical research studies

Please read this CC-220 Information Sheet before you start taking CC-220 and each time you get a new supply. This CC-220 Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about CC-220?

1. CC-220 may cause birth defects (deformed babies) or death of an unborn baby. CC 220 is similar to the medicine thalidomide. It is known that thalidomide causes life threatening birth defects. CC-220 was found to cause birth defects in experimental animals (rat and rabbit). CC-220 has not been tested in pregnant women but may cause birth defects.

If you are a female who is able to become pregnant:

- Do not take CC-220 if you are pregnant or plan to become pregnant
- You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:
  - for 28 days before starting CC-220
  - while taking CC-220
  - during breaks (dose interruptions) of CC-220
  - for at least 28 days after the last dose of CC-220
- You must have pregnancy testing done at the following times:
  - within 10 to 14 days prior to the first dose of CC-220
  - 24 hours prior to the first dose of CC-220
  - weekly for the first 28 days
  - if you have regular menstrual periods: every 28 days after the first month
  - if you have irregular menstrual periods: every 14 days after the first month
  - if you miss your period or have unusual menstrual bleeding
  - 28 days after the last dose of CC-220 (14 and 28 days after the last dose if menstrual periods are irregular)
- Stop taking CC-220 if you become pregnant while taking CC-220
  - If you suspect you are pregnant at any time during the study, you must stop CC 220 immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.
- Do not breastfeed while taking CC-220 and for at least 28 days after the last dose of CC-220
- The study doctor will be able to advise you how to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to CC-220, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

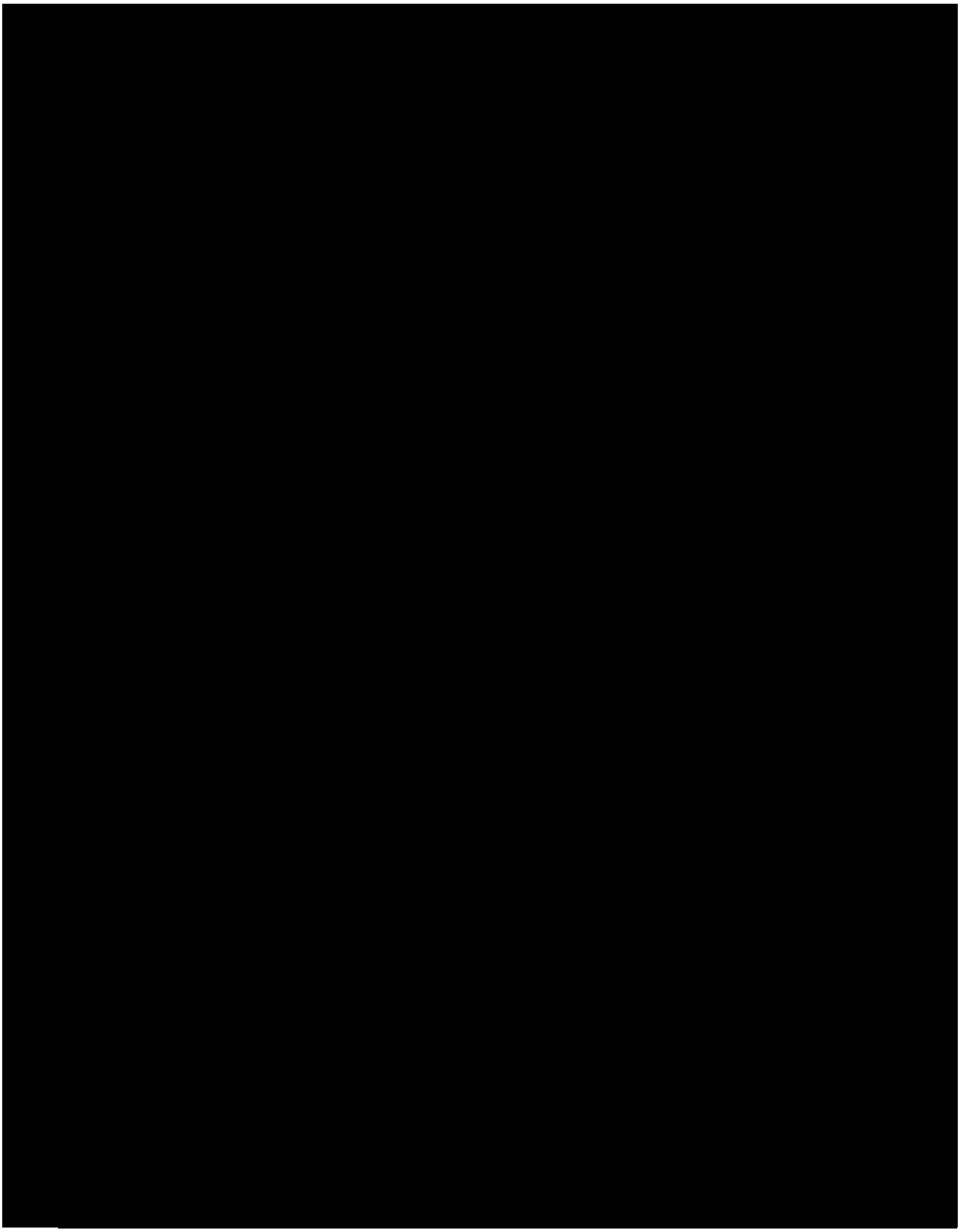
In a 9-month study in monkeys given CC-220 at doses higher than the highest dose in planned lupus and multiple myeloma studies in humans, male monkeys had a decrease in the amount of sperm producing cells. It is not known at this time if this finding can be reversed or at what time after start of CC-220 treatment this decrease will occur. It is not known if there might be a similar effect in men taking CC-220 and how this might affect their ability to father children. There were no observable effects in male sex organs in monkeys that received more than the highest dose given to humans. There were no effects of CC-220 in the sex organs of female monkeys.

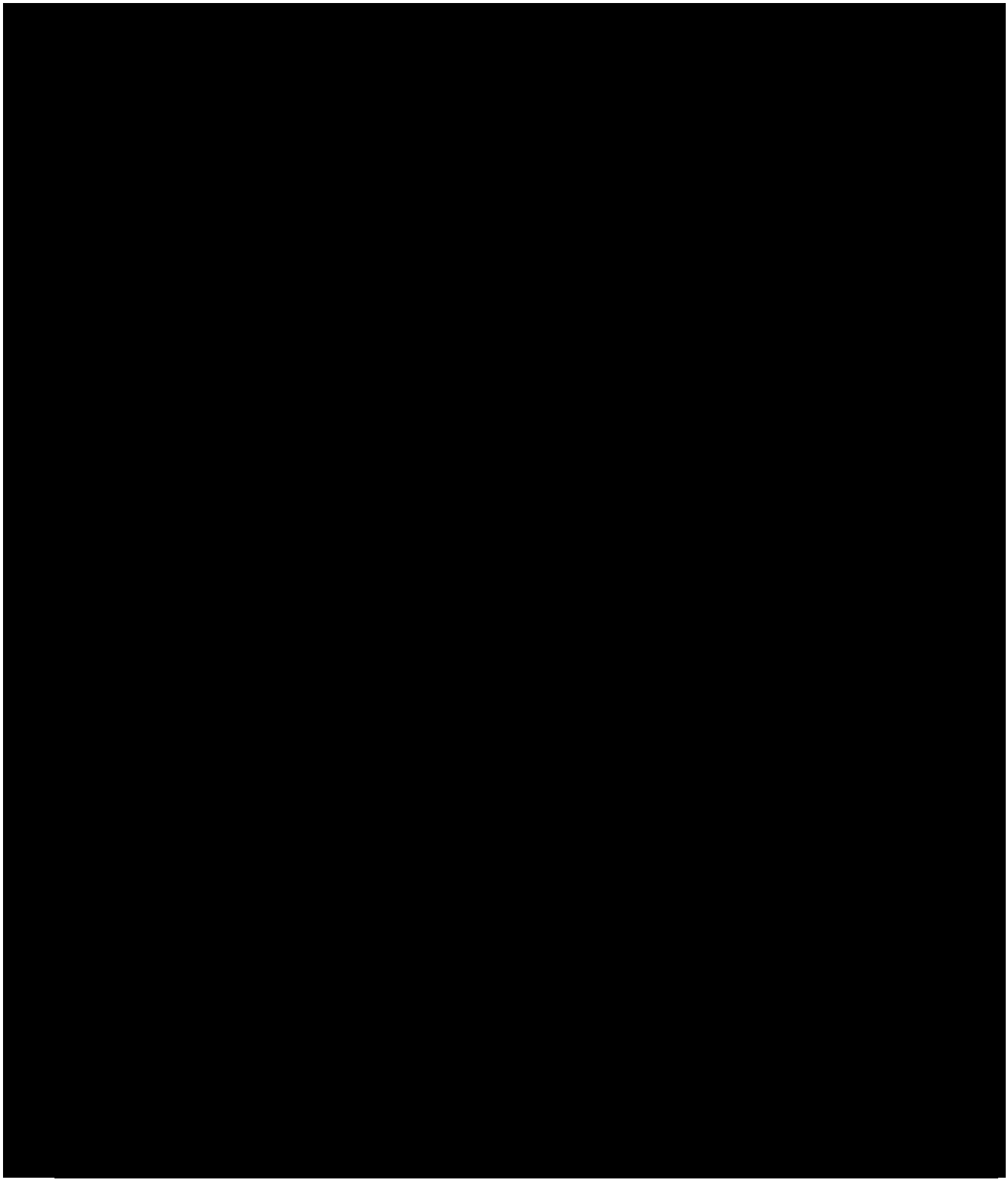
- Subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
    - While you are taking CC-220
    - During breaks (dose interruptions) of CC-220
    - For at least 90 days after the last dose of CC-220
- Male subjects should not donate sperm or semen while taking CC-220, during breaks (dose interruptions) and for at least 90 days after the last dose of CC-220.
- If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.

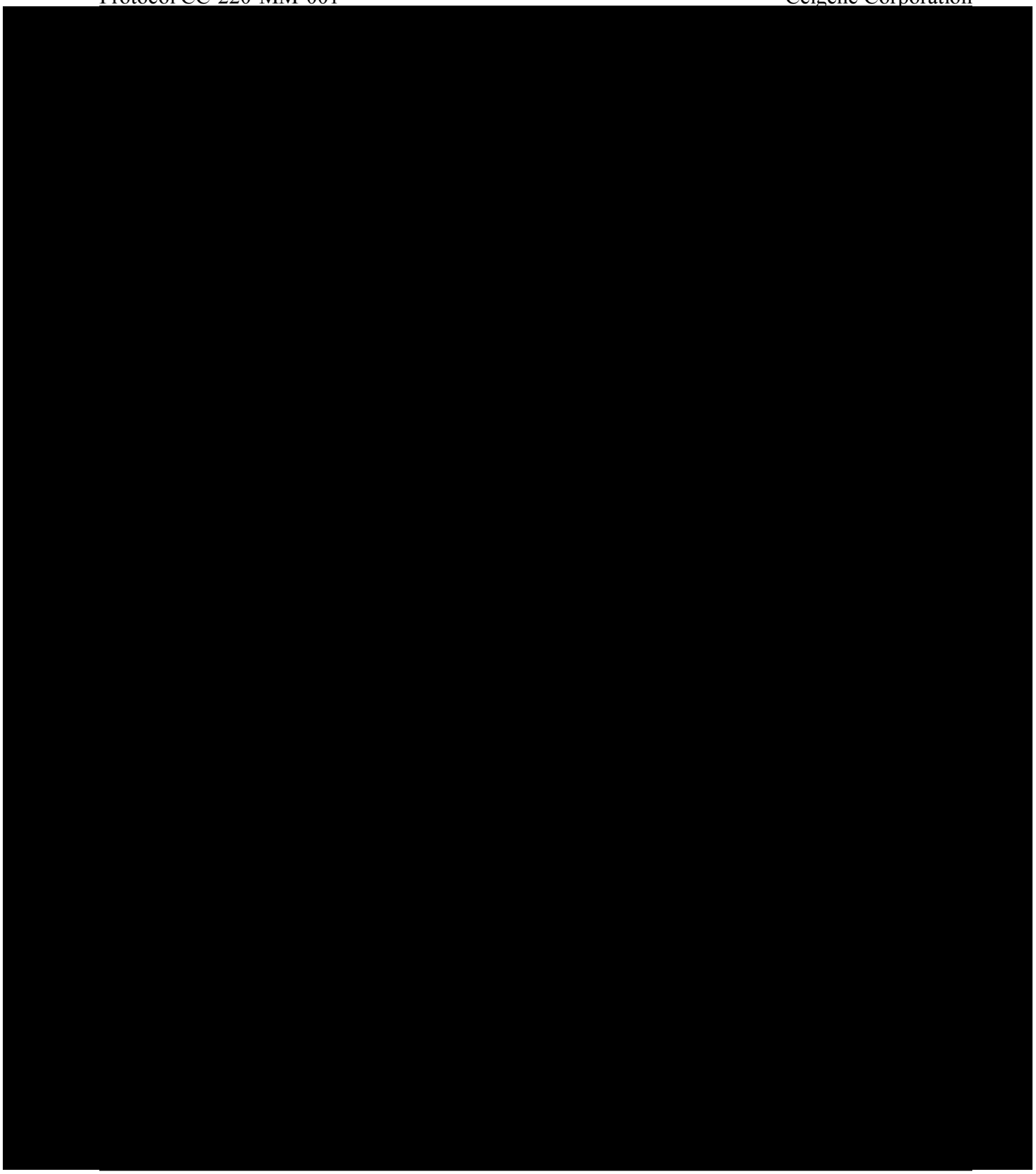
2. All subjects:

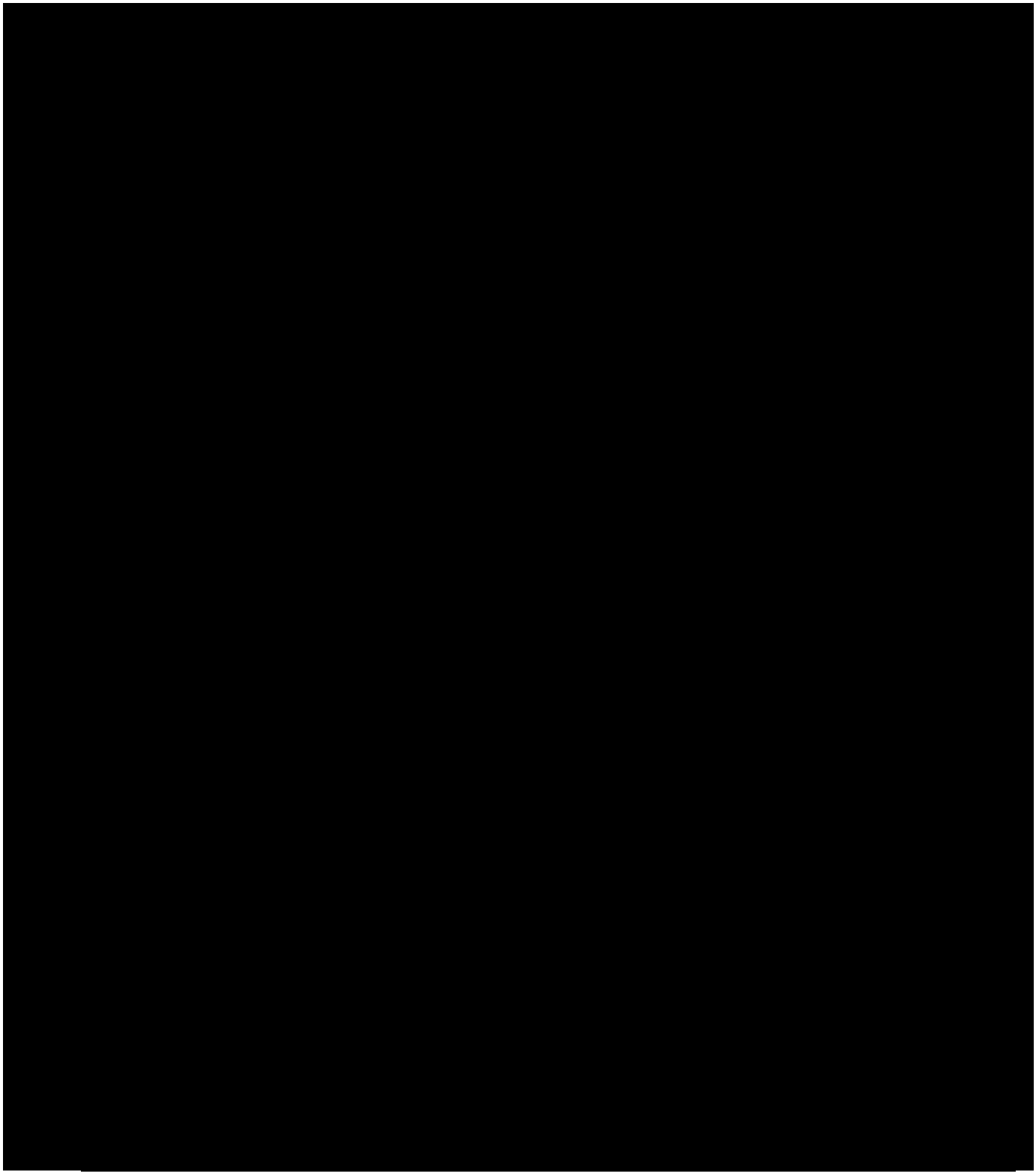
- Do not share CC-220 with other people. It must be kept out of the reach of children and should never be given to any other person.
- Do not donate blood while you take CC-220, during breaks (dose interruptions) and for at least 28 days after the last dose of CC-220.
- Do not break, chew, or open CC-220 capsules at any point.
- You will get no more than a 28-day supply of CC-220 at one time.
- Return unused CC-220 capsules to your study doctor.

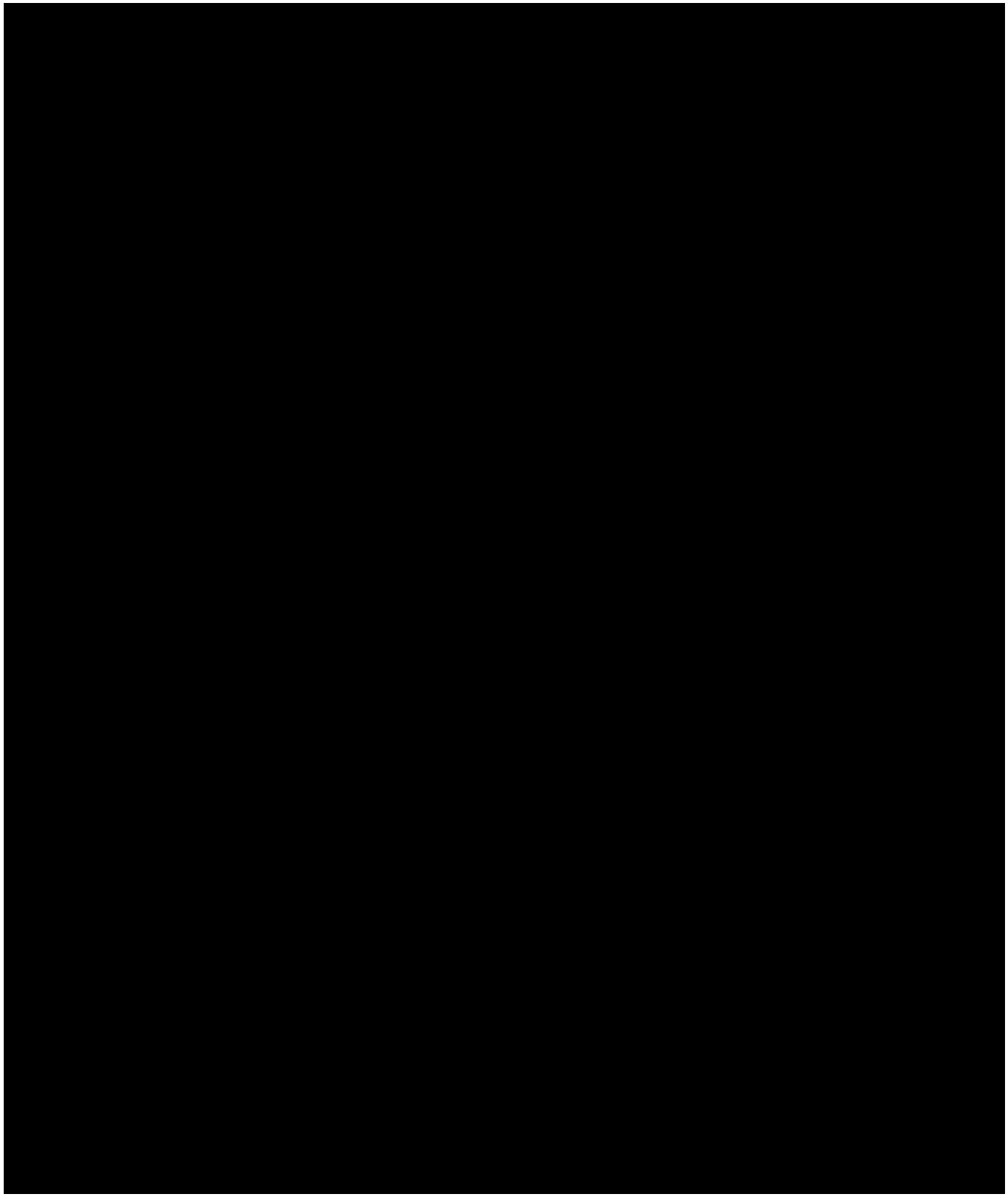
Additional information is provided in the informed consent form and you can ask your study doctor for more information.

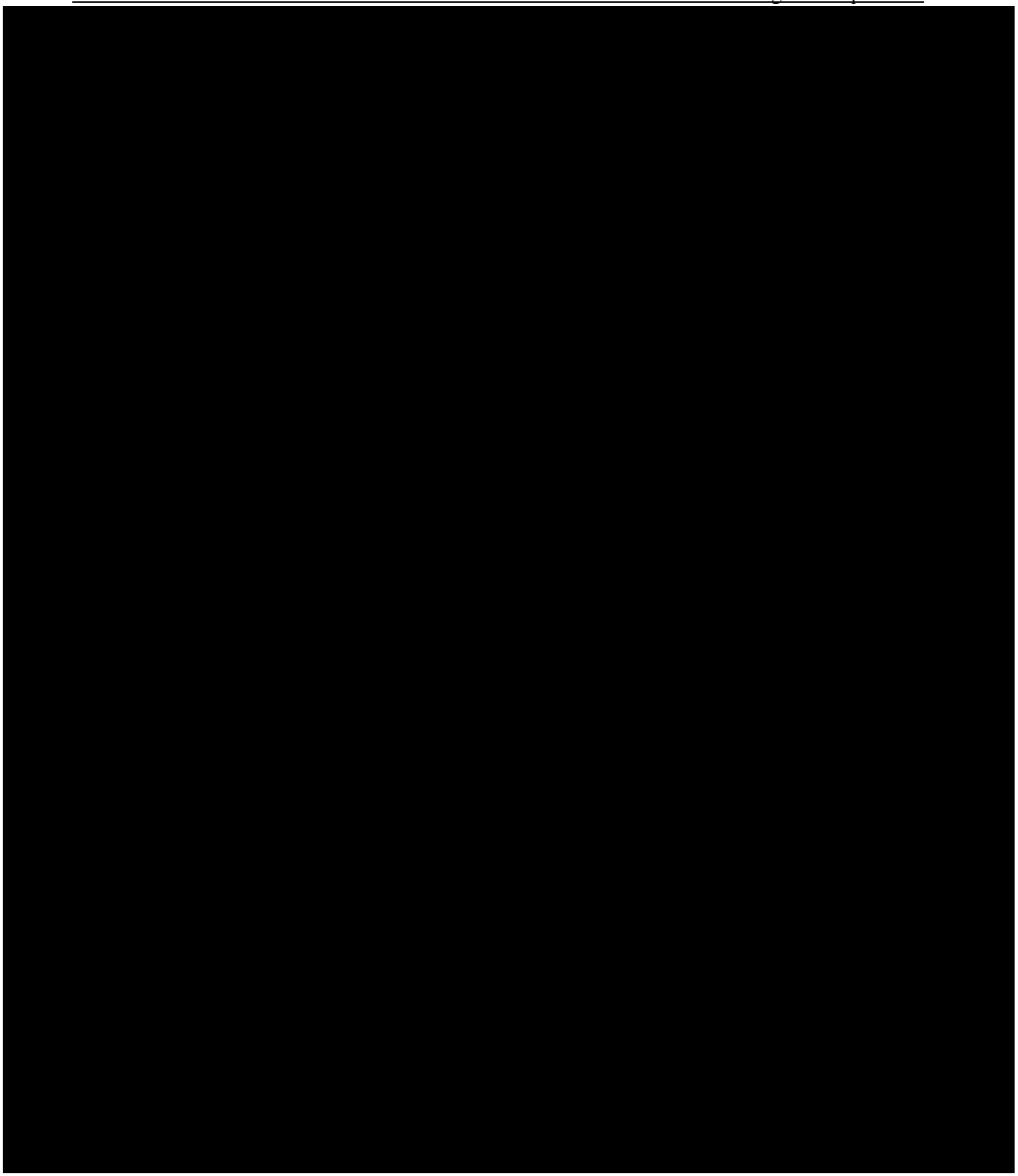












Appendix F: Risk/Benefit Assessment

In the RRMM cohorts, participants have already relapsed after or been refractory to the three major classes of treatment in multiple myeloma: immunomodulatory drugs (IMiDs), proteasome inhibitors, and anti-CD38 antibodies. Clinical outcomes in patients who failed treatment with these drugs are poor, with a median PFS between 3 to 4 months. These patients represent a population with high unmet medical need and novel therapies, especially ones that can add the convenience of oral administration, are greatly needed by these patients.

In NDMM progress has been made in improving the overall survival of patients. The increase in survival has been driven by more effective combination induction regimens composed primarily of combination regimens containing proteasome inhibitors, IMiDs, and more recently with the addition of a CD38-directed cytolytic antibody. However, despite a better understanding of the disease biology and the introduction of new and mechanistically different therapeutic options, MM is not curable with current therapies; thus, there remains a need to develop more efficacious and less toxic therapies for front-line treatment. IMiDs are a core component of these regimens in NDMM, and CC-220, a more potent cereblon-modulating agent with potentially better immunomodulatory properties, may confer further benefit to these patients.

The safety and tolerability profile of the IMiDs lenalidomide and pomalidomide has been well characterized through the extensive use of these drugs in MM. Given the similar mechanism of action, the safety and tolerability profile of CC-220 is anticipated to have common features with these IMiDs. This extensive prior experience with IMiDs was used to support the design and safety monitoring of this study. Additionally, the study CC-220-MM-001 has required close monitoring of participants' safety throughout via frequent visits during the clinical trial, and participants are encouraged to contact the Investigator if an intercurrent illness develops between study visits.

Testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice. The effectiveness and safety risk for the currently approved COVID-19 vaccines in RRMM participants, who are taking the study drugs in this trial, is unknown. Therefore, the Investigator and participant should carefully weigh the benefit to risk ratio prior to making the decision to give an approved COVID-19 vaccine during the Treatment Phase of this study. Investigators are encouraged to contact the Sponsor Medical Monitor to discuss any questions related to the selection or administration of COVID-19 vaccines.

Risk Assessment

Actual clinical risks of combination treatment are unknown but anticipated clinical risks may include some combination of the known clinical risks observed in each of the monotherapies and as noted in the IBs for CC-220, and approved, country-specific package inserts for bortezomib, daratumumab, carfilzomib, and dexamethasone. Human safety data, as detailed above, have shown all compounds to be safe and tolerable at the RP2Ds for CC-220 and at the approved doses and schedules of bortezomib, daratumumab, carfilzomib, and dexamethasone.

The potential risks of clinical significance and mitigation strategies associated with the use each of the novel combinations in this trial are presented in Table 35.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of CC-220, bortezomib, daratumumab, carfilzomib, and dexamethasone may be found in the respective IB or approved, country-specific package inserts for each compound.

Table 35: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study interventions		
Hematologic toxicity (eg, neutropenia, anemia, thrombocytopenia)	CC-220 IB Daratumumab USPI Bortezomib USPI Carfilzomib USPI	Exclusion Criteria (Section 4.3). Dose modification or interruptions per guidelines in Section 7.3. G-CSF, red blood cell and platelet transfusions per Investigator discretion.
Skin and subcutaneous tissue toxicity (eg, rash)	CC-220 IB Daratumumab USPI Bortezomib USPI Dexamethasone USPI	Exclusion Criteria (Section 4.3). Dose modification or interruptions per guidelines in Section 7.3
Vascular (eg, VTE, hypertension)	CC-220 IB Daratumumab USPI Bortezomib USPI Carfilzomib USPI Dexamethasone USPI	Exclusion Criteria (Section 4.3). Dose modification or interruptions per guidelines in Section 7.3
Hyperglycemia	CC-220 IB Carfilzomib USPI Dexamethasone USPI	Exclusion Criteria (Section 4.3). Dose modification or interruptions per guidelines in Section 7.3
Gastroenterological toxicity (eg, diarrhea, nausea, vomiting, colitis, and gastrointestinal perforation)	CC-220 IB Daratumumab USPI Bortezomib USPI Carfilzomib USPI Dexamethasone USPI	Exclusion Criteria (Section 4.3). Dose modification or interruptions per guidelines in Section 7.3
General disorders and administration site conditions (eg, fatigue, febrile neutropenia, pyrexia)	CC-220 IB Daratumumab USPI Bortezomib USPI Carfilzomib USPI Dexamethasone USPI	Exclusion Criteria (Section 4.3). Dose modification or interruptions per guidelines in Section 7.3
Increased risk of infection	CC-220 IB Daratumumab USPI Bortezomib USPI Dexamethasone USPI	Dose modification or interruptions per guidelines in Section 7.3
Metabolism and nutrition disorders (eg, decreased appetite)	CC-220 IB Daratumumab USPI Bortezomib USPI Carfilzomib USPI Dexamethasone USP	Dose modification or interruptions per guidelines in Section 7.3

Table 35: Risk Assessment (Continued)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Respiratory, thoracic, and mediastinal disorders (eg, ILD, pneumonitis, dyspnea)	CC-220 IB Daratumumab USPI Bortezomib USPI Carfilzomib USPI Dexamethasone USPI	Exclusion Criteria (Section 4.3). Dose modification or interruptions per guidelines in Section 7.3
Musculoskeletal and connective tissue toxicity (eg, pain)	CC-220 IB Daratumumab USPI Carfilzomib USPI Dexamethasone USPI	Dose modification or interruptions per guidelines in Section 7.3
Developmental toxicity	CC-220 IB	Inclusion Criteria (Section 4.2), Exclusion Criteria (Section 4.3), Pregnancy Surveillance (Section 10.4), Pregnancy Prevention Plan (Appendix D)
Second primary malignancy (SPM)	CC-220 IB	Exclusion Criteria (Section 4.3), SPM Surveillance (Section 10.7.1)
Study Procedures		
Bone marrow aspirate/biopsy (eg, pain, infection)	Not applicable	Per institutional protocol / Investigator discretion
Phlebotomy (eg, pain, ecchymosis, bleeding, syncope, infection)		
Other (if applicable)		
Allergy to contrast agent (eg, allergic reaction or anaphylaxis)	Not applicable	Prophylaxis and/or treatment per institutional protocol / Investigator discretion

Abbreviations: AE = adverse event; G-CSF = granulocyte colony-stimulating factor; IB = Investigator's Brochure; ILD = interstitial lung disease; SPM = second primary malignancy; USPI = United States Prescribing Information; VTE = venous thromboembolic event.

The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial participants in general. Immunocompromised patient populations such as those with MM, may be more susceptible to infections, including SARS-CoV-2 infections. In addition, the potential impact of study treatments administration on the frequency or severity of SARS- CoV-2 infections in participants with MM are currently unknown. Participants with recent or acute SARS-CoV-2 infections will be excluded or delay start of treatment as defined per Investigator. If a participant has a confirmed SARS-CoV-2 infection while on study treatment, dose delay or interruption of study treatment is per Investigator discretion.

Benefit Assessment

Immunomodulatory compounds are a key component in the treatment of multiple myeloma. CC-220 increased potency and unique pharmacokinetic properties may result in improved efficacy and tolerability over other cereblon-modulating agents. Although benefits may be hypothesized based on mechanisms of action and/or preclinical observations, actual clinical benefits to patients with RRMM have not been established. As noted previously, this population of RRMM

participants may have a median PFS of 3 to 4 months and would benefit from novel, efficacious therapeutics. It is expected that a large portion of the population of RRMM patients eligible for this trial will be amenable to treatment with a combination therapy to be evaluated within this clinical trial that may further extend the lives of these patients. NDMM patients may have a benefit with the use of a more potent cereblon-modulating agent like CC-220 in commonly used first-line combination regimens.

Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with the novel therapeutic combinations defined in this protocol are justified by the anticipated benefits that may be afforded to participants with RRMM and NDMM.

The Sponsor will evaluate the risk/benefit profile of the study on an ongoing basis in consultation with the DEC. This evaluation will be based on all available data – with particular attention to: (i) AEs or other safety trends in this or any other clinical study of the therapeutic agents evaluated in this protocol whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; (ii) new nonclinical data suggesting unreasonable and significant risk of illness or injury.

If such evaluation suggests that the risk/benefit profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data, and interaction with the appropriate Health Authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

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Date: Thursday, 06 January 2022, 01:07 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. One of the main purposes of this amendment is the addition of Cohort K with the goal to investigate CC-220Dd combination regimen in subjects with newly diagnosed multiple myeloma (NDMM) who are transplant non-eligible.

   The rationale for the addition of this cohort is supported by the preclinical data showing the synergy of this combination, the established clinical activity of combination therapy with daratumumab and immunomodulatory compounds (IMiDs) in the NDMM setting, and on the favorable tolerability and encouraging preliminary efficacy of CC-220 in combination with daratumumab and dexamethasone in relapsed and refractory multiple myeloma (RRMM). Refer to Protocol Section 1.3.13 for further details. Thus, the addition of daratumumab to CC-220 therapy may represent a highly effective regimen in NDMM subjects who are not eligible for autologous stem cell transplant (ASCT), and therefore, is chosen for further investigation.

   Revised sections: Protocol Summary; Section 1.3.6.4 Rationale for Dose Levels in NDMM Cohorts J1 and K; Section 1.3.6.5 Schedule; Section 1.3.13 Rationale for NDMM Cohorts (J1, J2 and K); Section 3.1 Study Design; Section 3.1.2 Expansion (Part 2); Figure 2; Section 3.2 Study Duration for Subjects; Section 4 Study Population; Section 5 Table 17; Section 6.2 Treatment Period; Section 6.3 Efficacy Assessment; Section 7.2.1.2 Part 2 (Expansion); Section 7.3 Dose Reduction and Interruption; Section 7.3.1 Table 22; Section 7.5 Method of Treatment Assignment; Section 8.3 Required Concomitant Medications and Procedures; Section 9.1 Overview; Section 9.3 Sample Size and Power Considerations; Section 9.8.2 Very Good Partial Response or Better Rate; Section 10.4 Pregnancy

2. An additional revision is the incorporation of 3 different CC-220 dose levels (1.0 mg, 1.3 mg, and 1.6 mg) in NDMM expansion Cohort J1 and newly added Cohort K. Approximately 75 subjects (up to approximately 25 subjects per dose level) will be enrolled. These doses were selected based on data available from both CC-220Vd (Cohort F) and CC-220Dd (Cohort E) in subjects with RRMM. In both Cohorts F and E, doses of CC-220 up to 1.6 mg have been investigated and considered safe and well tolerated by the Dose Escalation Committee. Based on an additional analysis showing clinical and pharmacodynamic activity of lower doses of CC-220 in these combinations, doses in this interval were selected for further investigation in subjects with NDMM who are not eligible for transplant. Refer to Protocol Section 1.3.6.4 for further details.

   Revised sections: Protocol Summary; Protocol Summary Table 3; Section 1.3.6.4. Rationale for Dose Levels in NDMM Cohorts J1 and K; Section 1.3.13 Rationale for NDMM Cohorts (J1, J2 and K); Section 3.1 Study Design; 3.1.2 Expansion (Part 2); Section 3 Figure 2; Section 4.1 Number of Subjects; Section 7.2.1.2. Part 2 (Expansion); Section 7.3.1 Table 22; Section 7.5 Method of Treatment Assignment; Section 9.3 Sample Size and Power Considerations

3. [redacted]

   Revised sections: Protocol Summary; Section 3.1.2 Expansion (Part 2)

4. [redacted]

   Revised sections: Protocol Summary; Section 3.1.2 Expansion (Part 2)

5. A revision was made to the laboratory exclusion criterion #6 to reflect the limited effect of renal function on CC-220 pharmacokinetics (PK). The role of renal impairment (RI) on CC-220 PK was assessed by an integrated population pharmacokinetic (PopPK) analysis including heathy subjects and patients with relapsed and refractory multiple myeloma. Creatinine clearance (CrCl: 36.2 to 234 mL/min) was not a statistically significant covariate in the final PopPK model and the data suggested that mild/moderate RI (CrCl ≥ 30 to < 90 mL/min) is unlikely to impact CC-220 PK. Additionally, based on the human radiolabeled absorption, distribution, metabolism, and excretion (ADME) study, the intact CC-220 only accounted for 16% and 11% of dose in urine and feces, respectively, indicating the absorbed drug is extensively metabolized and excreted mostly as metabolites with nearly equal contribution from urinary and fecal excretion routes.

   The update was made as follows:

   - Exclusionary criterion #6 was modified to update the exclusionary CrCl value to <30 mL/min (previously <45 mL/min)

   Revised section: Section 4.3 Exclusion Criteria

6. A revision was made to the inclusion criterion #20 to include subjects for who ASCT is not planned for initial therapy.

   Revised sections: Protocol Summary; Section 4.2 Inclusion Criteria

7. The protocol objectives have been updated to reflect the modifications to Cohort J1 and addition of Cohort K.

   Revised sections: Protocol Summary; Section 2 Table 7

8. Modifications were made to existing biomarker assessments to reflect the addition of Cohort K.

   Revised sections: Protocol Summary; Section 6.6 Biomarkers, Pharmacodynamics and Pharmacogenomics

9. Modifications were made to existing PK assessments to reflect the addition of Cohort K. Additional edits were made to provide further clarification to PK endpoints.

   Revised sections: Protocol Summary; Section 2 Table 8; Section 6.5 Pharmacokinetics; Section 9.11.1 Pharmacokinetic Analysis

10. The protocol was updated to include a Risk/Benefit Assessment for CC-220.

Added section: Appendix F

11. Language was revised to provide further clarity regarding investigational product (IP) supply at the end of the study.

    Revised sections: Protocol Summary; Section 3.3 End of Trial; Section 13.8 Termination of the Study

12. The protocol was updated to reflect updated reporting for Product Quality Complaint.

    Revised section: Section 15.3 Product Quality Complaint

13. The Rationale section has been updated to include updated indications for daratumumab and bortezomib.

    Revised sections: Section 1.3.2 Daratumumab; Section 1.3.3 Bortezomib

14. The Permitted Concomitant Medications and Procedures section was modified to clarify the use of granulocyte colony-stimulating factor (GCSF) and similar hematopoietic growth factors to prevent or treat neutropenia.

    Revised section: Section 8.1 Permitted Concomitant Medications and Procedures

15. The amendment also includes other minor clarifications and corrections.
16. Contact details were added for the Medical Monitors [redacted] and [redacted].
17. Additional references were added.

    Revised section: Section 17 References

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. Subcutaneous daratumumab (SC DARA) has recently been approved in the United States (US) and European Union, and is anticipated to be a standard of care option in the future. For this reason, once the recommended Phase 2 dose (RP2D) is determined in Cohort E (CC-220 + daratumumab + dexamethasone [CC-220Dd]) utilizing intravenous DARA, 13 subjects will be enrolled at this dose level using SC DARA to evaluate its safety and tolerability when combined with CC-220 and dexamethasone.

   Revised sections: Protocol Summary; Protocol Summary Table 3; Section 1.3.2 Daratumumab; Section 1.3.14 Schedule; Section 1.3.14 Rationale for Addition of Subcutaneous Daratumumab; Section 2 Table 7; Section 3.1 Study Design; Section 4.1 Number of Subjects; Section 5 Table 10; Section 7.1 Description of Investigational Product(s); Section 7.2.1.1 Part 1 (Dose Escalation); Section 7.2.3 Daratumumab; Section 7.2.3 Table 18; Section 7.2.3.1 Subcutaneous Daratumumab; Section 7.2.3.1.1 Management of Injection-site and Injection-related Reactions; Section 7.2.3.1.1.1 Injection-related Reactions; Section 7.2.3.1.1.2 Injection-related Reactions of Grade 1 or Grade 2; Section 7.2.3.1.1.3 Injection-related Reactions of Grade 3 or Higher; Section 7.2.3.1.1.4 Recurrent Injection-related Reactions; Section 7.4 Overdose

2. The protocol has been updated throughout to reflect the RP2D of 1.6 mg for CC-220 plus DEX, based on the 18 Oct 2019 Dose Escalation Committee recommendation.

   Revised sections: Protocol Summary; Protocol Summary Table 2; Section 1.3.11 Rationale for Cohort D Updated Design; Section 3.1 Study Design; Section 3.1.2 Expansion (Part 2); Section 7.3.1 Table 21

3. The protocol has been updated to reflect that Cohort C monotherapy (Part 2) will no longer be opened. Following the 08 Nov 2019 Dose Escalation Committee review of Cohort A, the 1 mg dose level was deemed tolerable and it was agreed that further investigation of CC-220 monotherapy was more appropriate in a newly diagnosed multiple myeloma maintenance setting. This will be evaluated in a separate protocol.

   Revised sections: Protocol Summary; Section 3.1.2 Expansion (Part 2); Section 4.1 Number of Subjects

4. The protocol objectives have been updated to correctly reflect study cohorts.

   Revised sections: Protocol Summary; Section 2 Table 7

5. A modification was made to existing biomarker assessments:

   The number of subjects enrolled in Cohort D at select US sites, in which the pharmacodynamic (Pd) effects of CC-220 on Aiolos and Ikaros in mononuclear cells will be evaluated, was increased to approximately N=20.

   Revised sections: Protocol Summary; Section 6.6 Biomarkers, Pharmacodynamics and Pharmacogenomics

6. The background section has been updated.

   Revised sections: Section 1.2.1.1 Mechanism of Action of CC-220

7. The International Myeloma Working Group (IMWG) Uniform Response Criteria is updated to the current 2016 criteria (Kumar, 2016).

   Revised sections: Table 8 Study Endpoints; Section 6.3.4 Assessment of Response; Section 9.8.3 Time to Response (TTR); Section 9.8.4 Response Duration (DoR); Section 17 References; Appendix B International Myeloma Working Group Uniform Response Criteria 2016

8. The amendment also includes other minor clarifications and corrections.
9. Contact details were added for the Medical Monitors [redacted] and [redacted].
10. [redacted]
11. Additional references were added.

    Revised section: Section 17 References

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. The primary purpose of this protocol amendment is the implementation of the following three expansion cohorts: CC-220 + dexamethasone (DEX) in relapsed refractory multiple myeloma subjects who have progressed following B-cell maturation antigen (BCMA) therapy (Cohort I), CC-220 + bortezomib + DEX in newly diagnosed multiple myeloma subjects (NDMM) not eligible for autologous stem cell transplantation (ASCT) (Cohort J1), and CC-220 + bortezomib + DEX in NDMM subjects eligible for ASCT (Cohort J2). Accordingly, the study title is revised to "A Phase 1B/2A Multicenter, Open-label, Dose-escalation Study to Determine the Maximum Tolerated Dose, Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of CC-220 as Monotherapy and in Combination with Other Treatments in Subjects with Multiple Myeloma".

   Revised sections: Protocol Summary; Table 1; Table 2; Table 3; Section 1.1 Disease Background; Section 1.3.13 Rationale for NDMM Cohorts (J1 and J2); Section 1.3.6.4 Schedule; Section 2 Study Objectives and Endpoints; Table 7; Table 8; Section 3.1 Study Design; Section 3.1.2 Expansion (Part 2); Figure 2; Section 4.2 Inclusion Criteria; Section 4.3 Exclusion Criteria; Table 14; Table 15; Table 16; Section 9.3 Sample Size and Power Considerations

2. The rationale for the addition of the transplant non-eligible NDMM (Cohort J1) and the transplant eligible NDMM (Cohort J2) is supported by the preclinical synergy data, the positive clinical activity of combination therapy with bortezomib and immunomodulatory compounds (IMiD) in the NDMM setting, and on the favorable tolerability and encouraging preliminary efficacy of CC-220 + DEX.

   Despite a better understanding of the disease biology and the introduction of new and mechanistically different therapeutic options (refer to Protocol Section 1.3.13), multiple myeloma (MM) is not curable with current therapies; thus, there is still a need to develop more efficacious and less toxic treatments for front line treatment (Willenbacher, 2018). As described in Protocol Section 1.3.7, preclinical studies in myeloma cell lines have shown CC-220, like immunomodulatory compounds, to have synergistic antiproliferative activity in combination with bortezomib (Amatangelo, 2018). CC-220 treatment in combination with bortezomib also induces degradation of Aiolos and Ikaros to a greater depth and leads to deeper cell killing than IMiD compounds in combination with bortezomib. Further, in preclinical models CC-220 has been shown to induce degradation of Aiolos and Ikaros with faster kinetics than other IMiD compounds.

   As of 15 April 2019, a total of 101 subjects were enrolled in the CC-220-MM-001 study; 26 subjects in the Cohort A (CC-220 monotherapy, from 0.3 to 1 mg), 66 subjects in Cohort B (CC-220 + DEX, from 0.3 to 1.3 mg), 6 subjects in Cohort E (CC-220Dd, from 1 to 1.1 mg), and 3 subjects in Cohort F (CC-220Vd, 1 mg). The maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) was not yet reached in any cohort. In subjects receiving CC-220 + DEX, the median age was 65 years (range 33 to 79), and median number of prior regimens was 5 (range 2 to12). Prior therapies included autologous stem cell transplantation (79%), lenalidomide (100%), pomalidomide (68%), proteasome inhibitor (100%), and CD38 monoclonal antibody (74%). Clinical activity

was observed across all CC-220 + DEX dose levels with an ORR of 32%, a clinical benefit rate of 49%, and a disease control rate of 85%. The ORR was 35% and 30% in IMiD agent-refractory and daratumumab and pomalidomide-refractory subjects, respectively. CC-220 + DEX showed a favorable safety profile, with Grade 3/4 neutropenia, infections, and thrombocytopenia, occurring in 29%, 26%, and 12% of subjects, respectively. Grade 3/4 fatigue, neuropathy and gastrointestinal disorders occurred in 0%, 1% of subjects, 3% of subjects, respectively. Thus far, data generated from the dose finding part of the study has reported preliminary favorable efficacy and safety of CC-220 + DEX in heavily pretreated subjects with relapsed and refractory multiple myeloma (RRMM) who failed multiple prior therapies (Lonial, 2019).

Taken together, based on the preclinical synergy data, the positive clinical activity of combination therapy with bortezomib and IMiD compounds in the NDMM setting, and on the favorable tolerability and encouraging preliminary efficacy of CC-220 + DEX, the addition of bortezomib to CC-220 therapy may represent a highly effective regimen in NDMM subjects who are eligible for ASCT and those who are not eligible for ASCT, and therefore, is chosen for further investigation.

Revised sections: Protocol Summary; Table 1; Table 3; Section 1.1 Disease Background; Section 1.3.6.4 Schedule; Section 1.3.13. Rationale for NDMM Cohorts (J1 and J2); Section 2 Study Objectives and Endpoints; Table 7; Table 8; Section 3.1 Study Design; Section 3.1.2 Expansion (Part 2); Figure 2; Section 4.2 Inclusion Criteria; Section 4.3 Exclusion Criteria; Table 14; Table 15; Table 16; Section 9.3 Sample Size and Power Considerations

3. Another major rationale for the amendment is the addition of Cohort I (CC-220 + DEX in RRMM subjects who have progressed following BCMA) therapy. Currently, there are multiple BCMA-targeted treatment modalities being investigated to treat MM, including: antibody drug conjugates (ADC), bispecific T-cell engagers, Chimeric Antigen Receptor T-cell Therapies (CAR T), bispecific and bi/trispecific antibodies, as well as cancer vaccines. (Shih-Feng Cho, 2018). The development of novel agents targeting BCMA is ongoing and data from early clinical trials have demonstrated significant anti-myeloma activity in heavily pre-treated RRMM subjects (Raje, 2019; Topp, 2019).

   Despite encouraging results, BCMA-targeted therapy is not curative, and the vast majority of subjects will ultimately relapse, thus highlighting the need for effective novel therapies in the post-BCMA setting. Cohort I will enroll up to 40 subjects who have received prior BCMA-targeted therapy to explore the safety and preliminary efficacy of CC-220 + DEX in this patient population. As CAR T therapy is anticipated to be a standard of care option in the future, Cohort I targets to enroll a minimum of 40% of subjects with prior BCMA-targeted CAR T therapy to ensure adequate representation of this population.

   Revised sections: Protocol Summary; Table 1; Table 3; Section 1.1 Disease Background; Section 1.3.12 Rationale for Cohort I; Section 2 Study Objectives and Endpoints; Table 7; Table 8; Section 3.1 Study Design; Section 3.1.2 Expansion (Part 2); Figure 2; Section 4.2 Inclusion Criteria; Section 4.3 Exclusion Criteria; Table 14; Section 1.3.6.4 Schedule; Section 9.3 Sample Size and Power Considerations

4. Several revisions are made to the study population, primarily to reflect the addition of Cohorts I, J1 and J2 to Part 2.

   Updates to account for the addition of Cohort I are as follows:

   - Inclusion criteria #4 is amended to clarify the measurable disease criteria applicable for RRMM subjects. The prior myeloma regimen requirements, which are outlined in inclusion criteria #5, #6, #7, #8, and #18 are amended to specify RRMM cohorts and/or to account for the addition of Cohort I. Inclusion criteria #9 is amended to specify that RRMM subjects who had CAR T therapy as their last myeloma therapy must have documented disease progression. Clarification is added to exclusion criteria #13 that the 28 days or 5 half-lives washout period from treatment with an investigational agent is not applicable for subjects who received CAR T as last prior regimen.

   Updates to account for the addition of Cohorts J1 and J2 are as follows:

   - Additional inclusion criteria #19, #20, and #21 are incorporated to reflect diagnostic and measurable disease criteria for NDMM Cohorts J1 and J2. Exclusion criteria #10 and #23 are amended to account for addition of Cohorts J1 and J2. Additional exclusion criteria #29 is incorporated to exclude any prior anti-myeloma therapy.

   Additional revisions are made to the laboratory exclusion criterion #6 to reflect the expected organ and bone marrow function of the multiple myeloma patient population. The changes are further supported by data generated from the dose finding part of this study, which has reported favorable safety of CC-220 + DEX (please refer to further details presented in Section 1.3.13).

   - Updates are made to exclusion criteria #6 to amend platelet counts for subjects in Part 2 to < 75,000/μL for subjects in whom < 50% of bone marrow nucleated cells are plasma cells; otherwise platelet count <50,000/μL. Creatinine clearance requirements are updated from 50 ml/min to 45 ml/min.

   Other changes include inclusion criteria #11 and #12 contraception requirements for bortezomib which were updated to align with the latest Velcade® prescribing information and to include Cohorts J1 and J2. A clarification is made to the cardiac history in exclusion criteria #26.

   Revised sections: Protocol Summary; Table 1; Section 4.2 Inclusion Criteria; Section 4.3 Exclusion Criteria

5. Primary, secondary, and exploratory objectives and endpoints are updated primarily to reflect the addition of the NDMM cohorts. The study endpoint table is modified to reflect the addition of a ≥Very Good Partial Response rate secondary endpoint. Additional minor modifications were made to objectives and endpoints to specify applicability to certain cohorts.

   Revised section: Protocol Summary; Section 2 Study Objectives and Endpoints; Table 7; Table 8; Section 6.6 Biomarkers, Pharmacodynamics and Pharmacogenomics; Section 9.8.2 Very Good Partial Response or Better Rate

6. The number of planned subjects is updated primarily to reflect the addition of Cohorts I, J1, and J2.

   Up to 40 total subjects may be enrolled to Cohort I.

   Approximately 100 total subjects (50 subjects each) may be enrolled to Cohorts J1 and J2. Sample size assumptions are further described in Protocol Section 9.3.

   Revised sections: Protocol Summary; Section 1.3.12 Rationale for Cohort I; Section 1.3.13 Rationale for NDMM Cohorts (J1 and J2); Section 3.1.2 Expansion (Part 2); Section 4.1 Number of Subjects; Section 9.3 Sample Size and Power Considerations

7. Response assessment requirements during treatment period is amended to specify that subjects in J1 will be followed every cycle for the first 2 years and thereafter, every 3 months until Progressive disease (PD) or a until a subsequent myeloma regimen has been started. Subjects in Cohort J2, following induction, ASCT with or without maintenance, will be followed for response assessment during the Post-Treatment Response follow-up every 3 months until PD or until a subsequent anti-myeloma regimen has been started.

   End of treatment visit is amended to specify for subjects in Cohort J2 who will not undergo an ASCT for whatever reason, an end of treatment (EOT) Visit should be performed. For those subjects in Cohort J2 who undergo an ASCT, the EOT Visit should be performed three months after the transplant.

   Follow-up criteria for Cohort J1 is added to include every cycle for the first 2 years and thereafter, every 3 months until PD or a until a subsequent myeloma regimen has been started. Follow-up criteria for Cohort J2 is added to include subject follow-up for response assessment following induction, ASCT with or without maintenance every 3 months until PD or until a subsequent anti-myeloma regimen has been started whereby a Post-Treatment Response Follow Up Discontinuation visit will be performed.

   Long-term follow-up criteria in Part 2 is amended to include Cohort I.

   Revised sections: Protocol Summary; Table 14; Table 15; Table 16; Section 3.1 Study Design; Section 3.2 Study Duration for Subjects; Section 6.2 Treatment Period; Section 6.2.1 End of Treatment Visit; Section 6.2.3 Post Treatment Response Assessment; Section 6.2.4 Long-term Follow-up; Section 6.3 Efficacy Assessment; Section 6.3.3 Extramedullary Plasmacytoma Assessments; Section 6.3.4 Assessment of Response

8. Table 14 is updated to include Cohort I (CC-220 + DEX in post-BCMA RRMM).

   Table 15 is created for Cohort J1 (CC-220Vd in NDMM not eligible for ASCT).

   Table 16 is created for Cohort J2 (CC-220Vd in NDMM eligible for ASCT).

   A clarification is added to Tables 9, 10, 11, 12, 13, 14 and 15 that during Post-Treatment Response Follow-up an extramedullary plasmacytoma (EMP) radiological assessment is only required every 3 months for those with a history of or clinical indication of EMPs only assessable radiographically.

   Revised sections: Tables 9, 10, 11, 12, 13,14, 15, and 16

9. The pharmacokinetic assessments section is revised to include both the sparse and intensive collection plan for Cohorts I, J1, and J2.

   Revised sections: Protocol Summary; Table 14; Table 15; Table 16; Section 6.5 Pharmacokinetics

10. Several revisions are made to the existing biomarker collection plan primarily to reflect the addition of Cohorts I, J1, and J2.

    [redacted]

    The bone marrow aspirate collection plan for minimal residual disease assessment is modified to include 6, 12, 18, and 24 months from C1D1 and yearly thereafter after achieving a response of VGPR or better until disease progression for Cohorts C, D, and I. For Cohort J1, the following bone marrow aspirate (BMA) collection plan is implemented: C7D1, 12, 18, 24 months from C1D1 and yearly thereafter after achieving a response of VGPR or better until disease progression. For Cohort J2 the following BMA collection plan for minimal residual disease (MRD) assessment is implemented: C4D1 of induction or end of induction, whichever comes first, after achieving VGPR or better and 100 days post-ASCT.

    Additional modifications are made to existing biomarker assessments to include Cohorts I, J1 and J2.

    Revised sections: Protocol Summary; Section 6.3.1 Bone Marrow Aspirate and/or Biopsy; Section 6.6 Biomarkers, Pharmacodynamics and Pharmacogenomics; Table 7; Table 8; Table 14; Table 15; Table 16; Table 17

11. Descriptions of treatment administration and schedule are modified to include Cohorts I, J1, and J2.

    Revised sections: Section 7.2 Treatment Administration and Schedule

12. Concomitant medications section is modified to clarify granulocyte colony stimulating factor (GCSF) use during the study.

    Revised sections: Section 8.1 Permitted Concomitant Medications and Procedures; Section 8.2 Prohibited Concomitant Medications and Procedures

13. The statistical plan, sample size, and study population definitions are amended to include Cohorts I, J1 and J2. Verbiage describing the Bayesian continuous monitoring method to monitor overall response rate (ORR) for futility and stopping rules for Cohort I is presented.

    The definition of very good partial response or better ($\geq$ VGPR) rate is added.

    Revised sections: Table 30; Section 9 Statistical Considerations; Section 9.3 Sample Size and Power Considerations; Section 9.8.2 Very Good Partial Response or Better Rate; 9.10 Interim Analysis

14. Additional references are added.

Revised section: Section 17 References

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. The primary purpose of this protocol amendment is the implementation of the following two triplet safety cohorts: CC-220 + dexamethasone (DEX) + weekly carfilzomib (CFZ) (Cohort G1) and CC-220 + DEX + twice weekly CFZ (Cohort G2). Accordingly, the study title is revised to "A Phase 1b/2a Multicenter, Open-label, Dose-escalation Study to Determine the Maximum Tolerated Dose, Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of CC-220 Monotherapy and in Combination with Other Treatments in Subjects with Relapsed and Refractory Multiple Myeloma". The basis for the combination with CFZ is supported by pre-clinical and clinical data that demonstrate the synergistic activity with proteasome inhibitors and immunomodulatory compounds. Improved outcomes with CFZ compared to bortezomib in relapsed and refractory multiple myeloma (RRMM) suggests the addition of CFZ to CC-220 therapy could be highly effective in RRMM, and therefore, is chosen for further investigation.

   A 3+3 dose escalation design, which is currently utilized for existing Part 1 cohorts, will also be utilized to establish the maximum tolerated dose and/or recommended phase 2 dose (MTD/RP2D) of CC-220 when administered in combination with DEX and CFZ. The primary objective is revised to include determination of the MTD/RP2D of CC-220 in combination with DEX and CFZ in subjects with RRMM. The secondary objectives are also revised to include both Cohorts G1 and G2 in the evaluation of safety and in the evaluation of preliminary efficacy. Consequently, the endpoints are modified to include these two additional cohorts, where applicable.

   Revised section: Protocol Summary, Table 1, Table 4, Section 2 Study Objectives and Endpoints, Table 7, Table 8, Section 3.1 Study Design, Section 3.1.1 Dose Escalation (Part 1), Section 3.1.1.2 Dose-limiting Toxicity, Figure 2, Section 4.2 Inclusion Criteria, Table 12, Table 13, Section 4.3 Exclusion Criteria, Section 1.3.5 Carfilzomib, Section 1.3.7.2 Dose of CC-220 in Triplet Regimens (Cohorts E, F, G1 and G2), Section 1.3.7.4 Schedule, Section 1.3.8. Rationale for Choice of Combination Compounds, Section 9.3 Sample Size and Power Considerations.

2. The amendment also implements a group sequential design to evaluate the efficacy and safety of CC-220 in combination with DEX in Cohort D. Once the RP2D is established for Cohort B and expansion is determined by the Dose Escalation Committee (DEC), Part 2 will be initiated to further evaluate the efficacy and safety of CC-220 plus DEX in Cohort D. This part of the study will implement a group sequential design, where a limited number of subjects will be enrolled in Stage 1 to ensure a sufficient efficacy signal is seen prior to potentially enrolling additional subjects in Stage 2.

   The rationale for this change is supported by data generated from the dose finding part of this study, which has reported favorable preliminary efficacy and safety of CC-220 in combination with DEX in heavily pretreated subjects with RRMM who failed multiple prior therapies. As of 11 January 2019, 58 subjects received CC-220 plus DEX in doses ranging from 0.3 to 1.2 mg in Cohort B. The median age was 64.5 years (range 33–79), and median number of prior regimens was 5 (2–12). Prior therapies included autologous stem cell transplant (79%), lenalidomide (100%), pomalidomide (69%), proteasome

inhibitors (100%), and daratumumab (66%). Median duration of therapy was 12+ weeks (range 4–109). Grade 3–4 AEs were reported in 41 (72%) subjects. The most frequently occurring Grade 3/4 AEs included neutropenia (26%), anemia (23%), infections (19%), and thrombocytopenia (11%). Of the 51 efficacy-evaluable subjects, 16 achieved a partial response or better (31%), 26 minimal response or better (51%), and 45 achieved stable disease or better (88%).

For this reason, a primary objective was added for Part 2 to determine the efficacy of CC-220 in combination with DEX in subjects with RRMM, as measured by overall response rate (ORR). Secondary objectives were amended to include evaluation of additional efficacy parameters of CC-220 in combination with DEX, including time-to-response (TTR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) in subjects with RRMM. Accordingly, endpoints are modified, where applicable.

Revised sections: Protocol Summary, Table 1, Section 1.3.12. Rationale for Cohort D Updated Design, Section 2 Study Objectives and Endpoints, Table 9, Section 3.1 Study Design, Section 3.1.2 Expansion (Part 2), Figure 2, Section 4.2 Inclusion Criteria, Section 4.3 Exclusion Criteria, Section 9 Statistical Considerations, Section 9.10 Interim Analysis.

3. Several revisions are made to the study population, primarily to reflect the addition of Cohorts G1 and G2 and to reflect the modifications to Part 2.

   Updates to account for the addition of Cohorts G1 and G2 are as follows:

   - Inclusion criteria #5 is amended to specify subjects in these cohorts must also have 2 prior regimens. The male and female contraception requirements, which are outlined in inclusion criteria #11 and #12, are updated in accordance with the latest carfilzomib prescribing information. Exclusion criteria #10 is revised to account for the addition of Cohorts G1 and G2. Exclusion criteria #24, #25, #26 and #27 are incorporated to reflect safety parameter exclusions for carfilzomib.

   Updates to account for the modifications to Part 2 are as follows:

   - Inclusion criteria #5, #6, and #16 are modified to update the prior exposure requirements for Cohort D. Subjects in this cohort are now required to receive at least three prior therapies including lenalidomide, pomalidomide, a proteasome inhibitor, a glucocorticoid and a CD38 antibody. Inclusion criterion #17 is added to require subjects in Cohort D be refractory to an immunomodulatory agent, a proteasome inhibitor, a glucocorticoid, and a CD38 antibody. Refractory is defined as disease that is nonresponsive on therapy (failure to achieve minimal response or development of progressive disease while on therapy) or progresses within 60 days of last dose. Exclusion criterion #28 is added to exclude subjects with prior history of treatment with gene therapy-based therapeutic for cancer or investigational cellular therapy for cancer or B-cell maturation antigen (BCMA) targeted therapy from Cohorts C and D.

   Other changes include the additions of exclusion criteria #23 to exclude subjects with acute diffuse infiltrative pulmonary and pericardial disease in accordance with the latest bortezomib prescribing information and exclusion criteria #11 to generally exclude

subjects with contraindications to other treatment regimens, as per local prescribing information.

Revised sections: Protocol Summary, Table 1, Section 4.2 Inclusion Criteria, Section 4.3 Exclusion Criteria.

4. The dose increments for all Part 1 dose escalation cohorts is modified to allow up to a 25% increase in dose from the prior dose level, as determined by the Dose Escalation Committee. In the present study, at doses above 0.9 mg, dosing ascends in increments of 0.1 mg. Based on estimated pharmacokinetic (PK) parameters from this study's data, historical data variability, and the less than 10% increases in dose, clinically significant differences in exposure are not being achieved with 0.1 mg dose escalations. In addition, based on the preliminary data generated from the dose finding part of the present study thus far, CC-220 as monotherapy and in combination with DEX appears to be generally well tolerated in heavily pretreated subjects with RRMM who failed multiple prior therapies. Therefore, based on the totality of the data, dose increases of up to 25% are implemented for subsequent dose level explorations. The rationale for the modification in dose increment increase is further detailed in in Section 1.3.7.3.

   Revised section: Protocol Summary, Table 2, Table 3, Table 4, Section 1.3.7.3 Rationale for Dose Increments in Dose Escalation, Figure 1, Table 5, Table 6, Section 3.1.1.1 Dose Escalation Committee.

5. The number of planned subjects is updated primarily to reflect the addition of Cohorts G1 and G2 and to reflect the modifications to the design of Cohort D.

   - Approximately 36 total subjects may be enrolled to Cohorts G1 and G2. The actual number of subjects will depend on the number of dose levels being tested (based on the occurrence of dose-limiting toxicity [DLT]) and may exceed these approximations.
   - In Cohort D, Stage 1, following the treatment of 40 subjects, an interim analysis will be performed to evaluate the preliminary efficacy of CC-220 plus DEX at the RP2D. If the results from Stage 1 does not cross the futility boundary, an additional 61 subjects may be treated to confirm the efficacy and safety of CC-220 plus DEX at the RP2D.

   Further, the number of subjects in Cohort A is modified to 34 subjects and in Cohort B to 72 subjects. As of 11 January 2019, the MTD/RP2D of CC-220 has not yet been reached at the dose levels studied in either cohort. Two DLTs, a Gr 3 lower respiratory tract infection and Gr 4 neutropenia, were observed in Cohort A at the 0.75 and 0.9 mg dose levels, respectively. One DLT of Gr 4 sepsis was observed in Cohort B at the 1.2 mg dose level. Consequently, 3 additional subjects were enrolled into each cohort dose level per the protocol DLT/MTD definition criteria. No further DLTs were observed, thus dose escalation in both cohorts is ongoing. The actual number of subjects in dose escalation part (Part 1) will depend on the number of dose levels being tested (based on the occurrence of DLT) and may exceed these approximations.

   Revised sections: Protocol Summary, Section 3.1.1 Dose Escalation (Part 1), Section 4.1 Number of Subjects, Section 9.3 Sample Size and Power Considerations.

6. [redacted]

   Revised sections: Protocol Summary, Section 2 Study Objectives and Endpoints, Table 7, Table 8, Table 14, Section 6.2 Treatment Period, Section 6.2.1 End of Treatment Visit, [redacted] Section 9 Statistical Considerations, [redacted].

7. Part 2 of the study may incorporate an independent response committee (IRC) to review efficacy data. The IRC will review efficacy data in accordance with the IRC Charter.

   Revised sections: Protocol Summary, Section 6.3.5 Independent Response Committee (IRC) Assessment, Section 9.8 Efficacy Analysis.

8. The long-term follow-up criteria for Part 2 cohorts (Cohort C and Cohort D) are modified to include subject contact every 3 months for 5 years from the date of the last subject enrollment in the study, or longer if clinically indicated. Subjects will be followed to collect the following information: survival, subsequent anti-myeloma therapies including date of progression, and second primary malignancies (SPM). [redacted]

   Revised sections: Protocol Summary, Section 2 Study Objectives and Endpoints, Table 7, Table 8, Section 3.1 Study Design, Section 3.2 Study Duration for Subjects, Table 14, Section 6.2.4 Long-term Follow-up, [redacted]

9. Primary, secondary, and exploratory are updated to reflect the changes in the study. The study endpoint table is modified to reflect the appropriate timeframes for all primary, secondary, and exploratory endpoints.

   Revised section: Protocol Summary, Section 2 Study Objectives and Endpoints, Table 7, Table 8, Table 9.

10. Multiple Table of Events are created to provide cohort specific information and improve clarity for sites. Table 9 is created for Part 1 Cohorts A (monotherapy) and B (CC-220+DEX). Table 10 is created for Part 1 Cohort E (CC-220Dd). Table 11 for Part 1 Cohort F (CC-220Vd) is updated to reflect relevant protocol changes. Table 12 is created

for Part 1 Cohort G1 (CC-220Kd). Table 13 is created for Part 1 Cohort G2 (CC-220Kd). Table 14 is created for Part 2 Cohort C (monotherapy) and Cohort D (CC-220+DEX).

Revised section: Tables 9, 10, 11, 12, 13, and 14.

11. Phosphate testing is now included in the chemistry panel that is utilized during the screening period, treatment period, and end of treatment visit.

    Revised section: Section 6.1 Screening Period, Section 6.2 Treatment Period, Section 6.2.1 End of Treatment Visit

12. A local hepatitis panel is incorporated during screening for all subjects. In addition, hepatitis B virus (HBV) DNA testing by polymerase chain reaction (PCR) is added to Cohort E subjects who have an indication for testing, as detailed in Table 10 (Table of Events for CC-220Dd) in accordance with updated daratumumab (DARA) safety information in the prescribing information (PI) and Summary of Product Characteristics (SmPC).

    Revised section: Tables 9, 10, 11, 12, 13, and 14, Section 6.1 Screening Period, Section 6.2 Treatment Period, Section 6.2.1 End of Treatment Visit.

13. An echocardiogram/multi-gated acquisition scan (ECHO/MUGA) is incorporated during screening for all subjects in Cohorts G1 and G2 in accordance with the safety considerations for carfilzomib.

    Revised section: Table 12, Table 13, Section 6.1 Screening Period.

14. The pharmacokinetic assessments section is revised to include both the sparse and intensive collection plan for Cohorts G1 and G2. Additionally, the number of subjects undergoing intensive PK in Cohorts C and D is modified to approximately 10 subjects in each cohort.

    Revised section: Protocol Summary, Table 12, Table 13, Table 14, Section 6.5 Pharmacokinetics.

15. Several revisions are made to the existing biomarker collection plan to reflect the addition of Cohorts G1 and G2. Additional modifications are made to various timepoints to account for cohort specific dosing schedules. Other modifications include the removal of the lymphocyte panel to explore T-cell counts from Part 2.

    New biomarker assessments are introduced for a subset of patients at select United States (US) sites. An assessment to evaluate the pharmacodynamic (Pd) effects of CC-220 on Aiolos and Ikaros using a novel exploratory assay is added for Cohorts B, D, F, G1, and G2. At one pre-identified US site, time-matched bone marrow aspirate (BMA) and whole blood will be collected to analyze PK/Pd in approximately 5 subjects in Cohort D.

    Lastly, an assessment [redacted] will be performed on approximately 20 subjects in Cohort D. Accordingly, changes were made to the study's exploratory objectives [redacted]. Rationale for the CAR-T cell products assay is outlined in Section 1.3.9.

Revised sections: Protocol Summary, Section 1.3.9 Rationale for Pharmacodynamics and Potential Predictive Biomarkers, Section 2 Study Objectives and Endpoints, Table 7, Table 8, Tables 9, 10, 11, 12, 13, and 14, Section 6.3.1 Bone Marrow Aspirate and/or Biopsy, Table 15, Section 6.6 Biomarkers, Pharmacodynamics and Pharmacogenomics.

16. Rationale and explanation for the DARA reflex assay is added.

    Revised section: Section 6.3 Efficacy Assessment.

17. Descriptions of treatment administration, schedule and supply/sourcing are added for CFZ. Section 7.2.4 is added to provide guidance on pre-infusion and post-infusion medications for infusion reaction prophylaxis in relation to CFZ dosing.

    Revised sections: Section 7.1 Description of Investigational Product, Section 7.2 Treatment Administration and Schedule, Section 7.2.4 Carfilzomib.

18. Table 18 clarifies that following a dose interruption, the dose of CC-220 may be maintained based on Investigator's discretion if neutropenia was the only CC-220-related toxicity requiring a dose modification and GCSF treatments are continued. This is consistent with experience and practice with other drugs of class (eg, pomalidomide) given bone marrow involvement by disease may worsen cytopenias early in treatment. The use of growth factors in early cycles without dose reduction was fairly common in pomalidomide studies and in practice and is supported by the literature (Expert panel consensus statement on the optimal use of pomalidomide in relapsed and refractory multiple myeloma. MA Dimopoulos, X Leleu, A Palumbo, P Moreau, M Delforge, M Cavo, et al. Leukemia (2014) 28, 1573–1585).

    Revised sections: Table 18 Dose Reduction Instructions for CC-220.

19. The text for dose level reductions for CC-220 in Part 2 is updated to clarify dose level reductions may be in one dose level decrease or as determined by the dose escalation committee.

    Revised section: Section 7.3.1 Dose Modification Instructions for CC-220, Table 19.

20. Dose modification instructions for daratumumab are updated to reflect the suggestions in the latest prescribing information, per PI and SmPC.

    Revised section: Section 7.3.3 Dose Modification Instructions for Daratumumab, Table 22.

21. Dose reduction and interruption instructions are added for Cohorts G1 and G2. Dose modification and dose level reduction instructions are added for CFZ.

    Revised section: Section 7.3 Dose Reduction and Interruption, Section 7.3.5 Dose Modification Instructions for Carfilzomib, Table 25, Table 26.

22. Verbiage for overdose, method of treatment assignment, and investigational product compliance is updated to account for the addition of Cohort G1 and Cohort G2. The definition of overdose is detailed for all study treatments.

    Revised sections: Section 7.4 Overdose, Section 7.5 Method of Treatment Assignment, Section 7.8 Investigational Product Compliance

23. The pregnancy language is updated to include CFZ.

    Revised Section: Section 4.2 Inclusion Criteria, Section 10.4 Pregnancy.

24. Concomitant medications section is updated to include CFZ antiviral prophylaxis as a required medication. A sentence was added to highlight that CYP2C19 substrates should be utilized with caution for subjects in Cohort F (CC-220+DEX+BTZ) due to BTZ's effect on the CYP2C19 enzyme.

    Revised section: Section 8.2 Prohibited Concomitant Medications and Procedures, Section 8.3 Required Concomitant Medications and Procedures.

25. The statistical plan, sample size, and study population definitions are amended to include Cohorts G1 and G2. Verbiage describing the Full Analysis population and the DLT Evaluable population are updated. A description of the Patient Reported Outcomes Evaluable population is presented. The definitions of overall response rate (ORR), time to response (TTR), response duration (DoR), progression-free survival (PFS), and overall survival (OS) are updated.

    A description of the group sequential design that will be utilized for Cohort D is presented. An interim analysis in Cohort D is described.

    [redacted]

    Revised section: Section 9 Statistical Considerations.

26. Additional references are added.

    Revised section: Section 17 References.

27. Additional terms are added to the Table of Abbreviations.

    Revised section: Table 28.

[redacted]

1. JUSTIFICATION FOR AMENDMENT

1. The primary purpose of this amendment is the implementation of the following two triplet safety cohorts: CC-220 + daratumumab (DARA) + dexamethasone (DEX) (Cohort E) and CC-220 + bortezomib (BTZ) + DEX (Cohort F). A 3+3 dose escalation design, which is currently utilized for Cohorts A and B, will also be utilized to establish the MTD/RP2D of CC-220 when administered in combination with these agents. Consequently, the study title is revised to "A Phase 1b/2a Multicenter, Open-label, Dose-Escalation Study to Determine the Maximum Tolerated Dose, Assess the Safety and Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-220 Monotherapy, in Combination with Dexamethasone, and in Combination with Dexamethasone and Daratumumab or Bortezomib in Subjects with Relapsed and Refractory Multiple Myeloma". The primary objective is revised as follows "determine the maximum tolerated doses (MTDs) and/or recommended Phase 2 doses (RP2Ds) of CC-220 as monotherapy (MonoT), in combination with dexamethasone (DEX) (DoubleT), and in combination with dexamethasone and daratumumab (C220Dd TripleT) or bortezomib (C220Vd TripleT) in subjects with relapsed and refractory multiple myeloma (RRMM)". The secondary objectives are also revised to include TripleT cohorts in the evaluation of safety and in the evaluation of preliminary efficacy. Accordingly, the endpoints are modified to include TripleT cohorts, where applicable.

   Revised sections: Protocol Summary, Section 2 Table 3 Study Objectives and Table 4 Endpoints, Section 3.1 Study Design and Figure 1 Overall Study Design,

2. The description of the study design is amended to incorporate Cohorts E and F into the dose escalation phase of the study (Part 1). The number of allowable missed doses for DARA and BTZ impacting criteria for dose-limiting toxicity (DLT) evaluability is defined for these new cohorts. It is also clarified that the determination of RP2D may be based on safety, pharmacokinetic (PK), biomarker, and preliminary efficacy, as applicable.

   Revised sections: Protocol Summary, Section 3.1 Study Design and Figure 1 Overall Study Design

3. Several revisions are made to the study population, primarily to reflect the implementation of TripleT cohorts. The number of planned subjects is updated accordingly. Inclusion Criterion #5 is modified to allow subjects who have received at least 1 prior regimen into Cohort F. Inclusion Criterion #4 is modified to include subjects with light chain multiple myeloma without measurable disease in the serum or urine: serum immunoglobulin free light chain ≥ 10 mg/dL (100 mg/L) and abnormal serum immunoglobulin kappa lambda free light chain ratio. Exclusion Criteria # 20, 21, and 22 are added to reflect safety parameter exclusions for Cohort E. Additionally, Inclusion Criteria # 11, 12, 13, and 14 and Exclusion Criteria # 5, 10, and 11 were revised, primarily to account for the addition of the TripleT cohorts.

   Revised sections: Protocol Summary, Section 4.1 Number of Subjects, Section 4.2 Inclusion Criteria, Section 4.3 Exclusion Criteria

4. Multiple myeloma epidemiology data is updated to include incidence and mortality data from 2016.

   Revised section: Section 1.1 Disease Background

5. In Section 1.3.3, the background information on DARA is updated to include the latest regulatory approvals in the United States (US) and in the European Union (EU) and to reflect the Darzalex® Prescribing Information (PI) for the US and Summary of Product Characteristics (SmPC) for the EU.

   Revised section: Section 1.3.3 Anti-CD38 Therapy

6. Section 1.3.4 is added to provide background information on BTZ from the Velcade® PI for the US and SmPC for the EU.

   Added section: Section 1.3.4 Bortezomib

7. The rationale for the starting dose of CC-220 in TripleT cohorts and for the 28-day cycle in Cohort E and the 21-day cycle in Cohort F is added.

   Revised section: Section 1.3.6 Rationale for Dose, Schedule and Regimen Selection

8. The rationale for the choice of combination of CC-220 with DEX and DARA or BTZ is added. Details from preclinical data in conjunction with data supporting the clinical activity of DARA and BTZ with IMiDs (immunomodulatory compounds) combination therapy are provided.

   Revised section: Section 1.3.7 Rationale for Choice of Combination Compounds

9. Revisions are made to the rationale for pharmacodynamics and potential predictive markers section to include CD38 as a biomarker for further exploration in this study.

   Revised section: Section 1.3.8 Rationale for Pharmacodynamics and Potential Predictive Biomarkers

10. Table 5 (Table of Events) is modified to include Cohort E. Table 6 is created to reflect assessments on a 21-day schedule for Cohort F. Additionally, a Post-Treatment Response Follow-up phase is added to the Table of Events to outline the continued collection of response assessments in subjects with a minimal response (MR) or better who discontinue study treatment in Part 1 or Part 2 of the study for a reason other than progressive disease (PD) or withdrawal of consent from the study.

    Revised sections: Table of Events: Tables 5 and 6

11. The screening assessments section is updated to specify that the Celgene Medical Monitor or designee must be contacted if there is a discrepancy between central safety laboratory results and local safety laboratory results. Upon review of the local laboratory results, the Celgene Medical Monitor or designee may deem the subject eligible for the study if all other eligibility criteria are satisfied.

    Revised section: Section 6.1 Screening Period

12. An additional serum free light chain assay is added to Day 8 and Day 15 of Cycles 1 to 4 for Part 2 to align the current study's analyses of this data with that of other studies.

    Revised section: Table of Events: Table 5 and Section 6.3 Efficacy Assessment

13. The pharmacokinetic assessments section is revised to include the sampling plan for Cohorts E and F, as well as to provide revisions and clarifications to the existing sampling plan for Cohorts C and D for both sparse and intensive collection.

    Revised sections: Protocol Summary Overview of Pharmacokinetic Assessments, Table of Events: Tables 5 and 6, Section 6.4 Pharmacokinetics

14. The biomarker collection plan is modified to include an additional assessment for evaluation of the pharmacodynamic (Pd) effects of CC-220 on Aiolos and Ikaros in mononuclear cells with a novel exploratory assay. Further, an additional timepoint is added at C6D15 to the existing assessments of Pd effects of CC-220 on immune cell populations to further observe evolution of response over time. Additional clarifications are made to the blood collection time points for Cohort F which has a 21-day treatment cycle. Lastly, revisions and clarifications are made to existing assessments, including clarification of when the collection of a bone marrow aspirate (BMA) and/or bone marrow biopsy (BMB) is mandatory and clarification of which assessments are mandatory in Part 1 versus Part 2 of the study. Table 7 is added to summarize and outline the BMA/BMB sample collection plan.

    Revised sections: Protocol Summary Overview of Biomarkers for Pharmacodynamic Assessments, Table of Events: Tables 5 and 6, Section 6.3.1 Bone Marrow Aspirate and/or Biopsy, Section 6.5 Biomarkers, Pharmacodynamics and Pharmacogenomics

15. Additional strengths of CC-220 capsules are added. Details of the excipients of the gel formulation have been removed to allow more flexibility in usage of a different capsule formulation.

    Revised sections: Protocol Summary and Section 7.1 Description of Investigational Product(s)

16. Descriptions of treatment administration; schedule and supply/sourcing are added for DARA and BTZ. Table 8 is added to provide guidance on pre-infusion and post-infusion medications for infusion reaction prophylaxis in relation to DARA dosing. Table 9 provides conversion for glucocorticoid doses to aid with the various glucocorticoids that may be used for pre-infusion and post-infusion across different institutions.

    Revised sections: Section 7.1 Description of Investigational Product(s) and Section 7.2 Treatment Administration and Schedule

17. Dose reduction and interruption instructions are added for Cohorts B, D, E and F. Criteria for dose delay and guidance for DARA-related toxicity management are provided. Dose modification and dose level reductions are also added for BTZ. A footnote was added to the dose modification table for CC-220 to clarify that dose modification instructions are not applicable for $\geq$ Grade 3 Second Primary Malignancies, where dosing modification is at discretion of the Investigator.

    Revised section: Section 7.3

18. Verbiage for overdose, method of treatment assignment, investigational product compliance, and adverse events has been updated to account for the addition of Cohort E and Cohort F.

Revised sections: Section 7.4 Overdose, Section 7.5 Method of Treatment Assignment, Section 7.8 Investigational Product Compliance, Section 10 Adverse Events

19. The pregnancy language has been updated to include DARA and BTZ.

    Revised Section: Section 10.4 Pregnancy

20. Concomitant medications section has been updated to include DARA pre-infusion and post-infusion and antiviral prophylaxis as required medications. Table 17 is added to outline the list of medications that are CYP3A4/5 strong inhibitors and inducers. A sentence was also added to highlight that antibiotics (including prophylaxis use) may be administered.

    Revised section: Section 8 Concomitant Medications and Procedures

21. The statistical plan, sample size and study population definitions are amended to include Cohorts E and F. Further, the verbiage describing the exploratory analyses was simplified to indicate details will be presented in the statistical analysis plan.

    Revised section: Section 9.2 Study Population Definitions, Section 9.3 Sample Size and Power Considerations and Section 9.11.2 Exploratory Analysis

22. Additional terms were added to the Table of Abbreviations.

    Revised section: Section 18, Table 18

23. Additional references are added to Section 17 References.

1. JUSTIFICATION FOR AMENDMENT

1. The primary purpose of this amendment results from preliminary data reported by the Celgene Translational Development team showing changes of T lymphocytes at the higher doses of CC-220. Consequently, an additional exploratory objective, "To evaluate dose-related immune effects of CC-220", has been added to the protocol. To support this objective, a lymphocyte panel containing CD4/CD8 counts will be added to the already scheduled hematology sampling. An additional hematology sample will be drawn on Day 15 of each cycle from Cycle 5 onward. No additional blood will be required at each sampling.

   Revised sections: Protocol Summary Exploratory Objectives, Overview of Biomarkers for Pharmacodynamic Assessments, Section 1.3.7, Section 2 Table 2, Section 2 Table 3, Section 5 Table 4, Section 6.1, Section 6.5, Section 9.11.2

2. To further understand the association between response and residual disease status, another exploratory objective has been added, "In Part 2 of the study, to explore minimal residual disease (MRD) in subjects who achieve a very good partial response (VGPR) or better and its correlation to clinical outcome measures". To support this objective, all subjects enrolled in Part 2 of the study will have a Screening bone marrow aspirate sample taken and stored. If the subject achieves a VGPR or better, another bone marrow aspirate sample will be taken and the two samples then analyzed. If a subject achieves a MRD negative state, a bone marrow aspirate sample will be collected every six months until progression of disease (PD) to determine the duration of the MRD negative state. A rationale for MRD assessments has been added.

   Revised sections: Protocol Summary Exploratory Objectives, Protocol Summary Overview of Key Efficacy Assessments, Protocol Summary Overview of Biomarkers for Pharmacodynamic Assessments, Section 1.3.9, Section 2 Table 2, Section 2 Table 3, Section 5 Table 4, Section 6.1, Section 6.2, Section 6.3.1, Section 6.5, Section 9.11.2

3. An existing exploratory objective has been edited to include immune activation/ exhaustion markers and cytokines.

   Revised sections: Protocol Summary Exploratory Objectives, Section 2 Table 2, Section 2 Table 3, Section 9.11.2

4. Cytogenetic data is collected at Screening for all subjects enrolled. These data are reported by local labs at the investigative sites. To enable consistent and complete results, a central laboratory will be used for this analysis.

   Revised sections: Section 5 Table 4, Section 6.3.1

5. A rational for cytogenetic assessments has been added.

   Revised section: 1.3.8

6. The section Overview of Biomarkers for Pharmacodynamic Assessments has been expanded to provide greater clarity of what markers are being studied and the sample collection time points:

Revised sections: Protocol Summary Overview of Biomarkers for Pharmacodynamic Assessments, Section 6.5

7. The following statement was added to assist investigator's in the management of dosing their elderly subjects greater than 75 years with dexamethasone, "Subjects who surpass the age of 75 years while on treatment may be switched to the 20 mg once daily (QD) dosage based on the investigator's best judgement".

   Revised sections: Protocol Summary, Section 1.3.5.3, Section 3.1, Section 7.2.1, Section 7.2.2

8. References have been updated to support the new objectives and additional text for the rational of cytogenetic assessment.

   Revised section: Section 1.3.7 Section 1.3.8, Section 1.3.9, Section 17

9. The eligibility criteria regarding contraception have been updated in line with the current Pregnancy Prevention Plan.

   Revised section: Section 4.2 Inclusion Criteria #11 and #12

10. Additional information has been provided on the prescribing information for dexamethasone.

    Revised section: Section 7.1

11. The Method of Treatment Assignment has been edited to provide a more efficient process.

    Revised section: Section 7.5

12. The Concomitant Medications and Procedures was updated to include analgesics, antihistamines and/or antibiotic medications for use during the study at the discretion of the investigator.

    Revised section: Section 8

13. The Prohibited Concomitant Medications and Procedures was updated to provide further information of prohibited medications that are strong inhibitors or inducers of CYP3A/5.

    Revised section: Section 8.2

14. A new section was included to provide sites with information regarding product quality complaints

    Revised section: Section 15.3

    The amendment also includes other minor clarifications or corrections:

    - The Study Design of Part 2 (Expansion) section has been corrected to include dosing with dexamethasone in Cohort D.
      - Revised section: Protocol Summary
    - A label of cohort study treatment was added to Part 2 of Table 1.
      - Revised section: Protocol Summary

- Timeframes have been added to all study endpoints.
  - Revised section: Section 2 Table 3
- A sentence was corrected to indicate all subjects with a minimal response or better who discontinue study treatment for a reason other than PD will be followed for response assessment every 28 days until PD or a new myeloma regimen has been started.
  - Revised sections: Protocol Summary, Sections 3.1, 3.2
- A sentence was edited to provide clarity regarding the need to record all local tests that determined a dose interruption and/or reduction of study treatment.
  - Revised section: Section 6.1
- Within the section of Efficacy Analysis, a subsection was relabeled for greater clarity.
  - Revised section: 9.8.1
- Additional abbreviations were added to the Table of Abbreviations
  - Revised sections: Section 18 Table 9, Section 1.3.9, Section 15.3

1. JUSTIFICATION FOR AMENDMENT

1. The primary purpose of this amendment is to provide additional dose-level cohorts to extend the planned dose escalation during Part 1 of this study. All dose levels have been enrolled with no safety concerns or dose-limiting toxicities observed. Further dose levels are necessary to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D).

   Revised sections: Protocol Summary, Figure 1, Section 7.3.1 Table 6

2. In the Part 2 expansion phase of the study, subjects will be required to have been treated with an anti-CD38 therapy in addition to lenalidomide or pomalidomide and a proteasome inhibitor to be eligible for this study. These changes have been made to more fully understand the efficacy profile of CC-220 in patients with advanced relapsed and refractory multiple myeloma (RRMM).

   Revised sections: Protocol Summary, Section 1.3.3, Section 4.2

3. Study endpoints have been changed to include progression-free survival and overall survival for the subjects enrolled in Part 2 of the study to further evaluate the preliminary efficacy of CC-220 as monotherapy and in combination with dexamethasone in subjects with RRMM. These changes have been made to more fully understand the efficacy profile of CC-220 in patients with advanced RRMM.

   Revised sections: Protocol Summary, Section 2, Figure 1, Table 4, Section 6.2.4, Section 9.8.4, Section 9.8.5

4. A long-term follow-up period of 2 years has been added to the length of the study to collect data for the overall survival endpoint and to include second primary malignancy (SPM) surveillance.

   Revised sections: Protocol Summary, Section 3.2, Section 3.3, Figure 1, Table 4, Section 6.2.4, Section 10.7.1

5. Several biomarker assessments that were optional in Part 1 or optional in Part 2 are now mandatory in both Parts 1 and 2. Additionally 2 sample collections were added to the immunophenotyping study to provide greater understanding of the data being collected.

   Revised sections: Protocol Summary, Section 5 Table 4, Section 6.5

6. The pregnancy section has been updated with new information released from the Global Risk Management Pregnancy Prevention Plan.

   Revised sections: Section 10.4, Section 10.4.1, Section 10.4.2

7. The size of the subject population to be enrolled for Cohort C and Cohort D was adjusted. Previously, the planned analysis would include the subjects treated at the recommended Phase 2 dose (RP2D) in Part 1 to be added to these cohorts in Part 2. This has been changed and the full planned population of subjects for analysis will be enrolled for these cohorts.

   Revised sections: Protocol Summary, Section 3.1.2, Section 4.1, Section 9.3

The amendment also includes some other minor clarifications or corrections:

- Reference to the MTD as determining the start of treatment with the RP2D in Part 2 of the study has been edited to read, MTD/RP2D since the RP2D may be achieved based on safety, pharmacokinetic (PK) and biomarker data prior to observing the MTD.
  - Revised sections: Protocol Summary, Section 1.3.5.1, Section 2, Section 9.3
- Clarification of creatinine clearance methods to determine eligibility and to measure creatinine clearance throughout the study.
  - Revised sections: Section 4.3, Section 6.1
- Description of Investigational Product – There has been an addition of two formulated capsules to accommodate the new dose escalating schedule.
  - Revised sections: Protocol Summary, Section 7.1
- Additional changes were made to the statistical section to further clarify data to be collected and analyzed.
  - Revised sections: Section 9.1, Section 9.4, Section 9.7
- The definition of the end of trial has been adjusted to accommodate the addition of the long-term follow-up phase of the study.
  - Revised sections: Protocol Summary, Section 3.3

1. JUSTIFICATION FOR AMENDMENT

This amendment is primarily being generated to provide updated information available with the publication of the Investigator's Brochure (IB) version 7. Section 6.3.6.1 Use in Pregnancy was revised to change the length of time that sexually active males must agree to use protocol-specified contraceptive methods after the last dose of investigational product from at least 28 days to at least 90 days after the last CC-220 dose. Changing the duration of use of contraceptive methods by male subjects from at least 28 days to at least 90 days after the last CC-220 dose aligns with no donation of sperm/semen by male subjects for at least 90 days after the last CC-220 dose (as stated in Section 6.3.6.1). In either case, a male subject who completed a CC-220 dose regimen presents the same risk of male-mediated developmental toxicity to the conceptus of a female sexual partner. The duration of at least 90 days for male contraception use is chosen based on the duration of one spermatogenic cycle in men and the residence time for unejaculated sperm. The 90-day duration for male contraception use after the last CC-220 dose would be considered sufficient to avoid risk to the conceptus of a female sexual partner.

In addition, this opportunity was used to include in the amendment the evaluation of the pharmacokinetic (PK) metabolite M12 as an exploratory objective of the study, include the evaluation of CC-220's R-enantiomer CC-17195 in the PK analysis, to more accurately address the assessment of duration of response study endpoint, insert regulatory review changes requested by the Medicines and Healthcare Products Regulatory Agency (MHRA), changes to the inclusion and exclusion criteria, change to the timing of the electrocardiogram (ECG) at steady state and to generally bring greater clarity and consistency to some sections.

Significant changes included in this amendment are summarized below:

- **Inclusion of the PK metabolite M12 was added as an exploratory objective of the study**

Revised sections: Protocol Summary, Table 2: Study Objectives, Table 3: Study Endpoints, Section 6.4 Pharmacokinetics, and Section 9.9.2 Exploratory Analysis

- **Clarification of the duration of response endpoint assessment**

To address the duration of response endpoint, all subjects with a minimal response (MR) or better who discontinue study treatment in Part 1 or Part 2 of the study for a reason other than progressive disease (PD) will be followed for response assessment every 28 days until PD or a new myeloma regimen has been started.

Revised sections: Protocol Summary, Section 3.1 Study Design, Section 3.2 Study Duration for Subjects, Table 4: Table of Events and Section 6.3.4 Assessment of Response

Added section: Section 6.2.3 Post Treatment Response Assessment

- **Removal of specific information regarding clinical experience**

The development of CC-220 is a dynamic process with ongoing studies resulting in changes to data. Consequently, the specific information about studies has been deleted and readers are referred to the IB for detailed and current information. Dose and safety summaries from these studies are still available in Section 1.3.4.1.

Revised sections: Section 1.2.1.5 Clinical Experience and Section 1.3.4.1 Dose

- **Change to the Table of Events**

The protocol includes an ECG assessment at Cycle 1 Day 7 after the first dose at steady state. This assessment has proven to be burdensome to the subjects who have to make a trip to the investigative site for the sole purpose of an ECG. Consequently, after consultation with the pharmacokineticist and the United States (US) Food and Drug Administration (FDA), the assessment has been moved to Cycle 1 Day 8 after the first dose at steady state. This will eliminate the need for the subject to make an additional trip to the investigative site and provide the safety data intended for this assessment.

Revised section: Table 4: Table of Events

- **Change to Inclusion Criteria**
    - A correction was made to inclusion criterion number 13. Subjects must agree to refrain from donating blood while on CC-220, during dose interruptions and for at least 28 days following the last dose of CC-220. The previous version stated 90 days.

Revised section: Section 4.2 Inclusion Criteria

- **Changes to the Exclusion Criteria**
    - The exclusion criterion (number 6) prohibiting a subject from participating in the study if their hemoglobin is <8 g/dL (<4.9 mmol/L) was removed since it is widely acknowledged that anemia is a hallmark of advanced multiple myeloma, the population being tested in this study. Further, anemia is not a dose-limiting toxicity in this study. Other sections were adjusted based on this change (eg, permitted and prohibited medications)

Revised sections: Section 4.3 Exclusion Criteria, Section 6.1 Screening Period, Section 8.1 Permitted Concomitant Medications and Procedures, and Section 8.2 Prohibited Concomitant Medications and Procedures

    - The exclusion criterion (number 13) prohibiting subjects from participating in the study if they have been treated with an investigational agent within 28 days or 5 half-lives (whichever is longer) of initiating IP has been clarified so that the term "investigational" is understood to be an agent being studied and for which the safety profile is not well developed. This differs from a commercially available agent that has been developed and has a known safety profile.

Revised section: Section 4.3 Exclusion Criteria

    - The exclusion criterion (number 16) has been edited to include grapefruit, St. John's Wort or related products within two weeks (changed from one week) prior to dosing and during the course of the study. This change is subsequent to a drug-drug interaction (DDI) study that showed that exposures of CC-220 change with alterations in CYP3A4. This change aligns with other studies being conducted with CC-220 in other indications.

Revised sections: Section 4.3 Exclusion Criteria and Section 8.2 Prohibited Concomitant Medications and Procedures

- **Timing of pregnancy tests has been adjusted for consistency**

It was noted that the timing of pre-study pregnancy tests was not aligned with the directions given in Appendix D.

Revised section: Section 6.1 Screening Period

- **Clarification of CC-220 Dose-level Reductions**

Table 6 has been expanded to clarify that subjects receiving CC-220 at higher doses are eligible to receive more than 2 dose reductions.

Revised section: Table 6: Dose-Level Reduction (DLR) for CC-220

- **Dose-limiting toxicity (DLT) Evaluable Population clarified**

To make the DLT definition consistent with other sections of the protocol, this definition was edited to include that subjects who miss more than 4 scheduled doses of CC-220 and/or 2 doses of dexamethasone (DEX) during Cycle 1 for reasons other than drug-related adverse events (AEs) will not be included in the DLT population.

Revised section: Section 9.2 Study Population Definitions

- **Regulatory Considerations - Protocol Amendments**

A request has been made by the MHRA that a statement be placed in the protocol that substantial protocol amendments would be submitted to national Competent Regulatory Authorities (as applicable) and approval must be obtained before implementation of the amended version occurs.

Revised section: Section 13.5 Protocol Amendments

- **Update to the CC-220 Pregnancy Prevention Plan for Subjects in Clinical Trials**
    - Based on new data published in the Investigator's Brochure version 7, a statement has been added to inform subjects that CC-220 was found to cause birth defects in experimental animals (rat and rabbit).

Revised section: Appendix D

    - Based on new data published in the Investigator's Brochure version 7, a statement has been added to inform male subjects that a 9-month toxicity study in monkeys indicates that there was a decrease in the amount of sperm producing cells. It is not known if this is reversible or what time after the start of CC-220 treatment this decrease will occur. It is not known if there might be a similar effect in men taking CC-220 and how this will affect their ability to father children. There were no observable effects in male sex organs in monkeys that received more than the highest dose given to humans. There were no effects of CC-220 in the sex organs of female monkeys.

- The requirement for male subjects to practice birth control after the last dose of CC-220 has been increased from 28 days to 90 days to account for the duration of one spermatogenic cycle in men and the residence time for unejaculated sperm.

Revised sections: Appendix D, Section 4.2 Inclusion Criteria

The amendment also includes minor corrections:

- The text, US and Canada, has been changed to North America since Canada is not participating in Part 1 of this study but may participate in Part 2.
- Clarification was made that the R-enantiomer (and not an active metabolite) would be analyzed as appropriate.
- The contact information for the Medical Monitor was updated.
- The International Conference on Harmonisation (ICH) was updated to read International Council for Harmonisation (ICH).
- Cytogenetic (FISH) testing has been changed to indicate that the analysis will be done by a local laboratory and not by a central laboratory.
- Abbreviations and Specialist Terms were updated.

1. JUSTIFICATION FOR AMENDMENT

This amendment is being generated to add to the prohibited concomitant medications during study participation medications that are strong inhibitors or inducers of CYP3A/5 as well as grapefruit and related products.

In addition, the role of an Independent Expert Review has been added to the Dose Escalation Committee (DEC) in Part 1, and in Part 2 of the study to ensure a robust review of safety during the expansion phase of this study where CC-220 as monotherapy and in combination with dexamethasone will be used at the recommended Phase 2 dose determined in Part 1 of the study.

Significant changes included in this amendment are summarized below:

- **Inclusion of strong inhibitors or inducers of CYP3A/5 as well as grapefruit and related products to the prohibited concomitant medications**

Exclusion criterion 16 of the protocol states that subjects who have taken a strong inhibitor or inducer of CYP3A4/5 at least one week prior to dosing with the intention of taking them during the course of the study and grapefruit or related products one week prior to dosing with the intention to eat these products throughout the study are excluded. This amendment adds such medications, grapefruit and related products to the prohibited concomitant medications and procedures listed in Section 8.2.

Revised section: Section 8.2

- **Addition of an Independent Expert Reviewer to the study**

The role of an Independent Expert Reviewer (IER) has been added to Part 1 of the study as part of the DEC and in Part 2 of the study to ensure subject safety. The review performed by the IER is dictated in the Dose Escalation Committee and Independent Expert Reviewer Charter.

Revised section: Protocol Summary, Section 3.1.1.1

Added: Section 3.1.3

The amendment also includes minor corrections:

- The Clinical Research Physician representing the EU has been added to the members of the DEC in Section 3.1.1.1.
- The Independent Expert Reviewer (IER) has been added to the List of Abbreviations.

1. JUSTIFICATION FOR AMENDMENT

This amendment is being generated to provide greater clarity to the pregnancy prevention requirements for this study, clinical pharmacology, and CC-220 dosing of monotherapy cohorts at the time of progressive disease. Additional clarifications have been made to pharmacokinetic and biomarker analyses and sampling.

Significant changes included in this amendment are summarized below:

- **Inclusion of a contraception requirement in the protocol inclusion criteria**

The protocol has been amended to add the requirement that any study subject who is a female of child bearing potential shall practice two forms of reliable contraception. One must be a highly effective method and one an additional effective (barrier) method. An additional eligibility criterion was added to require that both male and female subjects must follow all requirements defined in the Pregnancy Prevention Program.

Revised sections: Section 4.2

- **Addition of the CC-220 Pregnancy Prevention Plan for Subjects in Clinical Trials as a fixed appendix to the protocol**

Appendix D has been added to the protocol providing the full text of the CC-220 Pregnancy Prevention Plan for Subjects in Clinical Trials.

Revised sections: Section 4.2; Section 5; Section 6.1; Section 6.2; Section 10.4 Pregnancy; Appendix D

- **Additional pregnancy caution**

A statement was added to the section on pregnancy and reporting of pregnancies, suspected pregnancies or exposure of any pregnant female to CC-220.

Revised section: 10.4 Pregnancy

- **Clarification on the dosing of CC-220 for monotherapy cohorts at the time of PD**

Clarifying statements regarding the dose of CC-220 to be administered for subjects in the monotherapy cohorts who experience progression of disease and have the option of adding dexamethasone. The investigator will contact the Medical Monitor and be informed of the dose of CC-220 that is to be administered in this setting.

Revised sections: Protocol Summary, Study Design; Section 1.3.4.3; Section 3.1 Study Design; Section 7.2.1; Section 7.2.2

- **Table of Events has been corrected**

The Table of Events has been edited to more clearly show the pharmacokinetic sampling time points. Footnote “i” has been edited to indicate that intensive pharmacokinetic (PK) samples will be drawn on Cycle 1/Day 15 along with sparse PK samples.

Revised section: Section 5, Table 4; Section 5, Table 4 footnote ‘i’

- **CC-220 Food Effect**

A statement was added to indicate that there is no food effect associated with CC-220 dosing.

Revised section: Section 7.2

- **Characterization of the elimination half-life of CC-220**

The schedule of intensive PK sampling has been altered to demonstrate the requested characterization of elimination half-life of CC-220. Also, changes have been made to the text to clarify that subjects participating in intensive PK sampling will also participate in sparse PK sampling.

Revised sections: Protocol Summary; Section 5, Table 4, footnote 'i'; Section 6.4

- **Addition of further PK analyses**

The analyses of metabolites M12 and CC-17195 have been added to the PK parameters being studied in this protocol.

Revised section: Protocol Summary; Section 2, Table 3; Section 6.4

- **Addition of electrocardiogram (ECG) assessments**

The Table of Events has been updated to include ECG assessments at the maximal concentration of CC-220 (Day 1, 3-4 hours post first dose) and after the first dose at steady state (Cycle 1/Day 7). This is in addition to the scheduled ECGs at Screening and at End of Treatment. ECGs will also be conducted if clinically indicated.

Revised section: Section 5, Table 4 footnote "b"

- **Correction of biomarker collection time points and biomarker definition**

Pharmacodynamic time points for Cycle 1 Day 1 and Cycle 1 Day 12 at 1.5 hours has been changed to 3 hours. The Table of Events was updated to include the phrase "BMA and/or BMB", and footnote 'f' was revised. Analysis definitions of biomarkers were updated. Samples for testing bone marrow aspirate (BMA) and bone marrow biopsy (BMB)s were adjusted.

Revised section: Protocol Summary; Section 5, Table 4 footnote "f"; Section 6.3.1; Section 6.5

The amendment also includes several other minor clarifications and corrections:

- Table 1 was revised for clarity.
- Correction of footnote "c" for Table 4, Table of Events
- Frequency of assessments for serum and urine immunofixation tests was corrected (Section 5; Table 4; Section 6.3)
- Clarification of Immunoglobulin D (IgD) and immunoglobulin E (IgE) sample collection (Section 6.3)
- Text change in Section 3.1 to remove redundancy
- Two corrections made in Section 7.5 Method of Treatment Assignment:

- An Interactive Response Technology (IRT) system will be used to track subjects who are assigned to participate in the intensive PK sample collection. There is no substudy in this protocol.
- When both cohorts are open in Part 2, the IRT will assign subjects in a 1:2 ratio.