Official Title: An Open-Label, Randomized Phase IB/II Study Evaluating Safety, Tolerability, and Clinical Activity of Forimtamig-Based Treatment Combinations in Participants with Relapsed or Refractory Multiple Myeloma

NCT Number: NCT06055075

Document Date: Protocol Amendment Version 2: 17-May-2023

PROTOCOL

TITLE:	**AN OPEN-LABEL, RANDOMIZED PHASE IB/II STUDY EVALUATING SAFETY, TOLERABILITY, AND CLINICAL ACTIVITY OF FORIMTAMIG-BASED TREATMENT COMBINATIONS IN PARTICIPANTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA**
PROTOCOL NUMBER:	BP43437
VERSION:	2
REGULATORY AGENCY IDENTIFIER NUMBERS:	**IND Number**: 157685 **EudraCT Number**: Not applicable **EU Trial Number**: 2023-503689-21-00 **Clinical Investigation Identification Number (CIV ID)**: Not applicable
TEST PRODUCT:	Forimtamig, carfilzomib, daratumumab, and tocilizumab
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 21 Apr 2023
DATE AMENDED:	Version 2: See electronic signature and date stamp on the final page of this document

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PROTOCOL ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, RANDOMIZED PHASE IB/II STUDY EVALUATING SAFETY, TOLERABILITY, AND CLINICAL ACTIVITY OF FORIMTAMIG-BASED TREATMENT COMBINATIONS IN PARTICIPANTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA**
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TEST PRODUCT:	Forimtamig, carfilzomib, daratumumab, and tocilizumab
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files, and return a copy to your local Site Monitor.

PROTOCOL AMENDMENT, VERSION 2
RATIONALE

The main reason for amending Protocol BP43437 is to update assessments in the Schedule of Activities. Changes to the protocol, along with a rationale for each change, are summarized below.

- The SoA tables (Section 1.3) were updated as follows:
    - Harmonized the [redacted] across all tables.
    - Harmonized the [redacted] assessments across all tables.
    - Added the "[redacted]" column in all hourly SoA tables, which was missing.
    - Added the "[redacted]" row in the local MM response assessment part of the carfilzomib-specific Table 3, which was missing.
    - Added a clarification note for the [redacted] rows in the SoAs highlighting that [redacted] may be omitted for participants who are only eligible for the daratumumab or the carfilzomib arm, respectively (also updated in Sections 8.2.3 and 8.2.4).

Additional minor changes have been made to improve clarity and consistency. Substantial new information appears in *Book Antiqua* italics. This amendment represents cumulative changes to the original protocol.

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1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**AN OPEN-LABEL, RANDOMIZED PHASE IB/II STUDY EVALUATING SAFETY, TOLERABILITY, AND CLINICAL ACTIVITY OF FORIMTAMIG-BASED TREATMENT COMBINATIONS IN PARTICIPANTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA**
SHORT TITLE	**A PHASE Ib/II STUDY OF FORIMTAMIG-BASED TREATMENT COMBINATIONS IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA**
PROTOCOL NUMBER:	BP43437
VERSION:	2
REGULATORY AGENCY IDENTIFIER NUMBERS:	**IND Number**: 157685 **EudraCT Number**: Not applicable **EU Trial Number**: 2023-503689-21-00 **Clinical Investigation Identification Number (CIV ID)**: Not applicable
TEST PRODUCT:	Forimtamig, carfilzomib, daratumumab, and tocilizumab
PHASE:	Ib/II

RATIONALE

T-cell–mediated killing of multiple myeloma (MM) cells can result in clinical benefit. CAR-T cells directed against antigens expressed by MM cells have demonstrated promising activity in patients with relapsed or refractory (r/r) MM. However, these therapies have been associated with frequent and sometimes severe cytokine-mediated toxicity, neurotoxicity, as well as prolonged cytopenia without showing improved overall survival.

GPRC5D is differentially expressed by plasma cells in MM versus plasma cells from healthy donors and is rarely expressed in normal tissues, with the exception of testis and in highly keratinized structures such as hair follicles in skin. Bispecific T-cell redirecting antibodies targeting various cell surface proteins on MM cells are emerging with promising clinical activity. Forimtamig is a GPRC5D/cluster of differentiation (CD)3 T cell bispecific antibody (TCB) that recruits CD3-positive T-cells to GPRC5D-positive MM cells and induces killing of GPRC5D-positive MM cells.

In the ongoing first-in-human dose escalation Study BP42233, clinical activity for both subcutaneous (SC) and intravenous (IV) administrations of forimtamig monotherapy has been observed with an overall positive benefit/risk evaluation.

The aim of this study is to further evaluate the safety, tolerability, clinical activity, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of SC forimtamig when administered alone or in combination with carfilzomib or daratumumab in participants with r/r MM. These combination partners are standard of care (SoC) agents with a proven clinical benefit in monotherapy. [redacted] Taken together, the above mentioned SoC therapies may result in enhanced clinical activity when combined with forimtamig.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of forimtamig when given alone or in combination	• Incidence and severity of adverse events (AEs), with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) and of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) according to American Society of Transplantation and Cellular Therapy (ASTCT) Consensus Grading
To evaluate the preliminary anti-tumor activity of forimtamig when given alone or in combination	The International Myeloma Working Group (IMWG) criteria will be used for Investigator-assessed endpoints: • Objective response rate (ORR) • Complete response (CR)/stringent complete response (sCR) rate • Rate of very good partial response (VGPR) or better
Secondary	
To evaluate the preliminary anti-tumor activity of forimtamig when given alone or in combination	The IMWG criteria will be used for Investigator-assessed endpoints: • Progression-free survival (PFS) • Duration of response (DoR) for participants who achieve a partial response (PR) or better

Objectives	Endpoints
	• Time to first response • Time to best response • Overall survival (OS)
To characterize the pharmacokinetics (PK) of forimtamig when given alone or in combination	• To assess the serum concentrations and PK parameters of forimtamig including AUC, C_{max}, C_{min}, T_{max}, and other parameters, if appropriate alone or with combination partners
To evaluate the immune response to forimtamig	• Presence of anti-drug antibodies (ADAs) during the study relative to the presence of ADAs at baseline

OVERALL DESIGN AND STUDY POPULATION

This is a Phase Ib/II, randomized, controlled, open-label, multi-center study in which forimtamig will be administered alone or in combination with carfilzomib or daratumumab in participants with r/r MM to further evaluate the safety, tolerability, clinical activity, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of SC forimtamig.

The study consists of a dose exploration phase and a dose expansion phase. During the dose exploration phase, [redacted] will be tested in each combination arm on a [redacted] schedule in a randomized fashion.

Based on the data from the dose exploration phase (i.e., safety and clinical data from at least the first two treatment cycles, PK/PD data, and, if available, biomarker data), [redacted] to be tested during the expansion phase with the respective combination partner.

The forimtamig target dose selected for the expansion phase may vary between the combination arms (carfilzomib combination = Arm B; daratumumab combination = Arm C). In addition, a single agent forimtamig comparator arm (Arm A) will start when at least one combination arm enters the expansion phase.

The forimtamig target dose tested during the expansion phase (combination and single agent) will not exceed the highest forimtamig dose [redacted] tested during the dose exploration phase for any combination.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase Ib/II	**Population Type:**	Patients
Control Method:	Not applicable	**Population Diagnosis or Condition:**	Relapsed or refractory multiple myeloma
Interventional Study Design:	Randomized controlled study	**Population Age:**	≥ 18 years of age
Test Compounds:	Forimtamig, carfilzomib, daratumumab, and tocilizumab	**Site Distribution:**	Multicenter
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	Open label
Number of Arms:	1 comparator arm and up to 6 combination arms	**Number of Participants to be Enrolled:**	Approximately 36 to 316

STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are forimtamig, carfilzomib, daratumumab, and tocilizumab. In general, there will be no dose modifications for forimtamig or any of the combination partners. Study treatment administrations will be at the study center.

Study treatment name:	Forimtamig	Carfilzomib	Daratumumab	Tocilizumab[a]
Dose and regimen:	[redacted]	[redacted]	[redacted]	[redacted]
Route of administration:	SC	IV	SC	IV

C = cycle, D = day, [redacted]

[a] Note that tocilizumab is not a combination partner but an ad hoc treatment for cytokine release syndrome.

DURATION OF PARTICIPATION

The study duration per participant from screening until the safety follow-up visit will be approximately [redacted] (not including long-term follow-up), divided as follows:

- Screening: [redacted].
- Treatment period: Study treatment with forimtamig alone or in combination will be limited [redacted]. Participants in the combination arms who derive clinical benefit may continue treatment [redacted] with the respective combination partner alone until disease progression.
- Safety follow-up:
  - Participants in Arm A (forimtamig monotherapy) and Arm B (forimtamig + carfilzomib) will have their safety follow-up visit [redacted] after the last dose.
  - Participants in Arm C (forimtamig + daratumumab) will have their safety follow-up visit [redacted] after the last dose.
- Pre-progression follow-up: After the safety follow-up visit, participants will be followed every month after the last study treatment until confirmed progressive disease, death, the start of new anticancer therapy, withdrawal of consent, lost to follow up, or the end of the study, whichever occurs first.
- Post-progression follow-up: Survival status and start of new therapies for MM are to be checked every 3 months (e.g., via phone call or any other offline method as preferred by the site).

COMMITTEES

An internal monitoring committee (IMC) will be set up.

CONCOMITANT MEDICATIONS

For the use of permitted and/or prohibited concomitant medications in combination with carfilzomib and daratumumab, refer to the SmPC guidelines.

Prohibited Therapies:

- Cytotoxic chemotherapy intended for treatment of MM.
- Radiotherapy (except for limited field palliative radiotherapy for bone pain, for soft tissue lesions, or orthopedic surgery radiation after consultation with the Medical Monitor).
- Immunotherapy and/or hormone therapy for the treatment of cancer, whether approved by local regulatory authorities or investigational treatment. Adjuvant endocrine therapy for non-metastatic, hormone-receptor positive breast cancer is permitted.
- Any therapies for the treatment of MM, whether approved by local regulatory authorities or investigational treatment.
- Corticosteroids in excess of 10 mg daily of prednisone or equivalent is prohibited other than for the management of adverse events (AEs) or as premedication.
    - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for participants with orthostatic hypotension or adrenocortical insufficiency is allowed. Physiologic doses of corticosteroids for adrenal insufficiency are allowed. For use of other medications, the Medical Monitor is available to advise as needed.
- Continuation of the study treatment after emergency orthopedic surgery or radiotherapy is allowed only in the absence of disease progression and after consultation with and approval by the Sponsor. For participants for whom delay of systemic therapy is not appropriate, emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues. The circumstances must be reviewed by the Sponsor to determine whether study treatment may be continued.
- Nonsteroidal anti-inflammatory agents should be avoided to minimize the risk of exacerbation of potential sub-clinical myeloma-related kidney disease.

The above list of medications may not be comprehensive. The Investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1.

[redacted]

[redacted]

[redacted]

1.3 SCHEDULE OF ACTIVITIES

The schedule of activities (SoA) is provided in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6.

Table 1 Schedule of Activities for Forimtamig Comparator

Protocol Section	[redacted]	Screening	Cycle 1			Subsequent cycles		Treatment discontinuation	[redacted] safety FU visit	[redacted]	
	Day	[redacted]									
	Visit window		±1 day			±3 days			±7 days	±7 days	±14 days
	Hospitalization										
6.1.1.1			At least 36h	At least 36h	At least 36h	In case of ≥G3 CRS or TLS at C1					
	IMP administration										
	[redacted]										
	Clinical assessments										
5.1	Written informed consent and eligibility	X									
8.2.8	Medical history and demographic data	X									
8.2.1	Complete physical examination	X									
	Complete neurological examination (including ICE score)	X									
8.2.6	MRI of the brain	X									
8.2.3	Echo/MUGA (LVEF, not needed for patients who are only eligible for Arm A and Arm C)	X									
8.2.4	Pulmonary function test (FEV1, not needed for patients who are only eligible for Arm A and Arm B)	X									
8.2.3	Triplicate 12-lead ECG	X	X		X		X	C4 only	X	X		
8.2.1	Height (screening only) and weight	X	X				X	C2-4: D1, D15 C5 onward: D1	X	X		
	Targeted physical examination		X				X		X	X		
	Targeted neurological examination (incl ICE score)		X	X	X	X	X	X	X	X		
8.2.5	ECOG performance status	X	X				X		X	X		
8.2.2	Vital signs	X	X	X	X	X	X	X	X	X	X	X
8.1.2	PRO questionnaire	At screening or pre-dose					X	C2-3: D1, D15 Subsequent cycles: D1	X	X		
8.3	Adverse events	X	continuous									
5.1, 5.2, 6.5	Previous and concomitant treatments	X										
4.4	Survival follow-up and new anti-myeloma treatment										X	X

Table 1 Schedule of Activities for Forimtamig Comparator Continued

Protocol Section		Screening	Cycle 1						Subsequent cycles		Treatment discontinuation visit	[redacted] safety FU visit	[redacted]	
	Day	[redacted]												
	Visit window		±1 day						±3 days			±7 days	±7 days	±14 days
	Local Multiple Myeloma Response Assessment													
8.1.1	Skeletal survey	X	Repeat as clinically indicated											
	Local bone marrow biopsy and/or aspirate		X, to assess a CR/sCR (and if available progressive disease)											
	Imaging (PET/CT, CT scan, whole body MRI or a low dose whole-body CT)	X	Participants with plasmacytomas should be followed up with 12 weekly cross sectional imaging and as needed to confirm response or progression.											
	SPEP with SIFE	X	X						To be performed on Day 1 of each cycle prior to dosing		Only if not done within the [redacted]	X	X	
	[redacted]													
	Immunoglobulins (IgA, IgG, IgM [if applicable IgD, IgE])	X	X									X	X	
	Serum free light chains	X	X		X		X					X	X	
	Serum β-2 microglobulin	X	As clinically indicated											
	Peripheral plasma cell count	X												
	Central Multiple Myeloma Response Assessment													
	SPEP with SIFE	X	X						To be performed on Day 1 of each cycle prior to dosing		Only if not done within the [redacted]	X	X	
	[redacted]													
	Immunoglobulins (IgA, IgG, IgM [if applicable IgD, IgE])	X	X									X	X	
	Serum free light chains	X	X		X		X					X	X	
	Local laboratory assessments													
8.2.7 and Appendix 4	Hematology	X	X		X		X		X	X	X	X		
	Blood chemistry	X	X		X		X		X	X	X	X		
	Coagulation	X	X				X		X	X	X	X		
	Urinalysis	X	As clinically indicated											
	Lipids	X	As clinically indicated											
	Local viral serology	X												
	Hormones (male participants only)	X							C3		X	X		
	IgE and tryptase	X	In case of suspicion of type I hypersensitivity											
8.3.5 and Appendix 5	Pregnancy test	X	X						X		Only if not done within the [redacted]	X	[redacted]	
	Exploratory central laboratory assessments													
[redacted]														
	For Central PK/PD assessments refer to the hourly table													

Table 2 Hourly Schedule of Activities for Forimtamig Comparator

	[redacted]					Clinical genotyping If not collected on C1D1 pre-dose, it can be collected at any other scheduled visit at the earliest possible time.
Screening						
Cycle 1						X
Cycle 2						
Cycle 3						
Subsequent cycles						
Treatment Discontinuation visit						
[redacted] safety FU visit						
Overdose or AE leading to dose reduction or delay of study drug administration						
Unscheduled visit					As needed	

Table 2 Hourly Schedule of Activities for Forimtamig Comparator Continued

| | | |

Table 3 Schedule of Activities for Carfilzomib Combination

Protocol Section	[redacted]	Screening	Cycle 1					Cycle 2-3				
	Day	[redacted]										
	Visit window		±1 day					±3 days				
	Hospitalization											
6.1.1.1			at least 36h		at least 36h	at least 36h		In case of ≥G3 CRS or TLS at C1				
	IMP administration											
[redacted]												
	Clinical assessments											
5.1	Written informed consent and eligibility	X										
8.2.8	Medical history and demographic data	X										
8.2.3	Echo/MUGA (LVEF, not needed for patients who are only eligible for Arm A and Arm C)	X	Repeat if clinically indicated									
8.2.1	Complete physical examination	X										
	Complete neurological examination (including ICE score)	X										
8.2.6	MRI of the brain	X										
8.2.4	Pulmonary function test (FEV1, not needed for patients who are only eligible for Arm A and Arm B)	X										
8.2.3	Triplicate 12-lead ECG	X	X		X		X					
8.2.1	Height (screening only) and weight	X	X				X		X			X	
	Targeted physical examination		X				X		X	X		X	
	Targeted neurological examination (incl ICE score)		X	X	X	X	X	X	X		X	X	X
8.2.5	ECOG performance status	X	X				X		X			X	
8.2.2	Vital signs	X	X	X	X	X	X	X	X		X	X	X
8.1.2	PRO questionnaires	At screening or pre-dose					X		X			X	
8.3	Adverse events	X	continuous										
5.1, 5.2, 6.5	Previous and concomitant treatments	X											
4.4	Survival follow-up and new anti-myeloma treatment												
	Local Multiple Myeloma Response Assessment												
8.1.1	Skeletal survey	X	Repeat as clinically indicated										
	Local bone marrow biopsy and/or aspirate		X, to assess a CR/sCR (and if available progressive disease)										
	Imaging (PET/CT, CT scan, whole body MRI or a low dose whole-body CT)	X	Participants with plasmacytomas should be followed up with 12 weekly cross sectional imaging and as needed to confirm response or progression.										
	SPEP with SIFE	X	X										
	[redacted]		To be performed on Day 1 of each cycle prior to dosing										
	Immunoglobulins (IgA, IgG, IgM [if applicable IgD, IgE])	X	X										
	Serum free light chains	X	X		X		X						
	Serum β-2 microglobulin	X											
	Peripheral plasma cell count	X	As clinically indicated										
	Central Multiple Myeloma Response Assessment												
	SPEP with SIFE	X	X					To be performed on Day 1 of each cycle prior to dosing					
	[redacted]												
	Immunoglobulins (IgA, IgG, IgM [if applicable IgD, IgE])	X	X										
	Serum free light chains	X	X		X		X						
	Local laboratory assessments												
8.2.7 and Appendix 4	Hematology	X	X		X		X		X		X	X	
	Blood chemistry	X	X		X		X		X		X	X	
	BNP and/or NT-proBNP	X							X		X	X	X
	Troponine T/I	X							X		X	X	X
	Coagulation	X	X				X		X			X	
	Urinalysis	X	As clinically indicated										
	Lipids	X	As clinically indicated										
	Local viral serology	X											
	Hormones (male participants only)	X	C3										
	IgE and tryptase	X	In case of suspicion of type I hypersensitivity										
8.3.5 and Appendix 5	Pregnancy test	X	X					X					
	Exploratory central laboratory assessments												
[redacted]													
	For Central PK/PD assessments refer to the hourly table												

Table 3 Schedule of Activities for Carfilzomib Combination Continued

Protocol Section	[redacted]	Subsequent cycles			Carfilzomib single agent (protocol	Treatment Discontinuation visit	[redacted] safety FU visit	[redacted]	
	Day	[redacted]							
	Visit window	±3 days			±3 days		±7 days	±7 days	±14 days
	Hospitalization								
6.1.1.1									
	IMP administration								
[redacted]									
	Clinical assessments								
5.1	Written informed consent and eligibility								
8.2.8	Medical history and demographic data								
8.2.3	Echo/MUGA (LVEF, not needed for patients who are only eligible for Arm A and Arm C)	Repeat if clinically indicated							
8.2.1	Complete physical examination								
	Complete neurological examination (including ICE score)								
8.2.6	MRI of the brain								
8.2.4	Pulmonary function test (FEV1, not needed for patients who are only eligible for Arm A and Arm B)								
8.2.3	Triplicate 12-lead ECG	C4 only				X	X		
8.2.1	Height (screening only) and weight	C4: D1, D15 C5 onwards: D1			D1	X	X		
	Targeted physical examination				D1	X	X		
	Targeted neurological examination (incl ICE score)				D1	X	X		
8.2.5	ECOG performance status				D1	X	X		
8.2.2	Vital signs	X	X	X	D1, D8, D15	X	X		
8.1.2	PRO questionnaires	X			D1	X	X		
8.3	Adverse events	continuous							
5.1, 5.2, 6.5	Previous and concomitant treatments								
4.4	Survival follow-up and new anti-myeloma treatment							X	X
	Local Multiple Myeloma Response Assessment								
8.1.1	Skeletal survey	Repeat as clinically indicated							
	Local bone marrow biopsy and/or aspirate	X, to assess a CR/sCR (and if available progressive disease)							
	Imaging (PET/CT, CT scan, whole body MRI or a low dose whole-body CT)	Participants with plasmacytomas should be followed up with 12 weekly cross sectional imaging and as needed to confirm response or progression.							
	SPEP with SIFE	To be performed on Day 1 of each cycle prior to dosing				Only if not done within the [redacted]	X	X	
	[redacted]						[redacted]		
	Immunoglobulins (IgA, IgG, IgM [If applicable IgD, IgE])						X	X	
	Serum free light chains						X	X	
	Serum β-2 microglobulin								
	Peripheral plasma cell count	As clinically indicated							
	Central Multiple Myeloma Response Assessment								
	SPEP with SIFE	To be performed on Day 1 of each cycle prior to dosing				Only if not done within the [redacted]	X	X	
	[redacted]						[redacted]		
	Immunoglobulins (IgA, IgG, IgM [If applicable IgD, IgE])						X	X	
	Serum free light chains						X	X	
	Local laboratory assessments								
8.2.7 and Appendix 4	Hematology	X		X	D1	X	X		
	Blood chemistry	X		X	D1	X	X		
	BNP and/or NT-proBNP	As clinically indicated							
	Troponine T/I								
	Coagulation	X		X	D1	X	X		
	Urinalysis	As clinically indicated							
	Lipids	As clinically indicated							
	Local viral serology								
	Hormones (male participants only)					X	X		
	IgE and tryptase	In case of suspicion of type I hypersensitivity							
8.3.5 and Appendix 5	Pregnancy test	X			D1	Only if not done within the [redacted]	X	[redacted]	
	Exploratory central laboratory assessments								
[redacted]									
	For Central PK/PD assessments refer to the hourly table								

Table 4 Hourly Schedule of Activities for Carfilzomib Combination

	[redacted]
Screening	
Cycle 1	
Cycle 2	
Cycle 3	
Cycle 4	
Subsequent cycles	
Discontinuation visit	
At progression (if feasible)	
[redacted] safety FU visit	
Event of Grade ≥3 CRS/IRR or hypersensitivity reaction	
Overdose or AE leading to dose reduction or delay of study drug administration	
Unscheduled visit	As needed

Table 4 Hourly Schedule of Activities for Carfilzomib Combination Continued

	[redacted]	Clinical genotyping If not collected on C1D1 pre-dose, it can be collected at any other scheduled visit at the earliest possible time.	[redacted]	Serum forimtamig ADA	[redacted]
Screening					
Cycle 1		X		X	
Cycle 2				X	
Cycle 3				X	
Cycle 4				X	
Subsequent cycles				X	
Discontinuation visit				X	
At progression (if feasible)				X	
[redacted] safety FU visit				X	
Event of Grade ≥3 CRS/IRR or hypersensitivity reaction				X	
Overdose or AE leading to dose reduction or delay of study drug administration					
Unscheduled visit			As needed		

Table 5 Schedule of Activities for Daratumumab Combination

Protocol Section	[redacted]	Screening	Cycle 1										Cycle 2				Subsequent cycles		Daratumumab single agent (protocol Section 4.4)	Treatment Discontinuation visit	[redacted] safety FU visit	Pre-progression Follow-Up	Post-progression Survival Follow-Up
	Day	[redacted]																					
	Visit window		±1 day										±3 days						±3 days		±7 days	±7 days	±14 days
	Hospitalization																						
6.1.1.1				at least 36h		at least 36h		at least 36h				In case of ≥G3 CRS or TLS at C1											
	IMP administration																						
[redacted]																							
	Clinical assessments																						
8.2.7.1	ID card including blood profile	X																					
6.1	Written informed consent and eligibility	X																					
8.2.8	Medical history and demographic data	X																					
8.2.1	Complete physical examination	X																					
	Complete neurological examination (Incl ICE score)	X																					
8.2.6	MRI of the brain	X																					
8.2.3	Echo/MUGA (LVEF, not needed for patients who are only eligible for Arm A and Arm C)	X																					
8.2.4	Pulmonary function test (FEV1, not needed for patients who are only eligible for Arm A and Arm B)	X	Repeat if clinically indicated																				
8.2.3	Triplicate 12-lead ECG	X	X			X			X								C4 only			X	X		
8.2.1	Height (screening only) and weight	X	X						X				X			X			D1	X	X		
	Targeted physical examination		X						X				X	X		X	C4: D1, D16 C5 onwards: D1		D1	X	X		
	Targeted neurological examination (Incl ICE score)		X	X	X	X	X	X	X	X	X	X	X		X	X			D1	X	X		
8.2.5	ECOG performance status	X	X						X				X			X			D1	X	X		
8.2.2	Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	D1, D16	X	X		
8.1.2	PRO questionnaire	At screening or pre-dose							X				X			X	C3: D1, D15Subsequent cycles: D1		D1	X	X		
8.3	Adverse events	X	continuous																				
6.1, 6.2, 8.5	Previous and concomitant treatments	X																					
4.4	Survival follow-up and new anti-myeloma treatment																					X	X

Table 5 Schedule of Activities for Daratumumab Combination Continued

Protocol Section	[redacted]	Screening	Cycle 1									Cycle 2				Subsequent cycles		Daratumumab single agent (protocol Section 4.4)	Treatment Discontinuation visit	[redacted] safety FU visit	[redacted]	
	Day	[redacted]																				
	Visit window		±1 day									±3 days						±3 days		±7 days	±7 days	±14 days
	Local Multiple Myeloma Response Assessment																					
8.1.1	Skeletal survey	X	Repeat as clinically indicated																			
	Local bone marrow biopsy and/or aspirate		X, to assess a CR/sCR (and if available progressive disease)																			
	Imaging (PET/CT, CT scan, whole body MRI or a low dose whole-body CT)	X	Participants with plasmacytomas should be followed up with 12 weekly cross sectional imaging and as needed to confirm response or progression.																			
	SPEP with SIFE	X	X									To be performed on Day 1 of each cycle prior to dosing							Only if not done within the [redacted]	X	X	
	[redacted]																					
	Immunoglobulins (IgA, IgG, IgM [If applicable IgD, IgE])	X	X																	X	X	
	Serum free light chains	X	X			X			X											X	X	
	Serum β-2 microglobulin	X																				
	Peripheral plasma cell count	X	As clinically indicated																			
	Central Multiple Myeloma Response Assessment																					
	SPEP with SIFE	X	X									To be performed on Day 1 of each cycle prior to dosing							Only if not done within the [redacted]	X	X	
	[redacted]																					
	Immunoglobulins (IgA, IgG, IgM [If applicable IgD, IgE])	X	X																	X	X	
	Serum free light chains	X	X			X			X											X	X	
	Local laboratory assessments																					
8.2.7 and Appendix 4	Hematology	X	X			X			X			X	X			X	X	D1	X	X		
	Blood chemistry	X	X			X			X			X	X			X	X	D1	X	X		
	Coagulation	X	X						X			X	X			X	X	D1	X	X		
	Urinalysis	X	As clinically indicated																			
	Lipids	X	As clinically indicated																			
	Blood typing (section 8.2.7.1)	X																				
	Local viral serology	X																				
	Hormones (male participants only)	X										C3							X	X		
	IgE and tryptase	X	In case of suspicion of type I hypersensitivity																			
8.3.5 and Appendix 5	Pregnancy test	X	X									X				X		D1	Only if not done within the [redacted]	X	[redacted]	
	Exploratory central laboratory assessments																					
	[redacted]																					
	For Central PK/PD assessments refer to the hourly table																					

Table 6 Hourly Schedule of Activities for Daratumumab Combination

	[redacted]					
Screening						
Cycle 1						
Cycle 2						
Cycle 3-5						
Cycle 6 + and subsequent cycles						
Discontinuation visit						
At progression (if feasible)						
[redacted] safety FU visit						
Event of Grade ≥3 CRS/IRR or hypersensitivity reaction						
Overdose or AE leading to dose reduction or delay of study drug administration						
Unscheduled visit						As needed

Table 6 Hourly Schedule of Activities for Daratumumab Combination Continued

	[redacted]	Clinical genotyping If not collected on C1D1 pre-dose, it can be collected at any other scheduled visit at the earliest possible time.	[redacted]	Serum forimtamig ADA	[redacted]
Screening					
Cycle 1		X			
				X	
				X	
Cycle 2				X	
				X	
Cycle 3-5				X	
				X	
Cycle 6 + and subsequent cycles				X	
				X	
Discontinuation visit				X	
At progression (if feasible)					
[redacted] safety FU visit				X	
Event of Grade ≥3 CRS/IRR or hypersensitivity reaction				X	
Overdose or AE leading to dose reduction or delay of study drug administration					
Unscheduled visit				As needed	

2. INTRODUCTION

Multiple myeloma (MM) is a hematologic disorder defined by clonal expansion of malignant plasma cells in the bone marrow and/or extramedullary sites (Palumbo and Anderson 2011). Due to an aging population and an increase in the global population, there is an increase in the prevalence of MM. Moreover, both the incidence of MM and mortality associated with the disease are increasing globally, with a projected increase of over 70% in each from 2018 to 2040 (Globocan 2018).

Since 2014, increased survival has been achieved with the introduction of proteasome inhibitors (PI) such as bortezomib, immunomodulatory drugs (IMiDs) such as lenalidomide, and monoclonal antibodies (mAbs) such as daratumumab (anti-CD38), isatuximab (anti-CD38), and elotuzumab (anti-SLAMF7; SEER 2019). Despite this progress, most patients eventually relapse and the outcome for patients who have relapsed or are refractory (r/r) to a PI, an IMiD, and/or anti-CD38 mAb is quite poor, with median overall survival (OS) of approximately 1 year (Gandhi et al. 2019). Therefore, r/r MM represents an indication with a significant unmet medical need.

2.1 STUDY RATIONALE

T-cell–mediated killing of MM cells can result in clinical benefit. CAR-T cells directed against antigens expressed by MM cells have demonstrated promising activity in patients with relapsed/refractory (r/r) MM. However, these therapies have been associated with frequent and sometimes severe cytokine-mediated toxicity, neurotoxicity, as well as prolonged cytopenia without showing improved OS (Ali et al. 2016, Berdeja et al. 2016, Cohen et al. 2016).

GPRC5D is differentially expressed by plasma cells in MM versus plasma cells from healthy donors and is rarely expressed in normal tissues, with the exception of testis, and in highly keratinized structures such as hair follicles in skin (Smith et al. 2019, Atamaniuk et al. 2012, Inoue et al. 2004, Kodama et al. 2019, Pillarisetti et al. 2020). Bispecific T-cell redirecting antibodies targeting various cell surface proteins on MM cells are emerging with promising clinical activity (Costa et al. 2019, Caraccio et al. 2020, Cohen et al. 2020, Moreau et al.2022, Chari et al. 2022). Forimtamig is a GPRC5D/cluster of differentiation (CD)3 T cell bispecific antibody (TCB) that recruits CD3-positive T-cells to GPRC5D-positive MM cells and induces killing of GPRC5D-positive MM cells (Eckmann et al. 2022).

In the ongoing first-in-human dose escalation Study BP42233, clinical activity for both subcutaneous (SC) and intravenous (IV) administrations of forimtamig monotherapy has been observed with an overall positive benefit/risk evaluation (Hasselbalch Riley et al. 2022, Carlo-Stella et al. 2022, forimtamig Investigator's Brochure).

The aim of this study is to further evaluate the safety, tolerability, clinical activity, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of SC forimtamig

when administered alone or in combination with carfilzomib (K) or daratumumab (D) in participants with r/r MM. These combination partners are standard of care (SoC) agents with a proven clinical benefit in monotherapy (Cowan et al. 2022, Usmani et al. 2022, Mateos et al. 2022). [redacted] (Investigator's Brochure and further internal data). Taken together, the above mentioned SoC therapies may result in enhanced clinical activity when combined with forimtamig (Eckmann et al. 2022).

For further details on the study rationale, please refer to Section 4.2.

2.2 BACKGROUND

Most patients eligible for this study will have received frontline treatment with daratumumab, lenalidomide, and/or bortezomib, and will have relapsed or become refractory to these drugs during earlier lines of treatment. These patients represent a clinically relevant population because there is no SoC used in later lines of treatment.

Background on Forimtamig

Forimtamig is a novel TCB humanized IgG1 mAb targeting GPRC5D expressed on MM tumor cells and CD3Dε present on T-cells. Upon simultaneous binding to the CD3ε on T-cells and to GPRC5D expressed on MM target cells, T-cells are activated, release cytotoxic granules, and ultimately induce tumor cell lysis (TCL; killing) independent of the normal T-cell receptor major histocompatibility class interaction. Forimtamig efficiently induces T-cell proliferation and subsequently potentiates T-cell mediated anti-tumor responses by generating an increased effector-to-target ratio within the tumor.

A detailed description of the chemistry, non-clinical pharmacology, efficacy, and safety of forimtamig as well as clinical data from Study BP42233 are provided in the Investigator's Brochure.

Background on Carfilzomib

Carfilzomib is a second-generation PI with cytotoxic and potentially immunomodulatory effects, approved in combination with daratumumab and dexamethasone, lenalidomide and dexamethasone, or with dexamethasone for patients with second line or later (2L+) MM therapy (EMA SmPC, U.S. package insert). In the U.S., there is an additional label for single agent in r/r MM in 2L+. For the scientific rationale regarding the combination strategy with forimtamig, refer to Section 4.2.2.

Background on Daratumumab

Daratumumab is the first-in-class human IgG1 mAb targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action and was approved for MM in 2015 as monotherapy and subsequently in combination with other agents in MM (van de Donk et al. 2016). For the scientific rationale regarding the combination strategy with forimtamig, refer to Section 4.2.3.

2.3 BENEFIT/RISK ASSESSMENT

The benefit/risk assessment of forimtamig monotherapy in heavily pre-treated participants with r/r MM has been positive so far in the first-in-human Study BP42233. [redacted]

Safety risks based on the mechanism of action of forimtamig are cytokine release syndrome (CRS; [redacted]), infections, hair, skin and mucosal toxicity due to a probable on-target off-tumor expression of GPRC5D in highly keratinized structures, neurotoxicity, and hematologic toxicity. For more detailed information about the benefits, risks, and adverse events (AEs) of forimtamig observed to date, refer to the Investigator's Brochure.

In this study, forimtamig will be combined with carfilzomib or daratumumab. [redacted] Several risk mitigation strategies have been implemented in order to minimize and/or manage the risk of potential overlapping toxicities:

- Participant eligibility criteria tailored to exclude patients with a medical history that may pose a risk based on forimtamig's mechanism of action or the safety profile of the combination partners as described in their respective labels.
- Pre-medication and hospitalization guidelines to manage and monitor CRS toxicities.
- A dose exploration phase for each combination with randomized comparison of [redacted] together with a combination partner (see Figure 1) with predefined safety stopping rules (Section 4.1.3).
- Internal monitoring committee (IMC) reviewing the data, including safety, tolerability, and PK/PD data of the dose exploration phase prior to opening the dose expansion phase.

Monitoring of the safety profile during the dose exploration and expansion phases will be done every three months by the IMC.

In the expansion phase, the overall safety and efficacy profile of the studied combinations versus the forimtamig monotherapy will be evaluated to detect differences

in the safety profile as well as the potential contribution of the combination partners to the clinical activity of forimtamig.

The anticipated benefit/risk profile of combining forimtamig with carfilzomib or daratumumab or as monotherapy is considered acceptable given the poor prognosis of patients with r/r MM who have failed SoC therapies [redacted] and clinical data from Study BP42233.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of forimtamig is provided in the Investigator's Brochure.

COVID-19 Risk Assessment

Considering the early stage of development of this study and the limited number of participants, a conservative approach has been adopted. Patients with symptomatic disease (including coronavirus disease 2019 [COVID-19]) at screening will be excluded. Participants enrolled in this study will be closely monitored for new/emerging infections. Specific guidelines are provided in Section 8.3.8. In addition, vaccinations (including SARS-CoV-2/COVID-19 vaccination, if available) should be completed ideally prior to or during the course of the study as described in Section 6.5.1.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 7.

Table 7 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of forimtamig when given alone or in combination	• Incidence and severity of adverse events (AEs), with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) and of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) according to American Society of Transplantation and Cellular Therapy (ASTCT) Consensus Grading
To evaluate the preliminary anti-tumor activity of forimtamig when given alone or in combination	The International Myeloma Working Group (IMWG) criteria will be used for Investigator-assessed endpoints: • Objective response rate (ORR) • Complete response (CR)/stringent complete response (sCR) rate • Rate of very good partial response (VGPR) or better
Secondary	
To evaluate the preliminary anti-tumor activity of forimtamig when given alone or in combination	The IMWG criteria will be used for Investigator-assessed endpoints: • Progression-free survival (PFS) • Duration of response (DoR) for participants who achieve a partial response (PR) or better • Time to first response • Time to best response • Overall survival (OS)
To characterize the pharmacokinetics (PK) of forimtamig when given alone or in combination	• To assess the serum concentrations and PK parameters of forimtamig including AUC, C_{max}, C_{min}, T_{max}, and other parameters, if appropriate alone or with combination partners
To evaluate the immune response to forimtamig	• Presence of anti-drug antibodies (ADAs) during the study relative to the presence of ADAs at baseline
Exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase Ib/II, randomized, controlled, open-label, multi-center study in which forimtamig will be administered alone or in combination with carfilzomib or daratumumab to participants with r/r MM. An overview of the study design is provided in Section 1.2.

The study consists of a dose exploration phase and a dose expansion phase. During the dose exploration phase, [redacted] will be tested in each combination arm on [redacted] schedule in a randomized fashion (see also Section 4.3.1). For details on the randomization of eligible participants to the open and available treatment arms, refer to Section 6.3.1.

Based on the data from the dose exploration phase (i.e., safety and clinical data from at least the first two treatment cycles, PK/PD data, and, if available, biomarker data), [redacted] may be selected to be tested during the expansion phase with the respective combination partner.

During the exploration and expansion phases, the safety profile will be monitored every three months by the IMC. If a safety stopping criterion (Section 4.1.3) is met during the dose exploration or expansion phase, the IMC will conduct an ad hoc benefit/risk assessment and may recommend to either continue or pause enrollment or discontinue the treatment arm or all combination arms.

The forimtamig target dose selected for the expansion phase may vary between the combination arms [redacted] In addition, a single agent forimtamig comparator arm will start when at least one combination arm enters the expansion phase.

The forimtamig target dose tested during the expansion phase (combination and single agent) will not exceed the highest forimtamig dose [redacted] tested during the dose exploration phase for any combination.

Approximately 36 to 316 participants will be enrolled in this study: Approximately [redacted] participants in the dose exploration phase and approximately [redacted] participants in the expansion phase, depending on the number of forimtamig target doses expanded for each combination partner. In the expansion phase, each combination arm and the single agent forimtamig comparator arm will enroll up to approximately [redacted] efficacy-evaluable participants at their assigned target dose level of forimtamig.

4.1.1 Dose Exploration Phase

The forimtamig dosing regimen includes a [redacted]

[redacted]. The step-up doses will be the same in all arms. [redacted] will be tested with each combination partner during the dose exploration phase: [redacted]. Participants will be randomized between all open and eligible combination arms. Approximately [redacted] participants will be randomized per dose level within a combination arm.

The currently available clinical data from the forimtamig single agent Study BP42233 indicate that the safety profile for target doses up to [redacted] is similar, especially regarding [redacted]

Enrollment of the first 3 participants in each combination will be staggered such that their respective Cycle 1 Day 1 (C1D1) treatments are administered at least [redacted]. This will allow the assessment of unexpected acute and severe study treatment-related toxicities. Additional participants may be enrolled to account for participants who did not receive any dose of the combination partner treatment due to early discontinuation.

4.1.2 Dose Expansion Phase

After the IMC has reviewed all available clinical data from the dose exploration phase and established a positive benefit/risk assessment, an expansion phase may be opened with the combination partner. [redacted] The forimtamig comparator arm will be opened once at least one combination arm has started in the expansion phase.

For planned interim analyses, refer to Section 9.5.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

Most patients eligible for this study will have received frontline treatment with daratumumab, lenalidomide, and/or bortezomib, and will have relapsed or become refractory to these drugs during earlier lines of treatment. These patients represent a clinically relevant population because there is no SoC used in later lines of treatment. In Study BP42233, a favorable benefit/risk profile was demonstrated with forimtamig in patients with r/r MM.

In patients with r/r MM, the rechallenge of a drug used in prior treatment lines from which the patient did not partially benefit is not expected to be efficacious (Kumar et al. 2004). Therefore, patients who achieved at least a minimal response (MR) with carfilzomib and then progressed within 60 days of last therapy or did not respond to either of those while on salvage therapy, are excluded from the respective combination arm. Similarly, patients who are primarily refractory to carfilzomib will not be eligible for the respective combination arm (Rajkumar et al. 2011).

On the other hand, early clinical data suggest that patients previously exposed to or refractory to daratumumab treatment may be successfully rechallenged with anti-CD38 treatment after a treatment-free interval of several months. Therefore, implementing an anti-CD38 treatment-free interval is clinically indicated for patients eligible for the daratumumab combination arm (Nooka et al. 2019, Moreau et al. 2021, Mikhael et al. 2021).

Confirmation of GPRC5D expression will not be required prior to enrollment, based on the following rationale:

- GPRC5D is a cell-surface antigen whose expression is restricted to cells of the B lineage, including ubiquitous expression on plasma cells (Smith et al. 2019).
- [redacted]
- [redacted]

4.2.2 Rationale for Combining Forimtamig with Carfilzomib

Carfilzomib has cytotoxic and potentially immunostimulatory properties. Cytotoxic effects are mediated through proteasome inhibition (Carfilzomib SmPC). In contrast to IMiDs, PIs were reported to dampen T cell responses (Berges et al. 2008, Yanaba et al. 2010) and to induce lymphocytopenia in patients (Jung et al. 2013) potentially limiting their combination potential with T cell engaging therapies such as T cell bispecific antibodies.

Furthermore, recent preclinical data have shown that carfilzomib and other PIs could modulate the tumor microenvironment by inducing immunogenic properties in immune suppressive macrophages via an ER-stress-IRE1a-TRAF2-NK-κ B pathway (Zhou et al. 2022). In the same preclinical study, PIs increased macrophage and CD8 T cell infiltration into the tumor and synergized with anti-PD-1 treatment in a lung cancer mouse model.

[redacted]

[redacted]

4.2.3 Rationale for Combining Forimtamig with Daratumumab

Daratumumab is the first-in-class human IgG1 mAb targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action. It was approved for MM in 2015 as monotherapy (van de Donk et al. 2016).

Daratumumab has tumoricidal and immunomodulatory properties. Cytotoxic activity of daratumumab is mediated through multiple mechanisms by targeting CD38.

Immunomodulatory activities of daratumumab are mediated through depletion of CD38+ immune regulatory cells, promotion of T-cell expansion, skewing the T cell repertoire, and enhanced T cell cytotoxic potential (Krejcik et al. 2016).

[redacted]

Early clinical data suggest that patients previously exposed to or refractory to daratumumab treatment may be successfully rechallenged with anti-CD38 treatment after a treatment-free interval for several months (Nooka et al. 2019, Moreau et al. 2021, Mikhael et al. 2021). Therefore, implementing a daratumumab-free interval is clinically indicated for participants eligible for the daratumumab combination arm.

4.2.4 Rationale for Biomarker Assessments

Forimtamig is designed to target T cells and GPRC5D-positive tumor cells simultaneously. Binding of forimtamig to its two targets results in T cell activation and formation of an immunological synapse leading to TCL. This mode of action (MoA) was confirmed in nonclinical studies with forimtamig and in clinical studies of molecules with a similar format and MoA (Investigator's Brochure, Caraccio et al. 2020).

Pharmacodynamic (PD) and biomarker analyses will be conducted to demonstrate forimtamig's MoA and the impact of combination partners on forimtamig PD activity.

[redacted]

4.2.5 Rationale for Non-Standard Clinical Outcome Assessments

Cancer treatments, particularly combination therapies, can produce significant symptomatic AEs. Recent research has shown that clinicians may underreport the incidence and severity of symptoms experienced by patients receiving treatment for cancer (Fromme et al. 2004, Trotti et al. 2007, Pakhomov et al. 2008; Basch 2010, Quinten et al. 2011, Atkinson et al. 2012, Basch et al. 2014).

Collecting AE information directly from patients can provide a better understanding of treatment characteristics and their effects. In order to evaluate the tolerability of the study treatment, participants will be asked to report on their experience related to [redacted] selected from the validated [redacted] item bank (see Appendix 10).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.3.2 Carfilzomib Dose

A variety of different carfilzomib schedules and doses are described in the label, depending on the combination regimen (US label and EMA label). [redacted]

[redacted]

4.3.3 Daratumumab Dose

[redacted]

[redacted]

[redacted]

4.4 DURATION OF PARTICIPATION

The study duration per participant from screening until the safety follow-up visit will be approximately [redacted] (not including long-term follow-up), divided as follows:

- Screening: [redacted].
- Treatment period: Study treatment with forimtamig alone or in combination will be limited [redacted]. Participants in the combination arms who derive clinical benefit may continue treatment [redacted] with the respective combination partner alone until disease progression.
- Safety follow-up:
  - Participants in Arm A (forimtamig monotherapy) and Arm B (forimtamig + carfilzomib) will have their safety follow-up visit [redacted] after the last dose.
  - Participants in Arm C (forimtamig + daratumumab) will have their safety follow-up visit [redacted] after the last dose.
- Pre-progression follow-up: After the safety follow-up visit, participants will be followed every month after the last study treatment until confirmed progressive disease, death, the start of new anticancer therapy, withdrawal of consent, lost to follow up, or the end of the study, whichever occurs first.
- Post-progression follow-up: Survival status and start of new therapies for MM are to be checked every 3 months (e.g., via phone call or any other offline method as preferred by the site).

Additional follow-up will be required if the Investigator becomes aware of serious and related toxicity as per Appendix 3, Section 6.

4.5 END OF STUDY DEFINITION

The end of this study is defined as the date when the last participant's last visit (LPLV) occurs or the date at which the last data point required for statistical analysis, protocol-defined safety monitoring, or last survival follow-up is received from the last participant, whichever occurs later. Because of the exploratory nature of this clinical study, its conduct, including any or all treatment arms, can be discontinued at any time at the discretion of the Sponsor.

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants in this study will be adults with r/r MM who fulfill all of the given inclusion criteria and none of the exclusion criteria.

NOTE: Investigators should ensure that all study inclusion/exclusion criteria have been met at screening and prior to the first dose of study treatment. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment is given such that the participant no longer meets all eligibility criteria, supportive treatment may be administered according to local standards of care, if necessary, so that eligibility criteria may be met and laboratory tests may be repeated once, to determine if the patient qualifies for the study. If inclusion/exclusion criteria are not met after further evaluation, the patient should be excluded from participation in the study. Options for re-screening are described in Section 5.4.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

All participants must fulfill all general inclusion criteria. Additional inclusion criteria apply for the carfilzomib combination (Arm B) and the daratumumab combination (Arm C) as detailed in Section 5.1.1 and Section 5.1.2, respectively.

General Inclusion Criteria

1. Signed Informed Consent Form(s) (ICFs).
2. Age ≥ 18 years at time of signing ICF(s).
3. Ability to comply with the protocol in the Investigator's judgment.
4. Agreement to provide protocol-specific bone marrow biopsy and aspirate samples.
5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (Appendix 16).
6. Life expectancy of at least 12 weeks.
7. Documented diagnosis of MM according to the International Myeloma Working Group (IMWG) diagnostic criteria (Appendix 7).
8. Evidence of progressive disease based on Investigator's determination of response by IMWG criteria on or after last dosing regimen.
9. Participants with r/r MM who previously received therapy, including an IMiD and a PI. Both anti-CD38 naïve and anti-CD38 exposed/refractory participants are allowed.

For specific inclusion criteria for the carfilzomib combination (Arm B), refer to Section 5.1.1 and for the daratumumab combination (Arm C), refer to Section 5.1.2.

10. Measurable disease defined as at least one of the following:
    - Serum monoclonal protein (M-protein) ≥ 5 g/L.
    - Urine M-protein ≥ 200 mg/24 hours.
    - Serum free light chain (SFLC) assay: Involved SFLCs ≥ 100 mg/L and an abnormal SFLC ratio (< 0.26 or > 1.65).
11. AEs from prior anti-cancer therapy resolved to Grade ≤ 1, with the following exceptions:
    - Any grade alopecia.
    - [redacted]
12. Adequate organ functions:
    - Hepatic function:
      - AST and ALT ≤ 3 × upper limit of normal (ULN).
      - Total bilirubin ≤ 1.5 × ULN; participants with a documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible if total bilirubin ≤ 3 × ULN.
    - Hematologic function:
      - [redacted]
    - Renal function:

      Creatinine clearance (CrCl) ≥ 40 mL/min based:
      - On the Cockcroft-Gault formula (Appendix 13).
      - Or based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin calculation if cystatin C lab value is available (Appendix 1).
      - Or 24 hour urine collection.

- Serum calcium (corrected for albumin) level at or below the ULN (treatment of hypercalcemia is allowed and participants may enroll if hypercalcemia returns to normal with standard treatment).

13. **A biological female participant** is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:
    - Participant of non-childbearing potential (PONCBP), as defined in Appendix 5.

      AND/OR
    - Participant of childbearing potential (POCBP), who:
      - Agrees to remain abstinent (refrain from heterosexual intercourse) or use at least one highly effective contraceptive method that results in a failure rate of < 1% per year, preferably with low user dependency, from screening until [redacted] Biological female participants must refrain from breastfeeding during the same period. Examples of contraceptive methods are described in Appendix 5. The Investigator should evaluate with the participant the best contraceptive method based on anatomy and physiology. Hormonal contraceptive methods must be supplemented by a barrier method (preferably male condom). Biological female participants must refrain from donating eggs during this same period.

        Participants using oral contraceptives or hormonal contraception associated with a risk of thrombosis should be willing to switch to non-hormonal contraception or an alternative method of effective contraception during treatment with carfilzomib.
      - Have a negative pregnancy test (blood and additional urine test prior to first study treatment can be considered) within the 7 days prior to the first study treatment administration. Pregnancy tests (urine) should be performed monthly throughout the study until the end of the safety follow-up visit.
14. **A biological male participant** is eligible to participate if, during the treatment period [redacted] the participant agrees to:
    - Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom with a partner who is of childbearing potential (as defined in Section 1 of Appendix 5), or a pregnant partner to avoid exposure to the embryo. The Investigator should evaluate with the participant the best contraceptive method based on anatomy and physiology.
    - Refrain from donating semen during the same period.

5.1.1 Specific Inclusion Criteria for the Carfilzomib Combination

15. Cardiac function:

    Left ventricular ejection fraction (LVEF) > 40% as assessed by ECG or multiple-gated acquisition (MUGA) scan.

5.1.2 Specific Inclusion Criteria for the Daratumumab Combination

16. Must have a treatment-free interval of anti-CD38 directed therapies for 3 months.
17. Forced expiratory volume (FEV1)/forced vital capacity (FVC) ≥ 50% as assessed by spirometry.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following general exclusion criteria apply. Additional exclusion criteria apply for the carfilzomib combination (Arm B) as detailed in Section 5.2.1.

1. Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the last dose of forimtamig, tocilizumab, or carfilzomib, or [redacted] days after the last dose of daratumumab.
2. Plasma cell leukemia with circulating plasma cell count ≥ 5% or >500/μL.
3. Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary amyloid light-chain amyloidosis.
4. Participants with current amyloidosis (e.g., positive Congo Red stain or equivalent in tissue biopsy).
5. Participants with myelodysplastic syndrome.
6. Participants with (extramedullary) lesions in proximity of vital organs that may develop sudden decompensation/deterioration in the setting of a tumor flare. Participants may be eligible after discussion with the Medical Monitor.
7. Uncontrolled cancer pain. Participants requiring pain medication must be adequately controlled on a pain regimen at study entry. Symptomatic lesions amenable to palliative radiotherapy (e.g., bony lesions or plasmacytoma) should be treated prior to enrollment.
8. Hypersensitivity to any of the study-defined IMPs and/or history of severe allergic or anaphylactic reactions to mAb therapy or recombinant antibody-related fusion proteins.
9. Prior treatment with systemic immunotherapeutic agents, including, but not limited to, cytokine therapy, radioimmunoconjugate, gene modified adoptive cell therapy (e.g., chimeric antigen receptor modified T cells, natural killer [NK] cells), and bispecifics/trispecifics within 12 weeks or 5 half-lives of the drug, whichever is shorter, before first study treatment, except for the use of non-myeloma therapy (e.g., denosumab for hypercalcemia is allowed).

10. Prior treatment with mAb and antibody-drug conjugate within 4 weeks or 5 half-lives of the drug, whichever is shorter.
11. Prior anti-cancer therapy (chemotherapy, small molecule/tyrosine kinase inhibitors, radiotherapy) within 14 days prior to first forimtamig administration.
12. Major surgery within 2 weeks of the first dose, or not fully recovered from surgery, or has surgery planned during the time the patient is expected to participate in the study or within 2 weeks after the last dose of study treatment administration.

    Note: Patients with planned surgical procedures to be conducted under local anesthesia may participate.
13. [redacted]
14. [redacted]
15. Prior solid organ transplantation.
16. Received systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) greater than or equal to 140 mg of prednisone within the 14-day period before first dose of study treatment.
    - Participants who received acute, low-dose, systemic immunosuppressant medications (e.g., single dose of dexamethasone for nausea) may be enrolled in the study after discussion with the Medical Monitor.
    - The use of inhaled corticosteroids, mineralocorticoids for management of orthostatic hypotension, and physiologic doses of corticosteroids for management of adrenal insufficiency is permitted.
17. Active auto-immune disease or flare within 6 months prior to start of study treatment, as outlined in Appendix 8. The following exceptions apply:
    - Participants with a history of auto-immune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
    - Participants with a history of disease-related immune thrombocytopenic purpura are eligible.
    - Participants with a history of type I diabetes mellitus whose disease is controlled (defined as a screening hemoglobin A1c $< 8\%$ and no urinary ketoacidosis) are eligible.
    - Participants with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., participants with psoriatic arthritis are excluded) are eligible provided all of the following conditions are met:
        - Rash must cover $< 10\%$ of body surface area (BSA).
        - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.

- No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- Participants with transient autoimmune manifestations of an acute infectious disease (e.g., Lyme arthritis) that resolve upon treatment of the infectious agent are eligible.

18. History of other invasive malignancy that could affect compliance with the protocol or interpretation of results.
    - Participants with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are allowed.
    - Participants with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for ≥ 2 years prior to first forimtamig administration.
19. History of CNS disease, such as stroke, epilepsy, CNS vasculitis, progressive multifocal leukoencephalopathy (PML), neurodegenerative disease, or CNS involvement by MM with the following exceptions:
    - Participants with a history of stroke who have not experienced a stroke or transient ischemic attack in the past 6 months and have no residual neurologic deficits as judged by the Investigator.
    - Participants with a history of epilepsy who have had no seizures in the past 6 months while not receiving any anti-epileptic medications.
    - Stable neurodegenerative diseases such as controlled Parkinson's disease.
20. Significant cardiovascular disease or condition affecting cardiac function (such as, but not limited to, New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months prior to date of randomization, congestive heart failure, uncontrolled cardiac arrhythmias Grade 2 or higher by the National Cancer Institute (NCI) CTCAE Version 5.0, uncontrolled hypertension, unstable or poorly controlled angina pectoris, screening 12-lead ECG showing clinically significant ECG abnormalities, pericardial disease) that may limit a participant's ability to adequately respond to a CRS event.
21. Significant pulmonary disease such as known moderate or severe persistent asthma or a history of moderate or severe asthma within the last 2 years or currently has uncontrolled asthma of any classification. Participants who currently have controlled intermittent asthma, controlled mild persistent asthma or controlled COPD are allowed to participate in the study.
22. Known or suspected active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics within 14 days prior to first forimtamig administration.
23. Known or suspected chronic active Epstein-Barr virus (EBV) infection. Guidelines for diagnosing chronic active EBV infection are provided by Okano et al. (2005).

24. Hepatitis B virus (HBV) infection as defined according to the American Society of Clinical Oncology guidelines. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status (Appendix 14).
25. Acute or chronic hepatitis C virus (HCV) infection. Participants who are positive for HCV antibody at study entry or have a history of HCV antibody positivity must be negative for HCV by PCR to be eligible for study participation.
26. Known history of HIV seropositivity.
27. Live vaccine(s) within one month prior to start of the treatment.
28. Patients not fully vaccinated for SARS-CoV-2 as per local recommendations and taking into consideration previously demonstrated infection.
29. Patients who are only eligible for the forimtamig single agent comparator arm.

5.2.1 Specific Exclusion Criteria for Carfilzomib Combination

30. Previous refractoriness to carfilzomib. Participants are considered refractory to carfilzomib if they did not achieve at least an MR to most recent therapy with carfilzomib or if their disease relapsed within 60 days of the last dose of carfilzomib treatment (Rajkumar et al. 2011).
31. Participants who discontinued prior carfilzomib treatment due to treatment-related toxicity.
32. Participants with known liver cirrhosis.

5.3 LIFESTYLE CONSIDERATIONS

Participants are expected to follow protocol requirements for contraception. Exposure to sunlight should be avoided or skin should be protected with high UV light blocker. There are no study-specific restrictions on meals and dietary requirements.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized to study treatment and entered in the study.

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

The screening phase begins when the first screening assessment is performed. The screening window may be extended for participants who passed the screening process but could not be enrolled within the [redacted] screening window due to a study halt, logistical, personal, or technical reasons. In such an event, invasive assessments like biopsies do not have to be repeated, if agreed to by the Medical Monitor. In addition, results of tests such as skeletal survey, radiology (e.g., magnetic resonance imaging [MRI]) to document baseline size of known or suspected extramedullary plasmacytomas, chest x-rays, computed tomography (CT) scans, or bone marrow aspirate/biopsy

performed up to 6 weeks (42 days) before the start of treatment as routine follow-up for the participant's disease may be used to establish baseline status at screening.

Participants who did not meet the inclusion and exclusion criteria may be re-screened once and must sign a new ICF.

In case of uncertain or questionable results, any of the tests performed during screening may be repeated before study treatment administration to confirm eligibility (or clinical significance).

Biopsy samples will only be entered in the electronic case report form (eCRF) and analyzed for enrolled participants.

5.5 RECRUITMENT PROCEDURES

Participants may be identified for potential recruitment by the Investigator and referring physicians using various sources, such as pre-screening enrollment logs, clinical databases, and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved newspaper/radio/social-media advertisements prior to consenting to take place on this study.

6. TREATMENTS

Study treatment is defined as any investigational product (including placebo) or marketed product intended to be administered to a study participant according to the study protocol.

All investigational medicinal products (IMPs), auxiliary medicinal products (AxMPs), and non-investigational medicinal products (NIMPs) for this study are identified in Appendix 6. All IMPs required for completion of this study will be provided by the Sponsor.

Tocilizumab will be supplied by the Sponsor as an IMP. However, because of the urgent need to manage CRS and in case of accessibility limitations at the site, tocilizumab can be obtained locally by the study site for emergency use purposes if permitted by local regulations. It will be prepared, handled, and managed according to standard institutional practices. Irrespective of the sourcing method, all tocilizumab used in the study will be tracked and accounted for as required by ICH GCP. Tocilizumab supplied by the Sponsor will include a clinical study drug/IMP label and if obtained locally by the study site, it will have the marketed product label. For further instructions regarding recommended storage conditions and packaging configuration, refer to the local prescribing information, Investigator's Brochure, and pharmacy manual.

The use of commercial tocilizumab may be allowed in certain sites/countries, should this be requested by the site/country and approved by the country Health Authority. A record of this approval should be kept on site and a copy provided to the Sponsor.

Study treatment administrations will be at the study center. For more details, refer to Section 6.1.

Cases of accidental overdose or medication error overdose, along with any associated AEs, should be reported as described in Appendix 2, Section 5.2.

6.1 TREATMENTS ADMINISTERED

Study treatments must be administered in a clinic or hospital equipped for systemic (IV and SC) cancer treatment. Full emergency resuscitation facilities should be immediately available, and participants should be under close observation by the Investigator at all times. In case of infusion-related AEs, the signs and symptoms should have fully resolved before the participant is discharged.

The treatments administered are summarized in Table 8. For more details on forimtamig, refer to the Investigator's Brochure as well as the Pharmacy Manual. For more information on carfilzomib, daratumumab, and tocilizumab, see the local prescribing information.

Table 8 Summary of Treatments Administered

Study treatment name:	Forimtamig	Carfilzomib	Daratumumab	Tocilizumab
Dose formulation:	[redacted]	Lyophilized powder	Solution	Solution
Unit dose strength(s):	[redacted]	[redacted]	[redacted]	[redacted]
Dose and regimen:	[redacted]	[redacted]	[redacted]	[redacted]
Route of administration:	SC	IV	SC	IV
Source:	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor

6.1.1 Forimtamig Administration

Forimtamig will be administered as SC injection. The injection site shall be chosen by the Investigator and its location captured in the eCRF. In participants with lymphatic obstruction, forimtamig should not be administered to the affected area. For additional details, refer to the Pharmacy Manual.

[redacted]

6.1.1.1 Hospitalization for Forimtamig

All participants will be observed in a hospital setting for [redacted] during C1 after the completion of forimtamig administration. Before a participant is discharged, any sign or symptom of CRS must have improved to Grade 1 and the participant must not have any signs of infection.

Hospitalization requirements during subsequent cycles will be based on the clinical course during C1. Participants with e.g., Grade 3 CRS or tumor lysis syndrome (TLS) during C1 may be hospitalized following the subsequent injection of forimtamig. Decisions to modify or discontinue the requirement for hospitalization will be made based on the recommendation of the Sponsor and in consultation with the Investigators.

6.1.2 Premedication for Forimtamig

All IMPs must be administered to well-hydrated participants. The premedication guidelines in Table 9 are applicable if forimtamig is administered as single agent (arm A) [redacted].

Premedication with analgesic/anti-pyretic and antihistamine prior to each forimtamig injection is recommended in the first 3 cycles and can then be omitted at the discretion of the Investigator.

For carfilzomib and daratumumab premedication, refer to Section 6.1.3 and 6.1.4.

All premedications should be captured as concomitant medications in the participant's eCRF. Premedications may be changed based on emerging safety and other data as determined by the IMC/Sponsor.

[redacted]

6.1.3 Forimtamig and Carfilzomib Administration

Forimtamig in combination with carfilzomib is administered according to Table 10.

Carfilzomib is administered as IV infusion over 30 minutes.

Due to the risk of acute TLS, carfilzomib will only be administered in well hydrated participants. At least 250 mL of intravenous fluids should be administered prior to each administration in C2 and if needed, an addition 250 mL should be given at the discretion of the Investigator. Monitor participants for volume overload and adjust hydration to individual participant's needs.

Dexamethasone as Premedication for Carfilzomib

Premedication will be administered 30 minutes to 4 hours before carfilzomib administration. For C2, 10 mg of dexamethasone will be administered as premedication prior to carfilzomib. From C4 onward, dexamethasone will be administered at the discretion of the Investigator.

Thromboprophylaxis is recommended if carfilzomib is administered in combination with other therapies; the thromboprophylaxis regimen should be provided per Investigator's discretion based on an assessment of the participant's underlying risks.

For participants with a BSA of 2.2 m^2 or less, calculate the carfilzomib dose using actual BSA. Dose adjustments do not need to be made for weight changes of 20% or less. For participants with a BSA greater than 2.2 m^2, calculate the carfilzomib dose using a BSA of 2.2 m^2. For further details, refer to the carfilzomib label.

[redacted]

[redacted]

6.1.4 Forimtamig and Daratumumab Administration

Forimtamig in combination with daratumumab is administered according to Table 11.

Daratumumab will be administered SC [redacted] by manual push over approximately 3 to 5 minutes in the abdominal subcutaneous tissues in the left/right locations. The locations (left vs. right abdomen) for daratumumab and forimtamig injection must not be the same. [redacted]

Administration of daratumumab will be performed in a monitored setting with immediate access to trained personnel, adequate equipment, and medicine to manage potentially serious reactions. Guidelines for medical management of infusion-related reactions (IRRs) are provided in Section 8.3.8.1. No dose reduction for daratumumab is allowed. Dose delay may be allowed.

Premedication should be administered to reduce the risk of administration-related reactions, approximately 1 hour prior to every daratumumab injection as follows:

- Acetaminophen or paracetamol 650 to 1000 mg IV or oral.
- Diphenhydramine 50 mg (or equivalent) IV or oral.
- Dexamethasone 20 mg or equivalent of an intermediate or long-acting corticosteroid (IV for C1D1, oral or IV for the next daratumumab injections).

[redacted]

[redacted] From C2D15 onward, premedication may be discontinued at the discretion of the Investigator.

Post-medication: In addition, the Investigator may consider administering oral methylprednisolone at a dose of less than or equal to 20 mg (or an equivalent dose of an intermediate or long-acting corticosteroid) beginning on the day after administration of the first 3 doses of daratumumab (i.e., C1D2, C1D9, and C1D16), as per SmPC. If the participant does not experience a major systemic administration-related reaction after the first 3 doses of daratumumab, the post-medication may be discontinued.

For participants with a history of chronic obstructive pulmonary disease, short and long-acting bronchodilators and inhaled corticosteroids should be considered. These additional post-medications may be discontinued following the first 3 doses of daratumumab if the participant does not experience a major systemic IRR.

Antiviral prophylaxis should be initiated to prevent herpes zoster reactivation within 1 week after starting daratumumab and continue for 3 months following treatment.

[redacted]



6.1.5 Tocilizumab Administration

Tocilizumab should be administered for the treatment of CRS when necessary, as described in Section 8.3.8.1. Administration of tocilizumab should follow the guidelines defined in the SmPC and/or label. For additional details, refer to the tocilizumab Investigator's Brochure. If tocilizumab is administered, additional assessments are required as described in Appendix 15. Each study site must have two doses of tocilizumab at their disposal prior to administration of forimtamig.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

The packaging and labeling of the IMPs will be done in accordance with the Sponsor's standard and local regulations. IMP packaging will be overseen by the Sponsor's clinical study supplies department and bear a label with the identification required by local law, the protocol number, drug identification, and dosage.

The study site must follow all instructions included with each shipment of IMP. The Investigator or other authorized personnel (e.g., pharmacist) will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced. The Investigator or designee must confirm that appropriate temperature

conditions have been maintained during transit for all IMPs received and that any findings, product complaints, or discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

The Investigator is responsible for IMP accountability (i.e., receipt, reconciliation, and final disposition records). The authorized study personnel will maintain records of IMP delivery to the site, IMP inventory at the site, study treatment use by each participant, and disposition or return of unused IMP. This will enable reconciliation of all IMPs received, and ensure that participants are provided with the doses which are specified in the protocol.

IMP will either be disposed of at the study site according to the study site's institutional SOP or returned to the Sponsor with the appropriate documentation. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form. Accurate records of all IMP received at, dispensed from, returned to, and disposed of by the study site will be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Investigator's Brochure or local prescribing information for information on IMP formulation, IMP handling (including preparation and storage), and accountability.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

6.3.1 Method of Treatment Assignment

This is a randomized controlled open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number treatment assignment from the interactive voice or web-based response system (IxRS).

This study will employ a permuted-block randomization method with dynamically changing randomization ratios to account for fluctuation in the number of treatment arms that are open for enrollment over the course of the study. The randomization ratio will depend on the number of combination arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the dose exploration or expansion phase), with the stipulation that the likelihood of being allocated to the comparator arm will be no more than 50% in the expansion phase. The randomization ratios may be altered to increase enrollment in a particular arm.

Randomization will take into account general inclusion/exclusion criteria and arm-specific-inclusion/exclusion criteria (Section 5.1 and Section 5.2). For example, all daratumumab combinations in Arm C will be removed as an option for participants who are ineligible for that combination.

Additional patients may be enrolled to reach the target number of treated participants planned for analysis.

6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing each study treatment will prepare the correct dose according to the randomization schedule and respective pharmacy manual. This individual will record the date dispensed and participant number and any other relevant information.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, or nutritional supplements) used by a participant from [redacted] prior to screening until the last safety follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency). All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

6.5.1 Permitted Therapy

For the use of permitted and/or prohibited concomitant medications in combination with carfilzomib and daratumumab, refer to the SmPC guidelines.

6.5.1.1 Contraceptives

Participants who use hormone-replacement therapy, or other maintenance therapy should continue its use. The use of oral contraceptives is not recommended because oral contraceptives are metabolized by CYP450 enzymes and the transient release of cytokines during forimtamig treatment may cause drug-drug interactions, which may accentuate side effects associated with oral contraceptives. Regarding potential treatment effects on CYP enzymes, refer to “Substrates of CYP450 Enzymes” in this same section further below.

Participants using oral contraceptives or hormonal contraception associated with a risk of thrombosis should be willing to switch to non-hormonal contraception or an alternative method of effective contraception during treatment with carfilzomib.

6.5.1.2 Hematopoietic Growth Factors

Concomitant use of hematopoietic growth factors such as erythropoietin, granulocyte colony-stimulating factor (filgrastim, pegfilgrastim), granulocyte/macrophage colonystimulating factor (sargramostim), or thrombopoietin (oprelvekin, eltrombopag) is

allowed in accordance with instructions provided in the package inserts, institutional practice and/or published guidelines.

6.5.1.3 Infection Prophylaxis and Treatment

Anti-infective prophylaxis (including IV immunoglobulin replacement therapy) for viral, fungal or bacterial infections is highly recommended for participants at high risk of infections and should be instituted per institutional practice. Prophylaxis for pneumocystis infection and herpes zoster reactivation is mandated during the course of treatment according to the local institutional guidelines, unless contraindicated.

The use of IV-Ig replacement therapy is should be considered to reduce the risk of recurrent infection due to hypogammaglobulinemia per institutional guidelines.

Treatment for SARS-CoV-2 infection (including but not limited to tocilizumab, tixagevimab, cilgavimab, and other mAbs) or prophylaxis is permitted when used as authorized or approved by local health authorities and per institutional practice. Participants should be monitored for AEs for both forimtamig and COVID-19-directed therapies. COVID-19-directed therapies should not be administered on the same day as study treatment, when possible, to minimize the possibility of adverse drug-drug interactions. Study treatment should not be given during active infection, including COVID-19.

Infectious complications should be treated with oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

6.5.1.4 Vaccinations

Participants should not receive either primary or booster vaccination with live virus vaccines for at least four weeks before initiation of or at any time during study treatment. There is no data on potential interactions of non-live vaccines with forimtamig. In the absence of evidence-based recommendations, it would be advisable to space enough time (4 weeks) between the administration of the non-live vaccine and forimtamig in order to minimize the potential confounding effect of the non-live vaccine.

Available standard non-live vaccinations are strongly recommended (e.g., haemophilus influenzae, pneumococcus, meningococcus) before enrollment into the study. Investigators should review the vaccination status of participants being considered for this study and follow local guidelines for adult vaccination with non-live vaccines intended to prevent infectious diseases before study therapy.

Inactivated vaccines (e.g., COVID-19 mRNA vaccines) are allowed during the course of the study; however, they should be avoided in the first two cycles. The safety and efficacy of inactivated vaccines in participants receiving treatment with forimtamig is unknown. For each participant, the decision to receive a non-live vaccine will be a

benefit/risk discussion between the participant and treating physician. This decision will depend on a number of factors, such as the type of non-live vaccine, the potential risk of infection, and the underlying disease and age of the participant. Vaccination should not take place on dosing days. The timing of administration of a non-live vaccine during the course of the study can be further discussed with the Medical Monitor if warranted and should be documented if it occurs.

Influenza vaccination can be given during influenza season with non-live vaccines at any time during the study treatment.

6.5.1.5 Prophylaxis of Skeletal-related Events

Bisphosphonates or denosumab, as indicated for hypercalcemia or prevention of skeletal-related events, may be continued if the participant is already on either therapy prior to starting the study. In addition, initiation of these therapies during screening, pre-phase, or C1 is permitted. After C1, bisphosphonates or denosumab may be prescribed as long as there is no sign of disease progression.

6.5.1.6 Hematopoietic Growth Factors and Transfusions

Growth factor support, erythropoietin-stimulating agents, and transfusions are permitted to treat symptoms or signs of neutropenia, anemia, or thrombocytopenia according to local SoC. Growth factor support should be avoided during CRS and immune AEs. G-CSF should be considered for Grade 3 neutropenia with infection or fever or any Grade 4 neutropenia. For safety management guideline regarding hematopoietic toxicities, refer to Section 8.3.8.

6.5.1.7 Substrates of CYP450 Enzymes

Sustained elevation of cytokines, especially IL-6, has been shown to suppress CYP enzyme activity in humans; however, this is typically observed in chronically altered immunological states (Lee et al. 2010), such as chronic inflammatory diseases.

[redacted]

Nevertheless, the Investigator should consider that for participants treated with CYP substrates, potential AEs observed simultaneously with CRS might also be caused by elevated plasma exposures of the concomitantly administered CYP substrate.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
- [redacted]
- [redacted]

[redacted]

6.6 DOSE MODIFICATION, TEMPORARY INTERRUPTIONS, AND RECHALLENGE

In general, there will be no dose modifications for forimtamig or any of the combination partners. In the event a dose reduction is necessary for treatment-emergent AEs, documented consultation with the Medical Monitor and the Investigator of all decisions regarding dosing and dose-schedule modifications is required.

Temporary Interruptions

Temporary study treatment interruption is an acceptable method to manage AEs related to forimtamig or any of the combination partners. Treatment interruptions should be handled as described in Section 8.3.8.

6.6.1 Dose Modification, Temporary Interruptions, and Rechallenge for Forimtamig

[redacted]

- [redacted]

Supportive care such as transfusions or G-CSF may be provided per institutional standard practice to meet the hematology thresholds for dosing.

All considerations of dose and schedule modifications should be discussed with the Medical Monitor. The following guidelines regarding dose and schedule modifications should be followed:

- In general, participants receiving forimtamig who experience a Grade 4 AE that is not considered by the Investigator to be attributable to another clearly identifiable cause should permanently discontinue all study treatment. However, for participants with Grade 4 AEs of asymptomatic laboratory changes, study treatment may be resumed upon resolution to Grade≤1 or baseline after discussion with the Medical Monitor. Participants in a combination arm have the option to continue with the combination partner alone based on the benefit/risk assessment of the Investigator.
- [redacted]
- In general, participants who experience a Grade 3 AE that is not considered by the Investigator to be attributable to another clearly identifiable cause (e.g., disease progression, concomitant medication, or pre-existing medical condition) will be allowed to delay dosing [redacted] in order to recover from the toxicity.

  Participants may continue to receive additional administration of forimtamig, provided that the toxicity has resolved to Grade≤1 or baseline (for laboratory abnormalities, refer to the management guidelines in Section 8.3.8) within [redacted]. Exceptions may be allowed after careful clinical benefit/risk assessment by the Investigator and after discussion with the Medical Monitor.
- In case of treatment delay and depending on the length of treatment delay, the participant may be required to repeat step-up dosing. [redacted]

Participants who discontinue study treatment for reasons other than progressive disease should continue to be followed according to the schedule in Section 1.3.

6.6.2 Dose Modification, Temporary Interruptions, and Rechallenge for Carfilzomib

Guidelines for carfilzomib dose modification are described in Table 12 . For additional information, refer to the carfilzomib USPI.

Table 12 Carfilzomib Dose Modification

	Actual Carfilzomib Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Carfilzomib, forimtamig, and dexamethasone	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2

6.6.3 Dose Modification, Temporary Interruptions, and Rechallenge for Daratumumab

No dose modification of daratumumab will be allowed. AEs related to daratumumab may be managed by dose delay.

Administration of daratumumab may be restarted if the delay is within the timeframe specified in Table 13 . If daratumumab administration does not commence within the prespecified window 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.

If a dose delay occurs, PK and PD assessments should be performed on the actual day of study treatment administration, not on the originally scheduled administration day.

In the case of daratumumab interruption or missed dose(s), the other study treatments should continue to be administered per individual cohort schedule and not delayed. If daratumumab is permanently discontinued, other study treatments may be continued per individual arm dosing schedule.

For additional details, refer to the daratumumab local prescribing information.

[redacted]

6.7 TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not intend to provide forimtamig or any other study treatments to participants after conclusion of the study or any earlier participant withdrawal.

The Sponsor will evaluate whether to continue to provide forimtamig or any other study treatments to participants after the main study is over, in accordance with the Roche Global Policy on Continued Access to IMP, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

7. DISCONTINUATION OF STUDY OR STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of participant withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided, and efforts should be taken to motivate participants to comply with all the study-specific procedures as outlined in this protocol.

Reasons for early discontinuation may include disease progression or the participant being lost to follow-up (Section 7.3), withdrawing consent, or starting a new anti-cancer therapy, whichever occurs first.

Details on study and site closures are provided in Appendix 1, Section 4.

7.1 DISCONTINUATION OF STUDY TREATMENT

Participants must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he/she continues to receive study treatment.
- Investigator or Sponsor determines that it is in the best interest of the participant.
- Pregnancy.
- Use of an anti-cancer therapy for MM not required per protocol.
- Symptomatic deterioration attributed to disease progression.
- Disease progression during treatment per Investigator assessment according to IMWG criteria (Appendix 7).
- Participant decision.

Participants who discontinue study treatment will return to the clinic for a safety follow-up period as indicated in Section 1.3.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason and without justification.

In addition, the Investigator has the right to withdraw a participant from the study for medical conditions that the Investigator or Sponsor determines may jeopardize the participant's safety if he/she continues in the study.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate

eCRF. Participants will not be followed up with for any reason after consent has been withdrawn. This includes the assessments.

When a participant voluntarily withdraws from the study, or is discontinued by the Investigator, samples collected until the date of withdrawal/discontinuation will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will be used as part of the overall research data. A participant's withdrawal from this study does not, by itself, constitute withdrawal of samples donated to the Research Biosample Repository (RBR).

For data to be collected at the time of study discontinuation and any further evaluations that need to be completed, see the SoA (Section 1.3).

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

Discontinuation of sites or of study as a whole are handled according to Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timepoints are summarized in the SoA (Section 1.3). Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the SoA.

[redacted]

Results of standard-of-care tests or examinations performed prior to obtaining informed consent [redacted] may be used. These tests do not need to be repeated for screening.

Collection of any non-safety-related data or participant samples may be terminated by the Sponsor if further collection of such data or samples is not related to the study's primary objective(s) and additional data is not expected to add value to the existing analysis. The decision to discontinue any data collection will be communicated to study Investigators (and IRBs and ECs, according to local requirements) by means of a protocol clarification letter and will be incorporated into the next full protocol amendment. The decision to analyze samples that have been collected prior to the termination of sample collection will be documented by the Sponsor.

8.1 EFFICACY ASSESSMENTS

8.1.1 Disease and Response Evaluations

Participants will be evaluated for disease response and progression according to the IMWG response criteria (Appendix 7) during each cycle at timepoints identified in the SoAs (Section 1.3).

Disease evaluations scheduled for treatment days should be collected before study treatment is administered. In the event of prolonged treatment interruption, disease evaluations should continue every [redacted]. Disease evaluations will be performed until disease progression according to the IMWG criteria. For participants who discontinue study treatment before disease progression, disease evaluations should continue to be performed as described in the SoA (Section 1.3), until confirmed disease progression, death, the start of a new treatment for MM, withdrawal of consent for study participation, lost to follow-up, or the end of study, whichever occurs first.

Participants who progress, should not be taken off study treatment and disease evaluations should continue until disease progression according to the IMWG criteria is confirmed. Confirmation should be based on a second efficacy assessment. If imaging demonstrates progression, this does not need to be repeated.

[redacted] Disease evaluations scheduled for treatment days should be collected before study treatment is administered. Per IMWG criteria, participants will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status. [redacted]

Participants cannot move to a lower response category. Disease progression must be consistently documented across clinical study sites using the IMWG criteria in Appendix 7.

8.1.1.1 Myeloma Protein Measurements in Serum and Urine

Disease evaluations assessments will be performed [redacted] until disease progression according to the IMWG criteria (Appendix 7).

- Serum M-protein electrophoresis (SPEP) at baseline and all timepoints.
- Serum immunofixation electrophoresis (SIFE) at baseline and all timepoints.
- Serum free light chain (SFLC) assay (at baseline for all participants, all timepoints for participants with SFLC only disease and any participants with CR, and if necessary for other participants).
- [redacted]
- [redacted]
- Quantifiable Ig levels tested [redacted]
- [redacted]

Blood and 24-hour urine samples will be collected per SoA (Section 1.3) until the development of confirmed disease progression. Disease progression based on one of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. For participants with light chain MM, both serum and urine immunofixation tests will be performed routinely.

8.1.1.2 Bone Marrow Examination

Bone marrow (BM) is locally assessed as defined by IMWG response assessment criteria to confirm CR/sCR (Appendix 7).

Note: Per IMWG criteria, sCR must be confirmed by absence of clonal cells in BM by immunohistochemistry (κ/λ ratio $\leq$4:1 or $\geq$1:2 for κ and λ participants, respectively, after counting $\geq$100 plasma cells) or negative by 2 to 4 color flow cytometry.

8.1.1.3 Plasmacytoma

All participants with a history of plasmacytoma or clinically suspected plasmacytoma at the time of screening must undergo an imaging assessment to evaluate for the presence and/or extent of disease by radiological imaging or clinical examination.

A PET–CT scan should be performed as this is the preferred imaging modality to assess plasmacytoma. CT or whole-body MRI scans are also acceptable. Ultrasound tests are not acceptable to document the size of plasmacytomas.

Sites of known plasmacytomas must be documented during screening. The calculation of SPD/size of a paramedullary plasmacytoma (originating from bone) should only include the part of the plasmacytoma that extends beyond the bony cortex (i.e., the soft tissue component). The calculation of SPD/size of plasmacytoma originating from soft tissue should include the whole plasmacytoma.

Participants with radiologically assessed plasmacytoma will undergo repeat imaging every 12 weeks (±7 days) and when clinically indicated, using, the same imaging method as applied at screening/baseline. Lesions evaluated clinically should be assessed at every response assessment and when clinically indicated.

If assessment can only be performed radiologically, then evaluation of plasmacytomas may be done every 12 weeks. Clinical assessment of plasmacytoma will be performed, measured, and evaluated locally every 4 weeks for participants with a history of plasmacytomas or as clinically indicated until development of confirmed CR or confirmed disease progression. For every participant, the methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable, and will be monitored only for disease progression.

Imaging should also be performed upon clinical suspicion of progressive disease. Imaging assessments demonstrating progressive disease do not need to be confirmed. To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have increased by at least 50% or a new plasmacytoma must have developed. In the cases where not all existing extramedullary plasmacytomas are reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, this will also qualify as disease progression. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory imaging is necessary.

8.1.1.4 Skeletal Assessment

Participants must undergo imaging to evaluate skeletal disease during screening ([redacted]), and thereafter as clinically indicated based on symptoms, to document progression. Low-dose whole body CT scans are preferred for assessing skeletal disease, but conventional X-ray skeletal scans are also acceptable. Imaging should include the skull, long bones, chest, entire vertebral column, pelvis, and any other bones for which the Investigator suspects involvement by disease. The same imaging method should be used throughout the study.

If plasmacytomas are seen on skeletal scans, bi-dimensional tumor measurements should be recorded.

The X-ray skeletal scans may be omitted if a PET-CT scan or a separate whole-body CT scan (evaluable for bone disease) is performed as part of screening for extramedullary disease.

MRI is an acceptable method for evaluation of bone disease and may be included at the discretion of the Investigator; however, it does not replace the skeletal assessment at screening. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory imaging is necessary. In instances where changes may be more subtle, a repeat imaging may be needed in 1 to 3 weeks per Investigator's discretion.

8.1.2 Patient-reported Outcome Assessments

PRO instruments will be completed to more fully characterize the safety profile of the study treatment. In addition, PRO instruments will enable the capture of each participant's direct experience with the study treatment.

PRO data will be collected through use of the following instruments: [redacted].

8.1.2.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at the clinic at specific timepoints during the study (see Section 1.3). At the clinic, instruments will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

PRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be pre-programmed to the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device. The data will be available for access by appropriate study personnel.

During clinic visits, PRO instruments should be administered as follows:

- Instruments will be administered prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.
- Participants' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.

- Sites should allow sufficient time for participants to complete the instruments, estimated to be 20 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Participants should be instructed to answer questions to the best of their ability. There are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

Site staff should review all completed instruments and should ask the participants to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the participants to complete the item or confirm that the item was intentionally left blank.

8.1.2.2 Description of Clinical Outcome Assessment Instruments

[redacted]

[redacted]

[redacted]

[redacted]

8.2 SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoAs (Section 1.3). All participants will be closely monitored for AEs throughout the study and for at least [redacted] after the last dose of study treatment.

Safety assessments will consist of monitoring and recording AEs, including serious AEs (SAEs) and AEs of special interest (AESIs); measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, and ECGs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

8.2.1 Physical and Neurological Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, neurological systems, and weight and height.

A complete neurological examination, which includes an evaluation of mental status (Immune Effector Cell-Associated Encephalopathy [ICE] score; Appendix 12), cranial nerves, strength, sensation, and coordination should be performed and documented in the participant chart. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

A targeted symptom-directed physical examination should be performed at subsequent visits (or as clinically indicated). Targeted physical examinations should be

limited to systems of primary relevance (i.e., cardiovascular, respiratory, neurologic, and any system that might be associated with tumor assessment [e.g., those systems associated with symptoms] or potential drug-related toxicity; see Section 8.3.8).

Targeted neurologic examinations should include an evaluation of alertness and orientation to person, place, and time (ICE score; Appendix 12). [redacted] New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

The 10-point ICE score should be used for the grading of ICANS together with other neurologic domains, such as level of consciousness, motor symptoms, seizures, and signs of elevated intracranial pressure (ICP)/cerebral edema (Table 14). For ICANS grading, please refer to Appendix 12.

Table 14 10-point Immune Effector Cell-Associated Encephalopathy (ICE) score*

Orientation	Orientation to year, month, city, hospital: 4 points
Naming	Ability to name 3 objects (e.g., point to clock, pen, button): 3 points
Following command	Ability to follow simple commands (e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
Writing	Ability to write a standard sentence (e.g., "Our national bird is the bald eagle"): 1 point
Attention	Ability to count backwards from 100 by 10:1 point

Scoring: 10: no impairment; 7-9: Grade 1 ICANS; 3-6: Grade 2 ICANS; 0-2: Grade 3 ICANS; 0 due to patient unarousable to perform ICE assessment: Grade 4 ICANS
*Lee at al. 2019.

8.2.2 Vital Signs

On dosing days, the vital signs must be assessed prior to each individual drug administration and as needed per institutional guidelines.

Vital signs will include measurements of systolic and diastolic blood pressure, respiratory rate, pulse rate, and body temperature while the participant is in a sitting or semi-supine position. Every effort should be made to ensure that vital signs are obtained from participants in a consistent manner/position.

Additional vital signs will be assessed in the case of a CRS and whenever clinically indicated.

For all visits, vital signs should be captured in the eCRF only at the time points indicated in the SoAs (Section 1.3), unless abnormalities are observed. During infusion, vital signs are not required to be captured in the eCRF, unless abnormalities are observed.

8.2.3 Electrocardiograms and Cardiac Echocardiography

Triplicate 12-lead ECG recordings will be obtained on study days as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. On dosing-days, one pre-dose ECG and one post-dose ECG (4 to 4.5 hours after injection) will be obtained. Additional ECGs will be recorded in the case of a CRS and whenever clinically indicated.

To minimize variability, it is important that participants be in a resting and supine position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate.

Transthoracic Echocardiogram or Multiple-Gate Acquisition Scans

Transthoracic echocardiogram (TTE) or MUGA scans will be performed at screening for all participants in all [redacted]

8.2.4 Pulmonary Function Test

Spirometry will be performed at screening for all participants in all arms, [redacted]

8.2.5 ECOG Performance Status

ECOG performance status will be assessed at screening and before each study treatment administration as specified in the SoAs (Section 1.3). See also Appendix 16.

8.2.6 Baseline Brain MRI

A baseline brain MRI will be obtained from all participants unless medically contraindicated. The brain MRI should use gadolinium-based IV contrast unless contraindicated. Participants with a history of neurologic disease may be excluded from the study (Section 5.2).

8.2.7 Clinical Safety Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. A list of clinical laboratory tests to be performed is provided in

Appendix 4 and these assessments must be conducted in accordance with the SoAs (Section 1.3). The last result obtained prior to the first dose of study treatment will be used to determine eligibility. The measurements collected at the time closest to, but prior to, the start of study treatment administration will be defined as the baseline values for safety assessment and treatment decisions.

Retesting of abnormal screening values that lead to exclusion are allowed only once during the screening phase (to reassess eligibility).

Results of clinical laboratory testing will be recorded on the eCRF.

8.2.7.1 Effect of Daratumumab on Laboratory Tests

Indirect Anti-Globulin Test (Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross-matching. Blood type, Rh, and indirect antiglobulin test (IAT; indirect Coombs Test) assays should be performed before the first dose of daratumumab. Participant RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to the first daratumumab injection.



Participants assigned to Arm C (daratumumab) will receive a patient identification card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first injection of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Participants should be instructed to carry this card throughout the treatment period and for at least 6 months after the treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT; Chapuy et al. 2015).

Possible methods for blood banks to provide safe RBCs for transfusion to participants receiving daratumumab include:

- Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units.

- [redacted]

[redacted]

[redacted]

For interference with serum protein electrophoresis and immunofixation, refer to Section 8.1.1.

8.2.8 Medical History and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), and reproductive status (women only) will be recorded at baseline. In addition, all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant [redacted] prior to initiation of study treatment will be recorded. Results of tests performed as part of clinical practice are available in the participant file at screening and might be relevant for the r/r MM disease (e.g., cytogenetic profile, karyotyping, phenotype of malignant plasma cells, gene mutations), will be collected as part of the cancer history.

Demographic data will include age, sex, and self-reported race/ethnicity, where possible per local regulations.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. AESIs and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Sections 8.3.6 and 8.3.7.

The Investigator and any qualified designees are responsible for ensuring that all AEs (including assessment of seriousness, severity, and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording AEs are provided in Appendix 3.

8.3.1 Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Investigators will seek information on AEs at each participant's contact. All AEs, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study treatment**, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies). Any other AE should not be reported.

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until the safety follow-up visit (refer to Section 4.4).

Post-study AEs and SAEs: The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period.

However, if the Investigator learns of any SAE (including a death) or other AEs of concern that are believed to be related to prior treatment with study treatment, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all participant evaluation timepoints.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

The Investigator should follow up on each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow up on all SAEs considered to be related to study treatment or study-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return-to-baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed up on until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

8.3.3.2 Sponsor Follow-Up

For SAEs, AESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional event details and outcome information (e.g., from hospital discharge summaries, consultant reports, and/or autopsy reports) to perform an independent medical assessment of the reported event.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Immediate notification by the Investigator to the Sponsor of an SAE (regardless of relationship to study treatment) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

For immediate (i.e., no more than 24 hours after learning of the event) and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, Investigators, IRB and Ethics Committee (EC), see Appendix 2; Sections 5 and 6.

The reason for (prolonged) hospitalization should be captured in the eCRF.

8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be available separately.

8.3.5 Pregnancy

Participants of childbearing potential (POCBP) will be instructed to immediately inform the Investigator if they become pregnant during the study or [redacted].

Male participants will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or [redacted].

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (Appendix 5).

8.3.6 Adverse Events of Special Interest

AESIs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; for reporting instructions, see Appendix 2).

AESIs for this study include the following:

- Cases of an elevated ALT or AST value in combination with either an elevated bilirubin value or clinical jaundice, as defined in Appendix 3.
- Suspected transmission of an infectious agent by the study treatment, defined as any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Not applicable for this study.

8.3.8 Management of Specific Adverse Events

Toxicities associated or possibly associated with study treatment should be managed according to the management guidelines provided in this protocol or, if not specifically mentioned, according to standard medical practice. Clinical judgment should be applied and benefit/risk consideration may suggest deviating from these guidelines. In these specific cases, decisions regarding study treatments will be taken by the Investigator

upon consultation with the Medical Monitor. Consultation with the Medical Monitor may not, under any circumstances, lead to an unwanted delay in the provision of participant care.

For additional details on risks associated with forimtamig, refer to the Investigator's Brochure. For additional information on carfilzomib and daratumumab, refer to the respective local prescribing information (carfilzomib USPI and daratumumab SmPC).

8.3.8.1 Management of Systemic Injection-Related Reactions, Cytokine Release Syndrome, and Infusion-Related Reactions

8.3.8.1.1 Management of Systemic Injection-Related Reactions and Cytokine Release Syndrome Associated with Forimtamig

The mechanism of action of forimtamig is immune cell activation against GPRC5D-expressing cells. Therefore, a spectrum of events involving systemic injection-related reactions (referred to in this section as sIRR), target-mediated CRS, and/or anaphylaxis/hypersensitivity, with or without emergent anti-drug antibodies (ADAs), may occur. Also, other bispecific antibody therapeutics involving T-cell activation have been associated with sIRR, CRS, and/or anaphylaxis/hypersensitivity reactions.

CRS is an identified risk for forimtamig. CRS is characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and hypoxia (NCI CTCAE v.5.0) and manifestations of an IRR might be very similar. Therefore, these syndromes may be clinically indistinguishable.

Mild to moderate presentations of sIRR, CRS, and/or anaphylaxis/hypersensitivity reactions may include symptoms such as fever, headache, and myalgia, and may be treated symptomatically with analgesics, anti-pyretics, and antihistamines as indicated.

Severe or life-threatening presentations of CRS, such as hypotension, tachycardia, dyspnea, hypoxia, or chest discomfort, should be treated aggressively with supportive and resuscitative measures as indicated, including the use of high-dose corticosteroids, IV fluids, anti-cytokine therapy, admission to the intensive care unit, and other supportive measures per institutional practice. Severe CRS may be associated with other clinical sequelae such as disseminated intravascular coagulation, capillary leak syndrome, or macrophage activation syndrome (MAS; Section 8.3.8.5). Standard of care for severe or life-threatening CRS resulting from immune-based therapy has not been established. Case reports and recommendations using anti-cytokine therapy such as tocilizumab have been published (Teachey et al. 2013, Lee et al. 2014, Maude et al. 2014, Lee et al. 2019; see also Section 8.3.8.23).

Severe COVID-19 is associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ. If a participant develops severe CRS during the course of the study, a differential diagnosis with testing to rule out COVID-19 infection should be considered.

Monitor participants for sIRR, CRS, and/or anaphylaxis/hypersensitivity reactions, especially during C1. If this occurs during the injection, the injection should be interrupted immediately when observing signs of a severe reaction, and aggressive symptomatic/supportive treatment with corticosteroids and/or antihistamines as per institutional guidelines should be initiated.

Management guidelines for sIRR and CRS are summarized in Table 15 and Table 16, respectively, with the grading of CRS following the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system described in Appendix 11. Management of Grade ≥3 CRS should be immediately discussed between the Investigator and the Medical Monitor. Even moderate presentations of CRS in participants with extensive comorbidities should be monitored closely with consideration given to intensive care unit admission and tocilizumab administration (Table 16).

For AE reporting procedures related to CRS, refer to Appendix 2, Section 3.1. For tocilizumab treatment of CRS, refer to the SoA in Appendix 15. For anaphylaxis management, refer to Appendix 9.

Table 15 Recommendations for Management of Systemic Injection-Related Reactions Associated with Forimtamig

Event[a]	Action to be Taken
Grade 1 to 2	• Give supportive treatment.[b] • Pre-medicate with acetaminophen/paracetamol and an antihistamine, such as diphenhydramine, for all subsequent injections. Note: For Grade 2 wheezing or urticaria, the participant must be premedicated prior to subsequent doses.
Grade 3	• Give supportive treatment.[b] • Admission to ICU is recommended to monitor cardiopulmonary and other organ functions. • Provide oxygen for hypoxia and/or mechanical ventilation as needed. • Subsequent doses of forimtamig may be administered with steroid premedication in consultation with the Medical Monitor. • Participants who experience Grade 3 wheezing, bronchospasm, or generalized urticaria at first occurrence must be discontinued from study treatment. Note: If symptoms recur despite premedications with the same or greater severity at subsequent doses, the participant must be permanently discontinued from study treatment.
Grade 4	• Give supportive treatment.[b] • Admit to ICU to monitor cardiopulmonary and other organ functions. • Provide oxygen for hypoxia and/or mechanical ventilation as needed. • Permanently discontinue study treatment.

ICU = intensive care unit; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Refer to NCI CTCAE v5.0 for the grading of symptoms.

b [redacted]

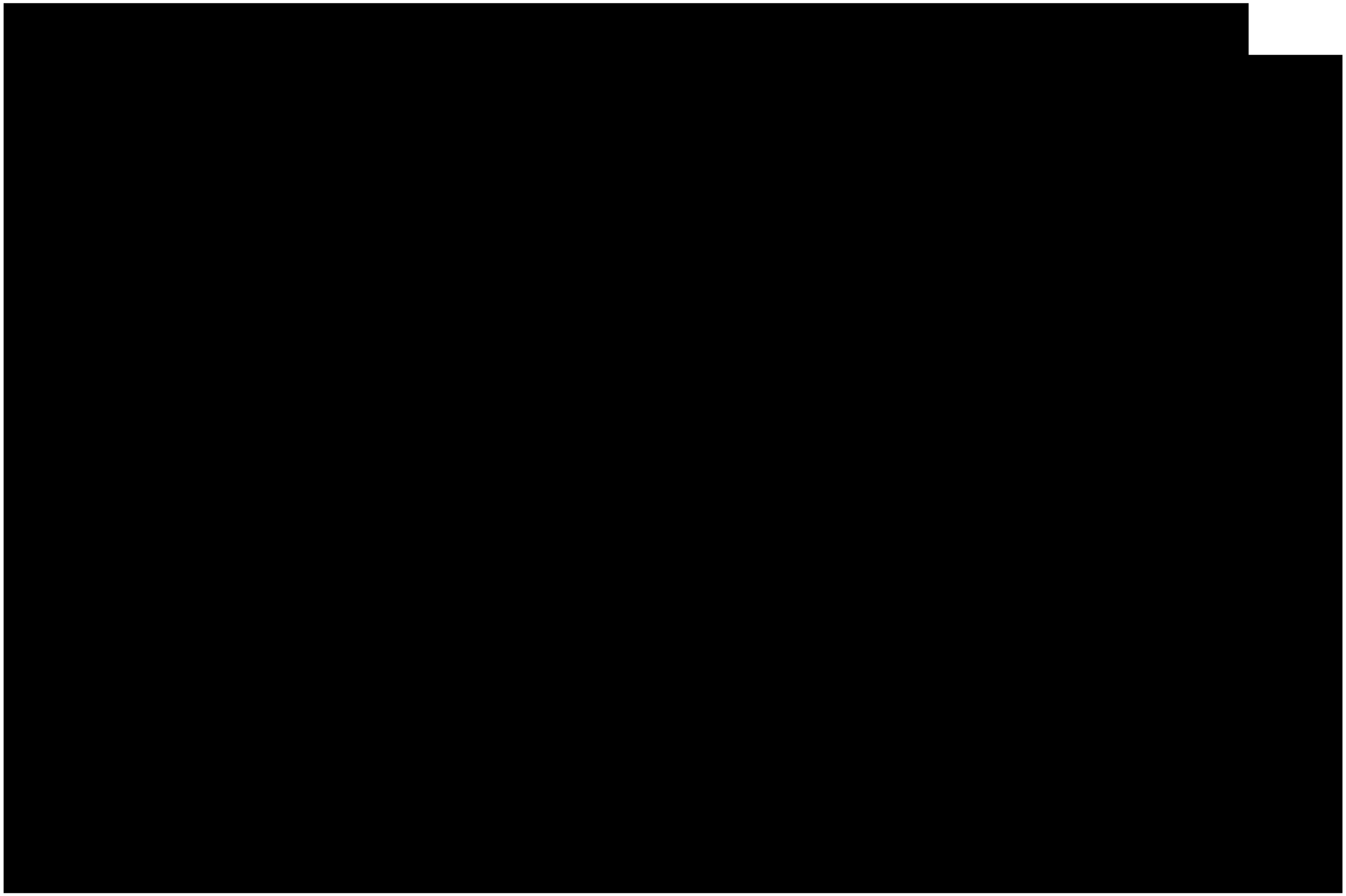
Additional and unscheduled blood samples should be taken at any time if signs and symptoms suggest a CRS event of Grade 3 or higher. Clinical decisions should be based on the results of the following local blood analyses: [redacted]

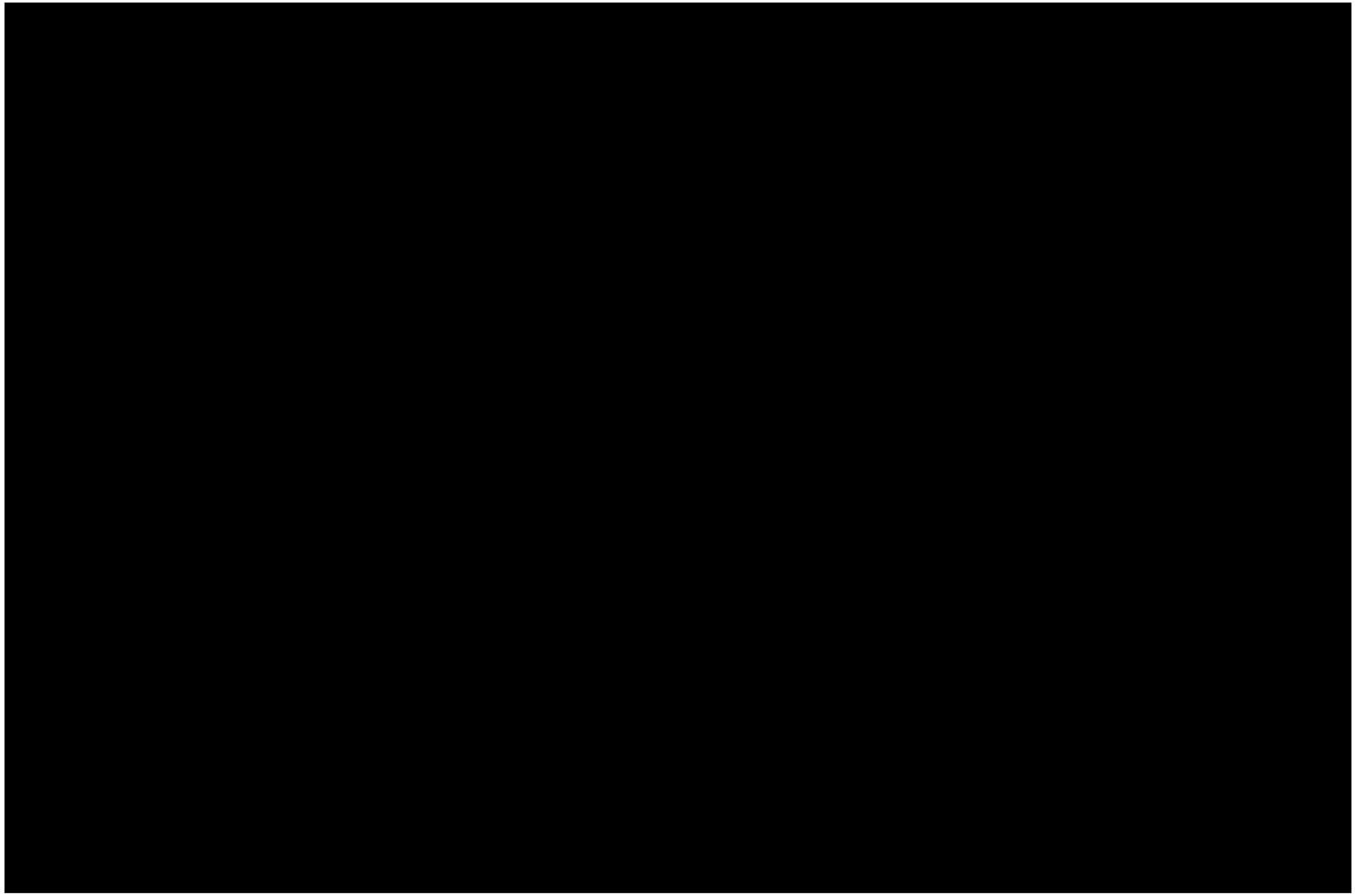
[redacted]

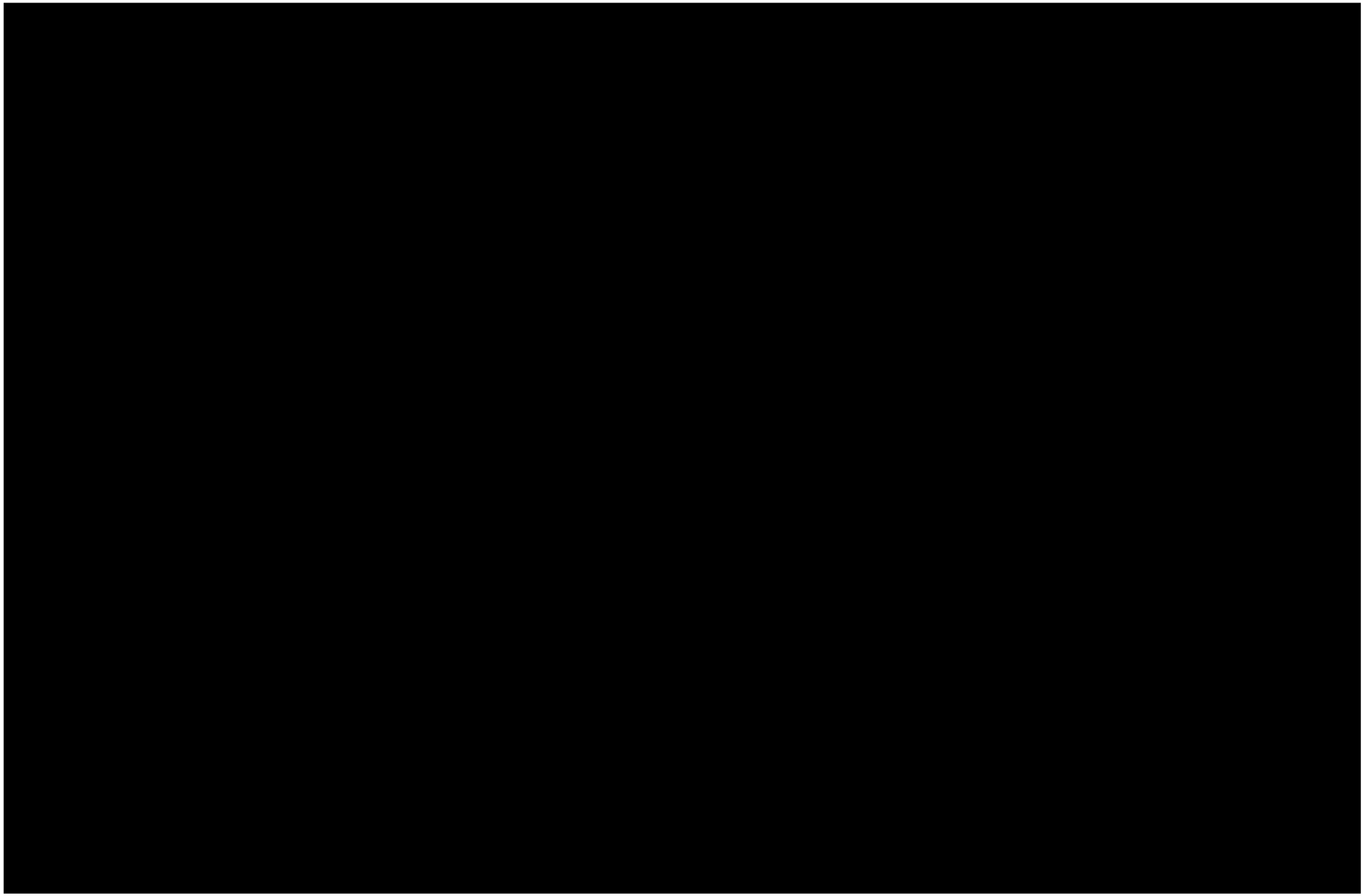
sIRRs may be indistinguishable from CRS based on the signs and symptoms. Therefore, the recommendation is to report the respective event as CRS by default and manage according to the guidelines for CRS in Table 16.

[redacted]

The management of CRS will be guided by the ASTCT CRS grading scale as shown in Appendix 11.









8.3.8.1.2 Management of Injection-Related Reaction/Cytokine Release Syndrome Associated with Daratumumab

Daratumumab solution for SC injection can cause severe and/or serious administration-related reactions, categorizes as IRRs, including anaphylactic [redacted].

The signs and symptoms of IRRs include respiratory symptoms such as nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as pyrexia chest pain, pruritus, chills, vomiting, nausea, and hypotension. [redacted]

If an administration-related reaction develops, SC daratumumab administration should be temporarily interrupted. Participants who experience AEs during SC daratumumab administration may be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. For bronchospasm, urticaria, or dyspnea, participants may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, participants may require IV fluid or vasopressors. In the event of a life-threatening administration-related reaction (which may include pulmonary or cardiac events) or an anaphylactic reaction, SC daratumumab should be discontinued.

Guidelines for the management of injection-related reactions associated with daratumumab are summarized in Table 17.

Table 17 Management Guidelines for Injection-Related Reactions Associated with Daratumumab

Event	Action to be Taken
Grade 1 to 2	• Interrupt SC daratumumab administration. • When the participant's condition is stable, SC daratumumab may be restarted at the Investigator's discretion. • If the participant experiences a Grade ≥ 2 event of laryngeal edema, or a Grade ≥ 2 event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, the participant must be permanently discontinued from SC daratumumab treatment.
Grade 3	• For administration-related reactions (other than laryngeal edema or bronchospasm) that are Grade 3, the SC daratumumab administration must be stopped and the participant must be observed carefully until resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the SC daratumumab administration may be restarted at the Investigator's discretion in consultation with the Medical Monitor.

Event	Action to be Taken
	• If the intensity of the adverse event returns to Grade 3 after restart of the SC daratumumab administration, the participant must be permanently discontinued from SC daratumumab treatment.
Grade 4	• SC daratumumab administration must be permanently discontinued.
Recurrent administration-related reactions	• If a Grade 3 administration-related reactions (or Grade ≥ 2 event of laryngeal edema or of bronchospasm) recurs during or within 24 hours after a subsequent SC daratumumab administration, the participant must be permanently discontinued from SC daratumumab treatment.

8.3.8.1.3 Management of Infusion-Related Reaction Associated with Carfilzomib

Infusion reactions, including life-threatening reactions, have occurred in patients receiving carfilzomib. Symptoms include fever, chills, arthralgia, myalgia, facial flush, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of carfilzomib. Administer premedication as outlined in Section 6.1.3.

For management of IRR associated with carfilzomib with onset during the infusion and prior to forimtamig administration, refer to Table 18 and for sIRR attributed to carfilzomib and/or carfilzomib and forimtamig with onset after the forimtamig administration, refer to Section 8.3.8.1.1.

Table 18 Management Guidelines for Infusion-Related Reactions

Event	Action to be Taken
Grade 1	• Monitor closely for infusion reaction. • If symptoms start: Stop infusion and do not restart until symptoms resolve completely. • Provide symptomatic treatment and restart infusion at half of the previous rate. If symptoms reoccur: Stop infusion and do not administer additional study treatment for the cycle.
Grade 2	• Monitor closely for infusion reaction. • If symptoms start: Stop infusion and do not restart. No additional study treatment will be administered for this cycle. • Provide symptomatic treatment and consider participant hospitalization.
Grade 3 and 4	• Manage as Grade 2. • The participant should receive an aggressive treatment including acetaminophen/paracetamol, antihistamine, IV saline, oxygen, bronchodilators, corticosteroids (hydrocortisone [200 mg IV] or equivalent) or vasopressors and adequate hydration as clinically indicated and depending on the symptoms. • Monitor participant until symptoms resolve completely and strongly consider ICU management.

8.3.8.2 Management of Local Injection-Site Reactions Associated with Subcutaneous Administration

8.3.8.2.1 Management of Local Injection-Related Reaction Associated with SC Administration of Forimtamig

Forimtamig will be administered SC, and thus local injection-site reactions are a potential risk. Skin samples/punch biopsies are recommended for participants who develop injection-site reactions following SC administration of forimtamig. Biopsies will be collected from both the injection site and the contralateral site to analyze biomarkers potentially associated with the reaction (e.g. GPRC5D expression) as described in Section 8.7.3.3.

Guidelines for the management of local injection-site reactions associated with forimtamig are summarized in Table 19.

Table 19 Management Guidelines for Local Injection-site Reactions with Forimtamig

Event	Action to be Taken
Grade 1	• Continue forimtamig in subsequent cycles and consider slowing down injection rate or change injection site in case of pain or erythema. • Initiate treatment with topical corticosteroids and continue until full resolution.
Grade 2	• Continue forimtamig SC in subsequent cycles after improvement to Grade ≤ 1. • Initiate treatment with topical corticosteroids. • [redacted] • Consider participant referral to dermatologist, if appropriate.
Grade 3	• Withhold forimtamig. • Refer participant to dermatologist. • [redacted] • Resume forimtamig if event resolves to Grade 1 or better.
Grade 4	• Refer participant to dermatologist. • Permanently discontinue forimtamig and contact the Medical Monitor. • Initiate treatment as per institutional guidelines.

8.3.8.2.2 Management of Local Injection-Related Reaction Associated with SC Administration of Daratumumab

Administration of SC daratumumab in abdominal tissue has been associated with local injection-site reactions, such as induration and erythema, in some patients. The reactions usually resolve within 60 minutes. Local injection site reactions should be managed per institutional standards.

8.3.8.3 Management of Hair and Skin Toxicity Associated with Forimtamig

[redacted]

To reduce the potential risk of the development of skin changes, participants should avoid sun exposure and use sun precautions. A dermatologist should evaluate persistent and/or severe skin toxicities. If appropriate, and if possible, photos of the skin toxicity should be obtained and submitted to the Sponsor. Investigators may consider obtaining skin samples/punch biopsies for participants who experience skin toxicities. Biopsies should be collected from an affected and unaffected skin area. The specimens will be used to analyze biomarkers potentially associated with the reaction (e.g., GPRC5D expression).

Guidelines for the management of dermatologic events associated with forimtamig are summarized in Table 20.

[redacted]

[redacted]

8.3.8.4 Management of Mucosal Toxicity Associated with Forimtamig

Mucosal toxicity has been determined as an identified risk for the treatment with forimtamig.

Clinical presentation usually follows the distribution pattern of the keratinized epithelium in the body, affecting the skin, its appendages (hair and nail), and/or the mucosa. Binding of forimtamig may cause mucosal impairment, which may be associated with oral toxicity and/or taste/smell alterations. Mucosal toxicity, mainly localized to oral cavity, most typically manifest as mucositis, dysgeusia, glossitis and oropharyngeal pain. Over time, these events might lead to decreased appetite and weight loss. After the initial evaluation for active infections, appropriate symptomatic management (e.g., mouth rinses, pain control), and nutrition consult as indicated and possibly a short course of corticosteroids after consultation with the Medical Monitor may be initiated.

Guidelines for the management of mucosal toxicities associated with forimtamig are summarized in Table 21.

Table 21 Management Guidelines for Mucosal Toxicities Associated with Forimtamig

Event	Action to be Taken
Any Grade	• Intervene early. • Oral hygiene to reduce the bioburden and moisturization of oral mucosal membranes (e.g., biotin spays, gels, candies). • Initiate mouth care with mouthwash formulations (e.g., combinations of local anesthetic, antihistamines, corticosteroids, antacid, antifungal and/or antibiotics, immunosuppressants) as per institutional routines. • Avoid alcohol-, hydrogen peroxide-, iodine, or thyme-containing products. Avoid harsh mouthwashes (e.g., Listerine®). • Initiate early treatment for oral candida as per institutional routine. • Diet should be modified (e.g., avoidance of spicy food, incorporation of thin liquids and good general hydration).
Grade 1	• Continue forimtamig. • Consider topical treatment with corticosteroids and/or other non-steroidal symptomatic therapy (e.g., salt water, mouth rinse formulations), as per institutional practice. • Consider treatment for local candida as per Institutional routines. • Initiate pain management, as indicated. • Monitor symptoms and re-evaluate within 48 to 72 hours. If no improvement, manage as Grade 2.
Grade 2	• Manage as Grade 1. • Initiate treatment with oral corticosteroids and/or other non-steroidal topical therapy, in consultation with the Medical Monitor.

Event	Action to be Taken
	• Consider treatment with higher-potency oral corticosteroids if toxicity does not improve.
Grade 3	• Withhold forimtamig.[a] • Initiate pain management, as indicated. • [redacted] • If event resolves to Grade 1 or better, resume forimtamig.[b] • If event does not resolve to Grade 1 or better while withholding forimtamig, permanently discontinue forimtamig after discussion with the Medical Monitor.
Grade 4	• Permanently discontinue forimtamig and contact Medical Monitor.

[a] Forimtamig may be withheld to allow for corticosteroids (if initiated) to be effective.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone.

8.3.8.5 Management of Macrophage Activation Syndrome and Hemophagocytic Lymphohistiocytosis Associated with Forimtamig

Severe CRS with features of adult-onset secondary or reactive MAS/hemophagocytic lymphohistiocytosis (HLH) has been reported with blinatumomab as well as CAR adoptive T cell therapy (Blincyto USPI, Teachey et al. 2013, Lee et al. 2014). While severe CRS and MAS/HLH have overlapping presentation and symptoms, MAS/HLH may be precipitated by other conditions including infections, autoimmune disease, and malignancies (Ramos-Casals et al. 2014).

The prevalence of these conditions in the study participant population makes the distinction between severe CRS and MAS/HLH and identification of inciting factors challenging. It remains unknown whether forimtamig treatment may further increase the risk of developing MAS/HLH in participants who have additional risk factors.

All cases of suspected MAS/HLH should be discussed with the Medical Monitor immediately. While there is currently no universally accepted set of criteria for diagnosing secondary or reactive MAS/HLH in the adult population, proposed criteria have been published (Fardet et al. 2014, Hejblum et al. 2014).

The supportive management of MAS/HLH is generally similar to that of IRR/CRS (see Section 8.3.8.1). Specific diagnostic, monitoring, and management guidelines for MAS/HLH are described below.

A diagnosis of MAS/HLH should be suspected in participants who present with:

- Signs and symptoms of sepsis.
- Fever of unknown origin.
- Grade ≥ 3 CRS at onset.

- CRS signs and symptoms, regardless of severity, which first present > 72 hours following forimtamig administration.
- CRS symptoms, regardless of severity, which persist > 24 hours following initial management as outlined in Section 8.3.8.1.

In all cases of suspected MAS/HLH, the Medical Monitor should be immediately notified. Participants should be hospitalized with the following diagnostic and monitoring measures initiated:

- Frequent (e.g., every 4 hours) vital signs and physical examination, including evaluation for splenomegaly.
- Serial (at least daily) monitoring of serum chemistries, complete blood counts, liver function tests (LFTs), ferritin, PT/partial thromboplastin time (PTT), fibrinogen, D-dimer, and triglycerides.
- [redacted]
- Complete infectious disease workup including:
  - Blood cultures (bacterial and fungal).
  - Urine cultures and urinalysis.
  - Radiographic assessments (e.g., chest x-ray or CT scan).
  - Assessment for active viral infections, including but not limited to, EBV, CMV, and HHV-6.
- If available, assessment for soluble CD25 and assessment of NK cell function.

Supportive and interventional care should follow the management guideline for CRS as described in Table 16 and considered between the Sponsor and Investigator on a case-by-case basis, given that there is no standard of care for MAS/HLH in these clinical situations.

8.3.8.6 Management of Infections Associated with Forimtamig and Daratumumab

Due to its anticipated MoA resulting in profound plasma-cell depletion, forimtamig may be associated with hypogammaglobulinemia and an increased risk of infections. Serum Ig levels will be monitored according to the SoA (Section 1.3).

Serious bacterial, fungal, and new or reactivated viral infections can also occur after the completion of forimtamig treatment.

[redacted]

exclusion criteria are not permitted to start study treatment (Section 5.2). Investigators should be cautious when considering the use of forimtamig in participants with a history of recurring or chronic infections or with underlying conditions that may predispose participants to infections, including devices disrupting natural barriers.

Participants should be closely monitored. Signs and symptoms of infection should result in timely collection of surveillance specimens (e.g. blood, urine, stool, sputum, body fluids, wound secret, nasal swab, rectal swab) and appropriate investigations (including culturing, multiplex PCR) prior to starting antibiotics or other treatment. Prompt intervention with empiric antibiotic regime tailored to local center epidemiology, particularly in the initial treatment cycles, is recommended at the onset of signs and symptoms suggestive of an infection.

In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Standard vaccinations should be performed as per institution guidelines before enrollment into the study (e.g., Hib, pneumococcus, meningococcus, VZV, SARS-CoV-2) or can be completed according to the guidelines in Section 6.5.1.

Anti-infective prophylaxis (including IGIV replacement therapy) for viral, fungal or bacterial infections is highly recommended for participants at high risk of infections and should be administered per institutional practice and at the discretion of the Investigator.

Prophylaxis for pneumocystis infections as well as herpes zoster are mandated during the course of study treatment as per institutional guidelines, unless contraindicated.

[redacted]

Daratumumab

Most infections with daratumumab are manageable and rarely lead to treatment discontinuation. Pneumonia is the most commonly reported (Grade 3 or 4) infection across clinical studies. Hypogammaglobulinemia is also commonly reported across clinical studies and may increase the risk of infection in participants. Hepatitis B virus reactivation, including fatal cases, has been reported in patients treated with daratumumab.

For management guidelines for infections, refer to Table 22.

Table 22 Management Guidelines for Infections

Event	Action to be Taken

General recommendations	• Standard vaccinations should be performed per institutional guidelines prior to enrollment into the study (e.g., haemophilus influenzae type B, pneumococcus, meningococcus, varicella, SARS-CoV-2 vaccines) and should be completed according to the provided guidelines in Section 6.5.1.
	• Anti-infective prophylaxis for viral, fungal or bacterial infections is highly recommended for participants at high risk of infections and should be administered per institutional practice.
	  ○ [redacted]
	  ○ For participants with severe neutropenia and febrile neutropenia, treatment with myeloid growth factors is recommended per institutional guidelines and as per Section 8.3.8.10.
	  ○ For participants with a history of infections or particular risk of infections (e.g., prior bronchiectasis, neutropenia or prior BCMA-targeted therapy, participants bearing devices breaking natural barriers) an antibiotic prophylaxis should be considered.
	• Prophylaxis for pneumocystis infections (e.g., trimethoprim-sulfamethoxazole) as well as herpes zoster (e.g., acyclovir) is mandated during the course of study treatment as per institutional guidelines, unless contraindicated.
	• Participants should be closely monitored. Infectious agent surveillance by repeated, various specimen collection, is highly recommended, particularly at early treatment cycles. Signs and symptoms of infections should result in prompt evaluation and therapeutic intervention. In case of subfebrile temperature, LFT increase, diarrhea or any other signs of infection, it is recommended to commence with a diagnostic workup (including e.g., multiplex PCR, blood, urine, stool, sputum, body fluids, and wound fluids culture, chest X-ray) immediately prior to starting antibiotic or other treatment. At the onset of signs and symptoms suggestive of an infection, a prompt short intervention with timely cessation with empiric antibiotic regime tailored to local center epidemiology is recommended. If the clinical status remains unclear, study treatment may be delayed and microbiological work up should be repeated.

Grade 1 (as applicable)	• Continue study treatment. • Treat as appropriate and monitor for signs/symptoms of worsening infection.
Grade 2	• Hold study treatment. • Treat as appropriate and monitor for signs/symptoms of worsening infection.

Event	Action to be Taken
	• Resume study treatment when resolved or improved at least to Grade 1 (if applicable).
Grade 3 to 4	• Hold study treatment. • Treat as appropriate and monitor for signs/symptoms of worsening infection. • Once infection has resolved or improved at least to Grade 1 (if applicable) and if ANC ≥ 500µL, resume study treatment.

8.3.8.7 Management of Tumor Lysis Syndrome

Management of Tumor Lysis Syndrome Associated with Forimtamig and Carfilzomib

TLS is a known effect of anti-tumor therapy in hematologic malignancies including MM (Fuente et al. 2004, Sezer et al. 2006). It is a potential risk for forimtamig, and cases of TLS including fatal outcomes have been reported in patients treated with carfilzomib.

There is a theoretical risk of TLS if treatment with forimtamig results in the rapid destruction of a large number of tumor cells.

Participants meeting any of the following criteria will be considered at high risk for TLS:

- Prior history of TLS caused by previous MM therapy.
- Preexisting renal insufficiency (serum creatinine > 1.5 mg/dL, or CrCl < 60 mL/min).

Participants must have a CrCl as defined in Section 5.1.

Participants should be informed about symptoms or signs of TLS (e.g., fever, chills, dysrhythmias, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures) and advised to contact the Investigator immediately if any such symptoms occur. If any clinical features are observed, re-check potassium, phosphate, uric acid, calcium, and creatinine within 1 hour.

If the Howard criteria for TLS (Howard et al. 2011) are fulfilled at any time during the study (two or more electrolyte laboratory abnormalities present simultaneously) or there is a medically relevant laboratory abnormality in TLS-related parameters or a sign of clinical TLS (e.g., increased serum creatinine or cardiac dysrhythmia), study treatment should be withheld, and participants should be hospitalized and adequately treated until normalization of laboratory abnormalities before study treatment is restarted.

The specific type of prophylaxis for TLS is generally selected based on the estimated risk of TLS (Cairo et al. 2010). Reducing the level of uric acid, with the use of allopurinol and particularly with the use of rasburicase, can preserve or improve renal function.

Rasburicase is more effective than allopurinol for the prevention and treatment of the TLS.

[redacted]

[redacted]

For participants at high risk, TLS prophylaxis and treatment should be administered according to local guidelines.

8.3.8.8 Management of Neurotoxicity

In this section, guidelines are provided for neurological toxicity (non-ICANS and ICANS).

8.3.8.8.1 Management of Neurotoxicity Associated with Forimtamig

Neurologic toxicity will be monitored closely during the study. All participants will be required to undergo a complete neurological examination at baseline prior to study treatment administration.

Participants should be routinely assessed for any signs or symptoms of neurological toxicity as part of the on-treatment clinical examination (Section 8.2.1). If new or worsening neurological toxicity is suspected, the participant should be referred to a neurologist for further evaluation of potential drug-related neurotoxicity. Treatable causes of neurological dysfunction such as infection or hemorrhage should be ruled out.

[redacted]

Management guidelines for non-immune mediated neurotoxicity AEs (non-ICANS) are summarized in Table 23.

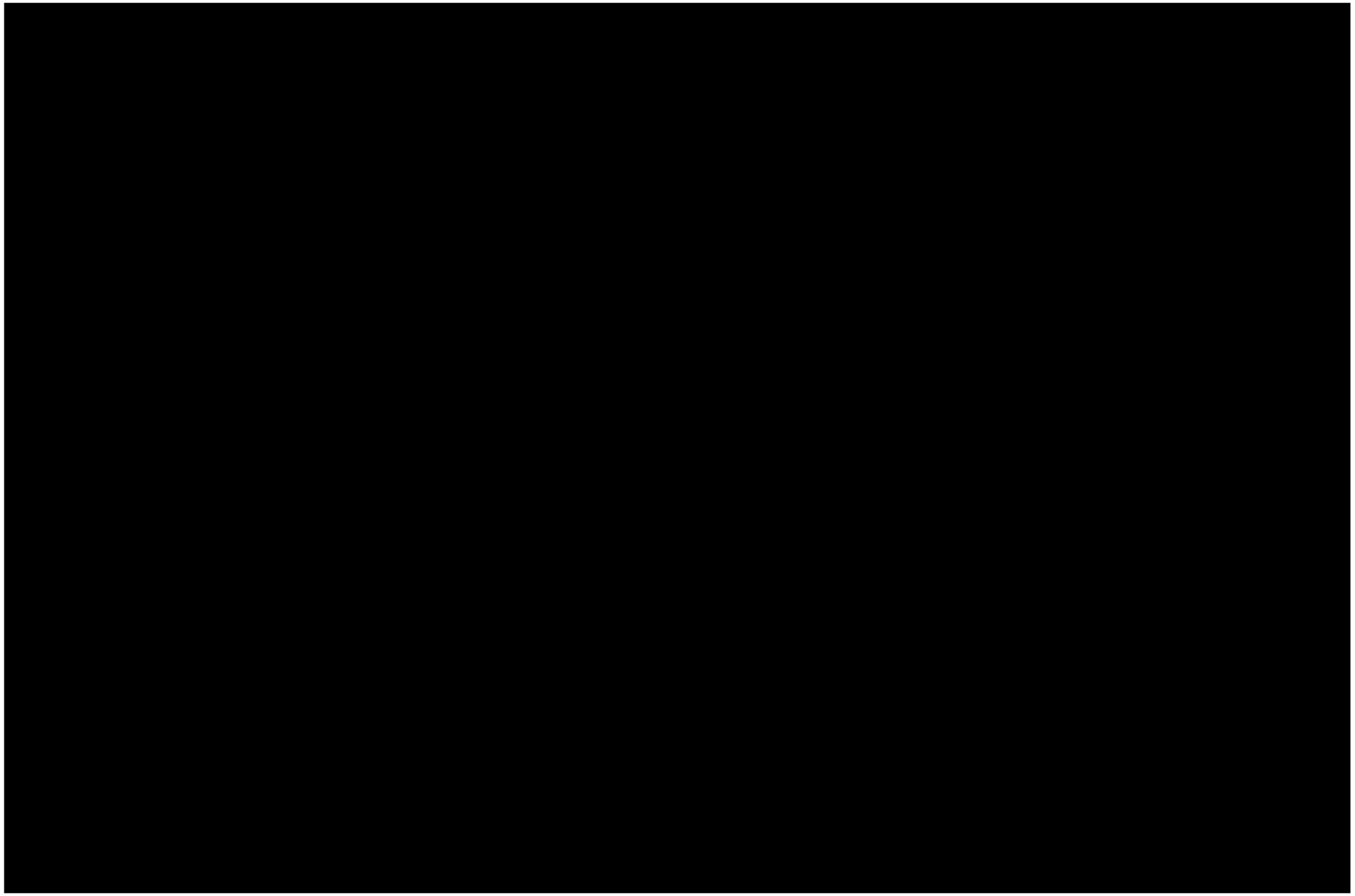
If immune-mediated mechanisms of neurotoxicity (ICANS) are suspected follow the management guidelines summarized in Table 24.

Participants with ICANS will be graded according to the guideline provided in Appendix 12 and symptoms of ICANS will be graded according to NCI CTCAE v5.0.

Participants with non-ICANS and all other neurotoxicities will be graded according to NCI CTCAE v5.0.

[redacted]

[redacted]



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8.3.8.8.2 Posterior Encephalopathy Syndrome (PRES) Associated with Carfilzomib

Cases of posterior reversible encephalopathy (PRES) have been reported in patients treated with carfilzomib. The presentation of this neurological disorder might involve seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension. The diagnosis is confirmed by neuro-radiological imaging (MRI).

8.3.8.9 Management of Tumor Inflammation/Tumor Flare

Tumor Inflammation/Tumor Flare Associated with Forimtamig

AEs associated with tumor inflammation have been reported with T-cell engaging therapies and are consistent with the MoA leading to influx of T-cells into tumor sites. Tumor flare may occur with a short time to onset following forimtamig administration and may present with varying degrees of severity. In addition, depending on tumor size and anatomic location, events associated with tumor inflammation/flare may potentially result in mass effects on vital structures, including airways, major blood vessels, and/or major organs. Participants should be closely monitored for tumor inflammation. Management guidelines for tumor inflammation/tumor flare associated with forimtamig are summarized in Table 25.

Table 25 Management of Suspected Tumor Inflammation/Flare

Grade[a]	Initial Management Recommendation	Action to be Taken with Forimtamig
Grade 1	• Manage pain with paracetamol and/or other pain medication.	• Continue treatment.
Grade 2	• Manage pain with weak opioids such as tramadol, dihydrocodeine, and codeine, which can be given in combination with non-opioid analgesics. • Monitor participant closely. • If no resolution to Grade ≤ 1 within 48 hours, administer 1 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until Grade ≤ 1.	• Hold until resolution to Grade ≤ 1.
Grade 3	• Manage pain with strong opioids such as oxycodone, hydromorphone, buprenorphine or similar at high dose if required. • Consider imaging the participant and perform differential diagnosis for disease progression. • Administer 2 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until resolution to Grade 1 or baseline. • Ensure participant access to an intensive care unit is available.	• Hold until resolution to Grade ≤ 1.

Grade[a]	Initial Management Recommendation	Action to be Taken with Forimtamig
Grade 4	• Follow all recommendations for Grade 3.	• Hold until resolution to Grade ≤ 1. • Consider permanent discontinuation after discussion with Medical Monitor.

IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = Nonsteroidal anti-inflammatory drugs.

[a] Grade of triggering event dependent on presenting sign/symptom of tumor inflammation; for events not specifically listed in NCI CTCAE, refer to Table 1 in Appendix 2 for corresponding grades.

8.3.8.10 Management of Neutropenia

8.3.8.10.1 Neutropenia Associated with Forimtamig

Neutropenia is a potential risk for forimtamig and the risk may increase with combination partners (Investigator's Brochure). All participants should be monitored at each cycle for cell blood counts and participants experiencing neutropenia should undergo blood cell monitoring until resolution of the event (Table 26). Participants with low neutrophil count at baseline (Grade 1 or 2) may be prophylactically treated as per local practice and institutional guidelines with growth factor support before the first administration of forimtamig, if needed. Participants who experience Grade 3 to 4 neutropenia should be closely monitored with more frequent assessments as applicable.

Participants who experience febrile neutropenia and/or infection should be managed per institutional guidelines.

Table 26 Management of Neutropenia Associated with Forimtamig

Event	Action to be Taken
Grade 1 or 2	• No dose reduction or delay in forimtamig is required.
Grade 3 or 4	• No dose reduction or delay in forimtamig is required for uncomplicated neutropenia. • [redacted] • Use of G-CSF is encouraged. • If the participant was not receiving G-CSF therapy previously, it is strongly recommended to initiate prophylactic G-CSF for current and subsequent cycles. • Follow blood cell counts weekly or as applicable until resolution to Grade 2 or lower.

G-CSF = granulocyte colony-stimulating factor.

8.3.8.10.2 Neutropenia Associated with Forimtamig and Carfilzomib

Management guidelines for neutropenia associated with forimtamig and carfilzomib are summarized in Table 27.

Table 27 Management of Neutropenia Associated with Forimtamig and Carfilzomib

Event	Action to be Taken
Grade 1 to 2	• No dose reduction or delay in forimtamig or carfilzomib is required for uncomplicated neutropenia.
Grade 3 to 4 ANC ≤ 500/mm^3 (Grade 4)	• No dose reduction or delay in forimtamig is required for uncomplicated neutropenia. For carfilzomib: Withhold dose • [redacted] •
Febrile neutropenia: ANC < 500/mm^3 and an oral temperature more than 38.5°C or two consecutive readings of more than 38°C for 2 hours	Withhold dose for both forimtamig and carfilzomib • If ANC returns to baseline grade and fever resolves, resume at the same dose. • For subsequent drops to <500/mm^3, follow the same recommendations as above and consider 1 dose level reduction when starting carfilzomib (see Section 6.1.3).

8.3.8.10.3 Neutropenia Associated with Forimtamig and Daratumumab

Management guidelines for neutropenia associated with forimtamig and daratumumab are summarized in Table 28.

Table 28 Management of Neutropenia Associated with Forimtamig and Daratumumab

Event	Action to be taken
Grade 1 or 2	• No dose reduction or delay in study treatment is required.
Grade 3 or 4	• No dose reduction or delay in forimtamig is required for uncomplicated neutropenia. • In case of Grade 4 neutropenia or Grade 3 or 4 febrile neutropenia, delay daratumumab administration to allow for recovery. When neutrophil count returns to ≥500/mm^3, daratumumab may be resumed. • Use of G-CSF is encouraged. • If the participant was not receiving G-CSF therapy, it is strongly recommended to initiate prophylactic G-CSF for current and subsequent cycles. • Follow CBC weekly or as appropriate.

CBC = complete blood count, G-CSF = granulocyte colony-stimulating factor.

8.3.8.11 Management of Thrombocytopenia

8.3.8.11.1 Thrombocytopenia Associated with Forimtamig

All participants should be closely monitored for thrombocytopenia. Regular monitoring of platelet counts should be performed until the event resolves and forimtamig dose delays

should be considered in cases of severe or life-threatening thrombocytopenia. Transfusion of blood products (e.g., platelet transfusion) according to institutional practice is at the discretion of the treating Investigator. Use of all concomitant therapies that could possibly worsen thrombocytopenia-related events, such as platelet inhibitors and anticoagulants, should also be taken into consideration.

8.3.8.11.2 Thrombocytopenia Associated with Forimtamig and Carfilzomib

All participants should be monitored at each cycle for thrombocytopenia. Transfusion of blood products (e.g., platelet transfusion) according to institutional practice is at the discretion of the treating Investigator. Carfilzomib dose interruption and/or modification may be required. Consider modifying the dose of carfilzomib or interrupting carfilzomib prior to adjusting forimtamig dose. If toxicities cannot be managed by dose modification or the participant cannot tolerate the lowest dose of carfilzomib ([redacted]), the participant should be discontinued from carfilzomib. If, however, the participant is benefitting from study treatment, treatment with forimtamig may be continued per forimtamig comparator arm (Arm A) schedule following consultation with the Medical Monitor. For additional details of recommended management guidelines, refer to the carfilzomib local prescribing information.

Management guidelines for thrombocytopenia associated with carfilzomib are summarized in Table 29.

Table 29 Management of Thrombocytopenia Associated with Forimtamig and Carfilzomib

Event	Action to be taken
Platelets $<10\times10^9$/L or evidence of bleeding with thrombocytopenia	• No dose reduction or delay in forimtamig is required. For carfilzomib: • Withhold dose. • If recovered to $\geq10\times10^9$/L and/or bleeding is controlled, continue at the same dose level. • For subsequent drops of $<10\times10^9$/L, follow the same recommendations as above and consider 1 dose level reduction when starting carfilzomib (refer to Table 12 in Section 6.6.2).

8.3.8.11.3 Thrombocytopenia Associated with Forimtamig and Daratumumab

All participants should be monitored at each cycle for thrombocytopenia. Transfusion of blood products (e.g., platelet transfusion) according to institutional practice is at the discretion of the treating Investigator. No modification of daratumumab dose is required. AEs related to daratumumab may be managed by dose delay. Consider delaying daratumumab prior to adjusting the forimtamig dose. If toxicities cannot be managed by dose delay of daratumumab, the participant is to be discontinued from daratumumab. If, however, the participant is benefitting from the therapy, continuation of forimtamig may

be continued per forimtamig comparator arm (Arm A) schedule following consultation with the Medical Monitor.

[redacted]

Management guidelines for uncomplicated thrombocytopenia that is not associated with bleeding are summarized in Table 30.

Table 30 Management for Thrombocytopenia Associated with Forimtamig and Daratumumab

Event	Action to be taken
Platelets ≥25,000/μL	• No dose reduction or delay in study treatment is required.
Platelets <25,000/μL	• Withhold daratumumab until platelet count is ≥50,000/μL. • Transfusion of blood products (e.g., platelet transfusion) according to institutional practice is at the discretion of the treating physician. • Follow CBC weekly.

8.3.8.12 Management of Testicular Toxicity

Testicular Toxicity Associated with Forimtamig

Male participants will undergo close monitoring for testicular toxicity. Clinical monitoring will include asking participants about signs or symptoms consistent with testicular toxicity. Laboratory monitoring will include assessment of serum testosterone, luteinizing hormone, and follicle-stimulating hormone.

Male participants who wish to have children in the future may consider cryopreservation of semen.

8.3.8.13 Management of Embryofetal Toxicity Associated with Carfilzomib

Based on the mechanism of action and findings in animals, carfilzomib can cause fetal harm when administered to a pregnant woman. No management guidelines are provided in the carfilzomib label.

8.3.8.14 Management of Thromboembolic Events

8.3.8.14.1 Venous Thrombosis Associated with Carfilzomib

Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with carfilzomib. Provide thromboprophylaxis for participants treated with carfilzomib in combination with dexamethasone. Select the thromboprophylaxis based on participant's underlying risk. For participants using oral contraceptives or hormonal contraception associated with a risk of thrombosis, consider non-hormonal contraception during treatment.

8.3.8.14.2 Thrombotic Microangiopathy Associated with Carfilzomib

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS) have been reported in patients receiving carfilzomib. Monitor for signs and symptoms of TTP/HUS.

8.3.8.15 Management of Hemorrhage Associated with Carfilzomib

Fatal or serous cases of hemorrhage have been reported in patients treated with carfilzomib. Hemorrhagic events include gastrointestinal, pulmonary and intracranial hemorrhage and epistaxis. The bleeding can be spontaneous and intracranial hemorrhage has occurred without trauma. Hemorrhage has been reported in patients having either low or normal platelet counts, in and patients who were not on antiplatelet therapy or anticoagulants. Promptly evaluate signs and symptoms of blood loss.

8.3.8.16 Management of Cardiovascular Events Associated with Carfilzomib

Pulmonary Hypertension

Pulmonary hypertension was reported in approximately 2% of patients who received carfilzomib. Evaluate with cardiac imaging and/or other tests as indicated. Withhold carfilzomib for pulmonary hypertension until resolved or returned to baseline and consider restarting carfilzomib based on a benefit/risk assessment.

Hypertension

Hypertension, including hypertensive crisis has been observed with carfilzomib. Optimize blood pressure prior to starting treatment with carfilzomib, and monitor blood pressure regularly. If hypertension cannot be adequately controlled, withhold carfilzomib and evaluate.

8.3.8.17 Management of Cardiac Toxicities Associated with Carfilzomib

New onset or worsening of pre-existing cardiac events, including congestive heart failure, pulmonary edema, decreased ejection fraction, restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction, including fatal cases, have occurred following carfilzomib administration. Some events occurred in patients with normal baseline ventricular function. In clinical studies with carfilzomib, these events occurred throughout the course of therapy with carfilzomib. Death due to cardiac arrest has occurred within one day of carfilzomib administration. The incidence of cardiac failure events in combination trials was 8%.

Monitor participants for clinical signs and symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold carfilzomib for Grade 3 or 4 cardiac AEs until recovery and consider restarting carfilzomib at a 1 dose level reduction based on a benefit/risk assessment.

8.3.8.18 Management of Acute Renal Failure Associated with Carfilzomib

Cases of acute renal failure, including fatal cases, have been reported in patients receiving carfilzomib. According to the carfilzomib label, approximately 9% of patients treated with carfilzomib were reported with renal insufficiency AEs (including renal failure). Acute renal failure was reported more frequently in patients with advanced relapsed and refractory myeloma who received carfilzomib monotherapy. The risk of renal failure was greater in patients with a baseline reduced estimated CrCl.

Monitor renal function with regular measurement of the serum creatinine and/or estimated CrCl. Reduce or withhold dose as appropriate.

8.3.8.19 Management of Pulmonary Toxicities Associated with Carfilzomib

Acute Respiratory Distress Syndrome (ARDS) and acute respiratory failure have occurred in approximately 2% of patients who received carfilzomib. In addition, acute diffuse infiltrative pulmonary disease, such as pneumonitis and interstitial lung disease, occurred in approximately 2% of patients who received carfilzomib. Some cases were fatal.

In the event of drug-induced pulmonary toxicity, discontinue carfilzomib.

8.3.8.20 Management of Toxicity and Hepatic Failure Associated with Carfilzomib

Cases of hepatic failure, including fatal cases, have been reported during treatment with carfilzomib. Carfilzomib can cause elevations of serum transaminases. Reduce or stop dose as appropriate. Liver enzymes and bilirubin should be monitored at treatment initiation and monthly during treatment with carfilzomib, regardless of baseline values.

8.3.8.21 Management of Progressive Multifocal Leukoencephalopathy Associated with Carfilzomib

Cases of PML, including fatal cases, have been reported with carfilzomib. In addition to carfilzomib, other possible contributory factors include prior or concurrent immunosuppressive therapy. Participants receiving carfilzomib should be monitored for any new or worsening neurologic, cognitive or behavioral signs and symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders.

If PML is suspected, further administration must be suspended until PML has been excluded by a specialist with appropriate diagnostic testing. If PML is confirmed, carfilzomib must be discontinued.

8.3.8.22 Management of Ocular Adverse Reactions Associated with Daratumumab

Ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma, have been noted in the daratumumab USPI. No management guidelines are provided in the daratumumab USPI.

8.3.8.23 Management of Adverse Events Related to Tocilizumab

Most of the risks reported with tocilizumab are based on long-term use of tocilizumab in rheumatologic indications.

Tocilizumab should be administered for the treatment of CRS when necessary, as described in Section 8.3.8.1. Administration of tocilizumab should follow the guidelines defined in the SmPC and/or label. For additional information, refer to the Tocilizumab Investigator's Brochure. *If tocilizumab is administered, additional assessments are required as described in Appendix 15.*

- [redacted]
- [redacted]
- [redacted]

8.4 TREATMENT OF OVERDOSE

Study treatment overdose is the accidental administration of a drug in a quantity that is higher than the assigned dose. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects (see Sections 5 and 5.2 of Appendix 2 for further details).

Decisions regarding dose-interruptions or modifications (if applicable) will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

Overdose with Forimtamig

In the event of an overdose, the Investigator should:

- Contact the Sponsor's Medical Monitor immediately.
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until resolved.
- Obtain a blood sample for PK analysis.

- Document the quantity of the excess dose, as well as the duration of the overdose, in the eCRF.

No antidote is available; the best supportive measures should be applied. The Sponsor does not recommend specific treatment for an overdose.

Overdose of Carfilzomib and Daratumumab

In case of any overdose, refer to the approved product label.

8.5 PHARMACOKINETICS

The PK sampling schedule for forimtamig is designed to provide a profile of the concentration-time curve for forimtamig administration and to provide data for PK modelling and immunogenicity assessments (ADA) with/without concomitant treatment with carfilzomib or daratumumab. In addition, this sampling schedule is expected to provide dynamic information on the magnitude and kinetics of PD alterations and their relationship to exposure, and may support PK- and/or PK/PD-based analysis of the contribution of the combination treatment on forimtamig safety and efficacy (see also Section 8.7).

Mandatory blood samples to evaluate concentrations of forimtamig will be collected from an IV line and processed to serum. When the study treatment is administered IV, the PK blood samples will be collected from the arm opposite to that used for study treatment administration. The blood samples for forimtamig PK will be collected as outlined in the SoAs (Section 1.3). If required for participants who receive tocilizumab, blood samples to determine the tocilizumab concentrations, ADA, and specific biomarkers will be collected at the timepoints indicated the SoAs (Section 1.3). The date and time of each sample collection will be recorded in the eCRF.

Forimtamig concentrations in serum will be analyzed with a validated bioanalytical electrochemiluminescent assay (dual binding competent assay). In addition, to support future PK/PD analysis and potential PK and PK/PD modeling, [redacted]

During the course of the study, the PK sampling timepoints may be modified based on emerging data to ensure optimal characterization of the forimtamig PK and disposition without increasing the overall blood collection volume for PK.

When a participant withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the participant specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been analyzed prior to withdrawal, the results will remain as part of the overall research data.

Additional (unscheduled) forimtamig blood PK samples will be taken:

- At the time of treatment discontinuation.
- If the participant experiences a Grade ≥ 3 CRS and IRR (see Section 8.3.8.1).
- If the participant experiences an AE leading to dose-reduction or delay of forimtamig administration (see Section 6.1.1).

Any volume of blood samples remaining after the specified analyses may also be used for further characterization of immune responses and for any forimtamig-related exploratory analyses or any assay development or validation experiments.

The PK blood samples will be destroyed within 2 years after the date of the final clinical study report. Details on sampling procedures, sample storage and shipment are given in the Sample Laboratory Flow Chart.

8.6 IMMUNOGENICITY ASSESSMENTS

As forimtamig is a human antibody, there is a risk that ADAs against this molecule will develop, potentially reducing its efficacy and/or potentially resulting in symptomatic hypersensitivity reaction in particular immune-complex reactions.

Antibodies against forimtamig will be evaluated in blood samples collected from all participants according to the SoAs (Section 1.3). Additional ADA samples should also be collected at the time of study treatment discontinuation or at the safety follow-up visit, in participants who experience a Grade≥3 IRR/CRS, and in participants with clinical signs of hypersensitivity reaction, in particular immune-complex reaction. For each collected ADA sample, a corresponding PK sample will be collected at the same timepoint for the determination of the forimtamig concentration.

Validated screening, confirmatory, and titer assays will be employed to detect ADAs against forimtamig. The date and time of each sample will be recorded in the eCRF.

If required, remaining ADA samples may also be used for assay development/validation experiments, for ADA characterization for compound-related exploratory analyses, or to help develop further blood tests.

The blood samples will be destroyed within 2 years after the date of the final clinical study report, unless the participant gives specific consent for the remainder of the sample(s) to be used for optional exploratory research within the RBR.

Details on sampling procedures, sample storage, and shipment are documented in separate sample handling documentation.

If used, blood samples needed to determine the presence of ADAs against tocilizumab, will be collected at the time points indicated in the SoAs (Section 1.3).

8.7 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

Blood and tissue samples ([redacted]) will be collected as specified in the SoAs (Section 1.3). The date and time of each sample collection should be recorded in the eCRF. Details on processes for collection and shipment of these samples can be found in the Laboratory Flow Chart.

These samples will be tested for protein, nucleic acid, or other tissue- or blood-derived biomarkers relating to the proposed mechanism of action of forimtamig and the resulting data will support PK/PD modeling.

Additional markers may be measured in the case that a strong scientific rationale develops. Note that as science and research are evolving, the list of biomarkers that will be evaluated cannot be fully defined.

When a participant withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the participant specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

8.7.1 Genetic and Genomic Analyses

The DNA extracted from the clinical genotyping samples may be used for, but is not limited to, determining whether alleles of genes [redacted], affect the PK, PD, efficacy, or safety of the study treatment. This may include germline whole genome sequencing (WGS) and targeted sequencing to investigate biomarkers that might predispose the participant to drug-associated autoimmunity or to a positive tumor response in response to the study treatment. These assessments will be performed if safety or efficacy rationales develop.

The blood and bone marrow samples collected for exploratory PD analysis at the visits specified in the SoA (Section 1.3) may be used for DNA and circulating cell-free tumor DNA extractions. The extracted DNA may be sent to one or more laboratories for next generation sequencing analysis for comprehensive characterization of the genome, which along with the clinical data collected in this study, may increase the opportunity for biomarker discovery. Data will be analyzed for exploratory research on genomic biomarkers including, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways, immune-related markers (e.g., T-cell receptor sequence), and other known MM drivers.

Any remaining blood or tissue samples (including any derivatives) after the specified analyses may also be used for additional assay validation experiments. These samples will be destroyed no later than 15 years after the date of the final clinical study report.

Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

Given the complexity and exploratory nature of these analyses, WGS/whole exome sequencing (WES)/targeted sequencing data and analyses will not be shared with Investigators or study participants unless required by law. Participants will not be identified by name or any other personally identifying information. Data arising from all biosamples, including samples for analyses of inherited DNA, will be subject to the confidentiality standards described in the sample documentation.

Analysis of RNA extracted from bone marrow samples and/or blood/peripheral blood mononuclear cell (PBMC) samples may include gene expression profiling to enable identification of PD biomarkers, response predictive biomarkers and assessment of treatment response (pharmacodynamics).

8.7.2 Pharmacodynamic and Biomarker Samples

Blood and tissue ([redacted]) samples will be collected from participants for PD and exploratory biomarkers, as specified in the SoAs (Section 1.3). The date and time of each sample collection should be recorded in the eCRF. Details on processes for collection and shipment of these samples can be found in the Laboratory Flow Chart.

The samples may also be used for research purposes to identify biomarkers useful for predicting and monitoring response to study treatment, assessing PD effects of study treatment, identifying biomarkers useful for predicting and monitoring study treatment safety, evaluating potential combination partners and investigating mechanism of therapy escape. Additional markers may be measured in case that a strong scientific rationale for these analyses develops.

Based on continuous analysis of the data in this and other studies, any sample type and/or analysis not considered critical for safety may be stopped at any time. Moreover, some samples that are collected may not be analyzed.

Unless otherwise specified below, samples (including blood, cell pellets, PBMCs, plasma, tissue samples, slides, etc.) will be destroyed no later than 5 years after the date of the final clinical study report, unless the participant provides specific consent for the remainder of the material to be stored for optional exploratory research in the RBR. For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.8).

Residual plasma/serum samples (e.g., from PK and/or PD assessments) may be used for longitudinal testing of bacterial or viral infection (e.g., SARS-CoV-2) by serological methods. This testing may be performed for each participant. In addition to serving as an important safety measure, these analyses will inform as to any association of bacterial or viral infection and response to treatment.

8.7.3 Mandatory Samples

The following samples for PD and biomarker research are required and will be collected from all participants, unless otherwise specified below.

8.7.3.1 Blood Sampling

The following blood samples will be collected from all participants as specified in the SoAs (Section 1.3) [redacted]

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.8 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

8.8.1 Overview of the Research Biosample Repository

The Roche RBR is a centrally administered group of facilities for the long-term storage of human biologic samples, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage and analysis of the RBR samples will facilitate the rationale design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional RBR. Samples collected for RBR can be used (but are not thus limited) to achieve the following objectives:

- [redacted]

8.8.2 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to forimtamig, diseases, or drug safety:

- [redacted]

The samples collected for DNA extraction include, but are not limited to, genomic analysis and may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, WES, NGS, or other molecular-based assays/genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

Participants will not be identified by name or any other personally identifying information. Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

If allowed by local laws, the participant may request access to the non-interpreted WGS/WES raw data from blood samples. Such a request must be conveyed to the Sponsor by the Investigator, using the email address: global.return-genomics-results@roche.com. The information, if available at the time of the request, would be shared with the Investigator in the form of a data file of raw genomic sequencing data. The Sponsor will not provide any interpretation of this raw genomic sequencing data. The interpretation of these data will require expertise in genomic and genetic analysis and an understanding of the variability of the technology used for data generation.

For all samples, dates of consent and sample collection should be recorded on the associated RBR page of the eCRF. Details on processes for collection and shipment of these samples can be found in separate sample documentation.

RBR samples will be stored until they are no longer needed or until they are depleted. The RBR storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., Health Authority requirements).

The repository samples will be subject to the confidentiality standards (as described under Confidentiality in Appendix 1).

8.9 HEALTH ECONOMICS/MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economic/medical resource utilization and health economic parameters are not evaluated in this study.

8.10 TIMING OF STUDY ASSESSMENTS

All assessments must be performed as per the SoA (Section 1.3).

Exceptional measures during the COVID-19 pandemic, such as adjustments in study visits, may be considered (see Section 8.10.2).

8.10.1 Assessments at Unscheduled Visits

If clinically indicated, any assessment or sample specified in the SoAs (Section 1.3) can be performed any time as an unscheduled assessment or sample at the discretion of the Investigator. Unscheduled eCRFs will be used to record any assessments performed during an unscheduled visit.

8.10.2 Exceptional Measures during COVID-19 Pandemic

Exceptional measures during the COVID-19 pandemic, such as adjustments in study visits, may be considered if in the overall best interest of the participant. Adjustments may include:

- Use of alternative facility for assessments (e.g., local laboratory or imaging centers).
- Replacement of a study visit with alternative methods for assessments (such as phone contacts or virtual visits to assess safety).
- Postponement of a study visit or of individual assessments.
- Temporary suspension of sample collection.

A robust benefit-risk assessment should be performed by the Investigator and discussed with the Medical Monitor. This assessment will be fully documented, and any deviations to the protocol will be recorded in accordance with the Sponsor standard procedure.

9. STATISTICAL CONSIDERATIONS

The data will be analyzed by the Sponsor and/or designated contract research organization. Any data analysis carried out independently by the Investigator should be submitted to the Sponsor before publication or presentation.

The analysis results will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and PK and biomarker measurements. Participants will be followed up until disease progression (according to the IMWG response criteria) or until discontinuation of treatment due to withdrawal from the study. All data will be listed by participant and summarized by treatment arm and dose. The primary objective of the study will be to evaluate the efficacy and safety profile of forimtamig-based treatment combinations.

Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and minimum and maximum values. Categorical variables will be summarized through use of counts and percentages. Listings will be used in place of tables in the event of small sample sizes.

9.1 STATISTICAL HYPOTHESES

Not applicable.

9.2 SAMPLE SIZE DETERMINATION

This study is not designed to make explicit power and Type I error considerations for a hypothesis test. Instead, this study is designed to obtain preliminary safety, efficacy, and PK data on forimtamig-based treatment combinations when administered to participants with r/r MM.

Approximately 36 to 316 participants will be enrolled in this study: Approximately [redacted] of these participants will be enrolled during the dose exploration phase to explore the combination treatments with different forimtamig target dose levels. Approximately [redacted] participants will be enrolled during the expansion phase, depending on the number of target forimtamig doses expanded for each of the combination partners.

In the expansion phase, each combination arm and the single agent forimtamig comparator arm will enroll up to approximately [redacted] efficacy-evaluable participants at their assigned target dose level of forimtamig.

This sample size [redacted]

[redacted]

9.3 ANALYSIS SETS

For purposes of analysis, the following populations are defined in Table 31.

Table 31 Analysis Sets

Population	Description
Safety	All participants enrolled in the study who receive any amount of any study treatment will be included in the safety population. Unless otherwise specified, the safety population will be the default analysis set for this study.
Pharmacokinetic	All participants in the safety population and who have PK data from at least one post-dose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria or deviate from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented with the reason for exclusion.
Immunogenicity	All participants with at least one ADA assessment, irrespective of whether the participant receives any treatment (Shankar et al. 2014).
Efficacy	The efficacy analysis population will include all response evaluable participants, i.e., participants who received at least one dose of one of their assigned study treatments and had at least one baseline and one on-treatment tumor assessment or participants who had one tumor assessment at baseline and discontinued their treatment for any reason before their first on-treatment tumor assessment.

Abbreviations: ADA = anti-drug antibody; PK = pharmacokinetics.

9.4 STATISTICAL ANALYSES

9.4.1 Demographics and Baseline Characteristics

Demography and baseline characteristics (including age, sex, participant disposition, previous therapies, and medical history, such as duration of malignancy) will be analyzed using descriptive statistics. The analysis will be based on the safety analysis population if not specified otherwise. Data will be summarized overall and by study treatment arm. Comparability between treatment arms will also be evaluated descriptively via tabulation by demographic characteristics.

9.4.2 Efficacy Analyses

The primary and secondary efficacy analyses will include all evaluable participants in the efficacy analysis population, with participants grouped according to their assigned study treatment at randomization as well as summarized overall.

9.4.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is objective response as assessed by the Investigator (by IMWG response criteria; Appendix 7), as defined in the objectives/endpoint Table 7. Participants with missing or no response assessments will be classified as non-

responders. Objective response rate (ORR), defined as the proportion of participants with a CR, very good partial response (VGPR), or PR, will be calculated for each arm, along with 95% confidence intervals (Clopper Pearson exact method). The difference in ORR between the combination arms and the corresponding comparator arm will also be calculated, along with 95% confidence intervals. The 95% CI for difference in rates will be constructed using Wald approximation with continuity correction to the binomial distribution.

9.4.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints time to response (TTR), DoR and progression-free survival (PFS), as well as overall survival (OS), if mature, will be summarized using time-to-event analysis and Kaplan-Meier curves. Definitions and handling of censoring (where applicable) for disease control rate (DCR), ORR, DoR, and PFS will be according to IMWG response criteria.

TTR is defined as the time from randomization until an objective response (PR or better according to IMWG response criteria). For participants who do not have documented objective response before the end of the study, TTR will be censored at the day of the last tumor assessment.

Time to best response (TTBR) is defined as the time from randomization until the best objective response (according to IMWG response criteria). For participants who do not have documented objective response before the end of the study, TTBR will be censored at the day of the last tumor assessment.

For participants with an objective response, DoR will be defined as the time from the initial objective response to the time of disease progression or death. If a participant does not experience disease progression or death before the end of the study, DoR will be censored at the day of the last tumor assessment. If no tumor assessments were performed after the time of first objective response, DoR will be censored at the time of first objective response.

For participants with an objective response (PR or better), TTR will be defined as the time from randomization until objective response.

PFS is defined as the time from randomization until disease progression or death from any cause. For participants who do not have documented disease progression or death before the end of the study, PFS will be censored at the day of the last tumor assessment.

OS is defined as the time from randomization to death from any cause. Participants who are still alive at the time of OS analysis will be censored at the last date they were known to be alive.

The Kaplan-Meier method will be used to estimate the median for PFS, OS, and DOR, with 95% confidence intervals constructed through use of the Brookmeyer and Crowley method. OS rate at specific timepoints will also be estimated through use of the Kaplan Meier method, with 95% confidence intervals calculated on the basis of the Greenwood estimate for the variance.

9.4.3 Safety Analyses

Safety analysis will be performed for all participants in the safety analysis population (for safety analysis methods, see Table 32). Descriptive statistics will be used to summarize all safety data by treatment arm and overall. Participant listings of all AEs will also be generated.

Safety will be determined by AEs, laboratory tests, vital signs, ECGs, physical and neurological examinations, and ECOG performance status. Exposure to combination treatment (by study treatment) will be summarized by treatment arm using total duration or study medication, number of cycles started, cumulative dose, and dose intensity using descriptive statistics. Dose modifications and interruptions, and their reasons will be presented.

Treatment-emergent AEs occurring after initiation of treatment will be summarized. For each participant, the maximum reported severity of each AE will be used in the summaries by severity grade. All treatment-emergent AEs, SAEs, AEs leading to withdrawal of study treatment, Grade $\geq$3 AEs, deaths, and causes of death will be listed and summarized by mapped term, appropriate thesaurus level, and NCI CTCAE severity grade.

Table 32 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for AEs will be standardized by the Sponsor. AEs will be summarized by mapped term and appropriate thesaurus level. The severity of AEs will be graded according to the NCI CTCAE v5.0, with the exception of cytokine release syndrome (CRS) and ICANS, which will be graded according to the ASTCT Consensus Grading (Lee et al. 2019). Summaries of AEs by grade, seriousness and relationship to study treatment will be presented, as well as summaries of AEs leading to death or premature withdrawal from study treatment. In addition, AEs leading to treatment discontinuation will be listed separately.

Endpoint	Statistical Analysis Methods
Clinical laboratory tests	All clinical laboratory data will be stored in the database in the units in which they were reported. Participant listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing. Laboratory test values will be presented by individual listings with flagging of values outside the normal ranges. Summary tables of change from baseline over time based on SI units will be displayed. Shifts in NCI CTCAE grades from baseline to worst grade observed during treatment will be presented for selected laboratory parameters.
Standard reference ranges and transformation data	The Sponsor's standard reference ranges, rather than the reference ranges of the Investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Sponsor's standard reference range. Certain laboratory parameters will be transformed to the Sponsor's standard reference ranges. A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, ALP, and total bilirubin. Because the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.
Definition of laboratory abnormalities	For all laboratory parameters included, there exists a Sponsor predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in participant listings of laboratory data. In addition to the standard reference range, a marked reference range has been predefined by the Sponsor for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.
Vital signs	Vital sign data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate.
ECG data analysis	ECG data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.
Concomitant medications	The original terms recorded on the participant's eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms. Concomitant medications will be presented in summary tables and listings.

AE = adverse events; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; ECG = electrocardiogram; eCRF = electronic case report form; ICANS = immune effector cell-associated neurotoxicity syndrome; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SI = Système International d'Unités.

9.4.4 Pharmacokinetic and Pharmacokinetic/Pharmacodynamics Relationships Analyses

Analyses will be carried out on the PK analysis population. Individual and mean serum forimtamig concentration versus time data will be tabulated and plotted by dose level, by dosing regimens, and/or by route of administration, as appropriate.

When data allow it, PK parameters will be derived from the serum concentrations of forimtamig with/without concomitant administration of the combo partner using standard non-compartmental methods or compartmental PK modeling, as most appropriate. Parameters may include:

- Total serum exposure area under the curve (AUC).
- Time to maximum concentration observed in serum (T_{max}).
- Maximum (C_{max}) and minimum (C_{min}) concentration observed in serum during C1 (step-up dosing).
- Forimtamig PK assessment in the bone marrow aspirate (if the sample's volume and quality allows it).
- Maximum and minimum concentration observed in serum under steady-state conditions within a dosing interval.
- Apparent clearance (CL_{ss}/F).
- All PK parameters will be presented by listings and descriptive summary statistics by dose level and by dosing regimens.

Additional PK parameters may be determined, as appropriate.

Population PK (popPK) modelling methodology may also be applied to PK and other data from this study (e.g., efficacy, safety, ADA). Data may be pooled from other clinical studies with forimtamig for popPK modelling. The popPK report will be separated from the clinical study report.

In addition, exploratory analysis of the dynamic relationships between exposure (PK) and PD markers, and safety and clinical activity data will be conducted, as data allow it, to inform on the potential contribution of the combination partners on the forimtamig exposure-efficacy and exposure-safety relationships.

[redacted]

[redacted]

9.4.6 Immunogenicity Analyses

Analyses of forimtamig immunogenicity will be carried out on the immunogenicity analysis population.

The number and proportions of ADA-positive and ADA-negative participants at baseline (baseline prevalence) and after study treatment administration (post-baseline incidence during both the treatment and follow-up periods) will be summarized by dose level, dosing regimens, and/or route of administration, as appropriate.

Participants are considered to be ADA-positive if they are ADA-negative at baseline or have missing data at baseline but develop an ADA response following study treatment administration (treatment-induced ADA response), or if they are ADA-positive at baseline and the titer of one or more post-baseline samples is greater than the titer of the baseline sample by at least 4-fold (treatment-enhanced ADA response).

Treatment-induced ADA responses will be further categorized as either:

- Transient ADA response, defined as a) ADA-negative or missing data at baseline, b) at least one post-treatment ADA-positive sample, c) only one ADA-positive sample or the time between the first and last ADA-positive sample is less than 16 weeks, and d) the last ADA sample is negative.
- Persistent ADA response, defined as a) ADA-negative or missing data at baseline and b) post-treatment ADA-positive samples over 16 weeks or more or the last ADA timepoint is positive (Shankar et al. 2014).

Participants are considered to be ADA-negative if they are ADA-negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA-positive at baseline but do not have any post-baseline samples with a titer that is greater than the titer of the baseline sample by at least 4-fold (treatment unaffected).

[redacted] The details of these analyses may be reported in a document separate from the clinical study report.

[redacted]

9.6 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol violations, and discontinuations from the study will be summarized overall and by cohort.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

This section includes the following appendices:

Appendix 1: Regulatory, Ethical and Study Oversight Considerations

Appendix 2: Adverse Event Definitions and Reporting

Appendix 3: Procedures for Recording Adverse Events

Appendix 4: Clinical Laboratory Tests

Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Appendix 6: Investigational Medicinal Product and Non-Investigational Medicinal Product Designations

Appendix 7: International Myeloma Working Group Uniform Response Criteria (2016)

Appendix 8: Preexisting Autoimmune Diseases and Immune Deficiencies

Appendix 9: Anaphylaxis Precautions

Appendix 10: Clinical Outcome Assessments

Appendix 11: ASTCT Cytokine-Release Syndrome Consensus Grading

Appendix 12: ASTCT ICANS Consensus Grading for Adults

Appendix 13: Cockcroft-Gault Formula/Creatinine Clearance

Appendix 14: Hepatitis B Virus Screening

Appendix 15: Schedule of Activities for Tocilizumab

Appendix 16: ECOG Performance Status

Appendix 17: Abbreviations

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the International Council for Harmonisation (ICH) E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the E.U./EEA will comply with the E.U. Clinical Trial Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations.

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Master Informed Consent Forms (ICFs), any information to be given to the participant (e.g., advertisements, diaries, etc.), and relevant supporting information must be submitted to the Institutional Review Board (IRB)/ethics committee (EC) by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (Section 2.3.1 of this appendix).

The Investigator should follow the requirements for reporting all adverse events (AEs) to the Sponsor. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC and archived in the site's study file.

1.3. INFORMED CONSENT

The Sponsor's Master ICF (and ancillary sample ICFs such as a Child's Assent or Caregiver's ICF, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of

informed consent that meets the requirements of 21 Code of Federal Regulations (CFR) Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant.

The ICFs must be signed and dated by the participant before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The ICFs should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IRB/EC-approved ICFs must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

If the ICFs are revised (through an amendment or an addendum) while a participant is participating in the study, the participant may be re-consented by signing the most current version of the ICFs or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised ICFs, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study. The study team will provide guidance for which participants need to re-consent in the event of an update to the ICF.

A copy of each signed ICF must be provided to the participant. All signed and dated ICFs must remain in each participant’s study file or in the site file and must be available for verification by study monitors at any time.

Participants who are re-screened are required to sign a new ICF.

Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the Research Biosample Repository (RBR). The Investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their samples at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant’s agreement to provide

optional RBR samples. Participants who decline to participate will not provide a separate signature.

The Investigator should document whether or not the participant has given consent to participate by completing the RBR Sample Informed Consent electronic case report form (eCRF).

In the event of death or loss of competence of a participant who is participating in the research, the participant's samples and data will continue to be used as part of the RBR.

For sites in the U.S., each ICF may also include participant authorization to allow use and disclosure of personal health information in compliance with the U.S. HIPAA. If the site utilizes a separate Authorization Form for participant authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply, except that IRB review and approval may not be required per study site policies.

Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site.

Withdrawal from the Research Biosample Repository

Participants who give consent to provide samples for the RBR have the right to withdraw their samples at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her samples, the Investigator must inform the Medical Monitor and Site Monitor in writing of the participant’s wishes using the RBR Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the study is closed. A participant's withdrawal from Study BP43437 does not, by itself, constitute withdrawal of samples from the RBR. Likewise, a participant’s withdrawal from the RBR does not constitute withdrawal from Study BP43437. Data already generated before time of withdrawal of consent to RBR will still be used.

1.4. CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

Confidentiality for Research Biosample Repository

Data generated from RBR samples must be available for inspection upon request by representatives of national and local Health Authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Participant medical information associated with RBR samples is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data derived from RBR sample analysis on individual participants will generally not be provided to study Investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by

name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with Investigators or participants unless required by law.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR sample data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

Monitoring and Oversight Research Biosample Repository

Samples collected for the RBR will be tracked in a manner consistent with GCP by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as compliance to authorized use of samples as specified in this protocol and in the ICF. The Sponsor's monitors and auditors will have direct access to appropriate parts of records relating to participant participation in RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

1.5. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (as defined in Section 4.5).

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on printed forms or eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

2.1.2. Clinical Outcome Assessment Data

As no diary data are collected, this is not applicable for this study.

2.1.2.1 Electronic Clinical Outcome Assessment Data

An electronic clinical outcome assessment (eCOA) device will be used to capture clinical outcome assessment (COA) data. The data will be transmitted automatically via web or wireless transmission after data entry to a centralized database at the eCOA vendor. The data may be reviewed by site staff via secure access to a web portal provided by the eCOA vendor.

The eCOA data will be collected using an electronic device provided by an eCOA vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

2.1.3. Source Data Records

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, COAs (paper or eCOA), evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable Health Authorities.

2.1.4. Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion or discontinuation of the study, or for the length of time required by relevant national or local Health Authorities, whichever is longer. After that period, the documents may be destroyed, subject to local regulations. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local Health Authorities.

2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IEC and competent authorities according to local regulatory requirements and timelines of each country participating in the study.

2.3.1. Protocol Amendments

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or any non-substantial changes, as defined by regulatory requirements.

2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. This allows the Sponsor to protect proprietary information and to provide comments on the basis of information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

2.3.3. Dissemination of Clinical Study Data

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to Study Investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

2.3.4. Management of Study Quality

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to first participant entry into the study, the Sponsor will identify and evaluate potential risks associated with critical study processes and data, as well as implement controls for the communication, review, and reporting of these risks. Details regarding the applied approach for the study will be provided in the integrated Risk Based Quality Management Plan.

2.3.5. Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

3. ADMINISTRATIVE STRUCTURE

3.1. INTERNAL MONITORING COMMITTEE

An IMC will be utilized to provide recommendations regarding study conduct to ensure enhanced participant monitoring while receiving study treatment. The IMC will evaluate the accumulating safety and efficacy data from all participants treated in this study periodically to ensure comprehensive evaluation of the overall benefit-risk profile of the study treatments. The IMC will operate according to a prespecified charter governing IMC composition, meeting requirements and frequency, and scope.

If a safety stopping criterion (Section 4.1.3 of the protocol) is met during either the safety run-in or expansion, the IMC may recommend discontinuing enrollment or discontinuing a treatment arm. If no safety stopping criterion is met during the safety run-in, the IMC may recommend enrolling participants in the corresponding expansion cohort and/or initiating the next expansion as described in Section 4.1.2 of the protocol.

In addition to the ongoing assessment of the incidence and nature of safety stopping criteria, AEs, SAEs, adverse events of special interest (AESIs), and laboratory abnormalities by the Investigator and the Medical Monitor, the IMC will review cumulative data at regular intervals during the study. In addition, the IMC will meet regularly and as needed at the request of the study Medical Monitor (e.g., based on unexpected safety signals).

The IMC may further make recommendations regarding study conduct, including, but not limited to, the following: Performing additional safety analyses, modifying the safety monitoring and/or eligibility criteria, amending the study protocol, holding participant enrollment pending further safety evaluations, holding/discontinuing study treatment, or terminating the study.

4. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

If the study is placed on hold, or if the Sponsor decides to discontinue the study or the development program, the Sponsor shall promptly inform the Investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigators shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

Appendix 2
Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting

1. DEFINITION OF ADVERSE EVENTS

According to the E2A International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP), an **adverse event** (AE) is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events Meeting the AE Definition:

- Deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, x−ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or serious AE (SAE) unless the progression is unexpectedly accelerated and not in line with the natural history of the disease. If the “lack of efficacy” does not require safety reporting, such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): The condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that at any dose:

- **Results in death.**
- **Is life-threatening.**

  The term "life-threatening" in the definition of "serious" refers to an event during which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- **Results in persistent or significant disability/incapacity**

  Disability means substantial disruption of the participant's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**.
- **Other significant events**:

  Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may

jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the electronic case report form (eCRF).

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by Sponsor In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor.

The Investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

3.1. ASSESSMENT OF SEVERITY

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, severe, or according to a predefined grading criteria [e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

If a participant experiences an isolated episode of fever temporarily associated with the injection of forimtamig, not accompanied by other cytokine release syndrome (CRS)-like

symptoms as described above, then the AE reporting term will be CRS of Grade 1. Fever attributed to an alternative documented cause, e.g., infection, should be reported as fever and not CRS.

The AE severity grading scale for the NCI CTCAE (v5.0) will be used for assessing AE severity. Table 2 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE. CRS should be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) criteria (Lee et al 2019, see Appendix 11). Participants with neurotoxicity (non- immune effector cell-associated neurotoxicity syndrome [ICANS]) will be graded according to NCI-CTCAE v5.0. ICANS will be graded according to ASTCT (guideline provided in Table 1) and symptoms of ICANS will be graded according to NCI-CTCAE v5.0.

Table 1 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to adverse event[d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 6 of this appendix for reporting instructions), per the definition of serious adverse event in Section 2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 6 for reporting instructions), per the definition of serious adverse event in Section 2. Grade 4 laboratory abnormalities would only be reported as SAEs if these meets one or more of the conditions outlined in Section 2 (Definition of Serious Adverse Events) of Appendix 2.

3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study treatment,

indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment.
- Course of the event, considering especially the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment.
- Known association of the event with the study treatment or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

For participant receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

4. FOLLOW-UP OF AES AND SAES

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, when possible the Investigator will provide sponsor with a copy of any post-mortem findings, including histopathology

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- SAEs.
- AEs of special interest (AESIs; see Section 8.3.6).

- Pregnancies (see Section 8.3.5).

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality on the basis of new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting SAEs to the local Health Authority and Institutional Review Board (IRB)/ethics committee (EC).

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

Events that Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. The Clinical Trial Adverse Event/Special Situations Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Events that Occur after Study Treatment Initiation

For reports of SAEs and AESIs (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Clinical Trial Adverse Event/Special Situations Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Reporting of Post-Study Adverse Events and Serious Adverse Events

If the Investigator becomes aware of any other SAE occurring after the end of the AE reporting period, and if the event is believed to be related to prior study treatment, the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to Investigators.

5.2 SPECIAL SITUATIONS: ACCIDENTAL OVERDOSE AND/OR MEDICATION ERROR

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: Accidental administration of a drug in a quantity that is higher than the assigned dose.
- Medication error: Accidental deviation in the administration of a drug (e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration).

After initiation of study treatment, special situations associated with forimtamig, carfilzomib, daratumumab, and tocilizumab (if applicable) and any associated AEs will be reported until [redacted] after the final dose of forimtamig, carfilzomib or tocilizumab (if applicable) and [redacted] after the last dose of daratumumab.

Special situations, regardless of whether they result in an AE, should be reported on the Special Situations eCRF. If there are any associated AEs, each event should be recorded separately on the Adverse Event eCRF.

Special situations and any associated AEs should be reported within 30 days after the investigator becomes aware of the situation. However, if an associated AE fulfills seriousness criteria or qualifies as an AESI, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the Investigator becomes aware of the event), as described in Section 5.1 of this appendix.

6. EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEE

The Sponsor will promptly evaluate all SAEs and AESIs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs/ECs, and applicable Health Authorities on the basis of applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events through use of the Reference Safety Information (RSI) in the documents listed below:

Drug	Document
Forimtamig	Forimtamig Investigator's Brochure
Carfilzomib	Carfilzomib EU SmPC
Daratumumab	Daratumumab EU SmPC
Tocilizumab	Tocilizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Appendix 3
Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events (AEs) on the Adverse Event electronic case report form (eCRF). Avoid colloquialisms and abbreviations. Only one AE term should be recorded in the event field on the Adverse Event eCRF.

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. INFUSION REACTIONS/INJECTION REACTIONS

AEs that occur during or after study treatment administration and are judged to be related to study treatment infusion or injection should be captured as a diagnosis (e.g., infusion-related reaction (IRR), cytokine release syndrome (CRS), injection-related reaction, injection site reaction or anaphylactic reaction) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction, CRS, or injection reaction, eCRF. If a participant experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the Infusion-Related Reaction, cytokine release syndrome or injection reaction, eCRF.

1.2. OTHER ADVERSE EVENTS

For AEs other than infusion-related reaction, CRS, injection related reaction, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.

- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

4. ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a

descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5. ABNORMAL VITAL SIGN VALUES

Not every vital sign abnormality qualifies as an AE. A vital sign result should be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator’s judgment.

It is the Investigator’s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

6. ABNORMAL LIVER FUNCTION TESTS

Drug-induced liver injury (DILI) has been the most frequent single cause of safety-related drug marketing withdrawals or limitation of use, as well as discontinuation of clinical development programs. Hence, detection and reporting of liver function abnormalities that might herald a signal of severe DILI are conducted for any product in clinical development, irrespective of its expected liability for this risk. This text is for studies involving all other patient populations or healthy volunteers.

DILI has been the most frequent single cause of safety-related drug marketing withdrawals or limitation of use, as well as discontinuation of clinical development programs. Hence, detection and reporting of liver function abnormalities that might herald a signal of severe DILI are conducted for any product in clinical development, irrespective of its expected liability for this risk. This text is for studies involving participants with chronic virological diseases, (e.g., hepatitis B or C, HIV) and studies involving oncology patients who have liver metastases or hepatocellular carcinoma or are receiving hepatotoxic concomitant medications.

The finding of an elevated ALT or AST in combination with either an elevated total bilirubin or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of potential severe liver injury. Therefore, Investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>5\times$ ULN value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin).
- Treatment-emergent ALT or AST $>5\times$ ULN value in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Appendix 2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious AE (SAE) or an AE of special interest (see Section 8.3.6).

7. DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified AE reporting period (see Section 5 of Appendix 2) that are attributed by the Investigator solely to progression of multiple myeloma should be recorded only on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5 of Appendix 2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

8. PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF. A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

9. LACK OF EFFICACY OR WORSENING OF MULTIPLE MYELOMA

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on International Myeloma Working Group (IMWG) response criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to progressive disease, it should be reported as an AE.

10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAEs in Appendix 2), except as outlined below. An event that leads to hospitalization under the following circumstances should not be reported as an AE or an SAE:

- Hospitalization for respite care.
- Planned hospitalization required by the protocol {(e.g., for study treatment administration or insertion of access device for study treatment administration)}
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study (e.g., when elective surgery became necessary because of the expected normal progression of the disease).
    - The participant has not suffered an AE.
- Hospitalization due solely to progression of the underlying cancer.

An event that leads to hospitalization under the following circumstances is not considered to be an SAE, but should be reported as an AE instead:

- Hospitalization for an AE that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the local laboratory at the time points indicated in the schedules of assessments (SoAs; protocol Section 1.3). The results must be captured in source documentation and entered into the eCRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2 of the protocol, respectively.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

The results of each test must be entered into the eCRF.

Investigators must document their review of each laboratory safety report.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Complete blood count, including red blood cell count (RBC), hemoglobin, hematocrit, white blood cell count (WBC) with differential count (i.e., neutrophils, bands are optional, neutrophils, lymphocytes, eosinophils, basophils, and monocytes), and platelet count.
Clinical chemistry	• Sodium, potassium, magnesium, chloride bicarbonate, calcium (corrected for albumin), phosphate, albumin, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatinine, creatinine clearance (Appendix 13) creatine kinase, blood urea nitrogen (BUN) or urea, uric acid, total protein, CRP, ferritin, glucose.
Blood typing and antibody screen	• As per Section 8.2.7.1.
Cardiac markers, only for Arm B (carfilzomib combination)	• Troponin T/I, BNP and/or NT pro-BNP
Coagulation	• INR or PT, aPTT.
Viral serology	• Hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb), hepatitis C virus (HCV) antibody; HCV RNA by PCR if the participant is HCV antibody positive. Participants whose hepatitis B serology results cannot rule out acute or chronic HBV infection must be negative for HBV by PCR to be eligible for study participation. • Participants who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation. EBV, CMV and HHV-6 by PCR will be tested in case of MAS/HLH only.

Laboratory Assessments	Parameters
Lipids	• Cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.
Hormone	• Free and total testosterone (in males)
IgE and tryptase	• IgE, tryptase at screening. • Tryptase and IgE samples will be collected in case of suspicion of type I hypersensitivity. A second sample for local IgE/tryptase analysis will be collected approximately 48 hours after onset of the reaction.
Pregnancy test	• As per Appendix 5.
Urinalysis	• Specific gravity. • Dipstick: pH, glucose, protein, blood, ketones, bilirubin • If there is a clinically significant positive result, urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded, and there is no need to perform microscopy and culture. • Microscopic examination (RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CMV = cytomegalovirus; CRP = C-reactive protein; EBV = Epstein-Barr virus; FSH = follicle-stimulating hormone; HBcAb = total hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HDL = high-density lipoprotein; HHV-6 = human herpesvirus 6; HLH = hemophagocytic lymphohistiocytosis; IgE = immunoglobulin E; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MAS = macrophage activation syndrome; NT pro-BNP = N-terminal pro-brain natriuretic peptide; PCR = polymerase chain reaction; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.

Additional Statistical Considerations for Clinical Laboratory Data

Standard Reference Ranges and Transformation of Data

Potential analysis considerations for analyzing laboratory data includes the use of standard reference ranges and potential transformation of data for specific laboratory tests.

In this scenario, Roche standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, ALP, and total bilirubin. The standard reference ranges for these parameters have a lower limit of zero; therefore, only the upper limits of the ranges will be used in transforming the data.

Definition of Laboratory Abnormalities

For all laboratory parameters included in the analysis described above, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled “H” for high or “L” for low in participant statistical outputs of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for these laboratory parameters. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant’s baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as “HH” for very high or “LL” for very low.

Additional Exploratory Central Laboratory Assessments

Herpes simplex virus (HSV)-8, human herpesvirus (HHV)-6, cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus, and varicella will be tested per SoA (Section 1.3). The data will be used for exploratory research.

Appendix 5
Contraceptive and Barrier Methods Guidance

1. DEFINITIONS

- **Participant of Childbearing Potential (POCBP)**

A participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

- **Participants in the following categories are considered to be of Non-Childbearing Potential (PONCBP)**

  - Pre-menarchal.
  - Premenopausal females with one of the following:
    - Documented hysterectomy.
    - Documented bilateral salpingectomy.
    - Documented bilateral oophorectomy.

      Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

  - Postmenopausal participants:
    - A postmenopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Participants on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal, highly effective contraception methods if they wish to continue their HRT during the study. Only discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

- **Female Participants**

POCBP are eligible to participate if they to remain abstinent (refrain from heterosexual intercourse) or use of at least one highly effective contraceptive method that results in a failure rate of <1% per year preferably with low user dependency, from screening until [redacted]

Per International Council for Harmonisation (ICH) M3(R2), highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly as described in Table 1 below. Effective or acceptable methods of birth control are defined as those, alone or in combination, that result in failure rate of > 1% per year when used consistently and correctly, as described in Table 1 below.

The Investigator should evaluate with the participant the best contraceptive method based on anatomy and physiology. Hormonal contraceptive methods must be supplemented by a barrier method (preferably male condom). Biological female participants must refrain from donating eggs during this same period.

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent[a] (Failure rate of < 1% per year when used consistently and correctly)
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: o Oral o Intravaginal o Transdermal Progestogen-only hormonal contraception associated with inhibition of ovulation: o Oral o Injectable
Highly Effective Methods That Are User-Independent (Failure rate of < 1% per year)
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a] Intrauterine device Intrauterine hormone-releasing system Bilateral tubal occlusion/ligation **Azoospermic partner (vasectomized or due to medical cause)** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the POCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Effective Birth Control Methods Which May Not Be Considered As Highly Effective (Failure rate of > 1% per year when used consistently and correctly)

Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
Male or female condom with or without spermicide[b]
Cap, diaphragm, or sponge with spermicide[b]

Abbreviations: POCBP = Participant of childbearing potential.

[a] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraception method.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods (i.e., when the risk of teratogenicity and genotoxicity is unlikely).

3. PREGNANCY TESTING

For POCBP enrolled in the study, blood sample and urine pregnancy tests will be performed according to the SoA (see Section 1.3). If a highly sensitive urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

4. COLLECTION OF PREGNANCY INFORMATION

- **Male participants with partners who become pregnant**

The Investigator will attempt to collect pregnancy information on any male participant's partner who becomes pregnant while the male participant is in this study [redacted]. (see Section 8.3.5 Pregnancy).

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information and an Authorization for Use and Disclosure of Infant Health Information to allow for follow-up on her pregnancy and the infant health information respectively If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available.

An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Information on the status of the infant health at the 6th and 12th month after the date of birth will be forwarded to the Sponsor by using Infant Clinical Trial Follow-up Reporting Form when the authorization for infant health follow-up has been obtained.

- **Participants who become pregnant**

The Investigator will collect pregnancy information on any participant who becomes pregnant while participating in this study (see Section 8.3.5 Pregnancy). Information will be recorded on the Clinical Trial Pregnancy Reporting Form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure. The Investigator will collect follow-up information on the participant and the neonate which will be forwarded to the Sponsor. When permitted by the site, the pregnant participant would need to sign an Authorization for the Use and Disclosure of Infant Health Information to allow for follow-up on the infant. Information on the status of the infant health at the 6th and 12th month after the date of birth will be forwarded to the Sponsor by using Infant Clinical Trial Follow-up Reporting Form when the authorization for infant health follow-up has been obtained.

While pregnancy itself is not considered to be an adverse event (AE) or serious AE (SAE) and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study, pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Appendix 2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will discontinue study treatment.

Additionally, attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5 ABORTIONS

Any spontaneous abortion in a participant exposed to study treatment or the partner of a male participant exposed to study treatment should be classified as an SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Any induced abortion due to maternal toxicity and/or embryofetal toxicity should also be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Elective or therapeutic abortion not associated with an underlying maternal or embryofetal toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting is not considered an AE but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form. All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a participant or partner of a male participant exposed to study treatment should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Appendix 6
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations

Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for the European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Forimtamig (RO7425781)	IMP (test product) [a]	Unauthorized	Not applicable
Carfilzomib	IMP (test product) [a]	Authorized	No [b]
Daratumumab	IMP (test product) [a]	Authorized	No [b]
Tocilizumab (RO4877533)	IMP (other)	Authorized	No [c]
Glucocorticoid	AxMP (other) [d]	Not applicable [e]	Not applicable [e]
Antihistamine	AxMP [d]	Not applicable [e]	Not applicable [e]

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product

[a] Forimtamig, carfilzomib, daratumumab, and tocilizumab are each considered to be an IMP.

[b] Carfilzomib and daratumumab are approved for the treatment of multiple myeloma, but not in combination with forimtamig.

[c] Tocilizumab is not approved for the treatment of cytokine release syndrome.

[d] Antihistamine and glucocorticoid do not fall within the definition of IMP in Regulation 536/2014, and are therefore classified as AxMPs. Participants must receive an antihistamine and a glucocorticoid prior to injection of forimtamig and daratumumab when premedication is required. Applicable premedication include, but are not limited to acetaminophen/paracetamol and diphenhydramine (antihistamine), and dexamethasone (oral or IV) or methylprednisolone (glucocorticoid).

[e] Antihistamine and glucocorticoid are classes of medicines and not individual products. Therefore, this field is not applicable. The Sponsor expects that the intended premedication is suitable for patients according to local prescribing information.

Table 2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in UK	Used within Marketing Authorization
Forimtamig (RO7425781)	IMP (test product) [a]	Unauthorized	Not applicable
Carfilzomib	IMP (test product) [a]	Authorized	No [b]
Daratumumab	IMP (test product) [a]	Authorized	No [b]
Tocilizumab (RO4877533)	IMP (other)	Authorized	No [c]
Glucocorticoid	NIMP (other) [d]	Not applicable [e]	Not applicable [e]
Antihistamine	NIMP [d]	Not applicable [e]	Not applicable [e]

IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

[a] Forimtamig, carfilzomib, daratumumab, and tocilizumab are each considered to be an IMP.

[b] Carfilzomib- and daratumumab are approved for the treatment of multiple myeloma, but not in combination with forimtamig.

[c] Tocilizumab is not approved for the treatment of cytokine release syndrome.

[d] Antihistamine and glucocorticoid do not fall within the definition of IMP and are therefore classified as NIMPs. Participants must receive an antihistamine and a glucocorticoid prior to injection of forimtamig and daratumumab when premedication is required. Applicable premedications include, but are not limited to acetaminophen/paracetamol and diphenhydramine (antihistamine), and dexamethasone or methylprednisolone (glucocorticoid).

[e] Antihistamine and glucocorticoid are classes of medicines and not individual products. Therefore, this field is not applicable. The Sponsor expects that the intended premedication is suitable for patients according to local prescribing information.

Appendix 7
International Myeloma Working Group Uniform Response Criteria (2016)

Response Subcategory	Response Criteria
sCR	**CR as defined below, *plus*** • Normal SFLC ratio, and • Absence of clonal cells in BM by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ participants, respectively, after counting ≥100 plasma cells) or negative by 2 to 4 color flow cytometry.[a]
CR	• No evidence of initial monoclonal protein isotype(s) on immunofixation of the serum and urine,[b, c] and • Disappearance of any soft tissue plasmacytomas, and • <5% plasma cells in BM. • For participants for whom the only measurable disease at baseline is by serum SFLC levels, a normal SFLC ratio of 0.26 to 1.65 (or reference range in testing laboratory) is also required.
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis,[c] *or* • ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24 hours.[c] • In addition to the above criteria, if present at baseline ≥90% reduction in the sum of the maximal perpendicular diameter (SPD) compared with baseline for soft tissue plasmacytoma. • For participants for whom the only measurable disease at baseline is by serum SFLC levels, VGPR is defined as ≥ 90% decrease in the difference between involved and uninvolved SFLC levels.
PR	• ≥50% reduction of serum M-protein and reduction in 24-hour urine M-protein by ≥90% or to <200 mg/24 hours.[d] • If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved SFLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are unmeasurable and SFLC assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline BM plasma cell percentage was ≥30%. • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)[e] of soft tissue plasmacytomas is also required.
MR	• ≥25% but ≤49% reductions of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89%.[d] • In addition to the above criteria, if present at baseline, ≥ 50%reduction in the size (SPD)[e] of soft tissue plasmacytomas is also required.
SD	• Not meeting criteria for sCR, MR, CR, VGPR, PR, or PD.

Response Subcategory	Response Criteria

Progressive disease [e,f]	Any one or more of the following criteria: .
	• Increase of 25% from lowest response value in any of the following:
	  ○ Serum M-component (absolute increase must be ≥ 0.5 g/dL) or serum-component increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL).
	  ○ Urine M-component (absolute increase must be ≥ 200 mg/24 hours).
	  ○ In participants without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL).
	• For non-secretory participants at study entry: In participants without measurable serum and urine M-protein levels and without measurable disease by FLC: BM plasma cell percentage irrespective of baseline status (absolute % 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.
	• Definite development of new bone lesions or definite increase in the size of existing bone lesions.
	• ≥ 50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease.

BM = bone marrow; CR = complete response; CT = computed tomography; Ig = immunoglobulin; mAb = monoclonal antibody; MR = minimal response; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PR = partial response; sCR = stringent complete response; SD = stable disease; SFLC = serum free-light chain; SPD = sum of the products of the maximal perpendicular diameters of measured lesions; VGPR = very good partial response.

[a] Special attention should be given to the emergence of a different M-protein following treatment, especially in the setting of participants having achieved a conventional CR, 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. Participants with positive serum IFE and confirmed daratumumab IFE interference, who meet all other clinical criteria for complete response or stringent complete response, will be considered CR/sCR.

[b] In some cases it is possible that the original M-protein light-chain isotype is still detected on immunofixation, but the accompanying heavy-chain component has disappeared; this would not be considered a CR even though the heavy-chain component is not detectable, since it is possible that the clone evolved to one that secreted only light chains. Thus, if a participant has IgA λ myeloma, then to qualify as a CR there should be no IgA detectable on serum or urine immunofixation; if free lambda is detected without IgA, then it must be accompanied by a different heavy-chain isotype (IgG, IgM, etc.). Modified from Durie et al. 2006. Requires two consecutive assessments to be carried out at any time before the institution of any new therapy (Durie et al. 2015).

[c] Clarifications to the criteria for classifying CR and VGPR in participants in whom the only measurable disease is by serum FLC levels: CR in such participants indicates a normal FLC ratio of 0.26 to 1.65 (or

reference range in testing laboratory) in addition to CR criteria listed above. VGPR in such participants requires a ≥ 90% decrease in the difference between involved and uninvolved FLC levels.

[d] Urine M-protein is not needed to document partial response or minor response if baseline urine M-protein was not measurable; however, it is still required for complete response and very good partial response

[e] Plasmacytoma measurements should be taken from the CT portion of the PET/CT or MRI scans, or dedicated CT scans where applicable. For participants with only skin involvement, the skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD. Any soft tissue plasmacytoma documented at baseline must undergo serial monitoring; otherwise, the participant is classified as not evaluable.

Notes:

- All response categories (CR, sCR, VGPR, PR, MR, and progressive disease) require 2 consecutive assessments made at any time before the institution of any new therapy.
- CR, sCR, VGPR, PR, MR, and stable disease categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed.
- VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.
- Radiographic studies are not required to satisfy these response requirements.
- Bone marrow assessments need not be confirmed.
- Participants should be categorized as having stable disease until they meet criteria for any response category or have PD. Participants will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; participants cannot move to a lower response category.
- Increase in bone marrow plasma cells (BMPCs) will not be considered progressive disease.
- Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. For participants with measurable disease by serum or urine M-protein at baseline, increases in SFLC or the SFLC ratio alone do not meet criteria for progressive disease.

References:

Durie BGM, Harousseau J-L, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–73.

Durie BGM, San Miguel J, Blade J, et al. Clarification of the definition of complete respose in multiple myeloma. Leukemia 2015;29:2416-7.

Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17:e328-46.

Appendix 8
Preexisting Autoimmune Diseases and Immune Deficiencies

Preexisting autoimmune diseases and immune deficiencies are listed in Table 1. Participants should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Table 1 Autoimmune Disease and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune nephritis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 9
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer.
- Oxygen.
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines.
- Antihistamines.
- Corticosteroids.
- Intravenous infusion solutions, tubing, catheters, and tape.

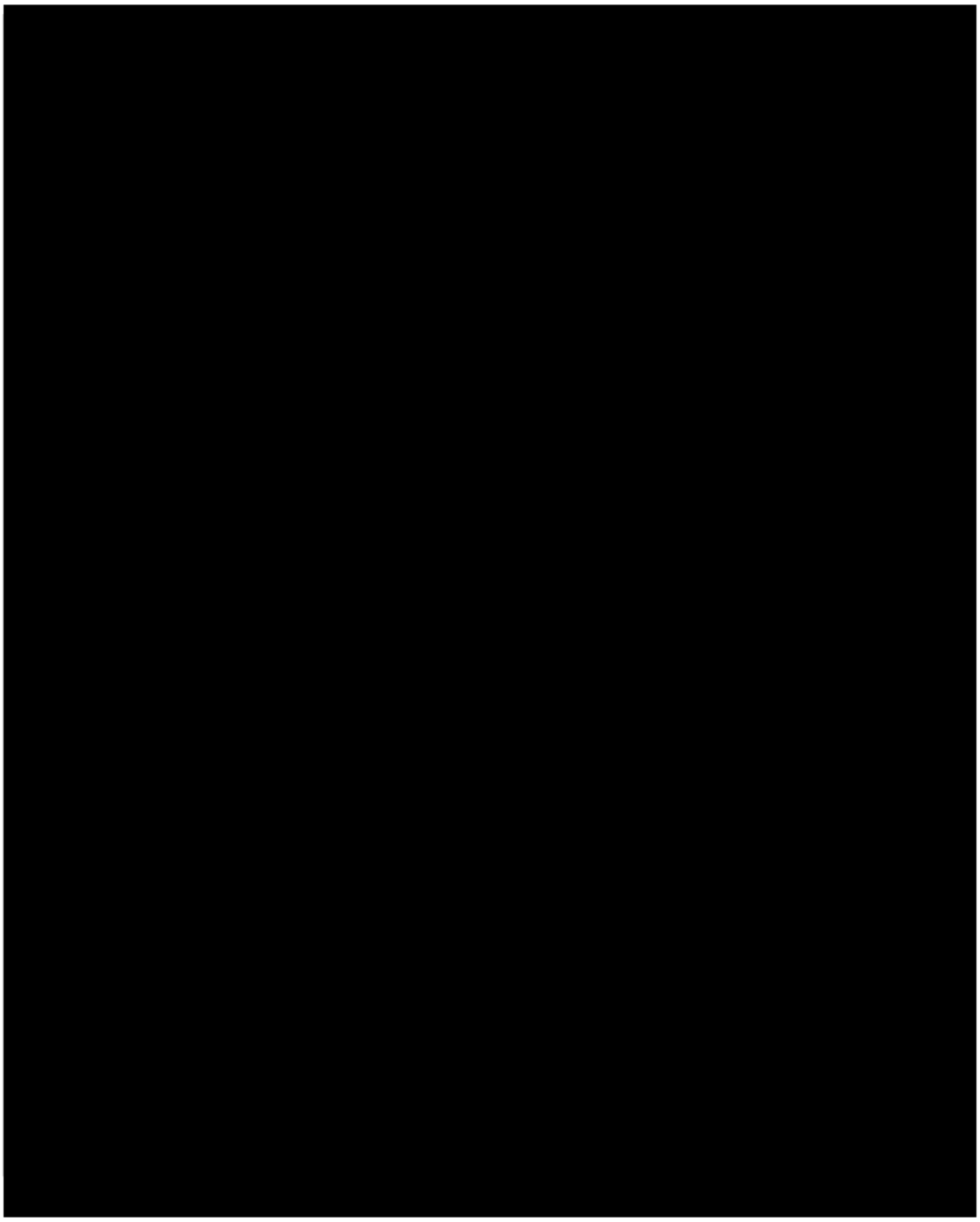
PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

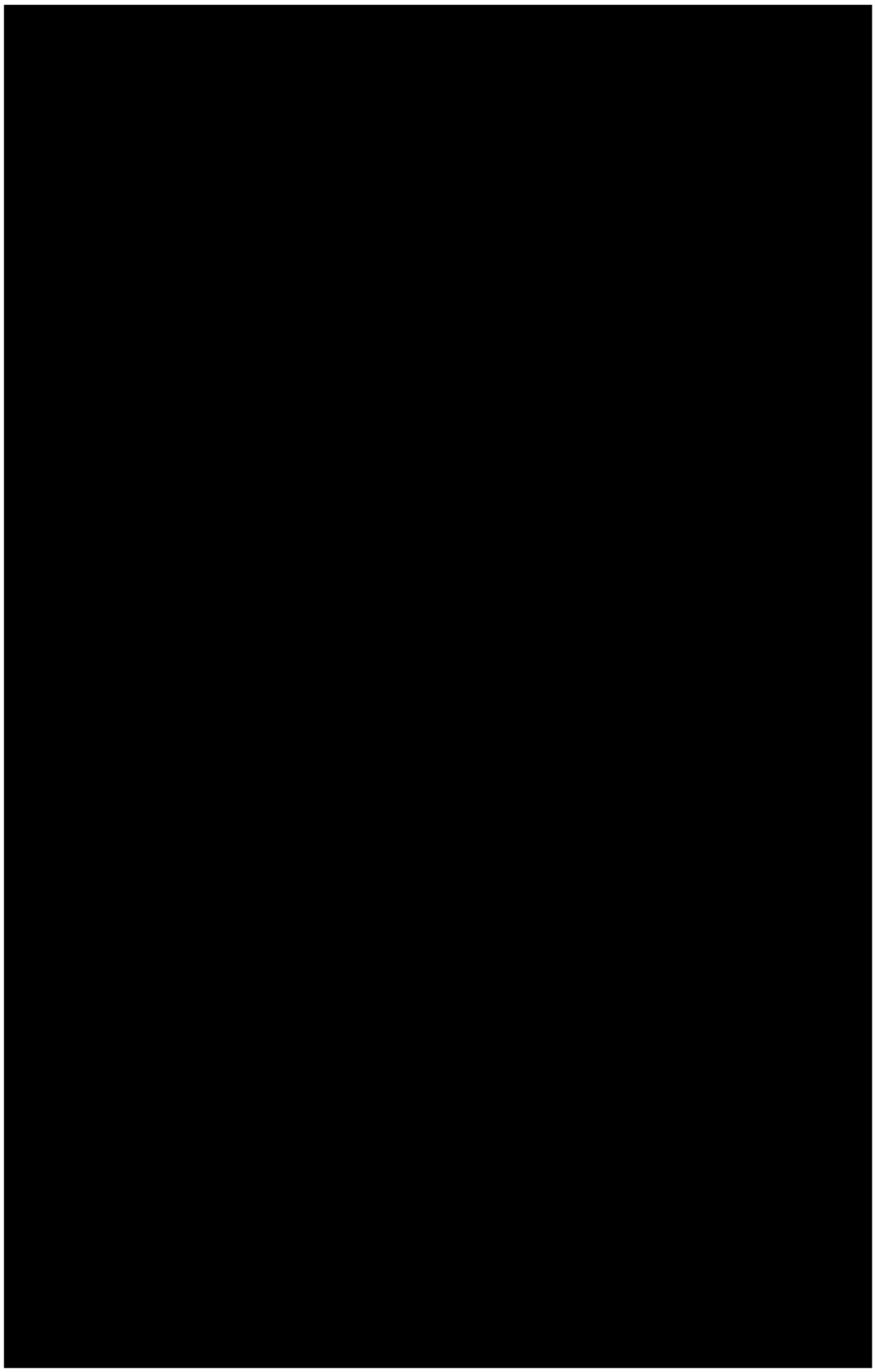
1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.

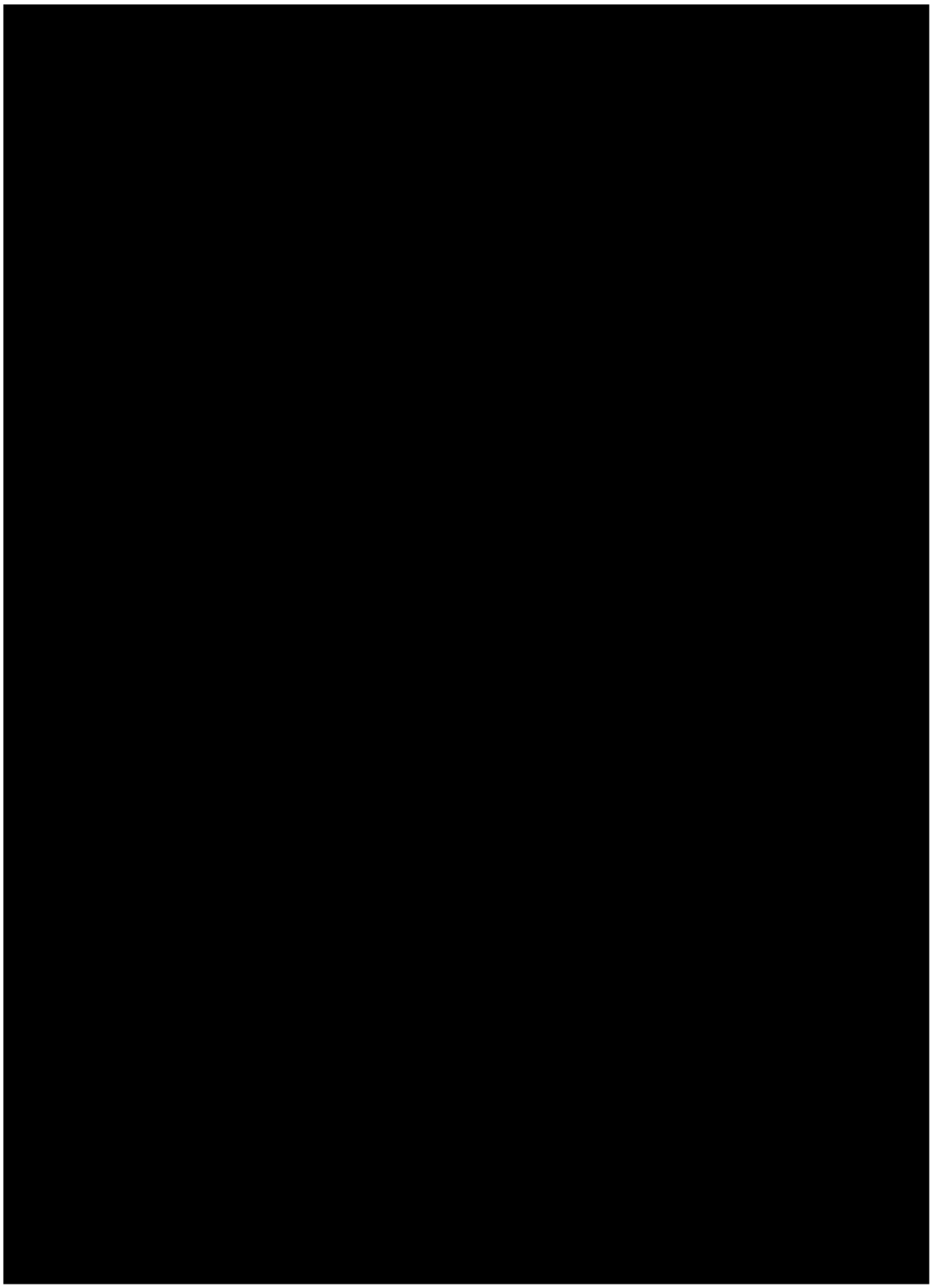
Appendix 10

[redacted]









Appendix 11
ASTCT Cytokine-Release Syndrome Consensus Grading

CRS Grade[a, e]	Clinical Parameter:				
	Fever[b]		Hypotension		Hypoxia
Grade 1	Temperature ≥ 38°C	with	None	and/or[c]	None
Grade 2	Temperature ≥ 38°C		Not requiring vasopressors		Requiring low-flow nasal cannula[d] or blow-by
Grade 3	Temperature ≥ 38°C		Requiring a vasopressor with or without vasopressin		Requiring high-flow nasal cannula, facemask, nonrebreather mask or Venturi mask
Grade 4	Temperature ≥ 38°C		Requiring multiple vasopressors (excluding vasopressin)		Requiring positive pressure ventilation (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome.

[a] CRS grading per ASTCT (Lee et al. 2019).

[b] Fever is defined as temperature ≥°38°C, not attributable to any other cause. In participants who develop CRS, and then receive anti-pyretic or anti-cytokine therapy (e.g., tocilizumab or steroids), fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[c] CRS grade is determined by the more severe event: hypotension or hypoxia, not attributable to any other cause.

[d] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

[e] Grade 5 CRS is defined as death due to CRS in which another cause is not the principal factor leading to this outcome.

Reference:

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.

Appendix 12

[redacted]

Appendix 13
Cockcroft-Gault Formula/Creatinine Clearance (mL/min)

Creatinine clearance (ml/min) for males

$$\text{Creatinine Clearance} = \frac{(140 - \text{age } \langle\text{years}\rangle) \times \text{body weight } \langle\text{kg}\rangle)}{(72) \times (\text{serum creatinine } \langle\text{mg/dL}\rangle)}$$

Creatinine Clearance (ml/min) for Females:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age } \langle\text{years}\rangle) \times \text{body weight } \langle\text{kg}\rangle)}{(72) \times (\text{serum creatinine } \langle\text{mg/dL}\rangle)} \times 0.85 \text{ (if female)}$$

For the Chronic Kidney Disease Epidemiology Collaboration **(CKD-EPI) Creatinine-Cystatin equation**, please refer to the following online tool (https://www.kidney.org/professionals/kdoqi/gfr_calculator) and use the results provided for the CKD-EPI creatinine-cystatin equation (2021).

Appendix 14
Hepatitis B Virus Screening

The following hepatitis B virus (HBV) screening guide is to be used to determine patient eligibility for the study:

Note: Patients with positive HBV-DNA should be excluded. Patients with negative HBV-DNA can be enrolled; however, HBV-DNA and AST/ALT laboratories should be performed every 3 months for the first 12 months after dosing.

Eligibility Based on Hepatitis B Virus Test Results			
Action	Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (anti-HBs)	Hepatitis B core antibody (anti-HBc total)
Exclude	+	– or +	– or +
Include	–	–	+, b
	–	+, a, b	+, b
	–	+, a	–

[a] Patients who are anti-HBs positive and without history of vaccination, should have HBV-DNA quantification test. Patients with positive HBV-DNA should be excluded. Patients with negative HBV-DNA can be enrolled. If required by local country guidelines on HBV prevention, HBV-DNA and AST/ALT laboratories should be performed every 3 months for the first 12 months after dosing.

[b] Patients with positive anti-HBc and patients with positive anti-HBc as well as positive anti-HBs must have a negative HBV-DNA quantification test result.

Appendix 15
Schedule of Activities for Tocilizumab

Table 1 Schedule of Activities in the Case of Tocilizumab Treatment for CRS or as Prophylaxis

Protocol Sections		Pre-tocilizumab	Tocilizumab	Post-tocilizumab						
	Time window relative to TCZ dosing	within 24 h		+15 min post EOI	6h (± 3h) post-EOI[a]	1 day (24h ± 4h) post-EOI	2 days (48h ± 4h) post-EOI[a]	3 days (72h ± 4h) post-EOI[a]	8 days (192 h ± 48h) post-EOI[a]	EoT
6.1	**TCZ administration** (8mg/kg for participants ≥30kg; 12mg/kg for participants <30kg; dose exceeding 800mg per infusion not recommended)		x							
8.2.2	**Vital signs** (respiratory rate, heart rate, systolic and diastolic blood pressure [in a seated or supine position], temperature and oxygen)			At least every 6 hours until resolution to baseline, then every 12 hours until end of hospitalization						
8.3.9.1	**Vasopressor** (document the type and dose in the concomitant medication eCRF)	x		Record at least every 6 hours until vasopressor are discontinued						
8.3.9.1	**FiO_2**	x		Record at least every 6 hours until patient on room air						
Local Laboratory Assessments										
8.2.6 and Appendix 4	**Hematology** (Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, and differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells])	x			x	x	x			
8.2.6 and Appendix 4	**Blood chemistry** (Sodium, potassium, chloride, bicarbonate, glucose, albumin, total protein, blood urea nitrogen, creatinine, creatinine clearance [by Cockcroft-Gault formula], calcium, magnesium, phosphorous, uric acid, ALP, ALT, AST, bilirubin, LDH, GGT, CRP and ferritin)	x			x	x	x			
8.2.6 and Appendix 4	**Coagulation** (INR, aPTT[or PTT], PT and fibrinogen)	x			x	x	x			
8.3.9.1	**Infection workup** (for bacterial, fungal and viral infections as clinically indicated)	x								
Central Laboratory Assessments										
8.8.1.1	**Serum IL-6 PD markers** (including IL-6, sIL-6R)	x		x[b]	x	x	x	x	x	
8.5.	**Serum TCZ PK**	x		x[b]	x	x	x	x	x	x
8.6	**Serum TCZ ADA**	x								x

ADA = anti-drug antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CRP = C-reactive protein; CRS = cytokine release syndrome; eCRF = electronic case report form; EoI = end of infusion; EoT = end of treatment visit; FiO_2 = fraction of inspired oxygen; GGT = gamma-glutamyltransferase; h = hour; ; INR = international normalized ratio; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; TCZ = tocilizumab.

[a] After first administration of tocilizumab for CRS only.

[b] Samples will be drawn from the arm not used for tocilizumab administration.

Appendix 16
ECOG Performance Status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., 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.

Reference:

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-5.

Appendix 17
Abbreviations

Abbreviation	Definition
2L+	second line or later
ABO/RhD	blood typing system
ADA	anti-drug antibody
AE	Adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BSA	body surface area
C1D1	Cycle 1 Day 1
CAR	chimeric antigen receptor
CD	cluster of differentiation
CNS	central nervous system
COVID-19	coronavirus disease 2019
COPD	chronic obstructive pulmonary disorder
CR	complete response
CrCl	creatinine clearance
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DoR	duration of response
DTT	dithiothreitol
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FEV1	forced expiratory volume

Abbreviation	Definition
FVC	Forced vital capacity
G-CSF	granulocyte colony-stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
IAT	indirect antiglobulin test
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	Immune Effector Cell-Associated Encephalopathy (score)
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFE	immunofixation electrophoresis
IFN-γ	interferon-gamma
IgA	immunoglobulin A
IgD	immunoglobulin D
IgE	immunoglobulin E
IgG	immunoglobulin G
IGIV	immune globulin intravenous
IgM	immunoglobulin M
IL	interleukin
IMC	Internal Monitoring Committee
IMiD	immunomodulatory drug
IMP	investigational medicinal product
IMWG	International Myeloma Working Group
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAS	macrophage activation syndrome
MoA	mode of action
MR	minimal response

Abbreviation	Definition
[redacted]	
MRI	magnetic resonance imaging
[redacted]	
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NGS	next-generation sequencing
NK	natural killer (cells)
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
POCBP	participant of childbearing potential
PONCBP	participant of non-childbearing potential
popPK	population pharmacokinetics
PR	partial response
PR	PR interval
[redacted]	
PT	prothrombin time
[redacted]	
QRS	QRS complex
QT	QT interval
RBR	Research Biosample Repository
RNA	ribonucleic acid
r/r	relapsed/refractory
SAE	serious adverse event
SC	subcutaneous
sCR	stringent complete response

Abbreviation	Definition
SCT	stem cell transplantation
SFLC	serum free light chain
SIFE	serum immunofixation electrophoresis
sIRR	systemic injection-related reaction
SmPC	summary of product characteristics
SoA	schedule of activities
SoC	standard of care
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reaction
TCB	T cell bispecific antibody
TCL	tumor cell lysis
TLS	tumor lysis syndrome
TTBR	time to best response
TTR	time to response
[redacted]	
ULN	upper limit of normal
[redacted]	
U.S.	United States
USPI	U.S. package insert
VGPR	very good partial response
WES	whole exome sequencing
WGS	whole genome sequencing

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