SUPPLEMENTARY APPENDIX

Targeting B-Cell Maturation Antigen with GSK2857916 Antibody-Drug Conjugate in Relapsed or Refractory Multiple Myeloma: A Dose-Escalation and Expansion Phase 1 Trial BMA117159

Suzanne Trudel, Nikoletta Lendvai, Rakesh Popat, Peter M. Voorhees, Brandi Reeves, Edward N. Libby, Paul G. Richardson, Larry D. Anderson Jr, Heather J. Sutherland, Kwee Yong, Axel Hoos, Michele M. Gorczyca, Soumi Lahiri, Zangdong He, Daren J. Austin, Joanna B. Opalinska, Adam D. Cohen

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Supplementary Methods: Further details on inclusion and exclusion criteria

Disease progression was defined as an increase of ≥25% from lowest response in either serum M-component or urine M-component; the difference between involved and uninvolved FLC levels (absolute increase >10 mg/dL) in patients without measurable M-protein; bone marrow plasma cell percentage ≥10%; development of new, or increase of existing bone lesions or soft tissue plasmacytomas; development of hypercalcaemia (corrected serum calcium >11·5 mg/dL or 2·65 mmol/L) attributable to plasma cell proliferative disorder on or within 60 days of completion of the last therapy.

Patients were excluded if they had received systemic anti-tumour therapy within 14 days, or plasmapheresis within 7 days prior to first dose, monoclonal antibody treatment within 30 days or an investigational drug within 14 days or 5 half-lives, whichever was shorter. Patients with a history of allogenic stem cell transplant, or with internal bleeding, surgery within last 4 weeks, any serious or unstable pre-existing medical, psychiatric disorder or laboratory abnormalities, active infections requiring antibiotic treatment, uncontrolled systemic diseases, at cardiovascular risk, known hypersensitivity reaction to drugs chemically related to GSK2857916, any HIV, Hepatitis B or C infection, current liver or biliary disease, or a history of corneal disease were excluded.

Supplementary Methods: Soluble BCMA assay

Free soluble BCMA was captured with anti-BCMA (GSK2857914) and detected with a distinct anti-BCMA antibody (BAF193). GSK2857916-bound soluble BCMA (i.e. complex soluble BCMA) was captured with anti-BCMA (BAF193) and detected with an anti-auristatin antibody. Validation with healthy donors was performed; individual data are presented in Table S1. The absolute values were broadly in line with those cited in the literature, which range from 2·57 to 20 ng/nL.[1,2] However, the expected change in levels is seen following drug administration (Figure S2).

Table S1. Soluble BCMA levels in healthy donors

Sample reference	Concentration (ng/mL)	% coefficient of variance
HD1	6·57	3·1
HD2	5·50	1·5
HD3	7·32	6·4
HD4	5·50	3·3
HD5	6·30	0·3
HD6	6·03	1·3
HD7	7·06	4·9
HD8	4·47	3·7
HD9	7·53	1·6
HD10	4·83	2·1
HD11	5·37	1·2
HD12	6·69	1·4
HD13	7·99	2·4
HD14	10·68	10·7
HD15	10·02	3·2
HD16	6·83	2·9
HD17	5·41	1·8
HD18	7·98	1·3
HD19	7·42	2·9
HD20	3·23	4·0
HD21	8·73	5·9
HD22	5·07	2·5
HD23	7·81	0·9
HD24	4·33	2·7
HD25	8·80	0·3

Table S2. Patient recruitment by Principal Investigator

Author	Centre	All Treated N=73
Trudel	Princess Margaret Cancer Centre	18
Lendvai	Memorial Sloan Kettering Cancer Center	12
Cohen	Univ. of Pennsylvania	12
Popat	Univ. College London	9
Voorhees and Reeves*	Univ. North Carolina	8
Libby	Seattle Cancer Care Alliance	6
Richardson	Dana Farber Cancer Center	5
Anderson	Univ. Texas Southwestern	2
Sutherland	Vancouver General Hospital	1

*Dr Voorhees was the initial Principal Investigator at University of North Carolina, and Dr Reeves became the Principle Investigator during the study.

Table S3. Patient baseline characteristics (prior daratumumab and refractory to IMiD and PI) (Part 2)

Characteristic	Prior daratumumab and refractory to IMiD and PI (n=12)
Age, median (range), years	58 (47 – 70)
Sex, male / female, n (%)	7 (58) / 5 (42)
Disease stage at diagnosis, I / II / III / unknown, n (%)	4 (33) / 3 (25) / 2 (17) / 3 (25)
Myeloma light chain, n (%)	
Kappa light chain	10 (83)
Lambda light chain	2 (17)
Myeloma immunoglobulin, n (%)	3 (25)
IgA	7 (58)
IgG	2 (17)
Other	
Genetics, n (%)*	
del13	2 (17)
del17p13	2 (17)
t(4:14)	3 (25)
1q21	2 (17)
Other	6 (50)
Missing	3 (25)
Prior therapies, n (%)	
Received ≥5 lines of therapy	10 (83)

FISH, fluorescent in situ hybridization; IgA/G; immunoglobulin A/G; IMiD, immunomodulatory drug; PI, protease inhibitor.

*As assessed by FISH. Multiple categories per patient possible; total may add to more than 100%.

Table S4. Response, adverse events, and dose modifications by dose level (Parts 1 and 2)

Dose level (mg/kg)	ORR, %	95% CI	Corneal events, % [Grade 3/4]	IRR, % [Grade 3/4]	Thrombocytopenia, platelet count decreased, % [Grade 3/4]	Dose delay, %	Dose reduction*, %
Part 1							
0·03 (n=1)	0	(0·0 – 97·5)	0	0	100 [100]	0	0
0·06 (n=1)	0	(0·0 – 97·5)	0	0	100 [100]	0	0
0·12 (n=4)	0	(0·0 – 60·2)	25 [0]	50 [0]	50 [25]	0	0
0·24 (n=4)	0	(0·0 – 60·2)	0	25 [0]	25 [25]	0	0
0·48 (n=4)	0	(0·0 – 60·2)	50 [0]	0	25 [25]	25	0
0·96 (n=3)	33	(0·8 – 90·6)	33 [0]	33 [0]	33 [33]	33	33
1·92 (n=4)	25	(0·6 – 80·6)	100 [25]	25 [0]	25 [0]	75	50
2·5 (n=8)	0	(0·0 – 36·9)	38 [0]	13 [0]	13 [0]	13	13
3·4 (n=3)	100	(29·2 – 100·0)	100 [33]	67 [0]	67 [67]	67	100
4·6 (n=6)	50	(11·8 – 88·2)	100 [0]	17 [0]	83 [83]	83	83
Part 2							
3·4 (n=35)	60	(42·1 – 76·1)	63 [9]	23 [9]	57 [34]	71	66

CI, confidence interval, IRR, infusion-related reaction, ORR: overall response rate.
*Adverse events leading to dose reductions.

Table S5. All adverse events (Grade 3, 4 and 5) by percentage and Grade 1 plus Grade 2 events occurring in ≥10% of patients, and all serious adverse events, in Part 1

	Maximum grade*			
	Grade 1–2†	**Grade 3**	**Grade 4**	**Total (n=38)**
Adverse events, n (%)	11 (29)	19 (50)	7 (18)	37 (97)
Nausea	18 (47)	0	0	18 (47)
Fatigue	16 (42)	1 (3)	0	17 (45)
Thrombocytopenia‡	3 (8)	79 (24)	4 (11)	16 (42)
Anaemia	5 (13)	6 (16)	0	11 (29)
Vision blurred	10 (26)	1 (3)	0	11 (29)
Chills	9 (24)	0	0	9 (24)
Dry eye	8 (21)	1 (3)	0	9 (24)
Aspartate aminotransferase increased	8 (21)	0	0	8 (21)
Pyrexia	8 (21)	0	0	8 (21)
Headache	6 (16)	0	0	6 (16)
Arthralgia	5 (13)	1 (3)	0	6 (16)
Epistaxis	6 (16)	0	0	6 (16)
Upper respiratory tract infection	6 (16)	0	0	6 (16)
Hypercalcaemia	3 (8)	3 (8)	0	6 (16)
Hyponatraemia	3 (8)	2 (5)	0	5 (13)
Neutropenia	1 (3)	3 (8)	1 (3)	5 (13)
Back pain	5 (13)	0	0	5 (13)
Pain in extremity	5 (13)	0	0	5 (13)
Cough	4 (11)	0	0	4 (11)
Musculoskeletal chest pain	3 (8)	1 (3)	0	4 (11)
Photophobia	4 (11)	0	0	4 (11)
Diarrhoea	3 (8)	1 (3)	0	4 (11)
Vomiting	3 (8)	1 (3)	0	4 (11)
Myalgia	4 (11)	0	0	4 (11)
Visual impairment	4 (11)	0	0	4 (11)
Blood creatine phosphokinase increased	4 (11)	0	0	4 (11)
Lymphocyte count decreased	1 (3)	0	2 (5)	3 (8)
Neutrophil count decreased	2 (5)	1 (3)	0	3 (8)
Gamma-glutamyl transferase increased	1 (3)	1 (3)	0	2 (5)
Influenza	1 (3)	1 (3)	0	2 (5)
Pneumonia	1 (3)	1 (3)	0	2 (5)
Hypotension	1 (3)	1 (3)	0	2 (5)
Pain	1 (3)	1 (3)	0	2 (5)
Hyperkalaemia	0	1 (3)	0	1 (3)
Hypokalaemia	0	1 (3)	0	1 (3)
Hypophosphataemia	0	1 (3)	0	1 (3)

Hyperviscosity syndrome	0	1 (3)	0	1 (3)
Limbal stem cell deficiency	0	1 (3)	0	1 (3)
Spinal cord compression	0	1 (3)	0	1 (3)
Syncope	0	1 (3)	0	1 (3)
Spinal cord injury thoracic	0	1 (3)	0	1 (3)
Hyperuricaemia	0	0	1 (3)	1 (3)
Serious adverse events, n (%)				13 (34)
Infusion-related reaction				1 (3)[§]
Pyrexia				2 (5)[¶]
Pain				1 (3)
Hyperviscosity syndrome				1 (3)
Neutropenia				1 (3)[§]
Thrombocytopenia				1 (3)[§]
Babesiosis				1 (3)
Pneumonia				1 (3)[§]
Deep vein thrombosis				1 (3)
Hypotension				1 (3)
Limbal stem cell deficiency				1 (3)[§]
Nausea				1 (3)
Vomiting				1 (3)
Hypercalcaemia				1 (3)
Spinal cord compression				1 (3)
Pharyngeal haemorrhage				1 (3)

[*]No Grade 5 events were reported.
[†]Grade 1 or 2 events are reported only where they occurred in ≥10% of patients.
[‡]Grouped term includes thrombocytopenia and platelet count decreased.
[§]Considered to be treatment-related.
[¶]n=1 considered to be treatment-related.

Table S6. Summary of corneal events by preferred term and maximum grade (Part 1)

	Maximum grade*		
	1–2	**3**	**Total**
Any event	18 (47%)	2 (5%)	20 (53%)
Vision blurred	10 (26%)	1 (3%)	11 (29%)
Dry eye	8 (21%)	1 (3%)	9 (24%)
Photophobia	4 (11%)	0	4 (11%)
Visual impairment	4 (11%)	0	4 (11%)
Corneal deposits	1 (3%)	0	1 (3%)
Corneal disorder	1 (3%)	0	1 (3%)
Corneal irritation	1 (3%)	0	1 (3%)
Corneal oedema	1 (3%)	0	1 (3%)
Corneal opacity	1 (3%)	0	1 (3%)
Diplopia	1 (3%)	0	1 (3%)
Eye pain	1 (3%)	0	1 (3%)
Eye pruritus	1 (3%)	0	1 (3%)
Foreign body sensation in eyes	1 (3%)	0	1 (3%)
Keratitis	1 (3%)	0	1 (3%)
Keratopathy	1 (3%)	0	1 (3%)
Limbal stem cell deficiency	0	1 (3%)	1 (3%)
Ocular toxicity	1 (3%)	0	1 (3%)
Photopsia	1 (3%)	0	1 (3%)
Punctate keratitis	1 (3%)	0	1 (3%)

*No Grade 4/5 corneal events were reported.

Table S7. Summary of corneal events by preferred term and maximum grade (Part 2)

	Maximum grade*		
	1–2	**3**	**Total**
Any event	19 (54%)	3(9%)	22 (63%)
Vision blurred	16 (46%)	0	16 (46%)
Dry eye	11 (31%)	1 (3%)	12 (34%)
Photophobia	8 (23%)	0	8 (23%)
Lacrimation increased	4 (11%)	0	4 (11%)
Keratitis	1 (3%)	2 (6%)	3 (9%)
Eye pain	1 (3%)	1 (3%)	2 (6%)
Keratopathy	2 (6%)	0	2 (6%)
Eye pruritus	1 (3%)	0	1 (3%)
Night blindness	1 (3%)	0	1 (3%)

*No Grade 4/5 corneal events were reported.

Table S8. Adverse events leading to dose delays, dose reductions and treatment discontinuation (Part 1 and Part 2)

	Part 1			Part 2		
	AEs leading to dose delay*, n (%)	**AEs leading to dose reductions*, n (%)**	**AEs leading to discontinuation, n (%)**	**AEs leading to dose delay*, n (%)**	**AEs leading to dose reductions*, n (%)**	**AEs leading to discontinuation, n (%)**
Vision blurred	4 (11)	2 (5)	0	12 (34)	11 (31)	0
Keratitis	1 (3)	1 (3)	0	3 (9)	3 (9)	0
Photophobia	2 (5)	1 (3)	0	2 (6)	2 (6)	0
Dry eye	2 (5)	3 (8)	0	3 (9)	1 (3)	0
Eye disorder	0	0	0	1 (3)	1 (3)	0
Keratopathy	0	0	0	1 (3)	1 (3)	0
Retinal detachment	0	0	0	1 (3)	1 (3)	0
Eye pain	0	0	0	1 (3)	0	0
Thrombocytopenia	2 (5)	2 (5)	1 (3)	4 (11)	4 (11)	2 (6)†
Platelet count decreased	0	0	0	1 (3)	2 (6)	0
Gamma-glutamyltransferase increased	0	0	0	1 (3)	1 (3)	0
Blood creatine phosphokinase increased	0	0	0	0	0	1 (3)†
Intraocular pressure increased	0	0	0	0	1 (3)	0
Visual acuity tests abnormal	0	0	0	0	1 (3)	0
Infusion related reaction	0	1 (3)	0	0	2 (6)	0
Proteinuria	0	0	0	1 (3)	1 (3)	0
Lung infection	0	0	0	2 (6)	0	0
Adenovirus infection	0	0	0	1 (3)	0	0
Bacteraemia	0	0	0	1 (3)	0	0
Cholecystitis infective	0	0	0	1 (3)	0	0
Pneumonia	0	0	0	1 (3)	0	0
Respiratory tract infection	0	0	0	1 (3)	0	0
Upper respiratory tract infection	2 (5)	0	0	0	0	0
Sinusitis	1 (3)	0	0	1 (3)	0	0
Pericardial effusion	0	0	0	1 (3)	0	0
Cough	0	0	0	1 (3)	0	0
Hyperkeratosis	0	0	0	1 (3)	0	0
Corneal disorder	0	1 (3)	0	0	0	0

Corneal opacity	0	1 (3)	0	0	0	0
Ocular toxicity	1 (3)	1 (3)	0	0	0	0
Visual impairment	0	1 (3)	0	0	0	0
Pyrexia	0	1 (3)	0	0	0	0
Babesiosis	1 (3)	1 (3)	0	0	0	0
Eye Pruritus	1 (3)	0	0	0	0	0
Alpha haemolytic streptococcal infection	1 (3)	0	0	0	0	0
Conjunctivitis	1 (3)	0	0	0	0	0
Pneumonia	1 (3)	0	0	0	0	0
Rhinitis	1 (3)	0	0	0	0	0
Asthenia	1 (3)	0	0	0	0	0
Fatigue	1 (3)	0	0	0	0	0
Pyrexia	1 (3)	0	0	0	0	0
Neutropenia	1 (3)	0	0	0	0	0
Spinal cord compression	1 (3)	0	0	0	0	0
Syncope	1 (3)	0	0	0	0	0
Bradycardia	1 (3)	0	0	0	0	0
Spinal cord injury thoracic	1 (3)	0	0	0	0	0
Weight decreased	1 (3)	0	0	0	0	0
Foreign body sensation in eye	0	0	1 (3)	0	0	0
Limbal stem cell deficiency	0	0	1 (3)	0	0	0
Hypercalcaemia	0	0	1 (3)	0	0	0

AE, adverse event.

[*]A patient may have experienced a dose delay and dose reduction as a result of the same adverse event.

[†]One patient experienced both thrombocytopenia and increased blood creatinine phosphokinase.

Figure S1. Duration of study treatment by individual subject and response (Part 1)

Treatment duration counts time difference between first dosing date and dosing end date without accounting for dosing interruptions. Triangles indicate ongoing patients. CR, complete response, MR, minimal response, NE, not evaluable, PD, progressive disease, PR, partial response, sCR, stringent complete response, SD, stable disease, VGPR, very good partial response.

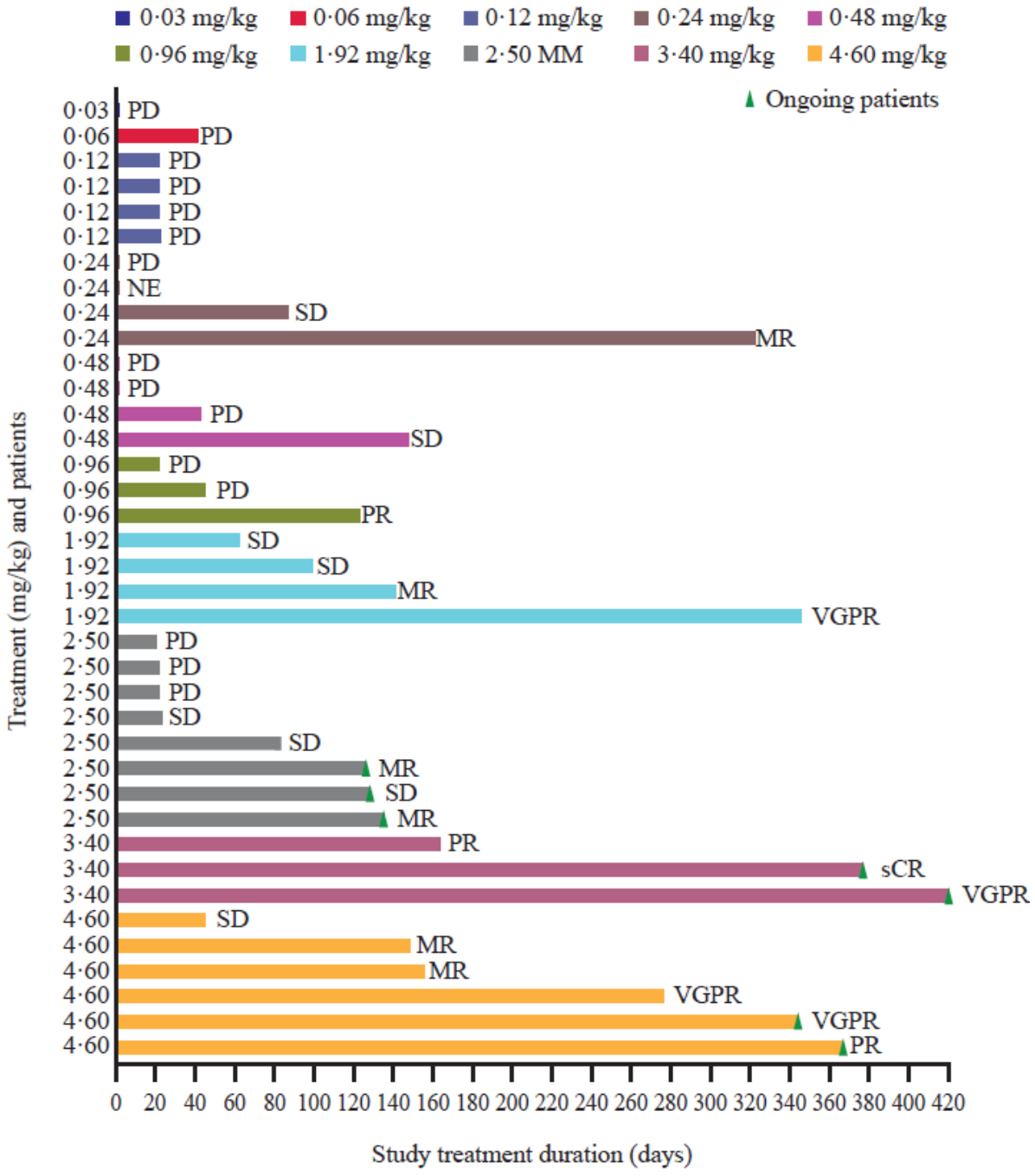
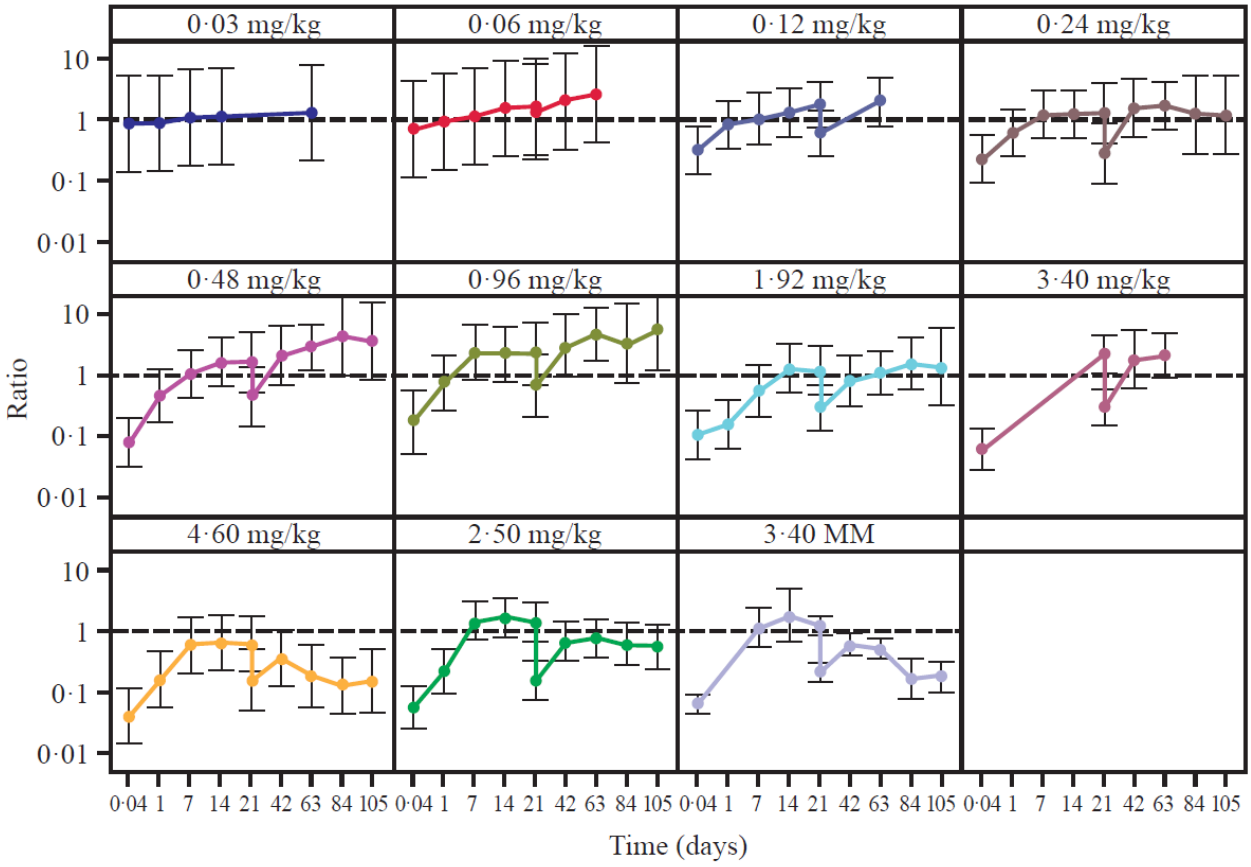


Figure S2. Summary of free soluble BCMA ratio to baseline over time by dose group (Parts 1 and 2)

Data show mean ratios of free soluble BCMA to pre-treatment baseline levels, for each treatment group, over 5 cycles. Part 2 patients (3·40 MM) had limited sampling during Cycle 1.

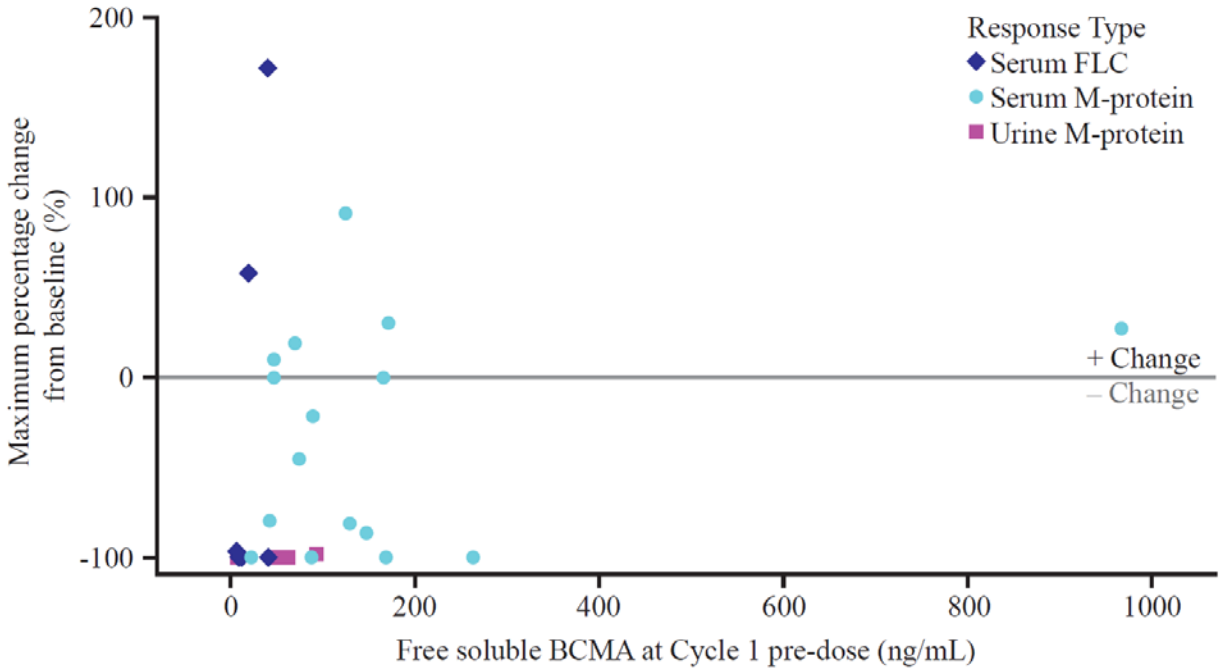


BCMA, B-cell maturation antigen.

Figure S3. Comparison of free soluble BCMA at pre-dose (Cycle 1) and maximum percentage change from baseline in serum M-protein, urine M-protein or serum FLC (Part 2)

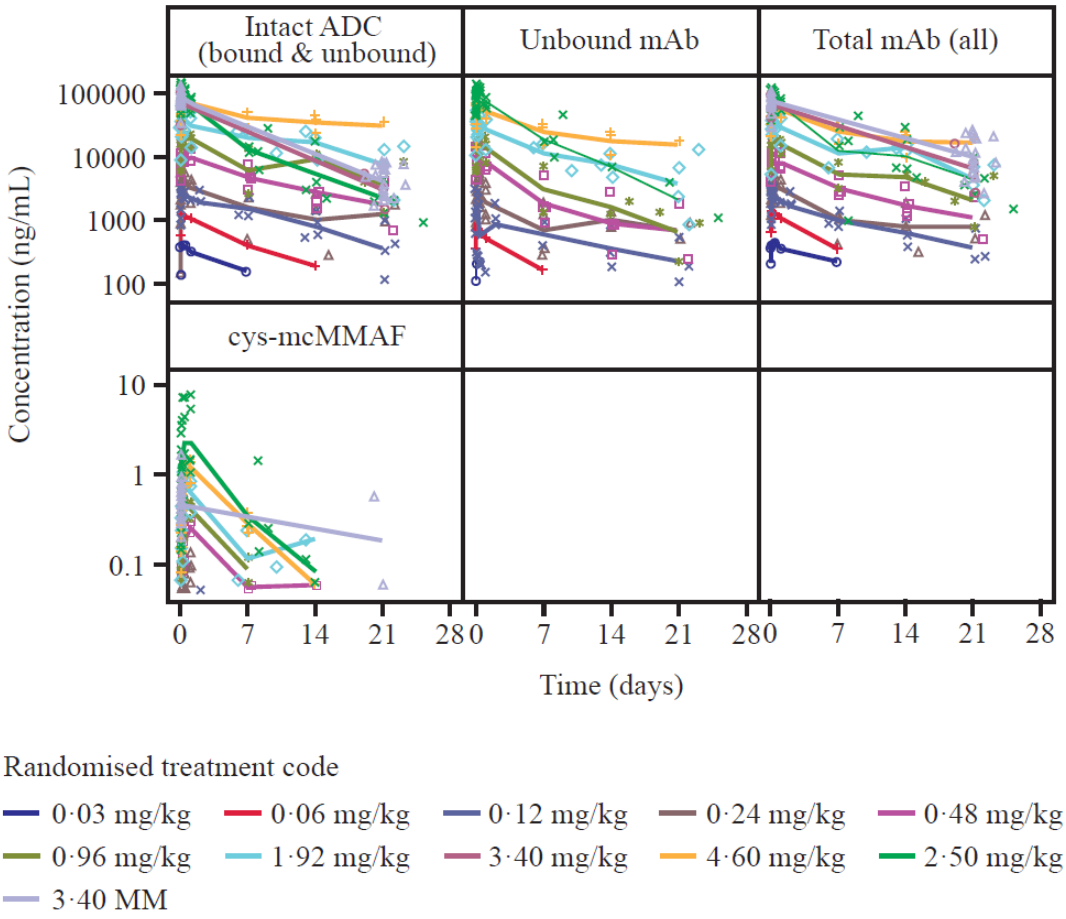
Serum M-protein depicted for patients with serum M-protein values. Urine M-protein depicted for patients without serum M-protein values. Changes in affected FLC depicted in patients with no measurable serum M-protein or urine M-protein values.

N=35



BCMA, B-cell maturation antigen, FLC, free light chain.

Figure S4. Mean plasma GSK2857916 concentration-time data at Cycle 1 by dose group



3·40 MM, subjects treated in Part 2 at RP2D of 3·40 mg/kg.
ADC, antibody-drug conjugate, mAb, monoclonal antibody; MMAF, monomethyl auristatin-F RP2D, recommended Phase 2 dose.

References

1. Sanchez E, Gillespie A, Tang G, et al. Soluble B-Cell Maturation Antigen Mediates Tumor-Induced Immune Deficiency in Multiple Myeloma. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2016; **22**(13): 3383-97.

2. Sanchez E, Li M, Kitto A, et al. Serum B-cell maturation antigen is elevated in multiple myeloma and correlates with disease status and survival. *British journal of haematology* 2012; **158**(6): 727-38.

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	DREAMM-1: A Phase I Open-label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, Immunogenicity and Clinical Activity of the Antibody Drug Conjugate GSK2857916 in Subjects with Relapsed/Refractory Multiple Myeloma and Other Advanced Hematologic Malignancies Expressing BCMA

Compound Number: GSK2857916

Development Phase: PHASE I

Effective Date: 02-NOV-2017

Protocol Amendment Number: 5

Author (s):

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2012N155299_00	2013-DEC-26	Original
2012N155299_01	2014-MAR-01	Amendment No. 1
Country specific Amendment for the United Kingdom to address required changes per MHRA. Updated Exclusion Criteria to exclude subjects with current corneal disease or history of corneal disease. Updated QTc withdrawal criterion to modify QTc withdrawal for QTc >500msec and to include > 60 msec increase from baseline. Updated Data Management Section 12 to include details on dissemination of data and communication plan.		
2012N155299_02	2014-MAR-20	Amendment No. 2
Global Amendment to address required changes per the FDA. Updated Inclusion Criteria with minimum weight requirement. Updated Blood Volumes. Revised Time and Events Tables. Corrected typographical errors.		
2012N155299_03	2014-MAY-05	Amendment No. 3
Country specific Amendment for Canada to address required changes per Health Canada. Updated preparation instructions of GSK2857916.		
2012N155299_04	2016-MAY-05	Amendment No. 4
Global Amendment to include patient reported outcome instruments in the Part 2 multiple myeloma cohort and refine the lymphoma histologies eligible in Part 2 BCMA-expressing lymphoma cohort. Additionally, the requirement for 60% of tumor cells staining positive for BCMA expression was removed. The total number of subjects that may be enrolled is presented by a range of 80 to 95 to provide an updated estimate based on the number of subjects who enrolled at the time of the amendment. Additional modifications include: changing the time-point specific blood specimens are collected for baseline/pre-treatment immunogenicity and biomarker measurements, and the visit window for certain assessments.		
2012N155299_05	2017-NOV-02	Amendment No. 5
Global amendment to include additional follow up of multiple myeloma subjects for ocular exams (for those whose corneal signs or symptoms have not resolved), additional patient reported outcome instruments, addition of time-to-event endpoints as exploratory objectives. Subjects who have completed treatment or the 3 month follow up visit (end of study) prior to amendment 5 will be reconsented for further follow up and survival status. Other administrative changes are also included		

SPONSOR SIGNATORY

PPD

Nov. 02. 2017

Joanna Opalinska, MD

Director, Oncology R&D

Date

PPD

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Regulatory Agency Identifying Number(s):

Compound Number	IND Number	EudraCT Number
GSK2857916	119333	2013-004549-18

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number BMA117159

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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LIST OF ABBREVIATIONS

ABC	Airway breathing and circulation
ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APRIL	A proliferation-inducing ligand
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC (0-∞)	Area under the concentration-time curve to infinity
AUC (0-τ)	Area under the concentration time curve over the dosing interval
AV	Atrioventricular
BAFF/BLyS	B-cell activating factor/B-lymphocyte stimulator
BAL	Bronchoaveolar lavage
BCMA	B cell maturation antigen
BCRP	Breast cancer resistant protein
BCVA	Best corrected visual acuity
BED	Biologically Effective Dose
BNP	B-type natriuretic peptide
BSA	Body surface area
BWT	Body weight
CBC	Complete blood count
CBR	Clinical benefit rate
CDISC	Clinical Data Interchange Standards Consortium
[redacted]	[redacted]
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase MB-isoenzyme
CL	Clearance
CLL	Chronic lymphocytic leukemia
Cmax	Maximum plasma drug concentration
CPMS	Clinical Pharmacology Modeling and Simulation
CPR	Cardio-pulmonary resuscitation
CR	Complete response
CRM	Continual Reassessment Method
CRP	C-reactive protein
CT	Computer tomography
cTn	Cardiac troponin
Ctrough	Trough plasma concentration
CYP	Cytochrome P450
CV%	Coefficient of variation percent
Cys-mcMMAF	cys Monomethyl auristatin F

DIC	Disseminated intravascular coagulation
DOR	Duration of response
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
DMPK	Drug metabolism and pharmacokinetics
DNA	Deoxyribonucleic acid
EC50	Concentration associated with 50% maximal effect
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eDiary	Electronic Diary
EM	Extramedullary
EOI	End of infusion
FACTS	Fixed and adapted clinical trials simulator
FLC	Free light chain
FSH	Follicle stimulating hormone
FTIH	First time in human
GLDH	Glutamate dehydrogenase
GLP	Good laboratory practice
GSK	GlaxoSmithKline
GSK2857914	GlaxoSmithKline anti-BCMA antibody (CA8 J6M0 Potelligent)
GSK2857916	GlaxoSmithKline anti-BCMA antibody drug conjugate (CA8 J6M0 Potelligent MMAF)
HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core
HBV	Hepatitis B
HCV	Hepatitis C
HNSTD	Highest non-severely toxic dose
HPLC	High performance liquid chromatography
HRT	Hormone replacement therapy
IC50	Concentration associated with 50% inhibition of maximal effect
IDSL	Integrated Data Standards Library
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMIDs	Immunomodulators
IMWG	International Myeloma Working Group
INR	International normalized ratio
IP	Intraperitoneal
IV	Intravenous
IVRS	Integrated voice response system
KIM-1	Kidney injury molecule-1
LBCL	Large B-cell lymphoma
LDH	Lactate dehydrogenase
MABEL	Minimum anticipated biological effect level

mc	Maleimidocaproyl
MDRD	Modified diet in renal disease
MI	Myocardial infarction
MM	Multiple Myeloma
MMAF	Monomethyl auristatin F
MR	Minimal response
MRI	Magnetic resonance Imaging
MTD	Maximum Tolerated Dose
NAG	N-Acetyl-β-D-glucosaminase
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
N-CRM	A modification of the Continual Reassessment Method (CRM) proposed by Neuenschwander et al.
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire - 25
NF-κB	Nuclear factor kappa light-chain enhancer of activated B cells
NK	Natural killer
NONMEM	Non linear mixed effects modelling
OAT	Organic anion transporter
OATP	Organic anion transporter polypeptide
ORR	Overall response rate
OSDI	Ocular Surface Disease Index
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PET	Probability of early termination
PFS	Progression-free survival
PFT	Pulmonary function test
Pgp	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient reported outcome
PT	Prothrombin time
PTS	Platform technologies and sciences
PTT	Partial thromboplastin time
QID	4 times a day
QoL	Quality of life
RAP	Reporting and analysis plan
RAMOS	Registration and medication ordering system
REML	Restricted maximum likelihood
RIBA	Recombinant immunoblot assay
RNA	Ribonucleic acid
Ro	Observed accumulation ratio
RO	Receptor occupancy
RPA-1	Renal papillary antigen-1
RP2	Recommended Phase 2

SAE	Serious adverse event
sBCMA	Soluble B-cell maturation antigen
sCR	Stringent complete response
SD	Stable disease
SOI	Start of infusion
SPEP	Serum protein electrophoresis
SPM	Study procedure manual
SPR	Surface plasmon resonance
t½	Half-life
TBNK	T-cell, B-cell and Natural Killer cells
T_{last}	Time of last quantifiable concentration
TLS	Tumor lysis syndrome
Tmax	Time to maximum drug concentration
TTP	Time to progression
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
Vd	Volume of distribution
Vss	Volume of distribution at steady state
WM	Waldenstrom's macroglobulinemia

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PROTOCOL SYNOPSIS

TITLE	A Phase I Open-label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, Immunogenicity and Clinical Activity of the Antibody Drug Conjugate GSK2857916 in Subjects with Relapsed/Refractory Multiple Myeloma and Other Advanced Hematologic Malignancies Expressing BCMA
PROTOCOL NUMBER	BMA117159
CLINICAL PHASE	I
COMPOUND(S)	GSK2857916
STUDY RATIONALE	This is a FTIH study that will assess the safety, pharmacokinetics (PK), pharmacodynamics (PD) and therapeutic potential of GSK2857916 in multiple myeloma (MM) and lymphomas that express BCMA. GSK2857916 is a humanized immunoglobulin (IgG1) antibody drug conjugate (ADC) which binds specifically to B cell maturation antigen (BCMA). The parent anti-BCMA antibody (J6M0) is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF) via a protease resistant maleimidocaproyl (mc) linker to produce the GSK2857916 ADC molecule. Upon binding to the cell surface, GSK2857916 is rapidly internalized and active drug (cys-mcMMAF) is released inside the cell. GSK2857916 has been produced in an afucosylated form to generate an enhanced antibody dependent cellular cytotoxicity (ADCC) response upon binding to FcγRIIIa receptors on the surface of human effector cells. This dual mechanism of action may improve efficacy by targeting dividing through ADC and non-dividing tumor cells through ADCC. Importantly, BCMA expression is maintained at the cell surface over time following GSK2857916 binding and internalization due to rapid BCMA receptor recycling and/or new protein synthesis. GSK2857916 has demonstrated dose-dependent cytotoxic activity in myeloma cell lines, ex vivo primary myeloma tumor samples, as well as preclinical myeloma mouse tumor models. GSK2857916 has also shown activity in B cell lymphoma cell lines that express BCMA. The hypothesis is that GSK2857916 can be safely administered to subjects with BCMA positive malignancies at doses where target engagement can be demonstrated. This study will determine if adequate target engagement of BCMA receptors translates into clinical benefit for subjects with MM and

<table>
<tr><td></td><td>BCMA positive lymphomas.</td></tr>
<tr><td>STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES</td><td>Hypothesis: GSK2857916 can be safely administered to subjects with MM and with BCMA positive lymphomas at doses where target engagement can be demonstrated.
<table>
<tr><th>Objective</th><th>Endpoint</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>• To determine safety, tolerability, maximum tolerated dose (MTD), and recommended phase (RP2) dose and schedule of GSK2857916 administered</td><td>• Adverse events (AE) and changes in clinical signs and laboratory parameters</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• To evaluate the pharmacokinetic (PK) profile of GSK2857916 and the breakdown product cys-mcMMAF) after intravenous (IV) single and repeat dose administration in subjects with relapsed/refractory MM and BCMA expressing lymphomas</td><td>• GSK2857916 and cys-mcMMAF PK parameters following IV single and repeat dose administration during dose escalation as data permit (e.g., AUCs Cmax, tmax, CL, V_{SS}, t½ [single dose], Cmax and Ctrough [repeat dose]). GSK2857916 population PK parameters in expansion cohorts at the RP2 dose (e.g. clearance (CL), volume of distribution (Vd), and relevant covariates which may influence exposure (e.g. age, weight, or disease-related covariates e.g. BCMA expression)</td></tr>
<tr><td>• To assess anti-drug antibody (ADA) formation after IV single and repeat dose administration of GSK2857916</td><td>• ADA incidence and titers after single and repeat IV dosing of GSK2857916</td></tr>
</table></td></tr>
</table>

	• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM and BCMA expressing lymphomas	• Clinical activity measured as Overall Response Rate (ORR) which is defined as follows: ○ For MM: the percentage of subjects achieving confirmed partial response or better (≥PR) ○ In addition, the percentage of subjects with minimal response (MR) will be assessed for clinical benefit rate (CBR) (Appendix 1) ○ For Lymphomas: the percentage of subjects achieving PR or better (≥PR) (Appendix 2)
	Exploratory	
	• To evaluate PD markers in MM after treatment with GSK2857916	• [redacted]
	• To explore relationships of GSK2857916 plasma concentrations/exposure with pharmacodynamics (PD), safety and clinical activity	• [redacted] • [redacted]

	• To characterize the relationship between clinical response and other biologic tumor characteristics (DNA, protein analysis)	• [redacted]
	• To investigate the relationship between genetic variants in the host and response to study medicine, or susceptibility, severity and progression of disease	• Relationship between host genetic variation and response to study medicine or susceptibility, severity and progression of disease
	• To explore the effect of GSK2857916 on symptoms (including bone pain, fatigue and visual symptoms) and impacts on HRQoL in subjects with relapsed/refractory MM (Part 2)	• Changes from baseline in bone pain/fatigue and analgesic use as measured by the eDiary • Interviews with subjects to further characterize changes in symptoms (including bone pain, fatigue and visual symptoms) and impacts on HRQoL
	• To explore changes in visual symptoms and function following discontinuation of treatment with GSK2857916	• Changes in visual symptoms and impacts as measured by the OSDI and NEI-VFQ-25 following treatment discontinuation • Follow-up telephone interviews conducted to further understand subjects experience with visual symptoms and changes in symptoms and related impacts following treatment discontinuation

	• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM in terms of time-to-event (TTE) endpoints (Part 2 MM)	• Time to progression (TTP), defined as: the time from first dose until the earliest date of PD per International Multiple Myeloma Working Group (IMWG), or death due to PD. • Duration of response (DOR), defined as: the time from first documented evidence of PR or better; until the time when disease progression (PD) is documented per IMWG; or death due to PD occurs in participants who achieve a response, i.e. confirmed PR or better. • Time to response (TTR), defined as: the time between the date of first dose and the first documented evidence of response (PR or better). • Progression-free survival (PFS), defined as: the time from first dose until the earliest date of disease progression (PD) per IMWG, or death due to any cause. • Number of deaths
STUDY DESIGN	This study is an open-label, dose escalation Phase I FTIH study to determine the RP2 dosing regimen of GSK2857916. The recommended dose and schedule will be selected based on the safety, pharmacokinetic (PK), and pharmacodynamic (PD) profiles observed after administering the study drug to subjects with multiple myeloma (MM). The study will consist of two parts and will enroll approximately 80-95 subjects. The Part 1 dose escalation phase will characterize the safety and	

	tolerability of respective dosing regimen for GSK2857916 utilizing the model based on the Neuenschwander continual reassessment method (N-CRM). Initially, GSK2857916 will be administered via 60 min intravenous (IV) infusion once every three weeks (21 days = 1 cycle). After a MTD or recommended phase 2 dose (RP2D) has been established on the once every three weeks schedule, the safety, tolerability, and PK of once-weekly dosing of GSK2857916 for three consecutive weeks with 1 week rest (28 days = 1 cycle) may be explored in an additional cohort(s). Part 2 will explore the safety, tolerability, PK, PD, and clinical activity of the RP2 dose of GSK2857916 identified in Part 1. Subjects with MM (n=40), and lymphomas expressing BCMA (n=10) will be enrolled in expansion cohort in Part 2. Futility analyses will be performed on the MM cohort after approximately 15, 22, 30 subjects have been enrolled. Sparse PK sampling will be collected to further characterize GSK2857916 exposures for the selected dose schedule. Although not required for MM, subjects with lymphomas will be enrolled in Part 2 based upon the detection of positive BCMA staining of tumor cells in a prospective immunohistochemistry screening assay performed at a central laboratory.
NUMBER OF SUBJECTS	Approximately 80-95 subjects will be enrolled. Up to 30 subjects with relapsed/refractory MM will be enrolled in Part 1, Schedule 1; Schedule 2, if explored, will enroll up to 15 additional subjects in Part 1. Up to 40 subjects with relapsed/refractory MM and up to 10 subjects with lymphomas expressing BCMA will be enrolled in Part 2.
INCLUSION/EXCLUSION CRITERIA	**Inclusion Criteria:** 1. Provide signed written informed consent, which includes compliance with the requirements and restrictions listed in the consent form. 2. Male or female, 18 years or older (at the time consent is obtained) 3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 6) 4. **Part 1/dose escalation:** • Histologically or cytologically confirmed diagnosis of: Multiple Myeloma in a subject who fulfills **all** of the following:

	• has undergone stem cell transplant, or is considered transplant ineligible, • has been pretreated with at least the 3 following classes of anti-myeloma drugs: alkylators, proteasome inhibitors and immunomodulators, • has demonstrated progression on, or within 60 days of completion of the last therapy. **Part 2 /MM cohort:** • Histologically or cytologically confirmed diagnosis of: Multiple Myeloma in a subject who fulfills **all** of the following: • has undergone stem cell transplant, or is considered transplant ineligible, • has been pretreated with at least the 3 following classes of anti-myeloma drugs: alkylators, proteasome inhibitors and immunomodulators, • and has demonstrated progression on, or within 60 days of completion of the last therapy. AND has measurable disease with at least one of the following: a. Serum M-pro**tein ≥0.5 g/dL (≥5** g/L) b. Urine M-protein ≥200 mg/24h c. Serum FLC assay: Involved FLC level ≥5 mg/dL (≥50 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65) d. Biopsy proven plasmacytoma (should be measured within 28 days of Screening Visit) **or** **Part 2/BCMA positive Lymphoma cohort:** a. Subject with one of the following lymphomas: Diffuse Large B-cell Lymphoma (DLBCL) or follicular lymphoma (FL) that exhibits positive BCMA expression on tumor cells as determined by a central laboratory using a validated IHC assay. Eligible subjects with BCMA positive lymphomas must also fulfill the prior treatment requirements as follows: b. DLBCL: at least 2 prior lines of systemic

therapy containing at least one line of chemo-immunotherapy with anti-CD20 antibody, and either has undergone stem cell transplant or is considered transplant ineligible

c. FL: at least 2 prior lines of systemic therapy

5. Subjects with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:

   a. transplant was > 100 days prior to study enrolment

   b. no active infection

   c. subject meets the remainder of the eligibility criteria outlined in this protocol

6. Adequate organ system functions as defined in Table below:

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)[1]	≥ 1.0 X 10^9/L
Hemoglobin	≥ 8.0 g/dL
Platelets	≥ 50 X 10^9/L
Coagulation	
INR	≤1.5
PTT	≤1.5 x ULN
Hepatic	
Total bilirubin	≤1.5 X ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
AST and ALT	≤ 1.5 X ULN
Renal	
Serum creatinine or Calculated creatinine clearance[2] Albuminuria	<1.2XULN ≥ 60 mL/min for Part 1; ≥50 mL/min for Part 2 if data supports loosening criteria ≤500mg/24hr
Cardiac	
LVEF (Echo) Troponin	≥50% ≤1xULN

	1. Without Growth factor support for the past 14 days, excluding erythropoietin 2. As calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 5) **NOTE:** Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the subject and the subsequent within range screening result may be used to confirm eligibility. 7. A female subject is eligible to participate if she is of: • Non-childbearing potential (i.e. physiologically incapable of becoming pregnant) defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MIU/mL and estradiol < 40 pg/mL (<147 pmol/L) is confirmatory]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods specified if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method. • Women of childbearing potential must have a negative serum pregnancy test within 72 hours of first dose of study treatment and agree to use effective contraception, as defined in Section 11.1.1, during the study and for 60 days following the last dose of study treatment. 8. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 11.1.2 from the time of first dose of study until 60 days after the last dose of study treatment to allow for clearance of any altered sperm. 9. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4) must be

	≤Grade 1 at the time of enrollment except for alopecia, and grade 2 neuropathy. **Exclusion Criteria:** 1. Systemic anti-tumor therapy within 14 days, or plasmapheresis within 7 days prior to the first dose of study drug. 2. Use of an investigational drug within 14 days or five half-lives, whichever is shorter, preceding the first dose of study drug. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drug. 3. History of an allogeneic stem cell transplant. Subjects with a history of an autologous stem cell transplant are NOT excluded if they meet Inclusion Criterion #5. 4. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect subject's safety). Subjects with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria given in Table 14. 5. Evidence of active mucosal or internal bleeding. 6. Any major surgery within the last four weeks. 7. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities) that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures. 8. Known active infection requiring antibiotic treatment. 9. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal or cardiac disease) 10. Subjects with previous or concurrent malignancies are allowed only if the second tumor is not contributing to the subject's illness. The subject must not be receiving active therapy, other than hormonal therapy for this disease and the disease must be considered medically stable for at least 2 years. 11. Evidence of cardiovascular risk including any of the following: a. QTc interval ≥ 470 msecs. b. Evidence of current clinically significant

	uncontrolled arrhythmias; i. including clinically significant ECG abnormalities including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block. c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening. d. Class III or IV heart failure as defined by the New York Heart Association functional classification system (Appendix 4) e. Uncontrolled hypertension f. Subjects with intra-cardiac defibrillators or permanent pacemakers; g. Abnormal cardiac valve morphology (≥Grade 2) documented by echocardiogram (subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study. 12. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2857916 or any of the components of the study treatment. 13. Pregnant or lactating female. 14. Known HIV infection. 15. Subjects with positive test for Hepatitis B surface (HBS-Ag) or Hepatitis B core (HBc)antigen 16. Subjects with positive test for hepatitis C (HCV) infection are excluded regardless of viral load. If hepatitis C antibody test is positive, a confirmatory polymerase chain reaction (PCR) or recombinant immunoblot assay (RIBA) test should be performed. If the PCR or RIBA test is negative, subject is eligible for this trial. 17. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator's assessment). 18. Current corneal disease or a history of corneal disease.

STUDY TREATMENT DOSE/ROUTE/REGIMEN	Product name :	**GSK2857916 Solution, 20 mg/mL, 1.5mL anti-BCMA-ADC**
	Formulation description:	Solution containing 20mg/mL **GSK2857916**
	Dosage form :	Supplied as frozen liquid. Recommended storage condition is -50°C to -15°C.
	Unit dose strength(s)/Dose Level(s):	20mg/mL, 1.5mL (Refer to Section 3.3.1.2.1 for dose levels)
	Physical Description:	GSK2857916 Solution for Infusion is clear or opalescent; colorless, yellow to brown liquid
	Route/ Administration/ Duration:	Delivered as IV solution (see Section 3.8)
	Dosing instructions:	Dilute GSK2857916 solution in normal 0.9% saline to the appropriate concentration for the dose. See Section 4.2 for compatible administration materials. Doses of GSK2857916 are to be administered as an IV infusion via an infusion pump that can ensure precision to the decimal point of a mL for the infusion rate at lower doses. It is recommended to prime the tubing with at least 15 mL prior to dosing.
	Manufacturer/ Source of Procurement:	GSK
	Manufacturer Lot number	132373860
SAFETY ASSESSMENTS	Measurements to evaluate safety will include height, weight, heart rate (HR), blood pressure (BP), temperature, echocardiogram, troponin I, 12-lead ECG, clinical chemistry, hematology, and other laboratory tests listed in Table 15 standard disease assessments for MM including bone marrow aspirate (cytology and flow	

	cytometry) and M protein analysis, ECOG performance status, and complete physical examination. AEs and laboratory results will be graded according to the NCI-CTCAE v4.0 [NCI, 2009]. Planned time points for all safety assessments are listed in the Time and Events Tables (Section 7.1).
PHARMACOKINETIC/ PHARMACODYNAMIC ASSESSMENT(S)	In Part 1 on Schedule 1 (i.e., GSK2857916 administered once every 21 days) PK samples will be taken in all subjects for both GSK2587916 and cys-mcMMAF measurement according to the Time and Events Tables in Section 7.1 In Part 1 on Schedule 2 (i.e., GSK2857916 administered once weekly for 3 consecutive weeks, 1 week rest) PK samples will be taken in all subjects for both GSK2857916 and cys-mcMMAF measurement according to the Time and Events Tables in Section 7.1. In the Part 2 dose expansion phase in subjects with MM PK samples will be taken for both GSK2587916 and cys-mcMMAF measurement according to the Time and Events Tables in Section 7.1. In the Part 2 dose expansion phase in subjects with BCMA positive lymphomas PK samples will be taken for both GSK2587916 and cys-mcMMAF measurement according to the Time and Events Tables in Section 7.1. Pharmacodynamic markers will be collected according to the schedule outlined in the Time and Events Tables in Section 7.1. Samples for immunogenicity assessment will be collected as outlined in the Time and Events Tables in Section 7.1.
CLINICAL ACTIVITY ASSESSMENT	Clinical activity will be measured as Overall Response Rate (ORR) which is defined as follows: For MM: the percentage of subjects with confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) as assessed by 2011 recommendation of the International Myeloma Working Group (IMWG) Panel I. Clinical benefit rate (CBR), including minimal response (MR), may be considered in addition to ORR (Appendix 1). For Lymphomas: the percentage of subjects with confirmed CR, PR, as described in the Revised Response Criteria for Malignant Lymphoma (Appendix 2)

TRANSLATIONAL RESEARCH	 Leukocyte population will be characterized and may be correlated with clinical outcome. A genetics samples will be collected in Part 2 and may be used to investigate variability in response that may be attributable to host genetic variation, if it emerges during this clinical study or a series of clinical studies of GSK2857916 (Appendix 7). Further, the genetic sample may be used to investigate the relationship between genetic variation and disease (susceptibility, severity or progression).
PATIENT REPORTED OUTCOMES	Part 2/MM cohort: changes in symptoms and health-related quality of life (HRQoL) will be assessed with the use of the Bone Pain/Fatigue diary. Changes in visual symptoms and impacts with the use of the OSDI and NEI-VFQ-25

STATISTICAL METHODS	Part1: After each dosing cohort, the N-CRM will be used to recommend the next dose level based on observed dose-limiting toxicities (DLTs). The dose escalation decisions will be based on this recommendation as well as the totality of the safety, pharmacokinetic, and pharmacodynamic data. Part 2: Futility analyses will be performed on the MM cohort after approximately 15, 22, and 30 evaluable subjects have been enrolled. The methodology utilized is based on the predictive probability of success if enrollment continues to 40 subjects [Lee, 2008]. **Clinical Activity** The exact 95% confidence interval (CI) for overall response rate (ORR) and clinical benefit rate (CBR) will be provided. Subjects with unknown or missing response will be treated as non-responders, i.e., these subjects will be included in the denominator when calculating percentages of response. For the Part 2 MM population, additional exploratory time-to-event (TTE) endpoint will include TTP, DOR, TTR, and PFS, as data permits. For all the TTE endpoints listed above, median TTE with 95% CI will be estimated employing the Kaplan-Meier method as data permits. A Kaplan-Meier survival curve will be generated. The number and percentage of subjects who had the event or were censored will also be reported. **Adverse Events**: Adverse events will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment. The incidence of deaths and the primary cause of death will be summarized. **Clinical Laboratory Evaluation**: The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel. Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit or worst-case post baseline, as appropriate. The worst-case- toxicity grade in hematology and chemistry result during the treatment will be summarized. Shift tables from baseline to the worst toxicity grade during treatment will

	be provided for each laboratory analyte. **Other Safety Measures**: Data for vital signs, electrocardiograms (ECGs), and echocardiograms (ECHOs) will be summarized. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages.

1. INTRODUCTION

1.1. Background

Multiple myeloma (MM) accounts for 1% of all cancers and for 10% of all hematologic malignancies. Approximately 20,000 people will be diagnosed with MM each year in the United States [Rajkumar, 2011a]. The median age at diagnosis is approximately 70 years. Newly diagnosed patients less than 60 years of age have a 30% probability for 10-year survival [Palumbo, 2011]. Recent progress in understanding the biology of the disease has resulted in significant improvements in treatment strategies for MM. Drugs that are currently approved for MM fall into three separate classes of agents: alkylating agents (melphalan, cyclophosphamide), proteasome inhibitors (bortezomib, carfilzomib), and immunomodulators (IMIDs: thalidomide, lenalidomide, pomalidomide). These highly active agents used in combination are providing tangible benefits for patients with MM [Rajkumar, 2011b]. Importantly, improvements in survival outcomes have been noted in patients with MM and current treatment strategies provide a very good chance for response in the first line. Unfortunately, duration of response and response rates decline dramatically in each subsequent line of treatment for this malignancy. MM remains incurable and the need for new treatment modalities is well recognized.

The normal function of B cell maturation antigen (BCMA) is to promote cell survival by transduction of signals from two known ligands (BAFF/BLyS and APRIL). The expression is restricted to B cells at later stages of differentiation, with expression on germinal center B cells in tonsil, blood plasma blasts and long lived plasma cells [Darce, 2007].

BCMA is expressed in various B-cell malignancies, including MM. The expression levels in MM vary from patient to patient, but our studies demonstrate that all patients tested express detectable levels of BCMA protein on their tumor cells. BCMA expression varies between MM patients and GlaxoSmithKline (GSK) studies have shown that in samples taken from MM patients (N=45), 31% have low expression, 38% moderate expression and 31% high expression of BCMA as detected by immunohistochemistry (IHC). BCMA was also analyzed by flow cytometry in tumor cells from 48 MM patients which aligned well with IHC results. In addition, other B-cell malignancies including Follicular Lymphoma (FL) [Basso, 2005; GSKin-house data], Diffuse Large B-Cell Lymphoma (DLBCL), Large B-Cell Lymphoma (LBCL), Chronic Lymphocytic Leukemia (CLL) and Waldenstrom's Macroglobulinemia (WM) [Montes-Moreno, 2012] [Elsawa, 2006] [Endo, 2007] were reported to express BCMA at varying frequencies; DLBCL and FL were among the B-cell hematologic malignancies exhibiting the highest frequency of BCMA expression.

A soluble form of BCMA has also been reported [Sanchez, 2012]. Higher amounts of this soluble form were found in supernatants isolated from cultures of MM-containing peripheral blood and bone marrow mononuclear cells compared to normal cells. Moreover, soluble BCMA (sBCMA) was higher in the sera of MM patients (n=209) compared to sera from age-matched, healthy controls (n=40; $P < 0.0001$). Measurement of serum levels of BCMA was conducted by immunoassay to confirm the prevalence and level of sBCMA expression in MM. Soluble BCMA is present in serum at a median

concentration of 9.28 ng/mL (range 6.10-14.09 ng/mL) in healthy volunteers (N=38) and is elevated in the serum of MM patients (N = 44) to median of 148.64 ng/mL (range 2.40-1062.48 ng/mL).

The restricted normal tissue expression profile of BCMA, along with its upregulation and survival function in MM and other BCMA-positive cancers makes it an attractive target for a therapeutic antibody with direct cell killing activity.

1.2. GSK2857916

1.2.1. Background

GSK2857916 is a humanized IgG1 antibody drug conjugate (ADC) which binds specifically to BCMA. The parent anti-BCMA antibody (J6M0) is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF) via a protease resistant maleimidocaproyl (mc) linker to produce the GSK2857916 ADC molecule. Upon binding to the cell surface, GSK2857916 is rapidly internalized and active drug (cys-mcMMAF) is released inside the cell.

GSK2857916 has been produced in an afucosylated form to generate an enhanced antibody dependent cellular cytotoxicity (ADCC) response upon binding to FcγRIIIa receptors on the surface of human effector cells. The rationale for this dual mechanism of action is to improve efficacy by targeting dividing and non-dividing tumor cells. Importantly, BCMA expression is maintained at the cell surface over time following GSK2857916 binding and internalization due to rapid BCMA receptor recycling and/or new protein synthesis. GSK2857916 has demonstrated dose-dependent cytotoxic activity in myeloma cell lines, *ex vivo* primary myeloma tumor samples, as well as preclinical myeloma mouse tumor models.

1.2.2. Preclinical Pharmacology

J6M0, the parent antibody for GSK2857916 binds specifically to human BCMA with an affinity of 1.61 nM as defined by surface plasmon resonance (SPR), and the binding properties were maintained following drug conjugation. J6M0 competes for binding to BCMA with both known ligands BAFF/BlyS and APRIL, and inhibits ligand-induced NF-κB signalling with an IC_{50} of 0.91 μg/mL and 2.43 μg/mL, respectively. However, in cell proliferation assays, GSK2857916 failed to inhibit cell growth directly.

A total of 16 cell lines were used to demonstrate the antitumor activity of GSK2857916 via the ADC mechanism in BCMA expressing cells and to investigate the relationship between BCMA expression and potency. The IC_{50} of GSK2857916 was determined for each cell line tested (Table 1). In general, the highest BCMA expressing cell lines (NCI-H929, MM.1R and JJN3) were most sensitive to GSK2857916 and the lowest expressing cell lines (ARH-77, MC/CAR and HuNS1) were least sensitive. In the 4 negative control cell lines (KU812, Raji, HUT78 and MOLT-4) where no expression or only trace expression of BCMA was observed by flow cytometry, there was no detectable growth-inhibitory activity at any of the concentrations tested. This demonstrates the specificity of GSK2857916 for BCMA expressing cells.

Table 1 Mean IC_{50} Values for GSK2857916

Cell Line	IC_{50} (ng/mL)	95% CI
U266	3.0	1.4 to 6.5
ARH77.10B5	3.4	2.5 to 4.8
MM.1R	11.5	10.9 to 12.1
NCI-H929	13.8	13.2 to 14.3
JJN3	26.0	24.1 to 28.1
MM.1S	53.2	49.5 to 57.0
LP1	55.7	44.3 to 70.1
ARH77	72.7	58.8 to 89.7
RPMI8226	79.1	60.1 to 104.1
L363	93.7	74.3 to 118.2
OPM2	114.3	97.0 to 134.9
KMS128M	148.4	124.1 to 177.5
HUNS1	244.2	198.4 to 300.5
MC/CAR	>1000	
Negative Control Cell Lines		
KU812	>1000	
Raji	>1000	
HUT78	>1000	
MOLT4	>1000	

GSK2857916 also had ADCC activity when tested against a panel of MM target cell lines using a fresh human PBM effector cells from healthy donors. The ADCC EC_{50} values were NCI-H929 [0.57 ng/mL], RPMI-8226 [4.09 ng/mL], JJN-3 [14.42 ng/mL], OPM-2 [4.15 ng/mL] and U266 [9.04 ng/mL], respectively.

GSK2857916 demonstrated dose dependent ADCC and ADC activity against primary CD138+ myeloma tumor cells from nine myeloma patients. These results demonstrate that GSK2857916 is capable of killing primary myeloma cells with potency similar to that observed in cell lines.

Myeloma tumor models in mice were also tested to ensure that GSK2857916 has activity *in vivo*. The cell lines selected for subcutaneous xenograft studies were NCI-H929 and OPM2. GSK2857916 administration resulted in complete tumor regression in both models at 4 mg/kg dosed by intraperitoneal (IP) route twice weekly for 4 weeks. In an orthotopic, bone marrow dissemination mouse model using MM.1S cells, treatment with GSK2857916 dosed at 0.4mg/kg or 4.0 mg/kg IP 9 times over the course of 1 month resulted in complete reduction of tumor burden and significantly increased survival of mice. These results demonstrate the anti-tumor activity of GSK2857916 at achievable *in vivo* dose levels.

1.2.3. Preclinical Pharmacokinetics and Metabolism of GSK2857916

1.2.3.1. Single dose pharmacokinetics

The pharmacokinetics of GSK2857916 (ADC) and cys-mcMMAF has been investigated following IV (bolus) administration to the rat and cynomolgus monkey. Plasma concentrations were quantifiable over the entire sampling period (144 hours in rat and 504 hours in cynomolgus monkey) at doses of 10, 30 and 100 mg/kg for the rat and 3, 10, and 30 mg/kg for the cynomolgus monkey. The maximum concentrations were observed at 0.25 hours (first sampling occasion) in the rat and between 0.25 and 6 hours in the cynomolgus monkey. Systemic exposure (C_{max} and AUC_{0-t}) for ADC and total increased approximately proportionally with increasing dose and there was no notable sex difference. Similar concentrations between ADC and total antibody suggest that GSK2857916 remains largely intact in circulation. This is further confirmed with the relatively low levels of cys-mcMMAF observed in both plasma and urine. GSK2857916 was cleared slowly (total plasma clearance; rat 0.333ml/hr/kg and cynomolgus monkey 1.07 ml/hr/kg). The mean steady state volume of distribution (V_{ss}) was low in both the rat and monkey being 97.6 mL/kg and 105 mL/kg, respectively; suggesting GSK2857916 is mainly confined to the systemic circulation.

1.2.3.2. Repeat dose pharmacokinetics

Rat

The pharmacokinetics of GSK2857916 and cys-mcMMAF has been investigated following IV infusion administration to male and female rats over 3-weeks (once weekly at 3, 10 or 30 mg/kg on Days 1, 8 and 15), followed by a 12-week off-dose period.

Systemic exposure (AUC_{0-168} and C_{max}) increased proportionally with increasing dose and there were no notable differences in the systemic exposure between sexes. The systemic exposure on Day 15 was slightly higher (up to 2.4-fold) than that on Day 1. T_{max} was observed at 0.25 hours, the first sampling point.

The AUC for ADC and total antibody were similar to one another at each dose level on Day 1 and was generally higher for total antibody on Day 15. The C_{max} was generally lower for total antibody than ADC on Day 1, but similar on Day 15. The average half-life was 11 days.

For cys-mcMMAF, there was insufficient data available to determine AUC on Day 1 in the low dose group (3 mg/kg). The systemic exposure increased proportionally with increasing dose and there were no notable differences in systemic exposure between sexes. The systemic exposure on Day 15 was higher (up to 6.4-fold) than that on Day 1. T_{max} ranged from 0.25 to 48 hours.

There were quantifiable concentrations of cys-mcMMAF in the urine samples collected on Day 7, 14, 22, 43R, 64R, 85R and 106R from toxicology animals. The mean total amount of cys-mcMMAF recovered in urine generally increased proportionally with increasing dose of GSK2857916. Cys-mcMMAF was not quantifiable in the urine samples collected on Days -6, -5 and -1 (pre-treatment) at any dose or in control group samples.

Cynomolgus Monkey

The pharmacokinetics of GSK2857916 and cys-mcMMAF has been investigated following IV bolus administration to male and female cynomolgus monkeys over 3-weeks (once weekly at 1, 3 or 10 mg/kg on Days 1, 8 and 15), followed by a 12-week off-dose period.

Gender-averaged systemic exposure increased proportionally with increasing dose and there were no notable differences in the systemic exposure between sexes. The gender-averaged systemic exposure increased 1.2- to 2.1-fold, respectively, from Week 1 to Week 3. Following IV bolus administration of GSK2857916, T_{max} was observed at 0.25 hour (the first sampling time point) in the majority of animals.

The systemic exposures for ADC and total antibody were similar, with total antibody consistently being slightly higher than ADC. The average half-life was 4 days.

For cys-mcMMAF, the gender averaged systemic exposure (AUC_{0-48hr}) increased proportionally with increasing dose and there were no notable differences in systemic exposure between sexes. The changes in gender-averaged systemic exposure from Week 1 to Week 3 were less than 2-fold. T_{max} was variable, although in most animals T_{max} was achieved within 6 hours after dosing during Weeks 1 and 3.

Table 2 Gender Averaged Pharmacokinetic Values for GSK2857916 (ADC) Following IV Administration to Cynomolgus Monkeys

PK Parameters	AUC_{0-167} (µg.h/mL)		C_{max} (µg/mL)		T_{max} (h)		$t_{½}$ (h)
Week / Dose (mg/Kg/week)	1	3	1	3	1	3	3
1	865	1240	22.3	27.5	0.25	0.25	N/A
3	2330	3760	58.8	63.3	0.25	0.25	96.4
10	11200	21500	249	292	0.25	0.25	N/A

1.2.3.3. Distribution, Metabolism, and Excretion

No studies have been performed at GSK specifically to evaluate the distribution, metabolism and excretion of GSK2857916.

A study performed on a similar antibody linked to MMAF has been performed [Alley, 2009] [Alley, 2010]. Distribution has shown using radio-labeled ADC that accumulation is rapid in the tumor with the proportion of released drug relative to conjugated drug increased over time in the tumor. In most normal tissues, both the mAb and drug decreased over time in conjunction with the serum concentrations, except in organs involved in hepatobiliary clearance where there was a 4 hour peak post dose followed by a rapid decrease. The difference between tumor versus normal biodistribution and release kinetics yielded a tumor exposure to released drug tens to hundreds of times higher than that of normal tissue.

Metabolism studies have shown the directly conjugated drug linker releases cys-mcMMAF after ADC catabolism, consistent with proteolytic degradation of the mAb to release the drug.

Cys-mcMMAF was detected in rat urine between 7 and 106 days following IV administration. However, it was not possible to make a quantitative assessment of renal excretion.

1.2.3.4. Pharmacokinetic drug interactions

1.2.3.4.1. Victim interaction potential

Victim PK interactions occur when a co-administered drug changes the PK of the investigational agent.

Elimination pathways (metabolism/catabolism and/or drug transporter) for GSK2587916 or cys-mcMMAF in humans have not been characterised. As a consequence, care should be exercised when GSK2857916 is co-administered with potent cytochrome P450 (CYP) inhibitors, CYP inducers, and transporter modulators. *In vitro* cys-mcMMAF was shown to be a substrate of P-glycoprotein (P-gp) with an efflux ratio of 31-fold in the presence of verapamil. As cys-mcMMAF has low permeability (<10 nm/s) changes in P-gp activity could potentially affect the pharmacokinetics of cys-mcMMAF *in vivo*.

Concomitant dosing of GSK2857916 with strong Pgp inhibitors should be avoided unless considered medically necessary (See Appendix 11: Pgp Inhibitors for list of relevant Pgp inhibitors).

1.2.3.4.2. Perpetrator interaction potential

Perpetrator interactions are changes in the PK of a co-administered drug caused by the investigational agent.

No clinical studies have been performed by GSK to evaluate the potential for cys-mcMMAF or GSK2587916 to interact with substrates of cytochrome P450 or drug transporters P-gp, OATP, BCRP or OAT. *In vitro*, Cys-mcMMAF did not appear to be a direct, time- or metabolism-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 and no induction of CYP 1A2, 2B6 or 3A4/5 enzyme activity or gene expression was observed. Therapeutic proteins have been shown to cause suppression of cytochrome P450 and drug transporter activities and expression however GSK2587916 is unlikely to modulate the cytokines which are known to elucidate this mechanism. Together these data suggest cys-mcMMAF and GSK2587916 have a low risk of being perpetrators of drug interactions.

1.2.4. Toxicology of GSK2857916 (anti-BCMA MMAF)

The potential toxicity of GSK2857916 [aBCMA antibody drug conjugate (CA8 J6M0 Potelligent MMAF)] has been evaluated in rat and cynomolgus monkeys in single dose range toxicity studies and in repeat dose studies of 3-weeks duration by the intravenous route of administration. An *in vitro* cross-reactivity study was conducted to evaluate the binding of GSK2857916 to human tissues.

1.2.5. Repeat dose toxicity

In the definitive 3 week rat and monkey toxicity studies, GSK2857916 was administered by the intravenous route formulated as a solution in 25mM aqueous Citrate buffer containing 0.05mM EDTA, 200mM Trehalose and 0.02% Polysorbate 80 (pH 6), and administered to rats at a dose volume of 10 mL/kg (10 minute infusion) and to monkeys at a dose volume of 4 mL/kg/dose (bolus, slow push).

1.2.5.1. Rat

GSK2857916 [0 (vehicle), 3, 10 or 30 mg/kg] was given once weekly for 3 weeks by IV infusion to male and female rats followed by a 12 week off dose period (0, 3 and 30 mg/kg/week). All changes presented are times control values.

One female given 30 mg/kg died in the restraint tube prior to dosing on Day 8; however, as 1 control animal died immediately after removal from the restraint tube on completion of dosing on Day 1, this death was considered not to be test article-related.

Adverse microscopic changes in the testes were noted at ≥10 mg/kg/week (degeneration and atrophy of seminiferous tubules which correlated with macroscopic findings of reduced size/flaccid testes and lower testes weights (down to 0.50X control). At 30 mg/kg/week, adverse microscopic changes were also noted in the kidney (tubular degeneration, characterised by basophilia, single cell necrosis and often, with hyaline cast formation) with associated increases in urine albumin (up to 549X), total protein (up to 14X), NAG (up to 1.3X), αGST (up to 5.4X), lipocalin-2 (up to 58X), KIM-1 (up to 3.4X) and RPA-1 (up to 2.4X); and plasma urea (up to 1.22X) and calcium concentrations (up to 1.13X) and sternum/bone marrow, decreased cellularity (minimal to moderate) accompanied by single cell necrosis with associated changes in red cell parameters [decreased red blood cells (down to 0.81X)], hemoglobin and hematocrit (down to 0.75X), mean cell volume and mean cell hemoglobin (down to 0.92X) and increased high absorption reticulocytes (1.97X) and decreased medium and low absorption reticulocyte counts (down to 0.45X)] at the end of the treatment period. In addition, in the lung, eosinophilic material (tubular-myelin) accompanied by multifocal macrophage aggregates, frequently subpleural, with alveolar wall thickening and in some foci, perivascular mononuclear inflammatory cell infiltration, was noted at the end of the off-dose period. Macroscopically many pale areas were noted in the lungs of these animals.

Non adverse microscopic and clinical pathology changes were noted at 30 mg/kg in the mandibular and mesenteric lymph nodes (multinucleate giant cells), femur/femorotibial joint (bone remodelling, characterised by osteoblast hypertrophy/hyperplasia, scalloped/uneven bone surfaces, fibrosis or early hyperostosis), and male mammary gland (epithelial single cell necrosis) as well as lower body weight gain (0.53X) and food consumption (0.91X) and increased total protein (1.29X), immunoglobulin A (1.78X) and higher alpha 1 and beta electrophoresis (up to 2.1X), cholesterol and potassium (1.47X) concentrations, changes in triglyceride concentrations, decreased bilirubin (0.59X) and lower WBCs (down to 0.47X), reflecting lower neutrophil, lymphocyte, monocyte, eosinophil and basophil counts.

At ≥10 mg/kg non-adverse findings were noted in the epididymides (aspermia/hypospermia, reduced size, mixed interstitial inflammatory cell infiltration), ovaries (luteinized nonovulatory follicles), spleen (lymphocytolysis, increased pigmented macrophages, congestion, higher weights), sternum/bone marrow (decreased cellularity/ single cell necrosis/ bone remodelling, characterised by osteoblast hypertrophy/hyperplasia, scalloped/uneven bone surfaces, fibrosis or early hyperostosis), liver (extramedullary haematopoeisis, increased weights), injection site (local epidermal hyperplasia/perivascular inflammation/skeletal muscle degeneration/necrosis), and thymus (lymphocytolysis accompanied by decreased cellularity and mixed inflammatory cell infiltration the interstitial and surrounding connective tissue and lower weights) as well as higher platelet counts (2.1X) and red cell distribution width (1.37X) higher neutrophil and basophil counts (2.5X) and increases in AST (6.8X), aldolase (3.4X),

creatinine kinase (2.8X), ALP (up to 3.0X), ALT(3.5X), glutamate dehydrogenase (GLDH) (8.6X), alpha 1 acid glycoprotein and IgM.

At all doses findings non-adverse findings were noted in the lung (eosinophilic material (tubular-myelin) accompanied with prominent alveolar macrophages) and eye (minimal bilateral corneal single cell necrosis, without ophthalmology findings) as well as higher albumin (1.13X), lipcalin-2 (7.5X) and alpha 2 macroglobulin (1.76X) concentrations.

In addition, increases in cytokine levels from 24 hours after the start of dosing on Day 1 was observed with higher monocyte chemoattractant protein-1 (up to 3.1X), IL-1β (up to 1.93X), IL-6 (up to 3.9X) and TNF-α concentrations (up to 3.1X) noted at 30 mg/kg, and IL-6 (up to 1.74X) and TNF-α (up to 2.3X) concentration in females only noted at 10 mg/kg. No associated treatment-related changes in body temperature or associated clinical signs were noted.

Following the 12 week off dose period, in animals previously given 30 mg/kg/week, there was recovery of the changes in all tissues except the lungs and testes/epididymides (seminiferous tubular atrophy and aspermia) together with additional clinical (discoloration, unevenly/abnormally worn, appearing longer, thicker or shorter) and microscopic changes (degeneration of ameloblast layer) in continuously growing incisor teeth. Body weight gain increased between Days 22R and 39R (1.21X) and lower from Day 39R (0.82X) onwards, food intake (0.94X) continued to be lower in males. Liver (1.14X) and spleen weights (1.23X) were still increased in males, thymus weights (0.78X) were reduced and some clinical pathology parameters were still altered in some animals after the off-dose period including increased urine albumin excretion levels (up to 40X), cholesterol (up to 1.27X), higher reticulocyte counts (up to 1.98X), red cell distribution width (up to 1.14X), WBC (up to 1.39X) and lymphocyte (up to 1.56X) counts.

Findings of uncertain relationship to treatment comprised a diffuse decrease in vacuolation in the brown adipose tissue of 1 female given 30 mg/kg at the end of the treatment period, and an increase in the incidence of hyaline casts in the kidneys of off-dose animals previously given 30 mg/kg.

There were no changes considered related to GSK2857916 administration in the stage dependent evaluation of spermatogenesis following treatment at 3 mg/kg/week. Changes in the testes at higher doses precluded sperm staging evaluation in these animals.

Due to the adverse microscopic changes in the testes at ≥10 mg/kg, the no observed adverse effect level (NOAEL) was 3 mg/kg [mean $AUC_{0\text{-}168h}$: 6100 μg.h/mL, range: 5960 to 6240 μg.h/mL, and mean C_{max}: 103 μg/mL, range: 101 to 105 μg/mL (based on gender averaged Day 15 values for GSK2857916 ADC)].

1.2.5.2. Cynomolgus monkey

In the 3-week definitive study in cynomolgus monkey, GSK2857916 was given to monkeys (3/sex/group) at 0 (vehicle), 1, 3 and 10 mg/kg/week once weekly for approximately 3 weeks by intravenous injection (bolus, slow push). An additional 2

monkeys/sex/group were added at doses of 0 and 3 mg/kg/week to evaluate the reversibility of potential test article related effects following a 12-week off-dose period.

Test article-related microscopic inflammatory changes were noted in the spleen and bone marrow. In the spleen and bone marrow, an increase in macrophages, characterized by increased numbers of vacuolated macrophages containing variable amounts of brown pigment, engulfed cellular and/or nuclear debris, was present in the red pulp of monkeys given ≥3 mg/kg/week (minimal to mild) or in the bone marrow of monkeys given 10 mg/kg/week (mild to moderate). These microscopic effects in spleen and bone marrow at ≥3 mg/kg/week were reflective of a systemic inflammatory response at increasing doses and were not noted following the off-dose period.

The inflammatory microscopic changes in spleen and bone marrow noted at terminal necropsy correlated with clinical pathology findings at Day 22 consistent with an inflammatory response including dose responsive increases in mean serum C-reactive protein concentrations (up to 36X baseline) at ≥3 mg/kg/week, decreased serum albumin concentrations for individual monkeys given ≥3 mg/kg/week, and increases in mean total white blood cells, principally neutrophils, monocytes and large unstained cell counts, at 10 mg/kg/week. The systemic inflammatory response was also associated with a mild decrease in red cell mass parameters (to 0.82X baseline) and platelet counts (to 0.70X baseline), with evidence of regenerative responses in individual monkeys including reticulocytosis and release of nucleated red blood cells at 10 mg/kg/week. These changes were noted with histologic splenic and marrow macrophage changes which, upon cytologic evaluation of bone marrow smears, were suggestive of hemophagocytosis. These clinical pathology changes noted in monkeys given 3 mg/kg/week were not noted at the end of the off-dose period.

In the liver, Kupffer cell effects characterized by an overall increase in visible Kupffer cells and with occasional presence of mitotic figures were noted in monkeys given ≥3 mg/kg/week. In the kidney, minimal increases in mitotic figures of mesangial cells were present in renal glomeruli of monkeys given 10 mg/kg/week. Also associated in some of the affected kidneys, was an increase in mitotic figures within interstitial histiocytic cells of the renal cortex.

In the kidney of a single male given 10 mg/kg/week, a mild glomerulopathy was noted microscopically, characterized by expansion of the mesangium by a homogenous eosinophilic matrix. Also present in the same monkey, there was mild degeneration/regeneration of the distal nephron, characterized by clustered distal tubules that were dilated and with basophilic cytoplasm and euchromatic nuclei. Single cell necrosis was present in the collecting duct epithelium. Rare tubules contained proteinaceous fluid or blood. These findings correlated with significantly elevated urine albumin and total protein excretion values in this animal on Day 22 and were considered an effect of the test article. The constellation of clinical pathology and microscopic findings are consistent with a primary, test article-related injury to glomeruli, with subsequent tubule/duct injury.

Increased tingible body macrophages were microscopically present in the thymic cortex of monkeys given ≥3 mg/kg/week and were often associated with intracytoplasmic

phagocytized cellular and nuclear debris (lymphocytolysis) or decreased cortical thickness. Several monkeys given 10 mg/kg/week additionally had decreased cellularity of the cortex associated with the tingible body macrophage finding and variable thymic weights at 10 mg/kg/week. These findings were not considered to be adverse.

Decreases in absolute number and percentage of natural killer (NK cells) were observed on Day 22 in monkeys given 10 mg/kg/week, as well as in individual monkeys given 3 mg/kg/week. There was evidence of reversibility at the end of the 12-week off-dose period in monkeys given 3 mg/kg/week. Additionally, minimal increases in absolute number and percentage of activated ($CD69^+$) B cells were observed on Day 22 in monkeys given 10 mg/kg/week; however, activated B cells represent a small proportion of total B cells (0.6 and 1.1% $CD69^+$ mean for males and females, respectively, at baseline) and changes were not detected in the absolute number or percentage of total B cells. There were no test article-related changes in absolute number or percentage of T cells, CD4 and CD8 T cell subsets, or NK T cells following administration of GSK2857916.

Mean serum immunoglobulin M (IgM) concentrations were decreased (0.77X to 0.48X baseline) for males given ≥3 mg/kg/week and females given ≥1 mg/kg/week on Day 22 and were also decreased (0.54 to 0.66X baseline) following the off-dose period. Mean serum immunoglobulin G (IgG) concentrations for individual females given 10 mg/kg/week were decreased (0.78X baseline) on Day 22. These decreases in IgM and IgG were expected changes consistent with the pharmacologic activity of the test article on plasma cells.

Mean serum aspartate aminotransferase (AST) (to 13X baseline), glutamate dehydrogenase (GLDH) (up to 3.3X baseline), gamma glutamyltransferase (GGT) (to 2.0X baseline), total bilirubin (to 1.7X baseline) and/or alanine aminotransferase values (ALT) (to 2.2X baseline) for male and female monkeys given 10 mg/kg/week were increased on Day 22, but were not associated with correlative hepatocyte or biliary microscopic findings.

The mean serum cholesterol concentration for males given 10 mg/kg/week was increased (1.52X baseline) and mean serum triglyceride concentration for females given 10 mg/kg/week was increased (2.2X baseline) on Day 22.

Increased mean activated partial thromboplastin times for males and females given 10 mg/kg/week were noted on Day 22 and were considered test article-related but non-adverse based on low magnitude and lack of correlate clinical findings.

Reduced eating (greater than half the daily allotment of food remaining) was noted sporadically throughout the dosing phase in monkeys given 10 mg/kg/week with a decrease in the consumption of citrus fruit in females given ≥3 mg/kg/week. Body weight loss was noted by 4 days following the last dose in 1 female at each dose level (non-fasted). A fasted terminal body weight prior to necropsy (8 days following the last dose) showed a slight increase from the previous weight for the female given 1 mg/kg/week, while that for the female given 10 mg/kg/week remained unchanged. The affected female given 3 mg/kg/week was maintained throughout the off-dose period and,

in the beginning of this phase, body weight continued to decrease. The body weight for this female generally increased throughout the remainder of the off-dose period and was comparable to Day 1 values by the end of the off-dose period.

Stage dependent qualitative evaluation of spermatogenesis in the testes was not performed on male monkeys due to immaturity of testes.

Based on glomerulopathy and degeneration/regeneration noted in the distal nephron in the kidney of the male given 10 mg/kg/week, the highest non-severely toxic dose was 3 mg/kg/week.

Based on adverse findings noted at ≥3 mg/kg/week and the transient nature of the body weight change noted in the monkey given 1 mg/kg/week, the no-observed-adverse effect level was 1 mg/kg/week [GSK2857916 (ADC): AUC_{0-167} 1240 μg.h/mL, range 893 to 1470 μg.h/mL; C_{max} 27.5 μg\mL, range 22.7 to 32.9 μg/mL; GSK2857916 (Total) AUC_{0-167} 1520 μg.h/mL, range 1210 to 1700 μg.h/mL; C_{max} 27.3 μg\mL, range 22.4 to 31.7 μg/mL; cys-mcMMAF: AUC_{0-167} 12.1 ng.h/mL, range 6.01 to 23.1 ng.h/mL; C_{max} 0.499 ng\mL, range 0.341 to 1.03 ng/mL (gender-averaged based on Week 3 values)].

1.2.6. Genotoxicity

Intact biopharmaceutical therapeutics, such as monoclonal antibodies and antibody drug conjugates, do not directly interact with DNA or other chromosomal material. Therefore, genetic toxicology studies with GSK2857916 were not performed. The active moiety of GSK2857916 is MMAF cytotoxin which is expected to be genotoxic in mammalian systems given it is a microtubule disrupting agent.

1.2.6.1. Route assessment for genotoxic impurities

An assessment of the route of synthesis for GSK2857916 has been carried out to determine the likelihood of mutagenic impurities being present in the drug substance. This indicated that there are no impurities of known or potential mutagenic concern that are considered likely to be present in final drug substance at a level that would exceed the threshold of toxicological concern at the planned clinical dose range.

1.2.7. Local tolerance

Clinical and histopathological analysis of injection sites was incorporated into the dose range toxicity and 3-week definitive repeat dose toxicity studies in rats and cynomolgus monkeys.

In the rat dose range toxicity study mild epidermal hyperplasia with single cell necrosis and mild degeneration/necrosis of skeletal muscle with inflammatory cell infiltrate was noted at the injection site in animals intravenously administered a bolus injection of GSK2857916 at ≥ 30 mg/kg (dose concentrations 6 and 16.1 mg/mL). In the rat 3-week study intravenous infusion of GSK2857916 at doses ≥ 10 mg/kg (dose concentrations 1 and 3 mg/mL) caused localised epidermal hyperplasia at the injection site. Focal skeletal muscle degeneration/necrosis was also observed in 1 male given 30 mg/kg. In addition,

the incidence of perivascular inflammation at the injection site was increased in GSK2857916 treated animals at doses of ≥3 mg/kg (dose concentration 0.3 mg/mL).

In the monkey dose range toxicity study mild to minimal hemorrhage with minimal to moderate subcutaneous inflammation characterised by necrosis, mixed inflammatory cell infiltrate including lymphocytes and large histiocytes/fibroblastic cells occasionally with multinucleation and mitotic figures and/or fibrosis was observed at ≥3 mg/kg (dose concentration 16.1 mg/mL) following bolus intravenous injection. In the female given 30 mg/kg epidermal squamous cell hyperplasia was also seen. No treatment related changes at the injection site were observed in the 3-week monkey study following repeated bolus intravenous administration of GSK2857916 at doses of 1, 3 and 10 mg/kg (dose concentrations 0.25, 0.75 and 2.5 mg/mL).

1.3. Benefit:Risk Assessment

Summaries of findings from non clinical studies conducted with GSK2857916 can be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2013N175128_02]. The following section outlines the risk assessment and mitigation strategy for this protocol:

1.3.1. Risk Assessment

Nephrotoxicity

Non clinical safety experiments have demonstrated primary glomerular injury and tubular degeneration (in rat at doses ≥30mg/kg, and in monkey at doses ≥10mg/kg). The morphologic changes were accompanied by large molecular proteinuria (albuminuria). The renal changes were dose dependent and reversible.

To minimize the risk of nephrotoxicity, only subjects with well-preserved kidney function will be allowed on study. During the study subjects will be monitored for kidney function by assessing creatinine value and clearance, electrolytes (Potassium, Calcium, Phosphorus, and Magnesium), protein and albumin excretion in 24 hr urine collection at every cycle, or more frequently if clinically indicated. Subjects will be educated about the need of maintaining adequate urinary output. Treatment will be implemented according to clinical practice. Dose reductions and treatment stopping criteria will be applied according to Section 3.10.

Hepatotoxicity

Non clinical safety experiments demonstrated increased liver weight and elevated liver enzymes at doses of ≥30 mg/kg in rats. Elevations in liver enzymes were also observed in monkeys at doses of 10 mg/kg, in addition at 3 mg/kg increased mitotic figures in Kupffer cells were also observed in monkeys. All of these changes were dose dependent and reversible.

Only subjects with well preserved liver function will be allowed on study. Subjects with Hepatitis B (HBV) and C will be excluded from the trial. Liver function tests will be frequently monitored in all subjects on study and in case of liver abnormalities

management will be implemented according to clinical practice. Subjects that meet liver stopping criteria (Section 3.9.1) will be withdrawn from the study.

Hematologic toxicity

Slight hemoglobin and platelet decrease together with an increase in numbers of neutrophils and monocytes have been noted in monkeys at doses of 10mg/kg. In rats, decrease in hemoglobin, white cells, lymphocytes and neutrophils were noted at doses of ≥30mg/kg. However, rats given 10mg/kg showed higher neutrophil counts, and increased platelets at doses of ≥10mg/kg.

The complete blood count (CBC) will be assessed frequently to monitor for hematologic toxicity. Supportive therapy (growth factors, transfusions, antibiotics, monitoring and active treatment of infections) will be provided according to standard medical practice and dose reductions or treatment discontinuations will follow recommendations in Section 3.10.1.

Immunosuppression

In non clinical studies GSK2857916 has been associated with decrease in immunoglobulins in monkeys (IgM at doses ≥1mg/kg, and IgG at >10 mg/kg). An increase in immunoglobulins was seen in rats (IgM ≥10mg/kg and IgA at 30 mg/kg). Note that rats are not an antigen specific species for GSK2857916.

Lymphocyte counts will be followed throughout the study by CBC and lymphocyte sub-population analysis. Subjects will be actively monitored for immunoglobulin levels and treated for infections according to standard practice.

Pulmonary toxicity

Preliminary non clinical safety experiments have demonstrated the presence of microscopic changes in the lungs (prominent alveolar macrophages associated with flocculent eosinophilic material; mixed perivascular inflammation) in rats at all doses tested.

Subjects will be monitored for clinical signs and symptoms potentially related to pulmonary toxicity. Further diagnostic tests and management will be implemented immediately according to recommendations provided in Section 3.10.1.

Ocular toxicity

There were no eye related findings in monkeys. Minimal corneal single cell necrosis was noted in rats treated at ≥3mg/kg.

Subjects will be actively monitored for ocular toxicity and will be instructed to use preventive steroid eye drops as outlined in Section 3.9.8. In case of developing eye-related symptoms, subjects will be evaluated by an ophthalmologist and appropriate management will be initiated immediately. Dose reduction and treatment stopping

recommendations will be followed according to recommendations provided in Section 3.10.

1.3.2. Benefit Assessment

Currently there is no clinical evidence that treatment with GSK2857916 will result in any benefit to subjects. However, based on data from non clinical studies there is a possibility that GSK2857916 might reduce tumor burden in subjects with MM and BCMA positive lymphomas.

1.3.3. Overall Benefit:Risk Conclusion

Overall, due to limited clinical experience with GSK2857916 benefit/risk cannot be asseesesed at this time. The safety of subject is the primary objective of this study and adequate monitoring and guidance for dose reductions/stopping criteria are provided in the protocol to minimize risks associated with exposure to GSK2857916.

2. OBJECTIVE(S), ENDPOINT(S) AND HYPOTHESIS

Hypothesis

GSK2857916 can be safely administered to subjects with MM and with other BCMA positive malignancies at doses where target engagement can be demonstrated.

Objective	Endpoint
Primary	
• To determine safety, tolerability, maximum tolerated dose (MTD), and recommended phase (RP2) dose and schedule of GSK2857916 administered	• Adverse events (AE) and changes in clinical signs and laboratory parameters
Secondary	
• To evaluate the pharmacokinetic (PK) profile of GSK2857916 and the breakdown product cys-mcMMAF) after intravenous (IV) single and repeat dose administration in subjects with relapsed/refractory MM and BCMA expressing lymphomas	• GSK2857916 and cys-mcMMAF PK parameters following IV single and repeat dose administration during dose escalation as data permit (e.g., AUCs Cmax, tmax, CL, V_{SS}, t½ [single dose], Cmax and Ctrough [repeat dose]). GSK2857916 population PK parameters in expansion cohorts at the RP2 dose (e.g. clearance (CL), volume of distribution (Vd)), and relevant covariates which may influence exposure (e.g. age, weight, or disease-related covariates e.g. BCMA expression)

Objective	Endpoint
• To assess anti-drug antibody (ADA) formation after IV single and repeat dose administration of GSK2857916	• ADA incidence and titers after single and repeat IV dosing of GSK2857916
• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM and BCMA expressing lymphomas	• Clinical activity measured as Overall Response Rate (ORR) which is defined as follows: o For MM: the percentage of subjects achieving confirmed partial response or better (≥PR) o In addition, the percentage of subjects with minimal response (MR) will be assessed for clinical benefit rate (CBR) (Appendix 1) o For Lymphomas: the percentage of subjects achieving PR or better (≥PR) (Appendix 2)
Exploratory	
• To evaluate PD markers in MM after treatment with GSK2857916	• [redacted]
• To explore relationships of GSK2857916 plasma concentrations/exposure with pharmacodynamics (PD), safety and clinical activity	• [redacted] • Relationship between safety/clinical activity (e.g. ORR) and GSK2857916 PK parameters
• To characterize the relationship between clinical response and other biologic tumor characteristics (DNA, protein analysis)	• [redacted]
• To investigate the relationship between genetic variants in the host and response to study medicine or susceptibility, severity and progression of disease	• Relationship between host genetic variation and response to study medicine or susceptibility, severity and progression of disease

Objective	Endpoint
• To explore the effect of GSK2857916 on symptoms (including bone pain, fatigue and visual symptoms) and impacts on HRQoL in subjects with relapsed/refractory MM (Part 2)	• Changes from baseline in bone pain/fatigue and analgesic use as measured by the eDiary • Interviews with subjects to further characterize changes in symptoms (including bone pain, fatigue and visual symptoms) and impacts on HRQoL
• To explore changes in visual symptoms and function following discontinuation of treatment with GSK2857916	• Changes in visual symptoms and impacts as measured by the OSDI and NEI-VFQ-25 following treatment discontinuation • Follow-up telephone interviews conducted to further understand subjects experience with visual symptoms and changes in symptoms and related impacts following treatment discontinuation
• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM in terms of time-to-event (TTE) endpoints (Part 2 MM)	• Time to progression (TTP), defined as: the time from first dose until the earliest date of PD per International Multiple Myeloma Working Group (IMWG), or death due to PD. • Duration of response (DOR), defined as: the time from first documented evidence of PR or better; until the time when disease progression (PD) is documented per IMWG; or death due to PD occurs in subjects who achieve a response, i.e. confirmed PR or better. • Time to response (TTR), defined as: the time between the date of first dose and the first documented evidence of response (PR or better). • Progression-free survival (PFS), defined as: the time from first dose until the earliest date of disease progression (PD) per IMWG, or death due to any cause. • Number of deaths

3. INVESTIGATIONAL PLAN

3.1. Discussion of Study Design

Table 3 Study Design

Part 1 Dose Escalation (n=up to 30 subjects) **Population: relapsed/refractory MM** Characterize safety, PK, PD, immunogenicity and establish RP2 dose of GSK2857916 Schedule 1: GSK2587916 once every 3 weeks (21-day cycle) (n=~20) Schedule 2: GSK2587916 once weekly for 3 consecutive weeks, 1-week rest (28-day cycle) (n=~9) Serial PK samples will be collected from all subjects in Part 1
Part 2 Expansion Cohort(s) (n=~50 subjects) **Population:** **1) Subjects with relapsed/refractory MM (up to 40 subjects)** **2) Subjects with lymphomas expressing BCMA (up to 10 subjects)** Cohort Expansion groups: Further evaluate the safety, PK, immunogenicity, and activity of GSK2857916 at the RP2 dose identified in Part 1 A futility analysis based on ORR data will be performed after approximately 15, 22 and 30 subjects have been evaluated for response in MM cohort Both Expansion groups will be analyzed separately Sparse PK samples will be collected from all subjects Genetics research samples will be collected predose from all subjects

This is a First Time in Human (FTIH), open-label, dose escalation trial consisting of two parts: a Part 1 dose escalation phase and a Part 2 expansion phase for safety, and clinical activity testing (Table 3 and Section 3.2). The study will enroll a total of approximately 80-95 subjects with relapsed/refractory MM or other BCMA-expressing lymphomas. The maximum dose to be administered in this trial will not exceed 5 mg/kg.

Part 1: Dose-escalation cohorts will characterize the safety, tolerability, PK, and PD of GSK2857916 given on a once every 21 days or a once weekly schedule. Only subjects with MM will be enrolled in Part 1 based on an N-CRM dose escalation model until MTD(s) or RP2D is/are established on an appropriate schedule(s). GSK2857916 and cys-mcMMAF PK parameters derived from extensive PK sampling and PD biomarkers (e.g.

[redacted] will be estimated/measured during dose escalation to inform the next cohort dose and the selection of a RP2 dose [Biologically effective dose (BED) or maximum tolerated dose (MTD)]. In case of insufficient sample quality or due to high variability in the measurement of PD biomarkers, up to 6 additional samples from subjects in expansion cohort might be collected for PD analysis. Initially, GSK2857916 will be administered (IV) via 60 min infusion once every three weeks (21 days = 1 cycle) on Schedule 1. Once an MTD1 or RP2D has been established on the once every 21-day (Schedule 1), the safety, tolerability, PK, and PD of once-weekly dosing (Schedule 2) of GSK2857916 may be explored as an additional cohort(s). Dose escalation decisions on each of these two dosing schedules will utilize a separate N-CRM model. The information gained from evaluation of Schedule 1 (once every three weeks; 21-day cycle) will be utilized to inform the model for Schedule 2 (once weekly for three consecutive weeks, 1 week rest; 28-day cycle).

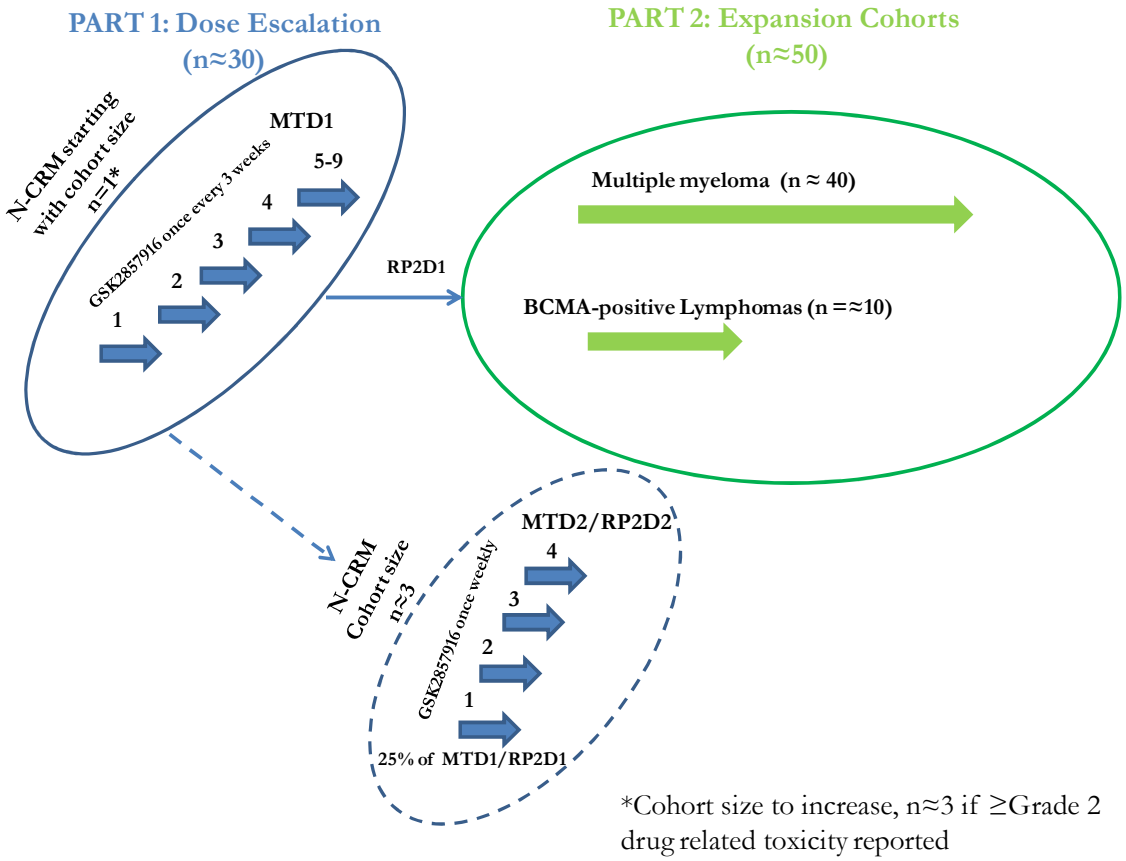
Part 2: Expansion cohorts will assess the safety, tolerability, PK (sparse sampling), and clinical activity of the GSK2857916 dose regimen identified in Part 1. A total of approximately 50 subjects will be enrolled in Part 2. A MM cohort (up to 40 subjects) will be enrolled with no prospective BCMA screening required (BCMA expression data collection and retrospective analysis will be performed). In addition, futility analyses will be performed on the MM cohort after approximately 15, 22 and 30 evaluable patients have been assessed for response. For more detailed information on the futility analysis, see Section 13.6.2. Sparse PK sampling will be collected to further characterize GSK2857916 exposure for the selected dose schedule.

A smaller cohort of subjects with BCMA positive lymphomas (up to 10 subjects) will be enrolled based upon prospective detection of positive BCMA tumor cell expression as determined by a central laboratory using a validated IHC assay.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables (Section 7.1) are essential.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.2. Study Schematic



Abbreviations: MTD=maximum tolerated dose; N-CRM= Neuenschwander Continual Reassessment Method; RP2D=recommended phase 2 dose

1. Part 2 to initiate after once every 3 week recommended dose is determined
2. Dose escalation with once weekly schedule may commence in parallel to Part 2 expansion

3.3. Part 1: Dose-Escalation Phase

Only subjects with MM will be enrolled in Part 1, and no prospective selection by BCMA expression level will be required. The MTD of GSK2857916 will be established first on Schedule 1; the once every three weeks (21 days) schedule as described in Section 3.3.1. Subjects on Schedule 1 will be enrolled into dose escalation cohorts based on an N-CRM dose escalation model generated for each schedule.

After the MTD1 or RP2D is established for the once every three weeks Schedule 1, once weekly dosing of GSK2857916 (Schedule 2) may be evaluated prior to, or in parallel with the expansion phase as described in Section 3.3.2. A weekly dosing regimen may be chosen for further evaluation if toxicity is felt to be related to Cmax and that equivalent or greater exposures in terms of AUC can be safely achieved with weekly dosing compared with the once every 3 weeks dosing regimen.

Note: For details on data dissemination and communication with sites (dose escalation meetings and safety update meetings), refer to Section 12.1.

3.3.1. Dose Escalation on Schedule 1 (GSK2857916 administered once every three weeks; 21 days = 1 cycle)

(Note: For details on scheduled procedures in subjects given GSK2857916 on Schedule 1 in Part 1 refer to Time and Events Section 7.1.1.1)

3.3.1.1. Single Subject Cohort Run-in (Schedule 1 only)

- A single subject will be enrolled at each dose level as outlined in Table 4 until occurrence of a ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out.
- Initially, GSK2857916 will be administered (IV) via 60 min infusion once every three weeks (21 days = 1 cycle) on Schedule 1. One subject or the sentinel subject i.e., the very first subject on the study; will initially be enrolled at the starting dose of 0.03 mg/kg in Cohort 1 (Refer to Section 3.6.4 for starting dose rationale). The initial dose will be given to the sentinel subject. Serial blood samples will be collected for PK. The sentinel subject must remain under observation for at least 24 hours after dosing before discharge. GSK2857916 (intact and total [intact + unconjugated antibody]) and cys-mcMMAF plasma concentrations will be analyzed and reviewed together with the safety data (DLT period). If the first dose is considered tolerated, the sentinel subject will be allowed to stay on the study and receive subsequent doses at the same dose level (i.e., 0.03 mg/kg) as scheduled, every three weeks (21 days interval) for up to 16 doses (or until disease progression, toxicity or withdrawal of consent).
- If the sentinel subject does not experience a ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out during the first cycle (within 21 days), the next subject will be allowed to enroll in the next cohort at a dose increased by ≤100% of the starting dose. Dose escalation with increments up to 100% of the previous dose will continue with enrolment of 1 subject per cohort until the occurrence of the first ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out. (run in procedure outlined in Table 4)
- The single subject (small cohort) run-in will be halted when the first ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out occurs in one subject in Cycle 1 (21 days). At this point, the cohort will be expanded to 3 or more subjects at the same dose level and the escalation will continue to follow the N-CRM procedure as outlined in Table 4

Table 4 Single Subject (Small Cohort) Run-In Procedure for GSK2857916 given on Schedule 1 (once every 21 days)

Dose Level	Number of subjects with ≥G2 toxicity	Dose Escalation/Action
Dose Level 1/Cohort 1	0 out of 1 subject (Sentinel subject)	Predicted starting dose 0.03 mg/kg every 21 days
Dose Level 2/Cohort 2	0 out of 1 subject	Escalate to the next dose level with increase ≤100% of the starting dose
Dose Level 3 and beyond/Cohort 3 and beyond	0 out of 1 subject	Escalate to the next dose level with increase of ≤100% of the dose tested in the previous cohort
	1 out of 1 subject*	Switch to Cohort size of 3 or more subjects

*Increase of doses **up to** 100% of the previous dose may continue until the first ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out occurs in one subject in Cycle 1 (21 days). At this point the single subject (small cohort) run-in is halted. Continue with N-CRM, with cohort sizes of 3 or more subjects. Increase of doses ≤100% will be considered for subsequent cohorts of 3 or more subjects.

- Dose escalation/de-escalations decisions will take into account all available data, including but not limited to the safety parameters, PD and PK data of all cohorts assessed. Dose escalation/de-escalation decisions will be informed by the N-CRM [Neuenschwander, 2008]. The N-CRM model used for Schedule 1 is described in detail in Section 3.3.1.2. The method is fully adaptive and makes use of all DLT information available at the time of each dose assignment. The Fixed and Adaptive Clinical Trial Simulator (FACTS) will be used to conduct the N-CRM. Dose-related decisions will occur following review of these data by the investigator(s), GSK medical monitor, clinical pharmacology modelling and simulation (CPMS) representative, and statistician. The decision and rationale will be documented in written format and distributed to the investigator(s), GSK medical monitor, CPMS representative, and statistician.

- The MTD will be defined as that dose which has the highest probability of having a DLT rate within the target toxicity interval, and for which the probability that the DLT rate lies within the excessive toxicity or the unacceptable toxicity window is less than 25% (see Section 3.3.3 for DLT definitions). The DLT assessment period on Schedule 1 will be 21 days.

- Dose adjustments/stopping criteria will adhere to guidelines provided in Section 3.10.1.

- Selected dose escalation cohorts may enroll additional subjects in order to further assess safety, PK and/or PD. The frequency and schedule of dosing may be adjusted based on emerging safety, PK and PD data e.g., a recovery period may be incorporated into the dosing. Additional, intermediate dose levels may also be explored.

- Subjects will receive GSK2857916 treatment until disease progression, unacceptable toxicity, withdrawal of consent, or until they have reached the end of the treatment period, which has been pre-specified as 16 cycles (48 weeks) for Schedule 1 (GSK2857916 given once every three weeks; 1 cycle = 21 days).

3.3.1.2. Description of N-CRM for Schedule 1

3.3.1.2.1. Planned Dose Levels

Prior to the start of the study, projected dose levels on Schedule 1 (in mg/kg) are 0.03, 0.06, 0.12, 0.24, 0.48, 0.96, 1.92, 2.8, 3.6, and 4.5 mg/kg; actual dose levels will be determined by N-CRM (Neuenschwander-Continuous Reassessment Method). Additional doses and schedules may be explored based on emerging safety, PK, and PD data. The maximum dose to be administered in this trial will not exceed 5 mg/kg.

Description of the New Continuous l Reassessment Method: After each cohort, a dosing recommendation for the next cohort will be made using the N-CRM [Neuenschwander, 2008]. All available data, including safety, PK and PD data from current and prior cohorts will be reviewed at the dose escalation meeting (see Section 12.1). Although the N-CRM will be used to recommend the next dosing level, clinical judgment by the Medical Monitor and internal dose-escalation committee in consultation with the investigators can halt enrolment into lower dose cohorts as deemed appropriate at any time during the trial.

The N-CRM design is a type of Bayesian adaptive dose escalation scheme that assumes a two-parameter logistic model for the toxicity rate based on dose. It is a modified version of the original Continuous Reassessment Method [O'Quigley, 1990]. A CRM-based design uses a statistical model for dose and toxicity, and is expected to locate the MTD efficiently while minimizing the number of subjects exposed to pharmacologically inactive dose levels.

The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment. In contrast, the 3+3 method only uses information from one dosing cohort at a time.

At the time of each dose escalation decision, the Fixed and Adaptive Clinical Trial Simulator (FACTS) will be used to obtain, for each potential dose, the posterior probabilities that the DLT rate for that dose lies in each of four toxicity intervals (under dosing, target dose range, excessive toxicity, and unacceptable toxicity). The four DLT toxicity intervals are defined as follows:

- [0%, 16%) Underdosing
- [16%, 33%) Target toxicity
- [33%, 60%) Excessive toxicity

- [60%, 100%) Unacceptable toxicity

The recommended dose will be the dose with the highest posterior probability of lying in the target toxicity interval with the additional requirement that the sum of the posterior probabilities of the DLT rate lying in the excessive toxicity or unacceptable toxicity range is less than 25%. Selection of the next dose cohort to be enrolled is also subject to the constraint that the next dose level can be no more than two times that of the current dose level. An updated estimate of the toxicity curve will be provided at the time of each dose escalation meeting (see Section 12.1).

Note that de-escalation as well as escalation is possible using this method.

Dose escalation will continue until:

i) Six subjects have been treated at the current target dose

AND

For the current dose level, the posterior probabilities of the DLT rate lying within the excessive toxicity interval or within the unacceptable toxicity interval sum to less than 25%.

AND

For the next higher dose, the posterior probabilities of the DLT rate lying within the excessive toxicity interval or within the unacceptable toxicity interval sum to less than 25%.

OR

ii) No doses are usable (i.e. For ALL doses, the posterior probabilities of the DLT rate lying within the excessive toxicity interval or within the unacceptable toxicity interval sum to more than 25%

AND

At least two DLTs have been observed.

The N-CRM model used to determine the MTD for Schedule 1 will utilize a single subject/cohort run-in phase.

3.3.1.2.2. Implementation of N-CRM

The N-CRM model implementation will be performed using Fixed and Adaptive Clinical Trial Simulator (FACTS) (Version 2.3 or higher) from Tessella.

3.3.1.2.3. Bayesian Prior

The N-CRM methodology requires that a Bayesian prior for the toxicity curve be pre-specified.

The proposed prior probabilities of DLT are an approximation on the potential toxicity profile based on the available non clinical toxicology package, dosing range being considered, and literature data available from clinical trials with other ADCs. Additionally, the prior is considered a 'weakly informative prior' and is defined with a fairly wide credible interval. This allows the model the freedom to estimate the observed probabilities of toxicity with minimal restriction.

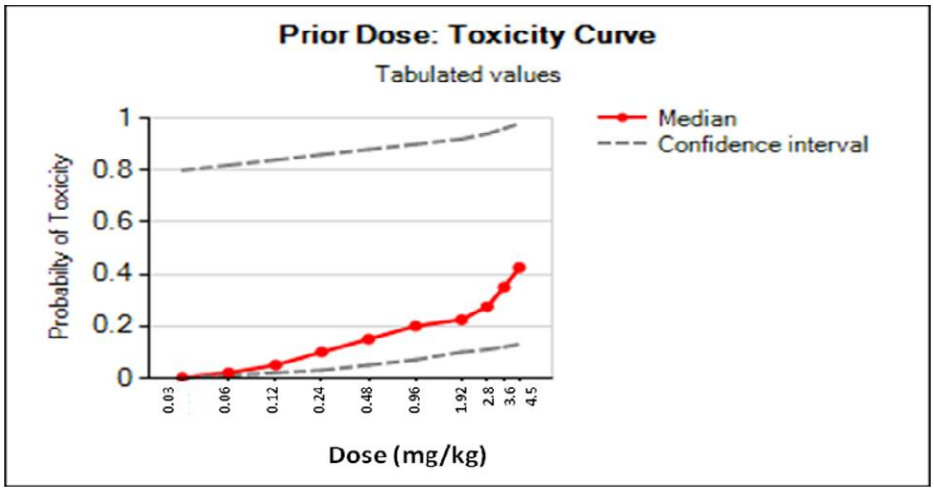
The initial Bayesian prior used for this design is determined by using the quantile method. For each dose, an estimate of the median probability of DLT was specified, along with a 95% credible interval. The 95% credible intervals are intentionally wide due to limited information about the toxicity profile of GSK2857916 in humans. Table 5 shows the median prior probability of experiencing a DLT at the given dose along with a 95% credible interval around the median:

Table 5 Table of Specified Prior Probability of DLT (with 95% Credible Interval)

Anticipated Dose (mg/kg)	2.5% Quantile for Probability of Toxicity	**Median Probability of Toxicity**	97.5% Quantile for Probability of Toxicity
0.03	0	**0.001**	0.80
0.06	0.01	**0.02**	0.82
0.12	0.02	**0.05**	0.84
0.24	0.03	**0.1**	0.86
0.48	0.05	**0.15**	0.88
0.96	0.07	**0.2**	0.90
1.92	0.1	**0.225**	0.92
2.8	0.11	**0.275**	0.94
3.6	0.12	**0.35**	0.96
4.5	0.13	**0.425**	0.98

A graphical presentation of the initial prior is displayed in Figure 1. Doses are the projected doses. Actual doses used during the conduct of the trial may vary. An intermediate prior will be derived based on the initial prior by FACTS (Version 2.3 or higher) from Tessella. The final prior is determined based on the intermediate prior and all available data.

Figure 1 Graphical display of the prior distribution for the probability of DLT given dose



3.3.2. Dose Escalation on Schedule 2 (GSK2857916 administered once weekly x3, 1 week rest; 28 days = 1 cycle)

(Note: For details on scheduled procedures in subjects given GSK2857916 on Schedule 2 in Part 1, refer to Time and Events Table in Section 7.1.1.2)

The MTD (MTD1) or RP2D (RP2D1) established for GSK2857916 on Schedule 1 i.e., once every three weeks schedule, will inform selection of the starting dose for Schedule 2 i.e., the once weekly schedule. Additional cohort(s) may be enrolled to evaluate the safety, PK, and PD of GSK2857916 for the once weekly dosing schedule to establish an MTD2. GSK2857916 will be dosed once weekly for 3 consecutive weeks, followed by 1 week off (Schedule 2 = 28-day cycle).

- The once weekly dosing cohorts may be explored prior to, or in parallel with, enrollment to the expansion cohorts (Part 2).
- The dose escalation of the once weekly schedule will utilize a separate N-CRM model from the model used for the once every three week schedule. The information gained from the evaluation of the once every three week schedule (Schedule 1) will be utilized to more accurately define the N-CRM model used for dose escalation on the once weekly schedule (Schedule 2).

- Depending on emerging safety signals, the proposed weekly starting dose will be 25% of MTD1 or RP2D1. If the initial dose of 25% of MTD1 or RP2D1 is not tolerated, dose escalation on the weekly schedule will be terminated and enrollment into Schedule 2 will be closed. If the starting dose is tolerated, escalation on the weekly schedule will continue at increments of ≤30% and will follow the N-CRM procedure until MTD2 or RP2D2 is reached.

- The MTD will be defined as that dose which has the highest probability of having a DLT rate within the target toxicity interval and for which the probability that the

DLT rate lies within the excessive toxicity or the unacceptable toxicity window is less than 25% (see Section 3.3.3 for DLT definitions). The DLT assessment period on Schedule 2 will be 28 days.

- The N-CRM procedure for the weekly schedule will not utilize a single subject/cohort run-in phase. Schedule 2 dose escalation cohorts will consist of 3 or more subjects due to higher starting dose and greater probability of toxicity.

- Dose escalation decisions will also take into account all available data. This includes, but is not limited to the safety and PK characteristics of all cohorts assessed. In addition, dose escalation decisions will be determined by the N-CRM [Neuenschwander, 2008]. The FACTS will be used to conduct the N-CRM. These decisions will occur following review of these data by the investigator(s), GSK medical monitor, CPMS representative, and statistician. The decision and rationale will be documented in written format and distributed to the investigator(s), GSK medical monitor, CPMS representative, and statistician.

- Dose adjustments/stopping criteria will adhere to guidelines provided in Section 3.10.

- Subjects will receive GSK2857916 in this weekly dosing cohort until disease progression, unacceptable toxicity, withdrawal of consent, or completion of the pre-specified treatment period of 48 doses (16 cycles on Schedule 2).

- If a subject misses a dose on the weekly schedule, the dose will be recorded as missing and the next dose will be administered according to the current cycle. The counting of days and cycles will continue regardless of whether or not the subject received the dose. Dose delays of + 3 days are allowed in order to accommodate scheduling conflicts/holidays, etc.

Additional alternative schedules may be evaluated based on emerging data. If an alternative schedule other than the weekly dosing schedule is evaluated, details on dosing and Time and Events will be updated in the Study Procedures Manual (SPM).

3.3.3. Dose-Limiting Toxicity - Part 1 only

Any subject in Part 1 (Dose Escalation) who received at least one dose of the drug (regardless of schedule) will be evaluated for DLTs. Safety data together with DLTs will be reviewed during the dose escalation meetings prior to opening enrollment into subsequent cohorts (see Section 12.1).

Subjects who have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced.An event will be considered a DLT if its relationship to the investigational agent cannot be ruled out occurs within the DLT reporting period (first 21 days of treatment for schedule 1, and first 28 days for schedule 2) and meets one of the following criteria:

- Albuminuria ≥2000 mg/24 hr which has been confirmed by repeat test at least 7 days apart and is not considered to be related to disease progression based on consultation of investigator with GSK medical monitor
- Grade 4 neutropenia (without fever) lasting ≥7 days
- Febrile neutropenia lasting ≥72 hours
- Grade ≥3 thrombocytopenia associated with bleeding where estimated blood loss is > 10mL or Grade 4 thrombocytopenia lasting >7 days and not responding to platelet transfusions
- Any Grade 3 or greater non-hematologic toxicity as described in Common National Cancer Institute-Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 [NCI, 2009] with the exception of the following Grade 3 events that can be controlled within 48 hours with routine supportive measures
    - Nausea and vomiting that can be controlled with anti-emetics
    - Diarrhea that can be controlled with anti-diarrheals
    - Rash or other skin reactions that can be controlled with antihistamines and steroids
    - Clinically asymptomatic electrolyte abnormalities which can be corrected within 48 hours)
- Liver toxicity meeting pre-specified GSK liver stopping criteria (see Liver in Section 3.9.1)

Tumor lysis syndrome does NOT constitute a DLT (Section 3.9.7).

A subject who develops a DLT will be allowed to stay on study only if the toxicity did not meet stopping criteria and recovered to ≤ Grade 1 within 14 days, or after a longer recovery time if benefit to subject can be demonstrated and if the investigator and medical monitor agree that for a given subject the benefits may outweigh the risks.

3.3.4. Maximum Tolerated Dose

The MTD will be defined as that dose which has the highest probability of having a DLT rate within the target toxicity interval and for which the probability that the DLT rate lies within the excessive toxicity or the unacceptable toxicity window is less than 25%.

3.4. RP2 Dose and Administration Schedule Selection for Part 2

All available safety, PK, and PD data from the once every 3 weeks schedule, and if available, the once weekly dosing schedule, will be analyzed. If a consistent level of 95-100% receptor occupancy is observed in evaluable subjects at a dose lower than the determined MTD with no evidence of target mediated disposition in the PK profile and where emerging signs of clinical activity can be demonstrated, a dose level below MTD may be defined as the biologically effective dose (BED).

This lower dose level, or an intermediate dose considered the BED, may be tested as the RP2 dose for further evaluation in Part 2. Part 2 may start enrolling once Part 1 has

completed enrollment of Schedule 1 (once every three weeks) and after the preliminary PK and relevant PD data have been analyzed. The once weekly schedule may be explored prior to or in parallel with the expansion cohorts. Data considered will include, but not be limited to, relationships between safety and exposure, the PK profiles, as well as any emerging PD information, and early signs of clinical activity observed for each schedule evaluated in Part 1. If the once weekly schedule is explored prior to initiating Part 2, the chosen dosing regimen would need to provide evidence of the following in order to be the preferred schedule in Part 2: a better safety and tolerability profile at an equivalent or higher dose, or greater clinical activity, or a more desirable PK profile (i.e. no evidence of target-mediated disposition observed over the dosing interval). A preference might be given to the weekly schedule if at MTD1, the receptor occupancy levels are considered sub-optimal and/or saturation of soluble sBCMA is not maintained long enough on the every 3 weeks dosing schedule.

Part 2: Expansion Cohort:

(Note: For details on scheduled procedures in subjects given GSK2857916 in Part 2, refer to Time and Events Tables Section 7.1.2. The Time and Events Table for GSK2857916 administered to MM subjects on Schedule 1 is represented in Section 7.1.2.1, and the Time and Events Table for GSK2857916 administered to MM subjects on Schedule 2 is represented in Section 7.1.2.2. Refer to Time and Events Tables Section 7.1.2.3 and Section 7.1.2.4 for GSK2857916 administered to subjects with lymphomas on Schedule 1 or Schedule 2, respectively).

Once the RP2 dose and schedule have been selected, expansion cohorts will be enrolled in order to better characterize the safety profile of the selected dose and schedule.

- The Part 2 expansion will enroll up to 50 subjects as summarized below:
    - Multiple Myeloma cohort (up to 40 subjects)- no prospective screening of BCMA is required for enrollment
        - Futility analyses based on ORR will take place after approximately 15, 22 and 30 subjects have been evaluated for response. Full details can be found in Section 13.6.2
        - BCMA expression data and retrospective analysis will be performed on samples collected in the MM population
        - PRO will be collected via eDiary in the MM population in Part 2 only
        - BCMA positive lymphomas (defined as BCMA positive staining by IHC) (up to 10 subjects) – prospective screening of BCMA expression is required for enrollment
- Sparse PK sampling will be collected from all subjects in Part 2 to explore exposures of GSK2857916 at the RP2 dose (BED or MTD) and schedule. Genetics research

samples will also be collected as outlined in Section 7.6 and in the Time and Events Table in Section 7.1.2.

Note: For details on data dissemination and communication with sites (safety update meetings), refer to Section 12.1.

3.5. Intra-Subject Dose Escalation

For the subjects enrolled in Part 1, intra-subject dose escalations may be considered on a case-by-case basis, provided that the subject completed at least 2 cycles at originally assigned dose, still fulfils eligibility criteria, has tolerated treatment well, and did not experience Grade 3 or higher toxicity. A subject's dose may be increased to that of a completed cohort that has not exceeded the MTD. Approval must be obtained from a GSK Medical Monitor. Dose-escalation decisions will be documented on a Dose Escalation/De-escalation Decision Form (see SPM).

3.6. Rationale

3.6.1. Rationale for Study

This study will assess the safety, PK, PD and the therapeutic potential of GSK2857916 in subjects with MM and lymphomas that express BCMA. GSK2857916 is a humanized IgG1 antibody drug conjugate (ADC) which binds specifically to BCMA. The parent anti-BCMA antibody (J6M0) is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF) via a protease resistant maleimidocaproyl (mc) linker to produce the GSK2857916 ADC molecule. Upon binding to the cell surface, GSK2857916 is rapidly internalized and active drug (cys-mcMMAF) is released inside the cell.

GSK2857916 has been produced in an afucosylated form to generate an enhanced antibody dependent cellular cytotoxicity (ADCC) response upon binding to FcγRIIIa receptors on the surface of human effector cells. This dual mechanism of action may improve efficacy by targeting dividing and non-dividing tumor cells. Importantly, BCMA expression is maintained at the cell surface over time following GSK2857916 binding and internalization due to rapid BCMA receptor recycling and/or new protein synthesis. GSK2857916 has demonstrated dose-dependent cytotoxic activity in myeloma cell lines, ex vivo primary myeloma tumor samples, as well as preclinical myeloma mouse tumor models. GSK2857916 has also shown activity in B cell lymphoma cell lines that express BCMA.

The hypothesis is that GSK2857916 can be safely administered to subjects with BCMA positive malignancies at doses where target engagement can be demonstrated. This study will determine if adequate target engagement of BCMA receptors translates into clinical benefit for subjects with MM and BCMA positive lymphomas.

3.6.2. Rationale for Population

The anti-tumor activity of GSK2857916 relies strictly on its binding to the BCMA cell surface receptor. Following binding to receptor the drug will be internalized and the toxin (MMAF) will be released inside the cell to cause cell cycle arrest and subsequent death.

In addition, the antibody on the cell surface will recruit effector cells via the ADCC mechanism to kill the tumor cells. It is prudent that the target population for this study is required to express BCMA. The MM population has been selected for this FTIH trial because this population has the highest likelihood of expressing BCMA. BCMA expression levels in MM vary from patient to patient, but our studies demonstrate that all MM patients tested express detectable levels of BCMA protein on their tumor cells. Specifically, GlaxoSmithKline (GSK) studies have shown that in samples taken from MM patients (N=45), 31% have low expression, 38% moderate expression and 31% high expression of BCMA as detected by immunohistochemistry (IHC). Subjects with lymphomas that exhibit BCMA expression have been selected as an exploratory cohort in this FTIH study; the frequency of BCMA expression in lymphomas is lower than that observed in MM, therefore prospective selection is required.

The target population for this study includes subjects with relapsed/refractory MM to establish the dose and characterize safety, PK and PD of GSK2857916. Subjects with BCMA expressing lymphomas will also be allowed on study after prospective screening by IHC demonstrates that BCMA is expressed on tumor cells. Potential subjects with B-cell lymphomas that will be tested for BCMA expression prior to study entry include subjects with the following diseases: Diffuse Large B-Cell Lymphoma (DLBCL), or Follicular Lymphoma (FL), that have progressed after 2 prior lines of systemic therapy for a given disease.

3.6.3. Rationale for Starting Dose

The dose selection of GSK2857916 in this proposed first time in human study (FTIH) took into consideration both the ADC and enhanced ADCC mechanisms that are combined in this molecule and was based on estimations derived from different approaches that included non clinical biology, toxicology as well as pharmacokinetic data collected in two species in particular mouse and monkey.

The following methods were used to support the determination of the starting dose:

- methods specific for oncology compounds based on results of toxicology studies (for ADC mechanism)

- Minimum Anticipated Biological Effect Level (MABEL) (for ADCC mechanism)

3.6.3.1. Human PK prediction

The human PK profile of GSK2857916 was predicted using the monkey pharmacokinetic data collected during the pre-clinical development of GSK2857916. Analysis of the monkey pharmacokinetic data using a 2-compartment PK model provided estimates of PK parameters in this species. In these conditions, the clearance of GSK2857916 in the monkey was 0.00242 L/h or 19.6 mL/day/kg, the volume of distribution was 0.310 L or 105 mL/kg and the half-life was approximately 5 days. An allometric scaling approach was used to predict the PK parameters in humans, with powers of unity for volume and 0.75 for clearance. Assuming a bodyweight of 70 kg for humans, the predicted human clearance (CL) is 0.0259 L/h or 8.89 mL/day/kg, the volume of distribution (Vss) is 7.33 L or 105 mL/kg and the plasma elimination half-life is approximately 12 days in the

absence of target. Predicted human exposure at different doses with the predicted safety cover in relation to the monkey (cross-reactive species) and rat (non-target specific) exposure was determined assuming no target mediated disposition and in the absence of soluble BCMA (most conservative case), therefore human predicted exposure (i.e. AUC and Cmax) as well as the ratio predicted Cmax/IC50 will be likely over-estimated in particular at the lower doses (i.e. <1 mg/kg) (Table 6 and Table 7).

Table 6 Safety margins when comparing monkey NOAEL data (cross-reactive species) with predicted human data for various doses of GSK2857916 administered IV ('safety cover')

Predicted Human Cmax and AUC			Safety cover (vs. Monkey NOAEL)			Ratio of predicted humanCmax/IC50[1]
Dose (mg/kg)	Cmax (µg/mL)	AUC (µg*h/mL)	Dose cover	Cmax cover	AUC cover	
0.03	0.593	81.0	33x	46.4x	15.3x	6.03x
0.05	0.988	135	20x	27.8x	9.2x	10.1x
0.1	1.98	270	10x	13.9x	4.6x	20.1x
0.2	3.95	540	5.0x	7.0x	2.3x	40.2x
1	19.8	2700	1.0x	1.4x	0.5x	201x
2	39.5	5400	0.5x	0.7x	0.2x	402x
5	98.8	13500	0.2x	0.3x	0.1x	1006x

1. IC50 = 0.1 µg/mL for depletion of CD19+/CD27hi/CD38hi plasmablasts in whole blood (ADCC mechanism)

Table 7 Safety margins when comparing rat NOAEL data (non-target specific) with predicted human data for various doses of GSK2857916 administered IV ('safety cover')

Predicted Human Cmax and AUC			Safety cover (vs.rat NOAEL)		
Dose (mg/kg)	Cmax (µg/mL)	AUC (µg*h/mL)	Dose Cover	Cmax Cover	AUC Cover
0.03	0.593	81.0	100x	174x	75x
0.05	0.988	135	60x	104x	45.2x
0.1	1.98	270	30x	52.1x	22.6x
0.2	3.95	540	15x	26.1x	11.3x
1	19.8	2700	3x	5.2x	2.3x
2	39.5	5400	2x	2.6x	1.1x
5	98.8	13500	1x	1.0x	0.5x

3.6.3.2. Starting dose determination

A summary of the *in-vitro* and *in-vivo* IC50s for both the ADC and ADCC mechanisms are summarized below (Table 8).

Table 8 GSK2857916 in-vitro – in-vivo IC50 Values

Mechanism	System	IC50 (ng/mL) (range)
ADCC (*In vitro*)	H929 target cells (n=8 PBMC donors) GSK	1.63[1] (0.57-4.79)
	JJN3 target cells (n=8 PBMC donors) GSK	9.42[1](1.01-111.3)
	primary human MM CD138+ tumor cells (n=10 donors) Farber	~100
	depletion of CD19+/CD27hi/CD38hi plasmablasts in whole blood (n=4 donors) GSK	98[1] (34-221)
	H929 in presence of sBCMA	116
Cytokine induction from effector cells *in vitro*	Cytokines induction from PMBC in presence of H929 target cells and GSK2857914 (ADCC enhanced only)	< 100[2]
ADC (*In vitro*)	Across various expressing cells lines (n=12)	45.6[1] (3-244)
	H929 target cells GSK	8.9 (8.0 – 9.8)[3]
	JJN3 target cells GSK	25.1 (18.2 – 34.8)[3]
ADC (*in vivo*)	Mouse xenograft	2540

1. Geometric mean
2. value reported is not an IC50, please refer to Section 5.6.3 of the IB for full description
3. (95% CI) The values reported are for GSK2857916

Based on *in-vitro* H929 cell lines experiments, the ADCC mechanism appears to be approximately 5.5-fold more potent than the ADC mechanism (1.63 ng/mL versus 8.9 ng/mL). The same pattern is observed with the JJN3 cell lines where the ADCC mechanism appears to be approximately 2.7-fold more potent than the ADC mechanism (9.42 ng/mL versus 25.1 ng/mL). Additionally, from the receptor occupancy curve and the killing activity curves for the ADCC and ADC mechanisms, it can be noted that maximum killing activity can be achieved at low binding.

- *Based on results of toxicology studies (ADC mechanism)*

Several methods were applied to look at the toxicologic aspect of GSK2857916 for the estimation of the starting dose based on the toxicology findings from the GLP toxicology studies conducted in both the rat and monkey species (refer to Section 1.2.4 for more details). A summary of the calculated starting dose from the different methods is provided in Table 9 below.

Table 9 Calculated starting dose from different approaches based on findings of toxicology studies

Methods	Starting dose
1/10th STD_{10} rat (BWT based)	1 mg/kg
1/6th HNSTD in monkey (BWT based)	0.5 mg/kg
1/6th HNSTD in monkey (**BSA** based)	0.15 mg/kg
1/10th NOAEL in monkey (BWT based)	0.1 mg/kg
1/10th NOAEL in monkey (**BSA** based)	0.03 mg/kg

- *Based on MABEL determination (ADCC mechanism)*

In order to investigate the pharmacology aspect of GSK2857916, predicted receptor occupancy (RO), based on the binding affinity of the drug for its target and BCMA receptor concentration, at the predicted Cmax (assuming no target mediated disposition and in the absence of soluble BCMA) of various doses were estimated and summarised in Table 10 below.

Table 10 Predicted receptor occupancy at Cmax for various doses

Dose (mg/kg)	Cmax (µg/mL)	RO
0.03	0.593	36%
0.05	0.988	55%
0.1	1.98	81%
0.2	3.95	93%
1	19.8	99%
2	39.5	99%
5	98.8	100%

To assess the excess of drug over target, the ratio of predicted Cmax at different doses to the BCMA receptor concentration in the bone marrow (Table 11) was also estimated

based on a published estimate of the number of multiple myeloma cells [Sullivan, 1972] an in-house determination of the number of BCMA receptor per cell.

Table 11 Ratio of predicted Cmax to the BCMA receptor concentration in the bone marrow at various doses of GSK2857916

Dose (mg/kg)	Cmax (nM)	Ratio of predicted human Cmax/BCMA Receptor concentration
0.03	3.95	0.45
0.05	6.58	0.74
0.1	13.2	1.49
0.2	26.3	2.97
1	132	15
2	263	30
5	658	74

Additionally, to incorporate the dynamic aspect, a drug-receptor binding PKPD model was developed that incorporates the major elements believed to be involved in the drug disposition process (e.g. tumor load, number of BCMA receptors on multiple myeloma cells, internalisation rate of the complex of drug-BCMA receptor formed, shedding rate of the BMA receptors (soluble BCMA) based on pre-clinical data (*in-vitro* as well as *in-vivo*) generated in house, and assumptions supported by published data in the literature. The model simulates the predicted level of receptor occupancy achieved over time, the accumulation of the molecule intracellularly via internalization of the ADC-receptor complex formed and consequently cys-mcMMAF, as well as the tumor regression. Mouse xenograft data generated during the pre-clinical development of GSK2857916 for which PK samples were also collected were modeled in order to derive an IC50 for tumor regression in relation to the cytotoxic agent (MMAF) of the molecule (ADC mechanism). This information was used in the drug-receptor binding PKPD model. Predicted Cmax and receptor occupancy assuming a high and low tumor burden at various doses are presented below. Prediction incorporates target-mediated disposition and presence of soluble BCMA.

Table 12 Predicted Cmax and receptor occupancy assuming a high and low tumor burden at various doses

	High tumor load		Low tumor load (10-fold lower)	
Dose (mg/kg)	Cmax (µg/mL)	RO	Cmax (µg/mL)	RO
0.03	0.037	2%	0.30	22%
0.1	0.21	8%	1.7	52%
1	15.7	91%	21	96%
5	104	99%	108	99%

Selection of starting dose:

In light of the potent ADCC mechanism in this unprecedented combination of enhanced ADCC and ADC mechanism in GSK2857916 and the novelty of the target (BCMA receptor), the MABEL approach to determine the starting dose was felt more appropriate. This is further supported by the fact that the monkey GLP toxicology study was conducted in healthy monkey (i.e. with no tumor) and that the mouse xenograft experiments did not fully explore the enhanced ADCC mechanism (human tumor but mouse effector cells). Furthermore, with both GSK2857916 (ADC molecule) and GSK2857914 (ADCC enhanced only) a general systemic inflammatory response was observed which could be attributable to the ADCC mechanism or related to the target binding. An increase in cytokine levels was observed with GSK2857914 which again could be attributed to the ADCC mechanism or to target binding. Finally, in the agonism assay, cross-linking with GSK2857914 induced NFκB signaling in H929 cells (with an EC50 in the range of 0.65-1.67 μg/mL). Taking into consideration all this information and the information derived from different methods looking at both the toxicology and pharmacology aspects of GSK2857916, a starting dose of **0.03 mg/kg** is proposed to account for the ADCC mechanism of the molecule that is anticipated to occur first and is believed to be the most important mechanism to consider in the determination of the starting dose. This dose is lower than the 1/6th HNSTD in the monkey, the most relevant species for this molecule as it cross-reacts with monkey BCMA, based on body surface area. Assuming no target mediated disposition and absence of soluble BCMA, this dose is predicted to provide 36% receptor occupancy. From a drug-receptor binding PKPD model that incorporates target mediated disposition and the presence of sBCMA, this dose is anticipated to confer between 2-22% receptor occupancy, depending on the tumor load.

3.6.3.3. Potential therapeutic dose determination

From the drug-receptor binding PKPD model (considering target mediated disposition and soluble BCMA), doses in the range 1-5 mg/kg (depending on tumor load) are anticipated to confer maximal therapeutic activity with an average predicted receptor occupancy of approximately 90% over the interval between two doses (i.e. 21 days) following the first dose and maximal anti-tumor effect afforded by the drug. This is also aligned with the *in-vivo* IC90 (approximately 20 μg/mL) for tumor regression in relation to the cytotoxic agent of the molecule (ADC mechanism) derived from the mouse xenograft data in the presence of soluble BCMA and the *in-vitro* IC90 for the ADCC mechanism of 0.5 μg/mL (depletion of CD19+/CD27hi/CD38hi plasmablasts in whole blood) or approximately 10 μg/mL (primary human MM CD138+ tumor cells).

Of note, competitor ADC molecules using MMAF as the cytotoxic agent have identified 3 mg/kg every 3 weeks as the MTD SGN-75 [Thompson, 2013] and AGS-16M8F doses up to 4.8 mg/kg every 3 weeks have been reported with no MTD identified yet [Beck, 2012].

3.6.4. Rationale for Endpoints

The endpoints of this study are designed to evaluate the safety, PK and PD of GSK2857916 in subjects with MM. Safety assessments will detect emerging safety signals and identify DLTs for determination of MTDs and a recommended dose and schedule of GSK2857916 for further exploration in expansion cohorts.

The collection of PK samples for determination of GSK2857916 plasma (intact, total antibody and cys-mcMMAF) concentrations will allow characterization of the PK profile and support investigation of its pharmacology.

Tumor biomarker selection was based on the dual mechanism of action of GSK2857916 (ADCC and ADC activity), the need for BCMA receptor expression for GSK2857916 to execute its action, and preclinical evidence that BCMA is a relevant therapeutic target. The study will seek to characterize the PD effects of GSK2857916 and to obtain preliminary data on the relationship between BCMA expression and other potential biomarkers (e.g., [redacted] that may influence clinical response.

Markers showing significant correlation between baseline levels and clinical outcome may have predictive value and maybe further explored for utility in patient selection in future trials.

Anti-tumor activity will be explored to evaluate the potential for clinical benefit from GSK2857916 treatment. In addition, patient report outcomes will also be studied in Part 2 (MM subjects only)

3.7. Study Treatment

3.7.1. Treatment Assignment

Dose level allocation will be performed by GSK after subjects have given their written informed consent and have completed the necessary screening assessments.

- The site staff will fax and/or email a complete Registration Form to the designated GSK study team member.

- Subjects will be identified by a unique subject number that will remain consistent for the duration of the study. The subject number will be used on all Case Report Form (CRF) pages and other trial-related documentation or correspondence referencing that subject.

- Upon completion of all the required screening assessments, eligible subjects will be registered into RAMOS (Registration and Medication Ordering System), the GSK interactive voice response system (IVRS), by the investigator or authorized site staff. All enrolled subjects will receive GSK2857916.

Additional details are outlined in the SPM.

3.8. Dosage and Administration of Study Treatment(s)

GSK2857916 will be administered intravenously over 60 minutes. Subjects enrolled in Schedule 1 will receive one dose every 3 weeks (21 days) for a maximum of 16 cycles (16 doses). Subjects enrolled in Schedule 2 will receive one dose per week for 3 consecutive weeks followed by 1 week rest (28 day cycle) for a maximum of 16 cycles (48 doses).

The maximum dose to be administered to subjects in this trial is 5 mg/kg.

Refer to Section 4 for details on preparation and handling, and administration instructions of GSK2857916.

3.8.1. Blinding

This is an open-label study.

3.9. Safety Management Guidelines

3.9.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of study treatment(s) and the follow-up period. Study treatment(s) will be stopped if any of the following liver chemistry stopping criteria is/are met:

1. Alanine aminotransferase (ALT) ≥3 X (times) upper limit of normal (ULN) and bilirubin ≥2 Xs ULN (or ALT ≥3 X ULN and international normalization ratio [INR] >1.5)

NOTE: Serum bilirubin fractionation should be performed.

2. ALT ≥5 X ULN.
3. ALT ≥3 X ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. ALT ≥3 X ULN persists for ≥4 weeks.
5. ALT ≥3 X ULN and cannot be monitored weekly for 4 weeks.

Subjects with ALT ≥3 X ULN **and** <5 Xs ULN **and** bilirubin <2 X ULN, who do not exhibit hepatitis symptoms or rash, can continue study treatment(s) as long as they can be monitored weekly for 4 weeks. See following section for details on weekly follow-up procedures for these subjects.

3.9.1.1. Liver Chemistry Follow-up Procedures

Refer to the diagram in Appendix 8 for a visual presentation of the procedures listed below.

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 3.9.1:

- Immediately and permanently withdraw the subject from study treatment
- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment(s) cessation and follow-up
- Complete the "Safety Follow-Up Procedures" listed below
- Complete the liver event electronic case report forms (eCRFs). If the event also meets the criteria of a serious adverse event (SAE) (see Section 8.2), the SAE data collection tool will be completed separately with the relevant details
- Upon completion of the safety follow-up permanently withdraw the subject from the study and do not rechallenge with study treatment(s)

Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN:

- Monitor subjects **weekly** until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], and bilirubin) resolve, stabilize or return to within baseline values

Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN and bilirubin ≥2 times ULN (or ALT ≥3 times ULN and INR >1.5):

- **This event is considered an SAE** (see Section 8.2). Serum bilirubin fractionation should be performed.
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended)
- Monitor subjects **twice weekly** until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

In addition, for <u>all</u> subjects with ALT ≥3 times ULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including:
  - Hepatitis A Immunoglobulin M (IgM) antibody
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
  - Hepatitis C ribonucleic acid (RNA)
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
  - Hepatitis E IgM antibody (if subject resides outside the United States (US) or Canada, or has traveled outside US or Canada in past 3 months)

- Blood sample for PK analysis. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment(s) prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected within 48 hours of learning of the abnormality, **do not obtain a PK sample**. Instructions for sample handling and shipping are included in the SPM.
- Serum creatine phosphokinase and lactate dehydrogenase
- Fractionate bilirubin, if total bilirubin ≥2 times ULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia, on the AE eCRF
- Record use of concomitant medication(s), acetaminophen, herbal remedies, other over-the-counter medication(s), or putative hepatotoxins on the Concomitant Medications eCRF
- Record alcohol use on the Liver Events eCRF

The following are required for subjects with ALT ≥3 times ULN **and** bilirubin ≥2 times ULN but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance imaging [MRI] or computed tomography [CT] scan) to evaluate liver disease
- Liver Imaging and/or Liver Biopsy eCRFs are also to be completed if these tests are performed
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE**: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793.

3.9.2. QTc Stopping Criteria

Study treatment will be withheld in a subject who meets the corrected QT (QTc)[1] interval duration criteria below.

- QT interval corrected for heart rate by Fridericia's formula (QTcF) >500 msec

or

- Increase in QTc of > 60 msec from baseline

[1]Based on average QTc value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment withheld.

3.9.3. Troponin Evaluation and Stopping Criteria

If post-screening, the local cTn is >Institutional ULN it is recommended that subjects undergo urgent evaluation of cardiac ischemia symptoms and ECG should be performed to rule out cardiac ischemia. An urgent repeat of cTn value and collection of sample for central lab evaluation should be obtained within 24 hours.

Asymptomatic subject:

If the second value of cTn is ≤ULN the subject can continue on study with close follow up of symptoms, ECG, and further cTn measurements as clinically indicated

If the second value of cTn remains >ULN treatment with GSK2857916 should be interrupted. The subject should undergo cardiac evaluation including ECHO testing for cardiac function. Any re-start of study treatment must be discussed with the GSK medical monitor who will consult with a member of the internal cardiotoxicity panel prior to re-start.

If the second value of cTn exceeds the threshold for MI according to local lab parameters, obtain cardiology consultation immediately. Permanently discontinue GSK2857916 and withdraw the subject from the study.

Symptomatic subject:

Obtain cardiology consultation immediately. Permanently discontinue GSK2857916 and withdraw the subject from the study.

3.9.4. Left Ventricular Ejection Fraction (LVEF)

3.9.4.1. LVEF Stopping Criteria

Echocardiography (ECHO) must be performed at Screening and as outlined in the Time and Events Tables (Section 7.1). Subjects who have an asymptomatic, absolute decrease of >15% in LVEF compared with baseline or an absolute decrease of >10% in LVEF compared with baseline and the ejection fraction is below 50% should temporarily interrupt GSK2857916 and have a repeat evaluation of LVEF within 1 week. ECHO should be repeated every 1 to 2 weeks for 4 weeks or until LVEF recovery to within 15% of baseline or to above 50% and within 10% of baseline depending on which stopping criteria above were met.

- If the LVEF recovers (defined as absolute decrease ≤15% compared to baseline or ≥50% and absolute decrease ≤10% compared with baseline) at any time during the next 4 weeks, after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK2857916 at a reduced dose. For such subjects, monitoring of LVEF will be performed 2, 4, and 8 weeks after rechallenge, and then per protocol
- If LVEF does not recover within 4 weeks, treatment with GSK2857916 should be permanently discontinued. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution

Subjects with Grade 3 or 4 symptomatic left ventricular systolic dysfunction must discontinue treatment with GSK2857916. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution.

Copies of all ECHOs and cardiology consultations performed on subjects who experience a >15% decrease in LVEF from baseline or >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <50% will require review by a GSK medical monitor. Instructions for submitting qualifying ECHOs/MUGAs are provided in the SPM.

3.9.4.2. Valvular Toxicity Stopping Criteria

Subjects who develop a new asymptomatic, moderate regurgitation or stenosis by echocardiogram (ECHO) (Grade 2 mitral/tricuspid/aortic valvular toxicity per National Cancer Institute- Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 4.0) should temporarily discontinue GSK2857916 and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1 to 2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the next 4 weeks after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK2857916 at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 8 weeks and then per protocol.
- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue GSK2857916. The valve should continue to be monitored via ECHO every 4 weeks for 8 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention) valvular toxicity must discontinue GSK2857916. Valvular toxicity should continue to be monitored every 4 weeks for 12 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the subject may restart GSK2857916at a reduced dose after consultation and approval of the GSK Medical Monitor.

ECHO must be performed at baseline and at the final study visit. Copies of all ECHO(s) and cardiology consultations performed on subjects who experience valvular toxicity will

be required by GSK for review. Instructions for submitting qualifying ECHOs are provided in the Study Procedures Manual (SPM).

3.9.5. Infusion-related Reactions and Cytokine Release Syndrome

Premedication is not allowed prior to first infusion unless deemed medically appropriate by the GSK Medical Monitor in consultation with investigators following evaluation of infusion related reactions across cohorts. Premedication should be considered in any subject who experienced an infusion related reaction at first or any subsequent infusion with GSK2857916.

If an infusion-related reaction occurs during administration, the infusion rate may be reduced or halted at the discretion of the investigator and/or GSK medical monitor depending on the severity of the symptoms. The subject will receive appropriate medical treatment. When the subject's condition is stable, the infusion may be restarted according to the judgment of the investigator. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused.

Blood for serum cytokines should be collected in each subject who developed infusion related reaction regardless whether the infusion has been completed or not. The time of serum collection will be documented in eCRF.

- Grade 1 allergic reactions or cytokine release syndrome
    - If infusion is ongoing, it may continue but subject should be monitored carefully to ensure that ongoing signs and symptoms do not progress and worsen warranting intervention as described below
- Grade 2 allergic reactions and/or cytokine release syndrome
    - Stop the infusion, follow subject frequently for clinical symptoms
    - Initiate symptoms treatment as clinically indicated
    - Once subject has recovered to baseline and if in the opinion of the investigator the safety/risk benefit is favorable, consideration can be given to restarting the infusion at 50% of the original rate after pre-medication with H1 receptor antagonist and acetaminophen
    - If treatment is continued, the subject should be pre-medicated prior to each subsequent dose and the infusion will be administered at 50% of the original rate
- Grade 3 or higher allergic reactions and/or cytokine release syndrome
    - Stop infusion immediately
    - Initiate symptoms treatment as clinically indicated
    - Do not resume infusion with GSK2857916

- Follow the subjects for safety as clinically indicated until toxicity resolves
- Complete safety documentation
- Subjects who experience ≥ Grade 3 allergic reaction will be withdrawn from study
- Further treatment with GSK2857916 in subjects who experience a ≥ Grade 3 infusion related reaction needs to be discussed with MM prior to next dose administration. Those subjects will be allowed to continue on study after recovery of the reaction to ≤ Grade 1 but will have to receive pre-medication prior to each subsequent dose of GSK2857916, and their infusion time will be extended to 2-4 hours (depending on severity of the reaction).

3.9.6. Allergic and Anaphylactic reaction

As GSK2857916 is a fully humanized ADC, it is considered unlikely for acute allergic reactions to occur in response to GSK2857916 exposure; however, all subjects will be monitored carefully for evidence of allergic response. A subject that exhibits signs or symptoms of severe hypersensitivity or anaphylaxis will receive appropriate medical treatment and be withdrawn from the study.

In accordance with the preparedness for treatment of anaphylaxis, emergency resuscitation equipment, advanced cardiac life support equipment, and medications must be readily accessible during GSK2857916 administration.

It is important to recognize early signs of an anaphylaxis reaction and appropriate treatment must begin immediately to prevent progression to severe anaphylaxis. Subjects will be closely monitored in an appropriate setting for early signs of dyspnea and edema. Antihistamines, such as diphenhydramine; and corticosteroids such as prednisone may be given to reduce symptoms.

If more severe clinical signs arise, immediate assessment of the ABC's (airway, breathing, and circulation from Basic Life Support) will be done in all suspected anaphylactic reactions. Cardio-Pulmonary Resuscitation (CPR) will be initiated if needed. Epinephrine will be given by injection without delay. Emergency interventions may include endotracheal intubation or tracheostomy. Treatment for shock will include IV fluids and medications that support the actions of the heart and circulatory system.

3.9.7. Tumor Lysis Syndrome (TLS) Prevention and Treatment Recommendations

Subjects with a high tumor burden with a high proliferative rate might be at risk for TLS and should be monitored for clinical and laboratory signs of tumor lysis. Specifically, all subjects with elevated uric acid (>8mg/dL, or >476mmol/L) should receive prophylaxis with allopurinol, or rasburicase. All subjects should be hydrated to reduce risks for renal toxicity and tumor lysis syndrome (TLS) with GSK2857916 treatment. Adequate fluid volume status should be maintained throughout treatment and blood chemistries should

be monitored as indicated in the Time and Events Tables in Section 7.1 or more frequently if clinically indicated. Prior to the first dose in Cycle 1, all subjects should receive at least 250- 500 mL of intravenous normal saline or other appropriate intravenous fluid. Additionally, 250-500 mL of intravenous fluid should be given as needed following GSK2857916 administration. Intravenous hydration should be continued, as needed, in subsequent cycles and subjects should be monitored for fluid overload during this period.

If the constellation of clinical and/or laboratory signs tested on Cycle 2 Day 1 indicates a possibility of developing TLS, subjects should be hospitalized with frequent monitoring of clinical signs and clinical chemistries and treated accordingly.

3.9.8. Ocular Toxicity and Stopping Criteria

All subjects will be advised to use prednisolone phosphate 1% or dexamethasone 0.1% eye drop 4 times a day (QID) for 4 days starting 1 day prior to each dose. Additional use of lubrication eye drops (artificial tears) QID PRN throughout the trial is recommended, especially if subject develops any ocular symptoms. Subjects who develop Grade 3 ocular or corneal toxicity will be allowed to continue study treatment after resolution to ≤ Grade 1; each case will be discussed individually between the investigator and the Medical Monitor. Subjects who develop ≥ Grade 4 ocular or corneal toxicity will be permanently removed from study. Refer to Section 3.10.2 for further guidance.

3.10. Guidelines for Events of Special Interest and Dose Modifications

3.10.1. Guidelines for Events of Special Interest

The severity of adverse events (AEs) will be graded utilizing the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment are provided in this section.

3.10.2. Predicted Toxicities and Proposed Dose Adjustments/Stopping Criteria

Toxicity	Grade/symptoms	Recommendations

Creatinine elevation which cannot be explained by concomitant sepsis, other severe infection with fever or dehydration	If absolute serum creatinine increase from baseline of > 0. 3 mg/dL (26 μmol/L) but ≤ 0.5 mg/dL (44 μmol/L)	Repeat within 48 hours
		• If creatinine returns to ≤0. 3 mg/dL (26 μmol/L) above baseline
		  o Continue GSK2857916 at current dose
		• If creatinine remains elevated: > 0. 3 mg/dL (26 μmol/L) but ≤ 0.5 mg/dL (44 μmol/L) from baseline
		  o Continue GSK2857916
		  o Monitor creatinine at least weekly
		  o Consider 25% dose reduction if creatinine remains elevated (after discussion with Medical Monitor)

	If absolute serum creatinine increase from baseline of >0. 5 mg/dL	Repeat within 48 hours: • If confirmed: withhold therapy, institute treatment and monitoring as clinically indicated, and follow for resolution • Discuss any further dosing with Medical Monitor* * Medical Monitor should consult GSK's nephrotoxicity panel about plans to continue therapy
Serum creatinine≥ Grade 3	>3.0mg/dL from baseline or 3.0-6.0xULN	• Provide appropriate medical treatment. • Permanently discontinue treatment with GSK2857916

Toxicity	Grade/symptoms	Recommendations
Albuminuria	>2000mg/24 hr	• Re-test (at least 7 days apart). o If not confirmed, continue GSK2857916 at 100% dose o If confirmed on re-test and no clear evidence of disease progression* ▪ Interrupt treatment with GSK2857916 ▪ Repeat testing within 4 weeks • If albuminuria ≤2000mg/24hr may restart GSK2857916 with 25% dose reduction • If albuminuria remains >2000mg/24hr after 4 weeks; Permanently discontinue GSK2857916 and withdraw subject from study; provide treatment as clinically indicated and follow for resolution * Medical Monitor should consult GSK's nephrotoxicity panel about plans to continue therapy
Thrombocytopenia	Grade 3: >25 and <50x10^9/L	• Where estimated blood loss is ≥ 10 mL: withhold the treatment: • No bleeding: continue treatment with 25% dose reduction
	Grade 4: ≤25x10^9/L	• Withhold the dose. Consider restarting with 25% dose reduction if recovered to >25x x10^9/L , only if there is no active bleeding at time of treatment re-start • If thrombocytopenia is considered disease related, is not accompanied by bleeding, and recovers with transfusion to >30 x10^9/L within 14 days, restarting treatment at 50% dose reduction may be considered after discussion with the GSK Medical Monitor
Febrile neutropenia	>38.3^{o}C for> 1 hr AND ANC < 1000/mm^3	• Withhold GSK2857916, implement treatment with antibiotics, antivirals and antifungals, as clinically indicated, • If resolved ≤ 14 days, may restart GSK2857916 treatment at 25% dose reduction

Toxicity	Grade/symptoms	Recommendations
INR prolongation	> 1.5	• Evaluate liver function and other possible causes for INR elevation (use of anticoagulants, work up for DIC and provide treatment as clinically indicated – If subject meets liver stopping criteria: Withdraw from study treatment as per liver stopping criteria – If subject has evidence of DIC: withdraw subject from study treatment – If isolated INR elevation and subject does not meet liver stopping criteria • Withhold the dose and re-test INR within 48hrs • Discuss the case with Medical Monitor and consider 25% dose reduction
	> 2.0	• Evaluate possible reasons as above, treat adequately if underlying condition has been identified • Restart treatment with GSK2857916 at 25-50% dose reduction if toxicity resolved to ≤1.5 baseline and after discussing the case with GSK Medical Monitor
	>2.5	• Evaluate and provide medical treatment if necessary • If INR prolongation is not related to use of anticoagulants withdraw subject from study treatment
Ocular/corneal toxicity	Grade 1	• Continue treatment with current dose of GSK2857916. • Consult ophthalmologist within 7 days
	Grade 2	• First occurrence: o Interrupt treatment with GSK2857916 o Consult ophthalmologist immediately o When recovered to G≤1 Restart treatment with GSK2857916 at 25% dose reduction upon resolution to ≤G1 • Second occurrence: o Interrupt treatment with GSK2857916 o Consult ophthalmologist immediately o Once resolved to≤ G1 or less: Restart treatment with GSK2857916

Toxicity	Grade/symptoms	Recommendations
		at additional 25% dose reduction • Third occurrence: o Further treatment with GSK2857916 only allowed after discussion and in agreement with medical monitor
	Grade 3	• First occurrence o Consult ophthalmologist immediately o Interrupt treatment with GSK2857916 o Once resolved to ≤ G1: Restart treatment with GSK2857916 at 25% -50% dose reduction if the investigator and Medical Monitor agree that the potential benefits outweigh the risks • Second occurrence o Consult ophthalmologist immediately o Permanently discontinue treatment with GSK2857916
	Grade 4	• Consult ophthalmologist immediately • Permanently discontinue treatment with GSK2857916
Pneumonitis	Grade 1	Withhold dose and follow recommendations below: Obtain high resolution chest CT if possible. • CT scan (high-resolution with lung windows) recommended • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation with pulmonologist recommended • If resolved: Retreatment at the full dose is possible
	Grade 2	Withhold treatment with GSK2857916 Follow recommendations below: Obtain high resolution chest CT if possible. • CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist

Toxicity	Grade/symptoms	Recommendations
		• Pulmonary function tests (PFT) – if abnormal, repeat every 8 weeks until back to baseline • Bronchoscopy with biopsy and/or bronchoalveolar lavage (BAL) recommended • Symptomatic therapy including corticosteroids if clinically indicated If resolved: Restart treatment with 50% dose reduction
	Grade 3/Grade 4	Permanently discontinue treatment with GSK2857916, and follow recommendations below. • Obtain CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • PFT – if abnormal, repeat every 8 weeks until back to baseline Bronchoscopy with biopsy and/or BAL if possible • Symptomatic therapy including corticosteroids as clinically indicated

3.10.3. Dose Modifications

For GSK2857916 toxicities not specifically addressed in the protocol follow the guidelines outlined in Table 13.

Table 13 Dose Adjustment/Stopping Criteria

Toxicity Grade[a]	Dose Modification of GSK2857916
Grade 1	• Continue at current dose level. Consider supportive care recommendations
Grade 2	• If toxicity is considered not clinically relevant, continue with 100% scheduled dose • If toxicity is considered clinically relevant withhold the dose until toxicity resolves to Grade 1 or baseline. If resolved within 14 days, then restart at current dose level. Consider supportive care recommendations • If not resolved within 14 days, discuss with GSK Medical Monitor
Grade 3	• Withhold dose until toxicity resolves to Grade 1 or baseline, unless condition fits exceptions noted below. If resolved within 14 days, resume treatment at dose reduced by 25% (first dose reduction), or 50% (second dose reduction). Consider supportive care recommendations. If toxicity is resolved within period longer than 14 days, continuation of treatment may be considered on an individual basis if benefit to subject can be demonstrated and if the investigator and medical monitor agree that for a given subject the benefits may outweigh the risks **Exceptions**: • Subjects who develop G3 toxicities which respond to standard treatment and resolve to ≤G1 within 48 hours may continue treatment at scheduled or reduced dose • Permanently discontinue for grade 3 or greater QTc prolongation i.e., QTcF >500 msec or QTcF increase by > 60 msec from baseline • Troponin elevations: See Section 3.9.3 for troponin stopping criteria
Grade 4	• Permanently discontinue study medication **Exceptions:** • G4 thrombocytopenia with no sign of bleeding, if recovered within 14 days. For dose reductions see Section 3.10 • G4 lymphopenia (dose reductions by 25-50% may be considered)

a. Possibly related to investigational drug.

4. INVESTIGATIONAL PRODUCT(S)

The term 'study treatment' is used throughout the protocol to describe GSK2857916 as the investigational product (IP) received by the subject as per the protocol design.

4.1. Description of Investigational Product

Product name :	**GSK2857916 Solution, 20 mg/mL, 1.5mL anti-BCMA-ADC**
Formulation description:	Solution containing 20mg/mL **GSK2857916**
Dosage form :	Supplied as frozen liquid. Recommended storage condition is -50°C to -15°C.
Unit dose strength(s)/Dose Level(s):	20mg/mL, 1.5mL (Refer to Section 3.3.1.2.1 for dose levels)
Physical Description:	GSK2857916 Solution for Infusion is clear or opalescent; colorless, yellow to brown liquid
Route/ Administration/ Duration:	Delivered as IV solution (see Section 3.8)
Dosing instructions:	Dilute GSK2857916 solution in normal 0.9% saline to the appropriate concentration for the dose. See Section 4.2 for compatible administration materials. Doses of GSK2857916 are to be administered as an IV infusion via an infusion pump that can ensure precision to the decimal point of a mL for the infusion rate at lower doses. It is recommended to prime the tubing with at least 15 mL prior to dosing.
Manufacturer/ Source of Procurement:	GSK
Batch Lot number	132373860

GSK2857916 will be provided to sites by GSK. **Only Batch Lot# 132373860 of drug product will be used for this trial.** The contents of the label will be in accordance with all applicable regulatory requirements. **The lot number indicated on the label refers to labelled lot number; the batch Lot# 132373860 may not be provided on the label.**

4.2. Preparation/Handling/Storage of GSK2857916 Investigational Product

Preparation

GSK2857916 Solution for Infusion, 20 mg/mL is supplied as a frozen liquid (Lot# 132373860). Before use, thaw each vial of GSK2857916 for Infusion, 20mg/mL, 1.5mL for up to 4 hours under refrigerated conditions (2-8°C), protected from light. Following thawing, gently swirl the vial to ensure uniformity. GSK2857916 should be diluted in normal saline (0.9%) to no more than 2 mg/mL and no less than 0.2 mg/mL. Refer to the Study Procedures Manual (SPM) for further details on preparation of GSK2857916.

The dosing solution of GSK2857916 can be held under refrigerated conditions (2-8°C), for up to 24 hours (**NOTE**: For centers in Canada up to 8 hours only) or 4 hours at

ambient temperature (diluted drug product in bag) from a stability perspective, but should be used as soon as possible as the product does not contain an antimicrobial preservative.

Handling

Under normal conditions of handling and administration, investigational product (IP) is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

In the case of unintentional occupational exposure notify the study monitor, the GSK Medical Monitor and/or the study manager.

Refer to the SPM for detailed procedures for the disposal and/or return of unused study treatment(s).

Administration

GSK2857916 is compatible with polyvinylchloride-lined or polyolefin-lined intravenous infusion administration sets, 0.2 micron polyethersulfone filters, or optionally a polyurethane catheter. Doses of GSK2857916 are to be administered as an IV infusion via an infusion pump that can ensure precision to the decimal point of a mL for the infusion rate at lower doses. It is recommended to prime the IV tubing with at least 15 mL prior to dosing.

Administration of drug product in this trial is restricted to Manufacturer Batch Lot#132373869.

Storage

GSK2857916 must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the GSK2857916 will be limited to the investigator and authorized site staff. GSK2857916 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

GSK2857916 is to be stored at a temperature range of -50°C to -15°C. Maintenance of a temperature log is required.

The expiry date, where required, is stated on the product label.

4.3. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product (IP) dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when

applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

4.4. Treatment Compliance

GSK2857916 will be intravenously administered to subjects at the study site. The dose to be administered is based on body weight calculation, and may be reduced for toxicity according to protocol guidelines. Only two dose reductions are allowed per subject; the first dose reduction by 25%, and the second by an additional 25%. If subject is not tolerating treatment at 50% of scheduled dose the subject will be withdrawn from study. Additional dose reductions (beyond 50% of the original scheduled dose) may be possible only for subjects who have been enrolled during dose escalation in Part 1 at the highest dose, which was subsequently deemed as exceeding the MTD.

The actual body weight in kg will be used for dose calculation in all subjects whose body weight is ≤100kg. For subjects with body weight >100kg, the dose to be administered should be the same as that calculated for a subject weighing 100kg. Administration will be documented in the source documents and reported in the electronic case report form (eCRF). The time of start and end of infusion will be documented in eCRF.

4.5. Treatment of Investigational Product Overdose

In the event of an overdose (defined as administration of more than the protocol-specified dose) of GSK2857916, the investigator should:

- contact the GSK Medical Monitor immediately
- closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK2857916 can no longer be detected systemically (at least 3 months for GSK2857916)
- obtain a plasma sample for pharmacokinetic (PK) analysis within 24 hours of the event if requested by the GSK Medical Monitor (determined on a case-by-case basis)
- document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the GSK Medical Monitor based on the clinical evaluation of the subject

5. STUDY POPULATION

5.1. Number of Subjects

The number of dose levels and the level at which the maximum tolerated dose (MTD) is reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish the recommended dose(s) for further study. It is estimated that approximately 30 subjects will be enrolled into Part 1, Schedule 1 (dose-

escalation) of the study. Up to 40 subjects with MM and up to 10 subjects with BCMA positive lymphomas (~50 subjects total) will be enrolled in Part 2 (expansion cohort). The number of subjects in the expansion cohort has been estimated based on expected variable expression of BCMA in those subjects (about 1/3 low, 1/3 medium, 1/3 high expression; approximately 13 subjects/group). The level of BCMA expression in a given subject is expected to impact target-mediated clearance, which as a consequence might be reflected in the PK/PD variability and safety profile of individual subjects. In addition, the sample size of 40 subjects in the MM cohort will allow for assessment of early signals of clinical activity and relationships (if any) to variable target expression levels. A total of approximately 80 subjects will be enrolled in the study. If Part 1, Schedule 2 (once weekly schedule) is explored, up to 15 additional subjects will be enrolled; then a total of approximately 95 subjects will be enrolled in the study.

In Part 1 (dose-escalation) of the study, if a subject has been withdrawn prior to expiration of the DLT observation period OR received less than 2/3 of the scheduled dose and is not evaluable for DLT, additional subjects may be enrolled as replacement subjects and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

5.2. Subject Selection Criteria

5.2.1. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events (AEs), and other pertinent information on the GSK study treatment that may impact subject eligibility is provided in the Investigator Brochure (IB)/IB supplement(s). Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Provide signed written informed consent, which includes compliance with the requirements and restrictions listed in the consent form
2. Male or female, 18 years or older (at the time consent is obtained)
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 6)

4. **Part 1/dose escalation:**
    - Histologically or cytologically confirmed diagnosis of: Multiple Myeloma in a subject who fulfills **all** of the following:
    - has undergone stem cell transplant, or is considered transplant ineligible,
    - has been pretreated with at least the 3 following classes of anti-myeloma drugs: alkylators, proteasome inhibitors and immunomodulators,

- has demonstrated progression on, or within 60 days of completion of the last therapy.

Part 2 /MM cohort:

- Histologically or cytologically confirmed diagnosis of: Multiple Myeloma in a subject who fulfills **all** of the following:
- has undergone stem cell transplant, or is considered transplant ineligible,
- has been pretreated with at least the 3 following classes of anti-myeloma drugs: alkylators, proteasome inhibitors and immunomodulators,
- and has demonstrated progression on, or within 60 days of completion of the last therapy.
- AND has measurable disease with at least one of the following:
    a. Serum M-pro**tein ≥0.5 g/dL (≥5** g/L)
    b. Urine M-protein ≥200 mg/24h
    c. Serum FLC assay: Involved FLC level ≥5 mg/dL (≥50 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65)
    d. Biopsy proven plasmacytoma (should be measured within 28 days of Screening Visit)

or

Part 2/ BCMA positive Lymphoma cohort:

a. Subject with one of the following hematologic malignancies: Diffuse Large B-cell Lymphoma DLBCL or Follicular Lymphoma that exhibits positive BCMA expression on tumor cells as determined by a central laboratory using a validated IHC assay. Eligible subjects with BCMA positive lymphomas must also fulfill the prior treatment requirements as follows:
b. DLBCL : at least 2 prior lines of systemic therapy containing at least one line of chemo-immunotherapy with anti-CD20 antibody, and either has undergone stem cell transplant or is considered transplant ineligible
c. FL: at least 2 prior lines of systemic therapies.

5. Subjects with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
    a. transplant was > 100 days prior to study enrolment
    b. no active infection
    c. subject meets the remainder of the eligibility criteria outlined in this protocol
6. Adequate organ system functions as defined in Table 14.

Table 14 Adequate Organ System Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)[1]	≥ 1.0 X 10^9/L
Hemoglobin	≥ 8.0 g/dL
Platelets	≥ 50 X 10^9/L
Coagulation	
INR	≤1.5
PTT	≤1.5 x ULN
Hepatic	
Total bilirubin	≤1.5 X ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
AST and ALT	≤ 1.5 X ULN
Renal	
Serum creatinine or Calculated creatinine clearance[2] Albuminuria	<1.2XULN ≥ 60 mL/min for Part 1; ≥50 mL/min for Part 2 if data supports loosening criteria ≤500mg/24hr
Cardiac	
LVEF (Echo) Troponin	≥50% ≤1xULN

1. Without Growth factor support for the past 14 days, excluding erythropoietin
2. As calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 5)

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the subject and the subsequent within range screening result may be used to confirm eligibility.

7. A female subject is eligible to participate if she is of:

- Non-childbearing potential (i.e. physiologically incapable of becoming pregnant) defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MIU/mL and estradiol < 40 pg/mL (<147 pmol/L) is confirmatory]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods specified if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their

post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

- Women of childbearing potential must have a negative serum pregnancy test within 72 hours of first dose of study treatment and agree to use effective contraception, as defined in Section 11.1.1, during the study and for 60 days following the last dose of study treatment.

8. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 11.1.2 from the time of first dose of study until 60 days after the last dose of study treatment to allow for clearance of any altered sperm.
9. All prior treatment-related toxicities (defined by National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4) must be ≤Grade 1 at the time of enrollment except for alopecia, and grade 2 neuropathy

5.2.2. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Systemic anti-tumor-therapy within 14 days, or plasmapheresis within 7 days prior to the first dose of study drug.
2. Use of an investigational drug within 14 days or five half-lives, whichever is shorter, preceding the first dose of study drug. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drug.
3. History of an allogeneic stem cell transplant. Subjects with a history of an autologous stem cell transplant are NOT excluded if they meet Inclusion Criterion #5.
4. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect subject's safety). Subjects with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria given in Table 14.
5. Evidence of active mucosal or internal bleeding.
6. Any major surgery within the last four weeks.
7. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions (including lab abnormalities) that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
8. Known active infection requiring antibiotic treatment.
9. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal or cardiac disease).
10. Subjects with previous or concurrent malignancies are allowed only if the second tumor is not contributing to the subject's illness. The subject must not be receiving

active therapy, other than hormonal therapy for this disease and the disease must be considered medically stable for at least 2 years.

11. Evidence of cardiovascular risk including any of the following:
    a. QTc interval ≥ 470 msecs.
    b. Evidence of current clinically significant uncontrolled arrhythmias;
        a. including clinically significant ECG abnormalities including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
    c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.
    d. Class III or IV heart failure as defined by the New York Heart Association functional classification system (Appendix 4)
    e. Uncontrolled hypertension
    f. Subjects with intra-cardiac defibrillators or permanent pacemakers;
    g. Abnormal cardiac valve morphology (≥Grade 2) documented by echocardiogram (subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.
12. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2857916 or any of the components of the study treatment.
13. Pregnant or lactating female.
14. Known HIV infection.
15. Subjects with positive test for Hepatitis B surface (HBS-Ag) or Hepatitis B core (HBc)antigen
16. Subjects with positive test for hepatitis C (HCV) infection are excluded regardless of viral load. If hepatitis C antibody test is positive, a confirmatory polymerase chain reaction (PCR) or recombinant immunoblot assay (RIBA) test should be performed. If the RIBA test is negative, subject is eligible for this trial.
17. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator's assessment).
18. Current corneal disease or a history of corneal disease.

6. COMPLETION OR WITHDRAWAL OF SUBJECTS

6.1. Screen and Baseline Failures

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to GSK.

6.2. Subject Completion Criteria

For Part 1 (dose-escalation phase), a completed subject is one who has completed at least 1 cycle of study treatment and an End of Study Visit without events causing them to withdraw or discontinue from the study for reasons listed in Section 6.3 For Part 2 (expansion cohort), a completed subject is one who has received at least one dose of study treatment without events causing them to withdraw or discontinue study treatment for reasons listed in Section 6.3 and completed an End of Study Visit.

A participant will be considered to have completed the study if he or she has received at least one dose of the study treatment and, has died before the end of the study, has not been lost to follow-up, or has not withdrawn consent from study participation.

6.3. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until disease progression, death or unacceptable toxicity, including meeting stopping criteria for significant toxicity as outlined in Section 3.10 and other relevant safety management guidelines outlined in the protocol, or until a maximum of 16 treatment cycles. In addition, study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- a dose delay of >14 days unless the investigator or GSK Medical Monitor agree that subject derives benefit and that further treatment benefits will outweigh the risks. Exceptions apply to nephrotoxicity as outlined in Section 3.10.2
- intercurrent illness that prevents further administration of study treatment(s)
- subject is lost to follow-up
- study is closed or terminated
- subject completes maximum number of treatment cycles per protocol
- The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF)

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event (AE)' will be recorded as the primary reason for permanently discontinuation on the eCRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Tables (see Section 7.1).

6.4. Subject Withdrawal

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

6.5. Study Completion

A study will be considered completed, having met the study objectives, when the last subject has received their last dose of study medication and completed the End of Study visit.

Per the EU Clinical Trial Directive, the end of the study is defined as the last subject's last visit.

6.6. Treatment after the End of Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition whether or not GSK is providing specific post-study treatment.

Subjects' survival and status of post-study treatment will be documented via medical charts analysis at 3 months following the last dose of study drug.

7. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments being performed.

The timing of each assessment is listed in the Time and Events Tables (Section 7.1). The timing and number of the planned study assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring for the following assessments: safety, pharmacokinetic (PK), pharmacodynamic (PD)/biomarker or other assessments. The change in timing or addition of time points for any of the planned study assessments listed above must be approved and documented by GSK, but this will not constitute a protocol amendment. The institutional review board (IRB) or ethics committee (EC) will be informed of any safety issues that require alteration of the safety monitoring scheme. The maximum amount of blood collected in Screening and during the first Cycle 1 from

each subject for the Dose Escalation and for the Dose Expansion is no more than 162 ml of blood (See Appendix 10).

Whenever vital signs, 12-lead electrocardiograms (ECGs) and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SPM.

7.1. Time and Events Tables

This section consists of the Time and Events Tables and supplemental footnotes to describe assessment windows and sequencing of study-specific assessments and procedures.

7.1.1. Dose Escalation

7.1.1.1. Every 3 Weeks Dosing Schedule for Multiple Myeloma

Time and Events Table for Full Study (Cycle = 21 days)									
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 2 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment**	**3-Month Off-study Follow-up**
Informed Consent	X								
Baseline Demographics	X								
Medical History	X								
Physical Exam	X	X				X	At the start of each cycle	X	
Ocular Exam	X[3]					X[4]	At the start of each cycle[4]	X[4]	
ECOG Performance Status	X					X	At the start of each cycle	X	
Vital Signs (BP, HR, Body Temperature)	X	X[5]		X	X	X[5]	At the start of each cycle[5]	X	
Weight and Height	X	Weight only				Weight only	Weight only - At the start of each cycle	Weight only	
Hematology	X	X[6]		X	X	X	At the start of each cycle	X	
Clinical chemistry	X	X[6]	X	X	X	X	At the start of each cycle	X	
Urine Dipstick	X	X[6]				X	At the start of each cycle	X	
INR, PTT	X	X[6]		X	X	X	At the start of each cycle		
HBV/HCV tests	X								
CK-MB, Troponin	X[7]			X[7]		X[7]	At the start of each cycle[7]	X[7]	
BNP	X[8]								
UPEP and urine Immunofixation	X					X	At the start of each cycle		
SPEP and serum Immunofixation, Serum M-protein Calculation	X					X	At the start of each cycle		
Kappa, lambda free LC, FLC ratio	X					X	At the start of each cycle		
24 hr urine protein and albumin	X					X	At the start of each cycle		

Time and Events Table for Full Study (Cycle = 21 days)									
Study Assessments[1]	**Screen**[2]	**Day 1 C1**	**Day 2 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment**	**3-Month Off-study Follow-up**
IgG, IgM, IgA	X					X	At the start of each cycle		
CRP, beta2 microglobulin	X					X	At the start of each cycle		
Pregnancy Test	X[9]						At the start of cycles 5[9], 9[9], 13[9]	X[9]	X[10]
Chest X-ray	X								
12-lead ECG	X[11]	X[11]		X[11]	X[11]	X[11]	At the start of each cycle[11]	X[11]	
LVEF and valves assessment (ECHO)	X[12]						At the start of cycles 4[12], 9[12]	X[12]	
Extramedullary plasmacytoma imaging	X[13]						At the start of cycles 5[13], 9[13], 13[13]	X[13]	
BM Aspirate (see below for each test required within procedure)**:**									
Disease assessment	X[14]						At the time of Complete Response		
BCMA assessment and PD (flow)	X[15]			X[15]					
FISH testing	X[16]								
BM biopsy for disease assessment and BCMA expression (IHC)	X[17]						At the time of CR (disease assessment only)		
Serum (soluble BCMA)		X[18]	X[18]	X[18]	X[18]	X[18]	Predose at the start of each cycle	X[18]	
Serum (cytokines/chemokines)		X[19]	X			X[19]	At predose and EOI on D1 of each cycle	X	
Serum (anti-drug-antibodies)	X					X[20]	At the start of cycles 3[20], 6[20], 9[20], 12[20] and 16[20]	X	
[redacted]	X							X	
Peripheral blood (flow for TBNK)	X[15]					X[15]	At the start of each cycle[15]	X[15]	
Serial Pharmacokinetics (blood)		X[21]	X[21]	X[21]	X[21]	X[21]	C3D1 only[21]	X[22]	
Urine PK	X[23]					X[23]	Day 1 of cycles 4[23], 7[23], 10[23], 13[23], 16[23]		
Premedication if needed		X				X	At the start of each cycle		
GSK2857916 administration		X[24]				X[24]	X[24]		
Steroid eye drops		X[25]				X[25]	X[25]		
Adverse Events		Continuous							

Time and Events Table for Full Study (Cycle = 21 days)									
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 2 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment**	**3-Month Off-study Follow-up**
Concomitant Medications	X	Continuous							
Survival Status									X[26]
Subsequent Treatment									X[26]

1. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All other assessments can be ± 3 days of scheduled occurrence unless otherwise specified.
2. All Screening assessments must be performed within 14 days prior to first dose unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed.
3. Screening examination to include BCVA (best-corrected visual acuity), slit lamp examination (with special focus on cornea), intraocular pressure, and dilated fundoscopic examination may be performed within 21 days prior to first dose.
4. On-study exams to include BCVA (best-corrected visual acuity) and slit lamp examination (with special focus on cornea); window for exams is up to 3 days prior to dosing.
5. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +10 minutes and +30 minutes (±5 min) after SOI, EOI, and 1 hour post EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +30 minutes after SOI, and EOI. The Sentinel Subject must be observed for at least 24 hours post EOI. **On days where vital sign timepoints align with PK sampling timepoints, vital signs should be assessed prior to PK samples being drawn.**
6. If completed within 72 hrs prior to the first dose, this assessment need not be repeated on Day 1 of Cycle 1. Refer to Table 15 for comprehensive list of lab tests.
7. Troponin will be measured at the local lab (troponin I or T) and a central lab (troponin I). CK-MB at the local lab or if not possible by a central laboratory.
8. BNP to be measured locally, or if not available by a central laboratory, at screening; if cardiac workup is required due to safety concerns during the study, BNP should be measured.
9. Perform only in women of child-bearing potential. A serum pregnancy test should be performed at screening, and subsequent pregnancy tests may be either serum or urine;
10. Final pregnancy test (serum or urine) must be performed in women of childbearing potential 60 days after last study treatment.
11. On dosing days, ECG to be performed in triplicate at predose (within 30 minutes prior to SOI) and EOI. **On days where ECG timepoints align with PK sampling timepoints, ECGs should be performed prior to PK samples being drawn (PK sample should be taken at the exact nominal time; refer to footnote 21).** At screening, on interim visits (C1D8 and C1D15) and End of Study obtain a single ECG measurement.
12. At Screening, LVEF may be performed within 30 days prior to first dose. All ECHOs indicated on dosing days may be performed up to 5 days before dosing. All ECHOs to be done locally and sent to GSK for central imaging storage.
13. May be performed up to 21 days prior to C1D1 as screening value. Needs to be performed by the same method throughout the study as was done at baseline (i.e. if PET scan was used as baseline, subject needs to be followed by PET scans). Selected target lesion needs to be measured and followed over time.
14. Samples from within 14 days prior to first dose are acceptable.
15. Sample(s) collected for analysis by central lab. The same sample will be used for BCMA (flow) and PD during Screening. On D8 only postdose PD assessment will be performed
16. FISH testing at least for: t(4;14), t(14;16), 17p13del. FISH results from samples taken within 60 days prior to first dose are acceptable.

17. Archival tissue from up to 60 days prior to study is acceptable
18. A single sample for sBCMA will be collected at C1D8, C1D15 and at the End of Study visit. sBCMA samples will also be collected on C1D1 at predose (within 30 minutes prior to SOI), at EOI (±5 minutes) and on C1D2 24h post SOI. On C2D1 sBCMA will be collected pre-dose (within 30 minutes prior to SOI) and at the EOI (±5 minutes)
19. Collect cytokines at predose (within 30 minutes prior to SOI) and EOI (±5 min) (even when infusion is interrupted or halted) to assess allergic reaction)
20. All ADA samples will be collected prior to each infusion
21. PK samples to be taken (in all subjects) for both GSK2857916 and cys-mcMMAF measurement: C1D1 at pre-dose (within 30 minutes prior to SOI), 0.5 h after the start of the infusion (SOI) (±5 min), at the end of infusion (EOI) just before EOI), 1 h after EOI, 3 h after EOI (±5 min), 8 h after EOI (±15 min), 24h after EOI (±1h) (Day 2); C1D8 1 sample; C1D15 1 sample; C2D1, at pre-dose (within 30 minutes prior to SOI) and at the EOI (just before EOI); C3D1 at pre-dose (within 30 minutes prior to SOI) and at the EOI (just before EOI).
22. Collect 1 PK sample at each subject's final visit.
23. Pre-specified amounts of urine will be collected for PK analysis from the 24 hour urine collection at Screening, C2D1, C4D1, C7D1, C10D1, C13D1, and C16D1. Refer to Section 7.4.2 for details.
24. Study drug administration ±3 day window only
25. Prophylaxis with prednisolone phosphate 1% or dexamethasone 0.1% 1 drop QID x 4 days starting 1 day prior to treatment
26. Record subject's survival status and whether subsequent treatment for disease was given. Subject does not need to come in for visit.

Abbreviations:
ADA = Antibody Drug Antibody; ALP = alkaline phosphatase; BCVA = best corrected visual acuity; BNP = B-type natriuretic peptide; C1D1 = Cycle 1 Day 1, etc.; [redacted] CK = creatinine kinase; CRP = C-reactive protein; EM = extramedullary; EOI = End of Infusion; FLC = free light chain; PD = Pharmacodynamics; PK = Pharmacokinetics; QID = 4 times a day; SOI = start of infusion; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

7.1.1.2. Weekly Dosing Schedule (Dose Escalation) for Multiple Myeloma

Time and Events Table for Full Study (Cycle = 28 days)									
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 2 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment**	**3-Month Off-study Follow-up**
Informed Consent	X								
Baseline Demographics	X								
Medical History	X								
Physical Exam	X	X				X	At the start of each cycle	X	

Time and Events Table for Full Study (Cycle = 28 days)									
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 2 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment**	**3-Month Off-study Follow-up**
Ocular Exam	X[3]					X[4]	At the start of each cycle[4]	X[4]	
ECOG Performance Status	X					X	At the start of each cycle	X	
Vital Signs (BP, HR, Body Temperature)	X	X[5]		X	X	X[5]	At the start of each cycle[5]	X	
Weight and Height	X	Weight only				Weight only	Weight only - At the start of each cycle	Weight only	
Hematology	X	X[6]		X	X	X	At the start of each cycle	X	
Clinical Chemistry	X	X[6]	X	X	X	X	At the start of each cycle	X	
Urine Dipstick	X	X[6]				X	At the start of each cycle	X	
INR, PTT	X	X[6]		X	X	X	At the start of each cycle		
HBV/HCV tests	X								
CK-MB , Troponin	X[7]			X[7]		X[7]	At the start of each cycle[7]	X[7]	
BNP	X[8]								
UPEP and urine Immunofixation	X					X	At the start of each cycle		
SPEP and serum Immunofixation and Serum-M protein Calculation	X					X	At the start of each cycle		
Kappa, lambda free LC, FLC ratio	X					X	At the start of each cycle		
24 hr urine protein and albumin	X					X	At the start of each cycle		
IgG, IgM, IgA	X					X	At the start of each cycle		
CRP, beta2 microglobulin	X			X		X	At the start of each cycle		
Pregnancy Test	X[9]						At the start of cycles 5[9], 9[9], 13[9]	X[9]	X[10]
Chest X-ray	X								
12-lead ECG	X[11]	X[11]		X[11]	X[11]	X[11]	At the start of each cycle[11]	X[11]	
LVEF and valves assessment (ECHO)	X[12]						At the start of cycles 4[12], 9[12]	X[12]	

Time and Events Table for Full Study (Cycle = 28 days)									
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 2 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment**	**3-Month Off-study Follow-up**
Extramedullary Plasmacytoma Imaging	X[13]						At the start of cycles 5[13], 9[13], 13[13]	X[13]	
BM Aspirate (see below for each test required within procedure)**:**									
Disease assessment	X[14]						At the time of Complete Response		
BCMA assessment and PD (flow)	X[15]			X[15, 17]					
FISH testing	X[16]								
BM biopsy for disease assessment	X[18]						At the time of Complete Response (disease assessment only)		
Serum (soluble BCMA)		X[19]	X[19]	X[19]	X[19]	X[19]	Predose at the start of each cycle	X	
Serum (cytokines/chemokines)		X[20]	X	X[20]	X[20]	X[20]	At predose and EOI on D1 of each cycle	X	
Serum (anti-drug-antibodies)		X[21]			X[21]	X[21]	At the start of cycles 3[21], 6[21], 9[21], 12[21] and 16[21]	X	
[redacted]		X						X	
Peripheral blood (flow for TBNK and intracellular cytokine testing)		X[15]		X[15]		X[15]	At the start of each cycle[15]	X[15]	
Serial Pharmacokinetics (blood)		X[22]	X[22]	X[22]	X[22]	X[22]	C3D1 only[22]	X[23]	
Urine PK	X[24]					X[24]	Day 1 of cycles 4[24], 7[24], 10[24], 13[24], 16[24]		
Premedication if needed		X		X	X	X	Each dosing week		
GSK2857916 administration		X[25]		X[25]	X[25]	X[25]	Each dosing week[25]		
Steroid eye drops		X[26]		X[26]	X[26]	X[26]	Each dosing week[26]		
Adverse Events		Continuous							
Concomitant Medications	X	Continuous							
Survival Status									X[27]
Subsequent Treatment									X[27]

1. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All other assessments can be done ± 3 days unless otherwise specified.
2. All Screening assessments must be performed within 14 days prior to first dose unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed.
3. Screening examination to include BCVA (best-corrected visual acuity), slit lamp examination (with special focus on cornea), intraocular pressure, dilated fundoscopic examination may be performed within 21 days prior to first dose
4. On-study exams, to include BCVA (best-corrected visual acuity) and slit lamp examination (with special focus on cornea); window for exams is up to 3 days prior to dosing.
5. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +10 minutes and +30 minutes (±5 min) after SOI, EOI, and 1 hour post EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +30 minutes after SOI, and EOI. **On days where vital sign time points align with PK sampling timepoints, vital signs should be assessed prior to PK samples being drawn.**
6. If completed within 72 hours prior to first dose, this assessment need not be repeated on Day 1 of Cycle 1. Refer to Table 15 for comprehensive list of lab tests.
7. Troponin will be measured at the local (troponin I or T) and central (troponin I) lab. CK-MB at the local lab or if not available by a central laboratory.
8. BNP to be measured locally, or if not available by a central laboratory, at screening; if cardiac workup is required due to safety concerns during the study, BNP should be measured.
9. Perform only in women of child-bearing potential. A serum pregnancy test should be performed at screening, and subsequent pregnancy tests may be either serum or urine.
10. Final pregnancy test (serum or urine) must be performed in women of childbearing potential 60 days after last study treatment.
11. On dosing days, ECG to be performed in triplicate at predose (within 30 minutes prior to SOI) and EOI. **On days where ECG timepoints align with PK sampling timepoints, ECGs should be performed prior to PK samples being drawn** (PK sample should be taken at the exact nominal time; refer to footnote 22). At screening and at End of Study, obtain a single ECG measurement.
12. At Screening, LVEF may be performed within 30 days prior to fi**rst dose;** All ECHOs indicated on dosing days may be performed up to 5 days before dosing**. ECHOs to be done locally and sent to GSK for central imaging storage.**
13. **May be performed up to 21 days prior to** C1D1 as screening value. Needs to be performed by the same method throughout the study as was done at baseline (i.e. if PET scan was used as baseline, subject needs to be followed by PET scans). Selected target lesion needs to be measured and followed over time.
14. Samples from within 14 days prior to first dose are acceptable.
15. Sample(s) collected for analysis by central lab. The same sample collected on Day 1 of cycle 1 prior to dosing will be used for BCMA (flow) and PD u.
16. FISH testing at least for t(4;14), t(14/16), 17p13del. FISH results from samples taken within 60 days prior to first dose are acceptable.
17. Collect sample prior to dosing.
18. Archival tissue from up to 60 days prior to study is acceptable.
19. A single sample for sBCMA will be collected at C1D8 predose, and at the End of Study visit. sBCMA samples will also be collected on C1D1 at predose (within 30 minutes prior to SOI), at EOI (±5 minutes) and on C1D2 24h post SOI. On C1D15 and C2D1 collect at predose (within 30 minutes prior to SOI) and EOI (±5 minutes)
20. Collect cytokines at predose (within 30 minutes prior to SOI) and EOI (±5 min) (even when infusion is interrupted or halted) to assess allergic reaction
21. All ADA samples will be collected prior to each infusion
22. PK samples to be taken (in all subjects) for both GSK2857916 and cys-mcMMAF measurement: C1D1 at predose (within 30 minutes prior to SOI), 0.5 h after the start of the infusion, at EOI (just before EOI), 1 h after EOI (±5 min), 3 h after EOI (±5 min), 8 h after EOI (± 15 min), and 24h after EOI (±1 h) (Day 2); C1D8 at predose (within 30 minutes prior to SOI), and at EOI (just before EOI); C1D15 at predose (within 30 minutes prior to SOI) and at EOI (just before EOI); C2D1 at predose (within 30 minutes prior to SOI), at EOI (just before EOI); C3D1 at predose (within 30 minutes prior to SOI) and at EOI (just before EOI).
23. Collect 1 PK sample at each subject's final visit.

24. Pre-specified amounts of urine will be collected for PK analysis from the 24 hour urine collection at Screening, C2D1, C4D1, C7D1, C10D1, C13D1, and C16D1. Refer to Section 7.4.2 for details.
25. Study drug administration ±1 day window only.
26. Prophylaxis with prednisolone phosphate 1% or dexamethasone 0.1% 1 drop QID x 4 days starting 1 day prior to treatment
27. Record subject's survival status and whether subsequent treatment for disease was given. Subject does not need to come in for visit.

Abbreviations:

ADA = Antibody Drug Antibody; ALP = alkaline phosphatase; BCVA = best corrected visual acuity; BNP = B-type natriuretic peptide; C1D1 = Cycle 1 Day 1, etc.; [redacted]CK = creatinine kinase; CRP = C-reactive protein; EM = extramedullary; EOI = End of Infusion; FLC = free light chain; PD = Pharmacodynamics; PK = Pharmacokinetics; QID = 4 times a day; SOI = start of infusion; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

7.1.2. Dose Expansion

7.1.2.1. Every 3 Weeks Dosing Schedule for Multiple Myeloma

	Time and Events Table for Full Study (Cycle = 21 days)								
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment[34]**	**Monthly Follow up[35]**	
Baseline Demographics	X								
Medical History	X								
Physical Exam	X	X			X	At the start of each cycle	X		
Ocular Exam	X[3]				X[4]	At the start of each cycle[4]	X[4]	X[35]	
ECOG Performance Status	X				X	At the start of each cycle	X		
Vital Signs (BP, HR, Body Temperature)	X	X[5]	X	X	X[5]	At the start of each cycle[5]	X		
Weight and Height	X	Weight only			Weight only	Weight only - At the start of each cycle	Weight only		
Hematology	X	X[6]	X	X	X	At the start of each cycle	X		
Clinical chemistry	X	X[6]	X	X	X	At the start of each cycle	X		
Urine Dipstick	X	X[6]			X	At the start of each cycle	X		
INR, PTT	X	X[6]	X	X	X	At the start of each cycle			
HBV/HCV tests	X								
CK-MB , Troponin	X[7,8]		X[7,8]		X[7,8]	At the start of each cycle[7, 8]	X[7,8]		
BNP	X[9]								
UPEP and urine Immunofixation	X				X	At the start of each cycle			
SPEP and serum immunofixation and Serum M-protein Calculation	X				X	At the start of each cycle			
Kappa, lambda free LC, FLC ratio	X				X	At the start of each cycle			

	Time and Events Table for Full Study (Cycle = 21 days)								
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment[34]**	**Monthly Follow up[35]**	
24 hr urine protein and albumin	X				X	At the start of each cycle			
IgG, IgM, IgA	X				X	At the start of each cycle			
CRP, beta2 microglobulin	X				X	At the start of each cycle			
Pregnancy Test	X[10]					At the start of cycles 5[10], 9[10], 13[10]	X[10]	X[11]	
Chest X-ray	X								
12-lead ECG	X[12]	X[12]	X[12]	X[12]	X[12]	At the start of each cycle[12]	X[12]		
LVEF and valves assessment (ECHO)	X[13]					At the start of cycles 4[13], 9[13]	X[13]		
Extramedullary Plasmacytoma Imaging	X[14]					At the start of cycles 5[14], 9[14], 13[14]	X[14]		
	BM Aspirate (see below for each test required within procedure)**:**								
Disease assessment	X[15]					At the time of Complete Response			
BCMA assessment and PD (flow)	X[16]		X[16, 18]						
FISH testing	X[17]								
BM biopsy for disease assessment	X[19]					At the time of CR (disease assessment only)			
Serum (soluble BCMA)		X[20]			X[20]	Predose at the start of each cycle	X		
Serum (cytokines/chemokines)		X[21]			X[21]	Predose and EOI on D1 of each cycle	X		
Serum (anti-drug-antibodies)		X[22]			X[22]	At the start of cycles 3[22], 6[22], 9[22], 12[22] and 16[22]	X		
[redacted]		X					X		
Peripheral blood (flow for TBNK and intracellular cytokine testing)		X[23]	X		X[23]	At the start of each cycle[23]	X[23]		
Sparse PK (blood)		X[24]			X[24]	C3D1[24] and C5D1[24] only	X[25]		
Genetics sample		X[26]							

	Time and Events Table for Full Study (Cycle = 21 days)								
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment[34]**	**Monthly Follow up[35]**	
Premedication if needed		X			X	X			
GSK2857916 administration		X[27]			X[27]	X[27]			
Steroid eye drops		X[28]			X[28]	X[28]			
Adverse Events			Continuous						
Concomitant Medications	X		Continuous						
e-Diary	X	X	X	X	X[30]	X[30]	X		
OSDI							X[31]	X[31]	
NEI-VFQ-25							X[31]	X[31]	
Exit Interview							X[32]		
Follow-up Interview								X[33]	
Survival Status								X[29]	
Subsequent Treatment								X[29]	

1. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All other assessments can be done ± 3 days unless otherwise specified
2. All Screening assessments must be performed within 14 days prior to first dose unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed.
3. Screening examination to include BCVA (best-corrected visual acuity), slit lamp examination (with special focus on cornea), intraocular pressure, and dilated fundoscopic examination may be performed within 21 days prior to first dose.
4. On-study exams, to include BCVA (best-corrected visual acuity) and slit lamp examination (with special focus on cornea); window for exams is up to 3 days prior to dosing. In the event that a subject has a dose delay due to a non-ocular toxicity and an ocular exam has been performed for that cycle, a repeat ocular exam 3 days prior to dosing may be omitted if the participant did not have corneal signs on the previous exam and does not have any new corneal symptoms.
5. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +10 minutes, +30 minutes (±15 min) after SOI, EOI, and 1 hour post EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +30 minutes after SOI, and EOI. **On days where vital sign timepoints align with PK sampling timepoints, vital signs should be assessed prior to PK samples being drawn.**
6. If completed within 72 hrs prior to the first dose, this assessment need not be repeated on Day 1 of Cycle 1. Refer to Table 15 for a comprehensive list of lab tests.
7. Troponin will be measured at the local (troponin I or T) and central (troponin I) lab.
8. CK-MB at the local lab or if not available by a central laboratory.
9. BNP to be measured locally, or if not available by a central laboratory, at screening; if cardiac workup is required due to safety concerns during the study, BNP should be measured.

10. Perform only in women of child-bearing potential. A serum pregnancy test should be performed at screening, and subsequent pregnancy tests may be either serum or urine.
11. Final pregnancy test (serum or urine) must be performed in women of childbearing potential 60 days after last study treatment.
12. ECGs to be performed in triplicate. On dosing days, ECG to be performed at predose (within 30 minutes prior to SOI) and EOI. At screening, on interim visits (C1D8 and C1D15) and End of Study, obtain a single ECG measurement. **On days where ECG timepoints align with PK sampling timepoints, ECGs should be performed prior to PK samples being drawn (PK sample should be taken at the exact nominal time; refer to footnote 24)**
13. At Screening, LVEF may be performed within 30 days prior to first dose. All ECHOs indicated on dosing days may be performed up to 5 days before dosing. ECHOs to be done locally and sent to GSK for central imaging storage.
14. May be performed up to 21 days prior to C1D1 as screening value. Needs to be performed with the same method throughout the study as was done at baseline (i.e. if PET scan was used as baseline, subject needs to be followed by PET scans). Selected target lesion needs to be measured and followed over time.
15. Samples from within 14 days prior to first dose are acceptable.
16. Sample(s) collected for analysis at central lab. The same sample will be used for BCMA (flow) and PD. On D8 only postdose PD assessment will be performed, if applicable (refer to footnote 18).
17. FISH testing at least for: t(4;14), t(14;16), 17p13del. FISH results from samples taken within 60 days prior to first dose are acceptable.
18. **Additional samples may be collected in some subjects (up to 6) for further exploration of PD.**
19. Archival tissue from up to 60 days prior to study is acceptable.
20. Collect sBCMA at C1D1 predose (within 30 minutes prior to SOI) and at EOI (±5 minutes), C2D1 at predose (within 30 minutes prior to SOI) and at EOI (+- 5 minutes).
21. Collect cytokines at predose (within 30 minutes prior to SOI) and EOI (±5 min) (even when infusion is interrupted or halted) to assess allergic reaction
22. All ADA samples will be collected prior to each infusion
23. Flow cytometry performed central laboratory.
24. PK samples to be taken for both GSK2587916 and cys-mcMMAF measurement on C1D1, C2D1, C3D1, and C5D1 at predose (within 30 minutes prior to SOI) and at EOI (just before EOI).
25. Collect 1 PK sample at each subject's final visit.
26. Informed consent for optional genetics research should be obtained before collecting a sample.
27. Study drug administration ±3 day window only.
28. Prophylaxis with prednisolone phosphate 1% or dexamethasone 0.1% 1 drop QID x 4 days starting 1 day prior to treatment
29. All participants should be followed for survival for 1 year from last subject last dose. and whether subsequent treatment for disease was given. Subject does not need to come in for visit. Participants who have completed treatment or the 3 month follow up visit (end of study) prior to amendment 5 will be reconsented for further follow up and survival status.
30. e-Diary to be completed at screening, then Days 1-7, 8, 15 of each treatment cycle. Upon implementation of the e-Diary, these assessments will be required.
31. OSDI and NEI-VFQ-25 to be administered during end of study treatment visit. Additional assessments for subjects who are experiencing corneal symptoms to be completed via telephone on a monthly basis for up to 1 year, or until resolution of symptoms (whichever comes first) during the follow-up period.
32. Exit interview to be performed within 21 days of end of study visit
33. Optional follow-up telephone interview to explore visual symptoms and changes in symptoms and related impacts following treatment discontinuation be performed at least 6 months following the End of Study Treatment visit. This interview would only be for those subjects who experienced corneal symptoms during treatment and consent to participate.
34. End of treatment visit should be performed within 30 days (+7 days) after the last dose or prior to the start of new anti-cancer treatment, whichever is earlier. In cases where more than 30 days (+7 days) have elapsed from the date of the subject's last dose due to dosing delays and a subsequent decision to take the subject off treatment, the end of study treatment visit should be scheduled as soon as possible to allow the final assessments to be performed at the earliest date.

35. Participants with corneal signs or symptoms at the end of study treatment visit should be monitored by ophthalmic exam once a month after the last study dose until deemed clinically stable by an eye care professional complete resolution or for 12 months (whichever comes first). Corneal exams to include BCVA and slit lamp examination (with special focus on cornea). Participants who have completed treatment or the 3 month follow up visit (end of study) will be reconsented for additional ophthalmology follow up.
Abbreviations:
ADA = Antibody Drug Antibody; ALP = alkaline phosphatase; BCVA = best corrected visual acuity; BNP = B-type natriuretic peptide; C1D1 = Cycle 1 Day 1, etc.; [redacted] CK = creatinine kinase; CRP = C-reactive protein; EM = extramedullary; EOI = End of Infusion; FLC = free light chain; PD = Pharmacodynamics; PK = Pharmacokinetics; QID = 4 times a day; SOI = start of infusion; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

7.1.2.2. Dose Expansion Weekly Dosing Schedule for Multiple Myeloma

Time and Events Table for Full Study (Cycle = 28 days)									
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**Day 15 C2**	**D1 of C3-C16**	**End of Study Treatment**	**3-Month Off-study Follow-up**
Informed Consent	X								
Baseline Demographics	X								
Medical History	X								
Physical Exam	X	X			X		At the start of each cycle	X	
Ocular Exam	X[3]				X[4]		At the start of each cycle[4]	X[4]	
ECOG Performance Status	X				X		At the start of each cycle	X	
Vital Signs (BP, HR, Body Temperature)	X	X[5]	X[5]	X[5]	X[5]		At the start of each cycle[5]	X	
Weight and Height	X	Weight only			Weight only		Weight only - At the start of each cycle	Weight	
Hematology	X	X[6]	X	X	X		At the start of each cycle	X	
Clinical chemistry	X	X[6]	X	X	X	X	At the start of each cycle	X	
Urine Dipstick	X	X[6]			X		At the start of each cycle	X	
INR, PTT	X	X[6]	X	X	X		At the start of each cycle		
HBV/HCV tests	X								
CK-MB , Troponin	X[7]		X[7]		X[7]		At the start of each cycle[7]	X[7]	
BNP	X[8]								
UPEP and urine immunofixation	X				X		At the start of each cycle		
SPEP and serum immunofixation and Serum M-protein Calculation	X				X		At the start of each cycle		
Kappa, lambda free LC, FLC ratio	X				X		At the start of each cycle		
24 hr urine protein and albumin	X				X		At the start of each cycle		
IgG, IgM, IgA	X				X		At the start of each cycle		

Time and Events Table for Full Study (Cycle = 28 days)									
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**Day 15 C2**	**D1 of C3-C16**	**End of Study Treatment**	**3-Month Off-study Follow-up**
CRP, beta2 microglobulin	X		X		X		At the start of each cycle		
Pregnancy Test	X[9]						At the start of cycles 5[9], 9[9], 13[9]	X[9]	X[10]
Chest X-ray	X								
12-lead ECG	X[11]	X[11]	X[11]	X[11]	X[11]		At the start of each cycle[11]	X[11]	
LVEF and valves assessment (ECHO)	X[12]						At the start of cycles 4[12], 9[12]	X[12]	
Extramedullary Plasmacytoma Imaging	X[13]						At the start of cycles 5[13], 9[13], 13[13]	X[13]	
BM Aspirate (see below for each test required within procedure)**:**									
Disease assessment	X[14]						At the time of Complete Response		
BCMA assessment and PD (flow)	X[15]		X[15, 17]						
FISH testing	X[16]								
BM biopsy for disease assessment	X[18]						At the time of Complete Response (disease assessment only)		
Serum (soluble BCMA)		X[19]	X[19]	X[19]	X[19]		Predose at the start of each cycle	X	
Serum (cytokines/chemokines)		X[20]	X[20]	X[20]	X[20]		Predose and EOI on D1 of each cycle	X	
Serum (anti-drug-antibodies)		X[21]		X[21]	X[21]		At the start of cycles 3[21], 6[21], 9[21], 12[21] and 16[21]	X	
[redacted]		X	X					X	
Peripheral blood (flow for TBNK and intracellular cytokine testing)		X[15]	X		X[15]		At the start of each cycle[15]	X[15]	
Sparse PK (blood)		X[22]	X[22]	X[22]	X[22]	X[22]	C3D1[22], C3D15[22], and C5D1[22] only	X[23]	
Genetics sample		X[24]							
Premedication if needed		X	X	X	X	X	Each dosing week		
GSK2857916 administration		X[25]	X[25]	X[25]	X[25]	X[25]	Each dosing week[25]		
Steroid eye drops		X[26]	X[26]	X[26]	X[26]	X[26]	Each dosing week[26]		
Adverse Events		Continuous							

Time and Events Table for Full Study (Cycle = 28 days)									
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**Day 15 C2**	**D1 of C3-C16**	**End of Study Treatment**	**3-Month Off-study Follow-up**
Concomitant Medications	X	Continuous							
e-Diary	X	X	X	X	X		X[28]	X	
Exit Interview								X[29]	
Survival Status									X[27]
Subsequent Treatment									X[27]

1. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All other assessments can be done ± 3 days unless otherwise specified
2. All Screening assessments must be performed within 14 days prior to first dose unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed.
3. Screening examination to include BCVA (best-corrected visual acuity), slit lamp examination (with special focus on cornea), intraocular pressure, and dilated fundoscopic examination may be performed within 21 days prior to first dose.
4. On-study exams, to include BCVA (best-corrected visual acuity) and slit lamp examination (with special focus on cornea); window for exams is up to 3 days prior to dosing.
5. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +10 minutes and +30 minutes (±5 min) after SOI, EOI, and 1 hour post EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +30 minutes after SOI, and EOI. **On days where vital sign timepoints align with PK sampling timepoints, vital signs should be assessed prior to PK samples being drawn.**
6. If completed within 72 hrs prior to the first dose, this assessment need not be repeated on Day 1 of Cycle 1. Refer to Table 15 for comprehensive list of lab tests.
7. Troponin will be measured at the local (troponin I or T) and central (troponin I) lab. CK-MB at the local lab, or if not available by a central laboratory.
8. BNP to be measured locally, or if not available by a central laboratory, at screening; if cardiac workup is required due to safety concerns during the study, BNP should be measured.
9. Perform only in women of child-bearing potential. A serum pregnancy test should be performed at screening, and subsequent pregnancy tests may be either serum or urine
10. Final pregnancy test (serum or urine) must be performed in women of childbearing potential 60 days after last study treatment.
11. ECGs to be performed in triplicate. On dosing days, ECG to be performed at predose (within 30 minutes prior to SOI) and EOI. **On days where ECG timepoints align with PK sampling timepoints, ECGs should be performed prior to PK samples being drawn (PK sample should be taken at the exact nominal time; refer to footnote 22).** At screening and End of Study, obtain a single ECG measurement.
12. At Screening, LVEF may be performed within 30 days prior to first dose. All ECHOs indicated on dosing days may be performed up to 7 days before dosing. ECHOs to be done locally and sent to GSK for central imaging storage.
13. May be performed up to 21 days prior to C1D1 as screening value. Needs to be performed with the same method throughout the study as was done at baseline (i.e. if PET scan was used as baseline, subject needs to be followed by PET scans). Selected target lesion needs to be measured and followed over time.
14. Samples from within 14 days prior to first dose are acceptable.
15. Sample(s) collected for analysis at central lab. The same sample collected on Day 1 of cycle1 prior to dosing will be used for BCMA (flow) and PD (refer to footnote 17).

16. FISH testing at least for: t(4;14), t(14;16), 17p13del. FISH results from samples taken within 60 days prior to first dose are acceptable.
17. Additional samples may be collected from 6 subjects in the MM cohort. Collect sample prior to dosing.
18. Archival tissue from up to 60 days prior to study is acceptable
19. A single sBCMA sample will be collected at C1D1 predose (within 30 minutes prior to SOI) unless otherwise specified. On C1D15 and C2D1 collect samples at predose (within 30 minutes prior to SOI) and at EOI (±5 minutes).
20. Collect cytokines at predose (within 30 minutes prior to SOI) and EOI (±5 min) (even when infusion is interrupted or halted) to assess allergic reaction
21. All ADA samples will be collected prior to each infusion
22. PK samples to be taken for both GSK2857916 and cys-mcMMAF measurement at C1D1 predose (within 30 minutes prior to SOI), EOI (just before EOI), 1 hour post EOI (±5 min), and 3 hours post EOI (±5 min); predose (within 30 minutes prior to SOI) and EOI (just before EOI) on C1D8, C1D15, C2D1, C2D15, C3D1, C3D15, and C5D1
23. Collect 1 PK sample at each subject's final visit
24. Informed consent for optional genetics research should be obtained before collecting a sample.
25. Study drug administration ±1 day window only
26. Prophylaxis with prednisolone phosphate 1% or dexamethasone 0.1% 1 drop QID x 4 days starting 1 day prior to treatment
27. Record subject's survival status and whether subsequent treatment for disease was given. Subject does not need to come in for visit.
28. e-Diary to be completed at screening, then Days 1-7, 8, 15 of each treatment cycle. Upon implementation of the e-Diary, these assessments will be required.
29. 29.Exit interview to be performed within 14 days of end of study visit

Abbreviations:
ADA = Antibody Drug Antibody; ALP = alkaline phosphatase; BCVA = best corrected visual acuity; BNP = B-type natriuretic peptide; C1D1 = Cycle 1 Day 1, etc.; [redacted]CK = creatinine kinase; CRP = C-reactive protein; EM = extramedullary; EOI = End of Infusion; FLC = free light chain; PD = Pharmacodynamics; PK = Pharmacokinetics; QID = 4 times a day; SOI = start of infusion; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

7.1.2.3. Dose Expansion Every 3 Weeks Dosing Schedule for Lymphomas

Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment[26]**	**Monthly Follow up[27]**	
Informed Consent	X								
Baseline Demographics	X								
Medical History	X								
Physical Exam	X	X			X	At the start of each cycle	X		
Ocular Exam	X[3]				X[4]	At the start of each cycle[4]	X[4]	X[27]	
ECOG Performance Status	X				X	At the start of each cycle	X		
Vital Signs (BP, HR, Body Temperature)	X	X[5]	X	X	X[5]	At the start of each cycle[5]	X		
Weight and Height	X	Weight only			Weight only	Weight only - At the start of each cycle	Weight only		
Hematology	X	X[6]	X	X	X	At the start of each cycle	X		
Clinical chemistry	X	X[6]	X	X	X	At the start of each cycle	X		
Urine Dipstick	X	X[6]			X	At the start of each cycle	X		
INR, PTT	X	X[6]	X	X	X	At the start of each cycle			
HBV/HCV tests	X								
CK-MB, Troponin	X[7,8]		X[7,8]		X[7,8]	At the start of each cycle[7]	X[7,8]		
BNP	X[9]								
24 hr urine protein and albumin	X				X	At the start of each cycle			
IgG, IgM, IgA	X				X	At the start of each cycle			
CRP, beta2 microglobulin	X				X	At the start of each cycle			
Pregnancy Test	X[10]					At the start of cycles 5[10], 9[10], 13[10]	X[10]	X[11]	
Chest X-ray	X								
12-lead ECG	X[12]	X[12]	X[12]	X[12]	X[12]	At the start of each cycle[12]	X[12]		
LVEF and valves assessment (ECHO)	X[13]					At the start of cycles 4[13], 9[13]	X[13]		
Serum (soluble BCMA)		X[14]			X[14]				

Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment[26]**	**Monthly Follow up[27]**	
Serum (cytokines/chemokines)		X[15]			X[15]	Predose and EOI on D1 of each cycle	X		
Serum (anti-drug-antibodies)		X[16]			X[16]	At the start of cycles 3[16], 6[16], 9[16], 12[16] and 16[16]	X		
[redacted]		X					X		
Peripheral blood (flow for TBNK and intracellular cytokine testing)		X[17]	X[17]		X[17]	At the start of each cycle[17]	X[17]		
Sparse PK (blood)		X[18]			X[18]	C3D1[18] and C5D1[18]	X[19]		
Genetics sample		X[20]							
CT Scan/PET Scan for disease assessments	X[21]					At the start of cycles 4, 7, 10, 13, and 16			
Premedication if needed		X			X	At the start of each cycle			
GSK2857916 administration		X[22]			X[22]	X[22]			
Steroid eye drops		X[23]			X[23]	At the start of each cycle[23]			
Tumor biopsy for BCMA expression	X[24]								
Adverse Events				Continuous					
Concomitant Medications	X			Continuous					
Survival Status								X[25]	
Subsequent Treatment								X[25]	

1. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All other assessments can be done ± 3 days of scheduled occurrence unless otherwise specified.
2. All Screening assessments must be performed within 14 days prior to first dose unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed.
3. Screening examination to include BCVA (best-corrected visual acuity), slit lamp examination (with special focus on cornea), intraocular pressure, and dilated fundoscopic examination may be performed within 21 days prior to first dose.
4. On-study exams to include BCVA (best-corrected visual acuity) and slit lamp examination (with special focus on cornea); window for exams is up to 3 days prior to dosing. In the event that a subject has a dose delay due to a non-ocular toxicity and an ocular exam has been performed for that cycle, a repeat ocular exam 3 days prior to dosing may be omitted if the participant did not have corneal signs on the previous exam and does not have any new corneal symptoms.

5. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +10 minutes, +30 minutes (±15 min) after SOI, EOI, and 1 hour post EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +30 minutes after SOI, and EOI. **On days where vital sign timepoints align with PK sampling timepoints, vital signs should be assessed prior to PK samples being drawn.**
6. If completed within 72 hrs prior to the first dose, this assessment need not be repeated on Day 1 of Cycle 1. Refer to Table 15 for a comprehensive list of lab tests.
7. Troponin will be measured at the local (troponin I or T) and central (troponin I) lab.
8. CK-MB at the local lab, or if not available by a central laboratory.
9. BNP to be measured locally at screening; if cardiac workup is required due to safety concerns during the study, BNP should be measured.
10. Perform only in women of child-bearing potential. A serum pregnancy test should be performed at screening, and subsequent pregnancy tests may be either serum or urine.
11. Final pregnancy test (serum or urine) must be performed in women of childbearing potential 60 days after last study treatment.
12. On dosing days, triplicate ECGs to be performed at predose (within 30 minutes prior to SOI) and EOI. **On days where ECG timepoints align with PK sampling timepoints, ECGs should be performed prior to PK samples being drawn (PK sample should be taken at the exact nominal time; refer to footnote 18).** At screening, on interim visits (C1D8 and C1D15) and End of Study, obtain a single ECG measurement.
13. At Screening, LVEF may be performed within 30 days prior to first dose. All ECHOs indicated on dosing days may be performed up to 5 days. ECHOs to be done locally and sent to GSK for central imaging storage.
14. A single sBCMA sample will be collected at C1D1 predose (within 30 minutes prior to SOI). On C2D1 sBCMA will be collected at predose (within 30 minutes prior to SOI) and at EOI (±5 minutes).
15. Collect cytokines at predose (within 30 minutes prior to SOI) and EOI (±5 min) (even when infusion is interrupted or halted) to assess allergic reaction.
16. All ADA samples will be collected prior to each infusion.
17. Sample(s) collected for analysis by central lab.
18. PK samples to be taken for both GSK2587916 and cys-mcMMAF measurement on C1D1 at pre-dose (within 30 minutes prior to SOI), at EOI (just before EOI), 1 h after EOI (±5 min), 3 h after EOI (±5 min); C2D1, C3D1, and C5D1 at pre-dose (within 30 minutes prior to SOI) and at EOI (just before EOI).
19. Collect 1 PK sample at each subject's final visit.
20. Informed consent for optional genetics research should be obtained before collecting a sample.
21. CT/PET or CT scans from within 21 days prior to first dose are acceptable. CT scans are acceptable at all restaging assessments unless CR is suspected, in which case a PET/CT scan will be obtained to confirm CR.
22. Study drug administration ±3 day window only.
23. Prophylaxis with prednisolone phosphate 1% or dexamethasone 0.1% 1 drops QID x 4 days starting 1 day prior to treatment.
24. Archived or fresh tissue required for BCMA testing. Refer to Section 5.2.1 Inclusion Criterion #4 for eligibility criteria.
25. Record subject's survival status until last subject completes or discontinues treatment and whether subsequent treatment for disease was given. Subject does not need to come in for visit.
26. End of treatment visit should be performed within 30 days (+7 days) after the last dose or prior to the start of new anti-cancer treatment, whichever is earlier. In cases where more than 30 days (+7 days) have elapsed from the date of the subject's last dose due to dosing delays and a subsequent decision to take the subject off treatment, the end of study treatment visit should be scheduled as soon as possible to allow the final assessments to be performed at the earliest date.
27. All participants should be followed for survival for 1 year from last dose. Participants with corneal signs or symptoms at the end of study treatment visit should be monitored by ophthalmic exam every month after the last study dose until deemed clinically stable by an eye care professional or for 12 months (whichever comes first). Corneal exams to include BCVA and slit lamp examination (with special focus on cornea).

Abbreviations:
ADA = Antibody Drug Antibody; ALP = alkaline phosphatase; BCVA = best corrected visual acuity; BNP = B-type natriuretic peptide; C1D1 = Cycle 1 Day 1, etc.; [redacted] CK = creatine kinase; CRP = C-reactive protein; EOI = End of Infusion; PD = Pharmacodynamics; PK = Pharmacokinetics; QID = 4 times a day; SOI = start of infusion

7.1.2.4. Dose Expansion Weekly Dosing Schedule for Lymphomas

Time and Events Table for Full Study (Cycle = 28 days)									
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**Day 15 C2**	**D1 of C3-C16**	**End of Study Treatment**	**3-Month Off-study Follow-up**
Informed Consent	X								
Baseline Demographics	X								
Medical History	X								
Physical Exam	X	X			X		At the start of each cycle	X	
Ocular Exam	X[3]				X[4]		At the start of each cycle[4]	X[4]	
ECOG Performance Status	X				X		At the start of each cycle	X	
Vital Signs (BP, HR, Body Temperature)	X	X[5]	X[5]	X[5]	X[5]		At the start of each cycle[5]	X	
Weight and Height	X	Weight only			Weight only		Weight only - At the start of each cycle	Weight	
Hematology	X	X[6]	X	X	X		At the start of each cycle	X	
Clinical chemistry	X	X[6]	X	X	X	X	At the start of each cycle	X	
Urine Dipstick	X	X[6]			X		At the start of each cycle	X	
INR, PTT	X	X[6]	X	X	X		At the start of each cycle		
HBV/HCV tests	X								
CK-MB , Troponin	X[7]		X[7]		X[7]		At the start of each cycle[7]	X[7]	
BNP	X[8]								
24 hr urine protein and albumin	X				X		At the start of each cycle		
IgG, IgM, IgA	X				X		At the start of every other cycle		
CRP, beta2 microglobulin	X				X		At the start of each cycle		
Pregnancy Test	X[9]						At the start of cycles 5[9], 9[9], 13[9]	X[9]	X[10]
Chest X-ray	X								
12-lead ECG	X[11]	X[11]	X[11]	X[11]	X[11]		At the start of each cycle[11]	X[11]	
LVEF and valves assessment (ECHO)	X[12]						At the start of cycles 4[12], 9[12]	X[12]	

Time and Events Table for Full Study (Cycle = 28 days)									
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**Day 15 C2**	**D1 of C3-C16**	**End of Study Treatment**	**3-Month Off-study Follow-up**
Serum (soluble BCMA)		X[13]	X[13]	X[13]	X[13]			X[13]	
Serum (cytokines/chemokines)		X[14]	X[14]	X[14]	X[14]		Predose and EOI on D1 of each cycle	X	
Serum (anti-drug-antibodies)		X[15]		X[15]	X[15]		At the start of cycles 3[15], 6[15], 9[15], 12[15] and 16[15]	X	
[redacted]		X						X	
Peripheral blood (flow for TBNK)		X[16]	X[16]		X[16]		At the start of each cycle[16]	X[16]	
Sparse PK (blood)		X[17]	X[17]	X[17]	X[17]	X[17]	C3D1[17], C3D15[17] and C5D1[17] only	X[18]	
Genetics sample		X[19]							
CT/PET Scan for disease assessments	X[20]						At the start of Cycles 3, 5, 7, 9, 11, 13, and 16		
Premedication if needed		X	X	X	X[24]	X	Each dosing week		
GSK2857916 administration		X[21]	X[21]	X[21]	X[21, 24]	X	Each dosing week[21]		
Steroid eye drops		X[22]	X[22]	X[22]	X[22, 24]	X[22]	Each dosing week[22]		
Tumor biopsy for BCMA expression	X[23]								
Adverse Events		Continuous							
Concomitant Medications	X	Continuous							
Survival Status									X[25]
Subsequent Treatment									X[25]

1. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All other assessments can be done ± 3 days unless otherwise specified
2. All Screening assessments must be performed within 14 days prior to first dose unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed.
3. Screening examination to include BCVA (best-corrected visual acuity), slit lamp examination (with special focus on cornea), intraocular pressure, and dilated fundoscopic examination may be performed within 21 days prior to first dose.
4. On-study exams, to include BCVA (best-corrected visual acuity) and slit lamp examination (with special focus on cornea); window for exams is up to 3 days prior to dosing. In the event that a subject has a dose delay due to a non-ocular toxicity and an ocular exam has been performed for that cycle, a repeat ocular exam 3 days prior to dosing may be omitted if the participant did not have corneal signs on the previous exam and does not have any new corneal symptoms.

5. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +10 minutes and +30 minutes after SOI (±5 min), EOI, and 1 hour post EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +30 minutes after SOI, and EOI**. On days where vital sign timepoints align with PK sampling timepoints, vital signs should be assessed prior to PK samples being drawn.**
6. If completed within 72 hrs prior to the first dose, this assessment need not be repeated on Day 1 of Cycle 1. Refer to Table 15 for comprehensive list of lab tests.
7. Troponin will be measured at the local (troponin I or T) and central (troponin I) lab. CK-MB at the local lab, or if not available by a central laboratory.
8. BNP to be measured locally, or if not available by a central laboratory, at screening; if cardiac workup is required due to safety concerns during the study, BNP should be measured.
9. Perform only in women of child-bearing potential. A serum pregnancy test should be performed at screening, and subsequent pregnancy tests may be either serum or urine
10. Final pregnancy test (serum or urine) must be performed in women of childbearing potential 60 days after last study treatment.
11. On dosing days, perform triplicate ECGs at predose (within 30 minutes prior to SOI) and EOI. **On days where ECG timepoints align with PK sampling timepoints, ECGs should be performed prior to PK samples being drawn (PK sample should be taken at the exact nominal time; refer to footnote 17).** At screening and End of Study, obtain a single ECG measurement.
12. At Screening, LVEF may be performed within 30 days prior to first dose. All ECHOs indicated on dosing days may be performed up to 7 days before dosing. ECHOs to be done locally and sent to GSK for central imaging storage.
13. A single sample for sBCMA will be collected at C1D8 predose, and at the End of Study visit. sBCMA samples will also be collected on C1D1 at predose (within 30 minutes prior to SOI) and EOI (±5 minutes). On C1D15 and C2D1 collect at predose (within 30 minutes prior to SOI) and EOI (±5 minutes)
14. Collect cytokines at predose (within 30 minutes prior to SOI) and EOI (±5 min) (even when infusion is interrupted or halted) to assess allergic reaction.
15. All ADA samples will be collected prior to each infusion.
16. Sample(s) collected for analysis by central lab.
17. PK samples to be taken for both GSK2857916 and cys-mcMMAF measurement at C1D1 predose (within 30 minutes prior to SOI), EOI (just before EOI), 1 hour post EOI (±5 min), and 3 hours post EOI (±5 min); predose (within 30 minutes prior to SOI) and EOI (just before EOI) on C1D8, C1D15, C2D1, C2D15, C3D1, C3D15, and C5D1.
18. Collect 1 PK sample at each subject's final visit.
19. Informed consent for optional genetics research should be obtained before collecting a sample.
20. CT/PET scans from within 21 days prior to first dose are acceptable.
21. Study drug administration ±1 day window only.
22. Prophylaxis with prednisolone phosphate 1% or dexamethasone 0.1% 1 drops QID x 4 days starting 1 day prior to treatment.
23. Archived or fresh tissue required for BCMA testing. Refer to Section 5.2.1 Inclusion Criterion #4 for eligibility criteria.
24. Also applies to C2D8.
25. Record subject's survival status and whether subsequent treatment for disease was given. Subject does not need to come in for visit.

Abbreviations:
ADA = Antibody Drug Antibody; ALP = alkaline phosphatase; BCVA = best corrected visual acuity; BNP = B-type natriuretic peptide; C1D1 = Cycle 1 Day 1, etc.; [redacted] CK = creatine kinase; CRP = C-reactive protein; EOI = End of Infusion; PD = Pharmacodynamics; PK = Pharmacokinetics; QID = 4 times a day; SOI = start of infusion

7.2. Demographic/Medical History and Baseline Assessments

The following demographic parameters will be captured during Screening: date of birth, gender, race and ethnicity.

Medical/medication history assessed as related to the eligibility criteria listed in Section 5.2.

Baseline (Screening) assessments obtained will include:

- Complete physical examination, including height (in cm) and weight (in kg).
- Vital signs (blood pressure, temperature, pulse rate)
- Chest x-ray
- Ocular exam
- Eastern Cooperative Oncology Group (ECOG) performance status
- Clinical laboratory tests outlined in Table 15
- Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test for female subjects of childbearing potential only
- 12-lead electrocardiogram (ECG)
- Echocardiogram (ECHO)
- Imaging studies (extramedullary disease for MM if indicated, or CT/PET scan for lymphomas)
- For MM: BM aspirate for FISH, BCMA (flow cytometry), PD (target engagement and caspase 3); BCMA expression (IHC)
- For MM: BM biopsy for disease assessment
- For Lymphomas: archival or fresh tissue evaluation for BCMA expression
- Review of concomitant medications

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.2.1. Critical Baseline Assessments

Cardiovascular medical history/risk factors will be assessed at baseline.

7.3. Safety Evaluations

Planned time points for all safety assessments are provided in the Time and Events Tables (Section 7.1).

7.3.1. Physical Examinations

At screening and on dosing days, a full physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.

During interim visits and at the end of study, a brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

7.3.2. ECOG Performance Status

The performance status will be assessed using the Eastern Cooperative Oncology Group (ECOG) scale (Appendix 6) as specified in the Time and Events Tables (Section 7.1).

7.3.3. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, temperature, and pulse rate. Vital signs should be measured after resting for at least 5 minutes. Vital signs will be measured more frequently if warranted by the clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

First Infusion:

Monitoring intervals: Vital signs must be monitored at predose (within 30 minutes prior to start of infusion), +10 and +30 minutes post start of infusion, and at the end of infusion, and 1 hour post end of infusion. In general, subjects must also be monitored for at least 1 hour after the completion of the first infusion and may be discharged if considered clinically stable and all other study procedures have been completed.

Sentinel subject: Subject must be monitored for at least 24 hours post first infusion.

Subsequent subjects: Subjects may be discharged if considered clinically stable and all other study procedures have been completed.

Subsequent Infusions:

Monitoring intervals: Vital signs must be monitored at predose (within 30 minutes prior to start of infusion), +30 minutes post start of infusion, and at the end of infusion.

Subjects may be discharged after the infusion has been completed if considered clinically stable and all other study procedures have been completed.

In case of infusion related reactions or cytokine storm, monitoring will be performed with higher frequency (as clinically indicated).

7.3.4. Electrocardiogram

Triple 12-lead electrocardiogram (ECGs) will be obtained at designated time points specified in the Time and Events Tables (Section 7.1) during the study using an ECG

machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals. At each assessment a 12-lead ECG will be performed by qualified personnel at the site after the subject has at least a 5 minute rest.

The QT interval should be corrected for heart rate by Fridericia's formula (QTcF). Refer to Section 3.9.2 for QTc withdrawal criteria. Refer to the Study Procedures Manual (SPM) for details regarding ECG procedures.

7.3.5. Echocardiogram

Echocardiograms (ECHOs) will be performed at baseline to assess cardiac ejection fraction and cardiac valve morphology for the purpose of study eligibility, as specified in the Time and Events Tables (Section 7.1). Additional ECHO assessments will be performed at specified timepoints indicated in the Time and Events Tables (Section 7.1) or if clinically warranted. The evaluation of the echocardiographer should include an evaluation for left ventricular ejection fraction (LVEF) and both right and left-sided valvular lesions.

Copies of all ECHOs performed on subjects will be stored in a central location if further evaluation is warranted.

7.3.6. Ocular Exam

An ocular exam to include BCVA (best-corrected visual acquity), slit lamp examination (with special focus on the cornea), intraocular pressure, and dilated funduscopic examination will be conducted for all subjects at screening. Additional exams will be performed as specified in the Time and Events Tables (Section 7.1) during the treatment period and at monthly follow-up visits as clinically indicated.

7.3.7. Laboratory Assessments

All protocol required laboratory assessments, as defined in (Table 15), should be performed according to the Time and Events Tables (Section 7.1). Details for the preparation and shipment of samples will be provided in the SPM.

Prior to administration of the first dose of study treatment, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range may be repeated (prior to the first dose) at the discretion of the investigator.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinical significant by the Investigator (for example SAE or AE or dose modification) the results must be recorded in the subject's CRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All laboratory tests with values that are significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 15:

Table 15 List of Clinical Laboratory Tests

Hematology			
Platelet Count	*RBC Indices*:	*Automated WBC Differential:*	
Red blood cell (RBC) Count	MCV	Neutrophils	
White blood cell (WBC) Count (absolute)	MCH	Lymphocytes	
Reticulocyte Count	MCHC	Monocytes	
Hemoglobin		Eosinophils	
Hematocrit		Basophils	
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric Acid
Glucose	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Phosphorous	Creatine kinase (CK)	LDH
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
24-hour urine protein and albumin			
Other screening tests			
Hepatitis B (HBsAg)			
Hepatitis C (Hep C antibody -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay or a validated HCV PCR viral test should be reflexively performed **on the same sample** to confirm the result)			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			
FISH analysis[1]			
Other Laboratory Tests			
Troponin	PTT	INR	IgG, IgM, IgA
CK-MB	B-type natriuretic peptide	C-reactive protein (CRP)	Beta2 microglobulin
Kappa, lambda free LC, FLC ratio	ADA	PGx[2]	Immunofixation
Serum Protein Electrophoresis (SPEP) and Serum M-protein calculation	Urine Protein Electrophoresis (UPEP)		
Biomarker Measurements			
[redacted]	[redacted]	[redacted]	[redacted]

1. FISH testing at least for: t(4;14), t(14/16), 17p13del. Biopsy samples from within 60 days prior to first dose are acceptable.
2. Samples to be collected from subjects in expansion cohorts only.

7.3.8. Pregnancy Testing and Reporting

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

If a female subject is of childbearing potential, she must have a serum β-HCG pregnancy test performed within 14 days prior to the first dose of study treatment. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described below during the study until 60 days following the last dose of study treatment(s).

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an adverse event (AE) or serious adverse event (SAE). Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described above.

7.3.9. Immunogenicity

Serum samples for determination of anti-GSK2857916 antibodies will be taken from all subjects in this study at the time-points specified in the Time and Events Tables in Section 7.1. Timing of the assessments may be adjusted based on emerging data. Details of sample preparation, storage and analysis will be provided in the SPM.

Samples will be analyzed for the presence of anti-GSK2857916 antibodies by a validated electrochemiluminescent immunoassay. All samples will be tested by a screening assay, and positive samples will be further characterized for specificity and antibody titers.

7.3.10. Visual Functioning Questionnaires

The impact of potential ocular toxicity on function and health-related quality of life will be assessed with the use of 2 visual function questionnaires: the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), and the Ocular Surface Disease Index (OSDI). Subjects will complete the self-administered versions of these two assessments during their End of Study Treatment visit. Subjects who are unable to complete the questionnaire on their own due to blurry vision, and require assistance can have the questionnaire read to them by an interviewer. If the questionnaires are

administrated by an Interviewer, then the questionnaire should be read to the subjects verbatim, and subject responses should be recorded directly without any interpretation.

Subjects who continue to experience visual symptoms after discontinuation of study treatment will complete additional interviewer-administered assessments via telephone on a monthly basis for up to 1 year during the Follow-up period or until the resolution of their visual symptoms, whichever comes first.

7.3.10.1. National Eye Institute Visual Functioning Questionnaire-25

The NEI-VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question [Mangione, 2001]. The NEIVFQ-25 generates the following vision-targeted sub-scales: global vision rating, difficulty with near vision activities; difficulty with distance vision activities; limitations in social functioning due to vision; role limitations due to vision; dependency on others due to vision; mental health symptoms due to vision; driving difficulties; limitations with peripheral vision, limitations with color vision; and corneal pain.

7.3.10.2. Ocular Surface Disease Index Questionnaire

The Ocular Surface Disease Index (OSDI) is a 12-item questionnaire designed to assess both the frequency of dry eye symptoms and their impact on vision-related functioning [Schiffman, 2000]. The OSDI has demonstrated good reliability, validity, sensitivity, and specificity, and can be used as a complement to other clinical and subjective measures of dry eye disease by providing a quantifiable assessment of dry eye symptom frequency and the impact of these symptoms on vision-related functioning.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection for Pharmacokinetics

Blood samples of approximately 5 mL for pharmacokinetic (PK) analysis of GSK2857916 (ADC and total antibody) and cys-mcMMAF will be collected at the time points indicated in the Time and Events Tables (Section 7.1). Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded.

Details on PK blood sample collection, processing, storage and shipping procedures are provided in the Study Procedures Manual (SPM). Blood volumes for PK samples are outlined in Appendix 10 (Section 16.9).

7.4.2. Urine Sample Collection for Pharmacokinetics

Urine samples of approximately 1 mL for pharmacokinetic (PK) analysis of cys-mcMMAF will be collected from the 24 hour urine collection sample as scheduled in the Dose Escalation Time and Events Tables (Section 7.1.1). The actual date and time of each urine sample collection as well as the urine volume collected will be recorded. In addition for qualitative analysis of any metabolite(s) approximately 20mL of control is required prior to dosing and a 400mL aliquot as described in the Time and Events Schedules (Section 7.1.1)

Details on PK urine sample collection, processing, storage and shipping procedures are provided in the Study Procedures Manual (SPM).

7.4.3. Pharmacokinetic Sample Analysis

Plasma and urine analysis will be performed under the control of GSK Platform Technologies and Science (PTS) Drug Metabolism and Pharmacokinetics (DMPK), the details of which will be included in the Study Procedures Manual. Concentrations of GSK2857916 (ADC and total antibody) and cys-mcMMAF will be determined in plasma and urine (cys-mcMMAF) samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the Study Procedures Manual).

Once the plasma and urine has been analysed for GSK2857916 (ADC and total antibody) and cys-mcMMAF any remaining plasma or urine may be analysed for other compound-related metabolites and the results reported under a separate GSK PTS-DMPK protocol.

7.5. Translational Research

7.5.1. Pharmacodynamics

Blood, bone marrow, and tumor tissue samples will be collected during this study and analysed pre and post GSK2857916 at the time points indicated in the Time and Events Tables (Section 7.1) to investigate pharmacodynamic response to GSK2857916. The timing of the collections may be adjusted on the basis of emerging PK or pharmacodynamic data from this study or other new information in order to ensure optimal evaluation of the pharmacodynamic endpoints. Details on PD blood and bone marrow sample collection, processing, storage and shipping procedures are provided in the SPM.

Pharmacodynamic markers may include but will not be limited to the following:

- [redacted]
- [redacted]

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

7.5.1.1. [redacted]

[redacted]

7.5.1.2. [redacted]

[redacted]

7.5.1.3. [redacted]

[redacted]

7.5.1.4. [redacted]

[redacted]

7.5.2. [redacted]

[redacted]

[redacted]

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

7.5.3. [redacted]

[redacted]

7.5.3.1. [redacted]

[redacted]

7.6. Genetics

An important exploratory objective of the clinical study is genetic research. Participation in genetics research is optional but all subjects who are eligible for the clinical study and are enrolled into part 2 (expansion cohort) will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for genetic research.

Information regarding genetic research is included in Appendix 7. In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the genetic research described in Appendix 7 unless otherwise indicated. Where required by regulatory authorities, approval of the genetic assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the genetic assessments is being deferred and the study, except for genetic assessments, can be initiated. When genetic assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, genetic assessments will not be conducted.

7.7. Evaluation of Anti-Cancer Activity

Standard disease assessments for MM will include laboratory tests, bone marrow aspirate (cytology, flow cytometry, FLC, etc.) and Bone Marrow biopsy for BCMA expression (IHC) during screening and at the time of CR. Evaluation will be according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (Appendix 1). Disease assessment for subjects with lymphomas will be evaluated at screening and every 9 weeks (for subjects on every 3 week dosing schedule) or every 8 weeks (for subjects on weekly dosing schedule), and at the end of study. Disease assessment for subjects with lymphomas will be according to the Revised Response Criteria for Malignant Lymphoma (Appendix 2).

- Clinical activity measured as Overall Response Rate (ORR) which is defined as follows:

    - For MM: the percentage of subjects with confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) as assessed by 2011 recommendation of the International Myeloma Working Group (IMWG) Panel I (Appendix 1). Other comparisons of interest may be considered (see Section 13.5.2)

- For lymphomas: the percentage of subjects with confirmed CR, PR, as described in the Revised Response Criteria for Malignant Lymphoma (Appendix 2).

Disease assessment may include imaging (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI], bone scan, plain radiography) and physical examination (as indicated for palpable/superficial lesions). Disease assessment will be completed within 4 weeks prior to the first dose of GSK2857916 then every 8 or 9 weeks thereafter, and at the final study visit. See the Time and Events Tables (Section 7.1) for the schedule of assessments of anti-cancer activity. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post-baseline assessments, a window of ±3 days is permitted to allow for flexible scheduling with the exception of dose administration days where a window of ± 3 days for Schedule 1 (once every 3 weeks) is permitted and ± 1 day for Schedule 2 (weekly) is permitted. If the last radiographic assessment was more than 8 or 9 weeks prior to the subject's withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

7.8. Health Outcomes: Quality of Life

7.8.1. Bone Pain/Fatigue Assessment (eDiary)

The patient reported outcome (PRO) instruments that will be used are the Bone Pain/Fatigue Assessment via an e-Diary. In the Part 2 multiple myeloma cohort, the implementation of this assessment will occur upon availability of the instruments.

Bone Pain/Fatigue Assessment: Bone pain burden will be measured by e-Diary consisting of certain modified questions from Brief Pain Inventory-Short Form (BPI-SF) which assesses pain intensity and the interference of pain with daily life [Atkinson, 2010; Cleeland, 1994] and Brief Fatigue Inventory (BFI) [Cleeland, 2010]. The BPI-SF is one of the most frequently used pain assessments [Cleeland, 2009] and has been used in various disease areas, including cancer pain and neuropathic pain [Daut, 1982; McDowell, 1996]. The questionnaire has demonstrated both reliability and validity across cultures and languages [Cleeland, 1994]. The BFI has also been used in cancer patients to measure fatigue [Mendoza, 1999; Chang, 2007].

Bone pain and fatigue burden will be measured by an e-Diary consisting of 7 short questions, including 4 questions to assess pain intensity (severity) and one question to assess the interference of pain with daily life activities. The items ask about pain experienced within the last 24 hours. It also includes 2 questions on use of pain medication. Fatigue will be measured by 2 short questions – one to assess the level of fatigue in the past 24 hours and the second to assess the interference of fatigue with general activity. Data from this e-Diary will be used to understand and characterize pain/fatigue experience and explore time to potential pain relief while controlling for the use of pain medication.

It is expected that the improvement in intensity of bone pain/fatigue and the impact of bone pain/fatigue on general activity will take place within the first 8 cycles of treatment

and the self-completion of the e-Diary during this period will accurately capture the changes in bone pain/fatigue.

Upon availability of the Bone Pain/Fatigue Assessment e-Diary, MM subjects will self-complete the assessments at the following times:

- Starting 2-4 days prior to Cycle 1 Day 1
- Daily from Day 1 through Day 8 for each Cycle to time of study treatment discontinuation
- Day 15 of each Cycle to time of study treatment discontinuation
- Study Treatment Discontinuation visit

7.8.2. Exit Interview and Follow-up Interview

To further evaluate disease and treatment related symptoms (including bone pain and fatigue, and visual symptoms) and associated impacts on function and health-related quality-of-life, participants in the Part 2 multiple myeloma cohort will complete an optional Exit Interview conducted via telephone. The interview will be conducted by a trained interviewer and will be audio recorded for transcription and analysis. The telephone interview should be conducted within 21 days following completion of the End of Study Treatment visit.

Subjects who have experienced ocular symptoms during the treatment period will have the option to also consent to participate in an optional Follow-up interview. The Follow-up interview will be conducted by a trained interview via telephone at least 6 months following the End of Study Treatment visit. The Follow-up interview will focus on visual symptoms experienced by the subject, impacts on function and health-related quality-of-life and management and resolution of their visual symptoms following discontinuation of study treatment.

Both the Exit Interview and Follow-Up interview are optional, and the failure to complete either interview will not constitute a protocol deviation.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an adverse event (AE) or serious adverse event (SAE) as outlined in Section 8.1 and Section 8.2, respectively.

8.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated)

temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/serious adverse event [SAE]).

"Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and 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 that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that led 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

8.2. Definition of an SAE

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject 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 out-subject setting. Complications that occur during hospitalization are adverse events (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.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person'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 or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgment should be exercised in deciding whether 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are 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.

g. Protocol-Specific SAEs:

- All events of possible study treatment-induced liver injury with hyperbilirubinemia defined as alanine aminotransferase (ALT) ≥3 times upper limit of normal (ULN) **and** bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and international normalization ratio (INR) >1.5, if INR is measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: Bilirubin fractionation should be performed.

- Any new primary cancers

8.2.1. Sentinel Events

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. The GSK Medical Monitor is accountable for reviewing all SAEs for possible Sentinel Events which is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia

- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrosis

8.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., electrocardiogram [ECGs], radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an adverse event (AE) or serious adverse event (SAE), in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as a SAE.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

8.3.1. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

8.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as a serious adverse event (SAE). Death due to disease under study is to be recorded on the Death electronic case report form (eCRF). However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design or procedures and the disease progression, then this must be reported as a SAE.

8.5. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an adverse event (AE) or serious adverse event (SAE).

AEs will be collected from the time the first dose of study treatment is administered until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 8.5.2.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days the investigator may report any AE that they believe possibly related to study treatment.

8.5.1. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

“How are you feeling?”

“Have you had any (other) medical problems since your last visit/contact?” or for pediatric studies, “Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?” or for pediatric studies, ”Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?”

8.5.2. Prompt Reporting of SAEs and Other Events to GSK

Serious adverse events (SAEs), pregnancies, and liver function abnormalities and any other events meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
"CV events" and/or "death"	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
Liver chemistry abnormalities:				
ALT ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5, if INR is measured)[c]	24 hours[a]	SAE data collection tool; Liver Event eCRF and liver imaging and/or biopsy eCRFs if applicable[b]	24 hours	Updated SAE data collection tool. Updated Liver Event eCRF[b]
ALT ≥5 times ULN; ALT ≥3 times ULN with hepatitis or rash **or** 3 times ULN ≥4 weeks	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥3 times ULN and <5 times ULN and bilirubin <2 times ULN	24 hours[a]	Liver Event eCRF does not need to be completed unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[b]		

a. GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
b. Liver event documents should be completed as soon as possible
c. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

Methods for detecting, recording, evaluating, and following up on adverse events (AEs) and serious adverse events (SAEs) are provided in the Study Procedures Manual (SPM).

8.5.3. Regulatory reporting requirements for SAEs

Prompt notification of serious adverse events (SAEs) by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)/ethics committee (EC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/EC, if appropriate according to local requirements.

9. LIVER CHEMISTRY FOLLOW-UP PROCEDURES

9.1. Liver Chemistry Testing Procedures

For subjects meeting any of the liver chemistry stopping criteria in Section 3.9.1, make every attempt to carry out the **liver event follow-up assessments** described below:

- Viral hepatitis serology, including:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
  - Hepatitis C RNA
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, then obtain heterophile antibody or monospot testing)
- Blood sample for pharmacokinetic (PK) analysis. Record the date and time of the PK blood sample draw and the date and time of the last dose of study drug prior the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date or time of the last dose cannot be approximated, or if a PK sample cannot be collected within 48 hours of the liver chemistry event, do not obtain a PK sample. Instructions for sample handling and shipping are found in the Study Procedures Manual (SPM).
- Serum creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH)

- Fractionate bilirubin, if total bilirubin ≥2 X upper limit of normal (ULN)
- Obtain a complete blood count (CBC) with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms indicative of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE eCRF
- Record the use of concomitant medications, including acetaminophen, herbal remedies or any other over the counter (OTC) medications, or any putative hepatotoxins, on the concomitant medication eCRF
- Record alcohol use on the liver event alcohol intake eCRF

The following assessments are required for subjects with ALT ≥3 X ULN and bilirubin ≥2X ULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance imaging [MRI] or computed tomography [CT]) to evaluate liver disease

9.2. Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3 X ULN **but** <5X ULN **and** bilirubin <2 X ULN, without symptoms indicative of hepatitis or rash, and who can be monitored safety for 4 weeks, the following actions should be taken:

- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety
- Continue administration of study drug
- Evaluate liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) weekly until they resolve, stabilize or return to within baseline levels
- If at any time the subject meets any of the liver chemistry stopping criteria 1 to 5 (Section 3.9.1), then proceed as described in Section 9)
- If, after 4 weeks of monitoring, ALT <3X ULN and bilirubin <2 X ULN, then monitor subjects twice monthly until liver chemistries normalize or return to within baseline values

9.3. Drug Restart/Rechallenge Following Liver Events that are Possibly Related to Study Drug

Approval by the GSK Medical Monitor to restart/rechallenge study drug may be considered where:

- The subject is receiving compelling benefit, the benefit exceeds the risk, and no effective alternative therapy is available. Approval of restart/rechallenge by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must be obtained, as required

- If the restart/rechallenge is approved by GSK in writing, then the subject must be provided with a clear description of the possible benefits and risks of administration of study drug, including the possibility of a recurrence, a more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study drug restart/rechallenge. Documentation of the informed consent must be recorded in the subject's study chart.
- Study drug must be administered at the dose specified by the GSK Medical Monitor.
- Subjects approved by GSK for restart/rechallenge of study drug must return to the clinic twice a week for evaluation of liver chemistry tests until stable liver chemistries have been demonstrated and laboratory monitoring may resume per protocol.

9.4. Drug Restart Following Transient, Resolving Liver Events Not Related to Study Drug

Approval by the GSK Medical Monitor to restart study drug(s) may be considered where:

- Liver chemistry abnormalities have a clear underlying cause (e.g., biliary obstruction, hypotension) and liver chemistries have improved to normal or are within 1.5 X baseline and ALT <3X ULN. Approval of restart by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) may be required.
- If the restart/rechallenge is approved by GSK in writing, then the subject must be provided with a clear description of the possible benefits and risks of administration of study drug(s), including the possibility of a recurrence, a more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study drug(s) restart/rechallenge. Documentation of the informed consent must be recorded in the subject's study chart.
- Study drug(s) must be administered at the dose specified by the GSK Medical Monitor.
- Subjects approved by GSK for restart/rechallenge of study drug(s) must return to the clinic once a week for evaluation of liver chemistry tests until stable liver chemistries have been demonstrated and laboratory monitoring may resume per protocol.
- If protocol-defined stopping criteria for liver chemistry abnormalities are met, study drug(s) administration must stop.

10. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the electronic case report form (eCRF). Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

Concomitant dosing of GSK2857916 with strong Pgp inhibitors should be avoided unless considered medically necessary (See Appendix 11: Pgp Inhibitors for list of relevant Pgp inhibitors).

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. The SPM will be updated to include this information. Any such changes will be communicated to the investigative sites in the form of a letter.

10.1. Permitted Medication(s)

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, growth factors, and treatment with antibiotics, anti-emetics, antidiarrheals, and analgesics, as appropriate.

Steroids are not allowed unless used for pre-medication prior to GSK2857916 infusion.

Concomitant therapy with biphosphonates is allowed.

Concomitant prophylactic treatment for tumor lysis syndrome (according to local standards) in subjects with high tumor load, where TLS may occur is permitted and should be considered.

10.2. Prohibited Medication(s)

Chronic treatment with oral steroids is prohibited while the subject is on study.

A short course (up to 7 days) of steroids can be used to manage rash, treatment induced diarrhea, or other acute complications. Steroids may be used to treat infusion related reactions. Inhaled steroids are allowed.

10.3. Permitted Non-Drug Therapies

Subjects may receive local irradiation for pain control or stability control.

10.4. Prohibited Non-Drug Therapies

Plasmapheresis is prohibited from 7 days prior to study entry through the end of study.

11. LIFESTYLE AND/OR DIETARY RESTRICTIONS

11.1. Contraception

11.1.1. Female Subjects

A female of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years in the absence of hormone replacement therapy (HRT). In questionable cases, the subject must have a follicular stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

A female of childbearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

Female subjects of childbearing potential must not become pregnant during the study and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of <1%.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least 60 days after the last dose of study treatment.

Contraceptive Methods with a Failure Rate of <1%

- Oral contraceptives (either combined or progesterone only) if not contraindicated for this subject population or per local practice.
- Estrogenic vaginal ring if not contraindicated for this subject population or per local practice.
- Percutaneous contraceptive patches if not contraindicated for this subject population or per local practice.
- Implants of levonorgestrel if not contraindicated for this subject population or per local practice.
- Injectable progesterone if not contraindicated for this subject population or per local practice.
- Intrauterine device or intrauterine system that meets the <1% failure rate as stated in the product label

- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus vaginal spermicidal agent (foam/gel/film/cream/suppository)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

11.1.2. Male Subjects

To prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods:

- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

  Complete abstinence from sexual intercourse from the first dose of study medication, throughout the study treatment period and for at least 60 days after the last dose of study treatment.
- Condom *(during non-vaginal intercourse with any partner - male or female)* **OR**
- Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository) *(during sexual intercourse with a female)*

11.2. Lactation Restrictions

Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for 4 months following the last dose of study treatment.

12. DATA MANAGEMENT

For this study, data will be collected using defined electronic case report forms (eCRFs), transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data. AEs and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal

validated medication dictionary, GSK Drug. Electronic CRFs (eCRFs), including queries and audit trails, will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

When laboratory samples (i.e., hematology and clinical chemistry) are analyzed by a central laboratory the results will be stored in a database maintained by the central laboratory and transferred to GSK at agreed times.

In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

12.1. Data Dissemination and Communication Plan

The GSK Medical Monitor will review screening packets to ensure that subjects being considered for enrolment meet eligibility criteria prior to entering the study. Subjects will not be assigned a study number until their screening packet is reviewed and approved by the GSK Medical Monitor. GSK will remain in constant contact with the clinical sites during the enrolment period to ensure that cohort enrolment in Parts 1 and 2 of this study are completed as per protocol. Investigators will be informed about available openings for enrolment on the trial and will be asked to pre-screen their subjects to determine potential eligibility, and to avoid over-enrolment. Enrollment will be offered to a given site for a limited period of time, and if the site chosen cannot successfully enrol a subject within a pre-specified time period then another site will be offered the opportunity to enrol a subject.

During Part 1 of the study, Study Team Safety Update Meetings will be held every three weeks to review relevant data with the Principal Investigators (or delegates) and site staff. These meetings will be held on an "as needed" basis (but no less frequent than once a month) during Part 2 (e.g., to share safety experience and to communicate results of scheduled futility analyses). Safety, PK, PD, and clinical outcome data available for all subjects at the time of the scheduled Safety Update Meeting will be reviewed and summarized. In addition, Dose Escalation Meetings will be scheduled at the conclusion of the DLT assessment period for subjects enrolled in each cohort to review safety PK, and PD data and determine the next dose level appropriate for study. Dose escalation decisions will be made with team and investigator agreement after review of available safety data from at least one cycle of therapy with GSK2867916 (i.e., 21 days for the once every 3 weeks schedule and 28 days for weekly schedule). All dose escalation or safety decisions will be documented in writing with copies maintained at each site and the Master Study Files at GSK. Available data will be provided to participants prior to each scheduled Safety or Dose Escalation Meeting.

Attendees of Safety Update and Dose Escalation Meetings will include but not limited to all clinical investigators (or designees) and site staff, the GSK Medical Monitor, Clinical Investigation Lead, Clinical Operations Study Lead (USA and Local Operating Company designees), Data Quality Leader, Global Clinical Safety and Pharmacovigilance Representative, Statistician, CPMS representative, and Translational Medicine Lead.

13. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

13.1. Hypothesis(es)

13.1.1. Part 1: Dose-Escalation Phase

No formal statistical hypotheses are being tested in Part 1. Analysis of the data obtained from Part 1 will only utilize descriptive methods.

13.1.2. Part 2: Expansion Cohort

For Part 2, hypothesized response rates are provided in Section 13.2.2 below. In this case, a test that the ORR is less than or equal to the null hypothesis rate versus the ORR is greater than or equal to the alternative rate will be performed using the stopping rules provided in Section 13.6.2. Descriptive statistics will be used to describe the observed ORRs at the RP2 dose used in the expanded cohorts.

13.2. Sample Size Determination

The sample size planned for Part 1 arises from the predefined criteria for dose selection and is not driven by statistical considerations. Based on simulations, the anticipated size of Part 1 will be approximately 20 subjects. See Section 13.2.1 and Section 13.2.2 for more details.

The additional 50 subjects in the expanded cohort for Part 2 of the study (which includes approximately 40 MM subjects and approximately 10 subjects with other BCMA positive malignancies) will provide additional safety and tolerability information about the treatment and a better precision around the response rate estimate.

13.2.1. Part 1: Dose-Escalation Phase

The total number of subjects to be enrolled in Part 1 will depend on the number of subjects needed to characterize the individual dose cohorts for determination of the MTD. Simulations were conducted to determine the average sample size and percentage of times each dose was selected under three different scenarios. These scenarios were designed to represent true toxicity profiles which are lower than expected, higher than expected, and in line with expectations. For each scenario, 1000 clinical trials were simulated. Details are provided in Table 16. Doses are the projected doses. Actual doses used during the conduct of the trial may vary.

The specified prior probabilities discussed in Section 3.3.1.2.3 were used to determine an explicit equation for the prior distribution using the FACTS software. The parameters (s.d.) of the explicit distribution are α=-1.3281 (1.7153), ln(β)=-0.795 (1), and ρ=-0.9352 where α and ln(β) are distributed as bivariate normal with correlation ρ.

Table 16 Simulation Results Under Various Scenarios

Dose (mg/kg)	Scenario 1: Below Level of Toxicity		Scenario 2: Expected Level of Toxicity		Scenario 3: Higher Level of Toxicity	
	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)
No Dose		0		0.7		6.8
0.03	0	0	0.001	0	0.05	0.2
0.06	0.01	0	0.02	0	0.075	0.1
0.12	0.025	0	0.05	0.4	0.1	2.6
0.24	0.05	0.1	0.1	1.4	0.15	5.3
0.48	0.075	0.7	0.15	6.7	0.2	20.3
0.96	0.1	4.3	0.2	20.3	0.3	29.0
1.92	0.125	14.1	0.225	30.3	0.35	24.6
2.8	0.15	22.6	0.275	27.9	0.375	9.5
3.6	0.175	22.4	0.35	9.1	0.45	1.2
4.5	0.225	35.8	0.425	3.2	0.55	0.4

The average sample size over the 1000 clinical trials simulated under each of Scenarios 1-3 was 20.55, 20.04, and 19.43 respectively.

13.2.2. Part 2: Expansion Cohort

Dose escalation will be used to establish the RP2 dose for GSK2857916. Once the RP2 dose is confirmed, at least 15 and up to 40 subjects in total will be enrolled into the MM cohort using decision rules defined in Table 17. The sample size and stopping rules are based on the methodology of Lee et al. [Lee, 2008]. The assumptions underlying the design are detailed below.

The null hypothesis is:

H_0: $p \leq 20\%$

The alternative hypothesis is:

H_A:$p \geq 40\%$

For the MM expansion cohort, starting with 15 subjects and allowing for a maximum sample size of 40, this design will have a type I error rate (α) of 0.075 and 89.8% power. The trial is not designed to stop early for efficacy, but is designed to stop early for futility if the predictive probability of success is less than 5%. The type I error rate, power, and predictive probability of success to stop early for futility were derived from explicitly stating the minimum and maximum sample size, allowing for the futility stopping rate to range from 5% to 20% within the predictive probability design software, and selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior probability used in determining the design was Beta (0.25, 0.75), a distribution with a mean response rate of 25%. Under the null hypothesis, if the true response rate is 20%, the expected sample size of the design is 23.4 subjects and probability of early termination (PET) is 88.9%. Under the alternative hypothesis, if the true response rate is 40%, the expected sample size of the design is 38.6 subjects and probability of early termination (PET) is 8.5%.

13.3. Sample Size Sensitivity

13.3.1. Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

13.4. Data Analysis Considerations

Data will be listed and summarized according to GSK integrated data standards library (IDSL) reporting standards and the Clinical Data Interchange Standards Consortium (CDISC) where applicable. Complete details will be provided in the Reporting and Analysis Plan (RAP).

13.4.1. Analysis Populations

The '**All Treated**' population is defined as all eligible subjects who receive at least 1dose of study treatment. An incorrect treatment schedule or drug administration or an early termination of treatment will not result in exclusion of subjects from this population. Subjects with major deviations from the eligibility criteria affecting safety or from the treatment schedule at the DLT evaluation period (1 cycle: 21 days for once every 3 weeks schedule or 28 days for once weekly schedule) for reasons other than toxicity may be presented in separate tables/listings.

The 'All Treated' population will further be classified in the following sub-populations.

- Part 1: all Part 1 subjects of All Treated population. Note, subjects in Part 1 are exclusively multiple myeloma patients.
- Part 2 MM: all Part 2 MM subjects of All Treated population
- All Treated MM: comprise of subjects in Part 1 and Part 2 MM.
- Part 2 NHL: all Part 2 lymphoma subjects of All Treated population.

The '**DLT Evaluable**' population in Part 1 enables an appropriate evaluation of study DLTs. It is defined as those subjects fulfilling the 'All Treated' population criteria, and having met the following adequate exposure criteria:

- For Schedule 1 (once every 3 weeks dosing) subjects received a complete infusion in cycle 1.

- For Schedule 2 (once weekly dosing for 3 consecutive weeks, 1 week rest) subjects receive three infusions, two of which must be complete infusions, in cycle 1. (as increases up to ≤30% are implemented between cohorts, less than 2 complete infusions would result in a total dose closer to the previous dose investigated).

Any subject in the "All Treated" population who experiences a DLT, as defined in Section 3.3.3 will also be included in the DLT evaluable population regardless of exposure.

The '**Evaluable (MM)'** population is a subset of the 'All Treated' population, who were initially treated at RP2D in the expansion cohort and have at least two post-baseline disease assessments or they have progressed or died or permanently discontinued treatment. This population will be used for the futility analysis of the MM expansion cohort.

The '**Pharmacokinetic (PK) Population**' is defined as those subjects in the "All Treated" population from whom at least one PK sample was obtained, analyzed, and was measurable.

The '**Pharmacodynamic (PD) Population**' is defined as those subjects in the "All Treated" population from whom at least one PD sample was obtained, analyzed, and was measurable.

13.5. Treatment Comparisons

13.5.1. Primary Comparisons of Interest

No formal hypothesis testing will be performed. Safety, PK, PD markers, and efficacy summaries will be provided by initial dose cohort in Part 1 and by expansion cohort in Part 2.

13.5.1.1. Primary Comparison of Interest

All available data, including adverse events, changes in laboratory values and other safety parameters will be evaluated for each dose cohort in Part 1 and for each expansion cohort in Part 2.

13.5.2. Other Comparisons of Interest

Pharmacokinetic: PK parameters will be evaluated and summarized for each dose cohort in Part 1 and in Part 2.

Pharmacodynamic markers: Changes from baseline in PD markers will be evaluated and summarized for each dose cohort in Part 1 and for Part 2.

Clinical anti-cancer activity: The number of Overall Responders (PR, VGPR, CR or sCR) for each dose cohort in Part 1 and for each expansion cohort in Part 2 will be listed and summarized if data warrant. Clinical Benefit Rate (CBR), as defined in Appendix 1, may also be explored. The results from the independently reviewed scans may also be reported if data are available.

13.6. Interim Analysis

13.6.1. Part 1

While no formal interim analysis is planned for Part 1, safety, pharmacokinetic and pharmacodynamic marker data will be examined on an ongoing basis to support dose escalation decisions. Prior to determining the GSK2857916 dose for the next cohort enrolled, exploratory analysis will be conducted to assess the relationship of GSK2857916 dose levels with safety, PK and PD parameters using all data from available cohorts. For more details of the dose escalation procedure, see Section 3.3.

13.6.2. Part 2

The methodology utilized is based on the predictive probability of success if enrollment continues to 40 subjects [Lee, 2008]. The predictive probability design is similar to a Green-Dahlberg design in that it allows for early stopping for futility. The differences are that the predictive probability design allows for evaluation of stopping rules as often as after each subject, rather than at only two stages. While the two designs have similar type I and type II error rates, the probability of early termination is greater with the predictive probability design. In this particular study, we will stop only for futility and evaluate the stopping rules once approximately 15, 22, and 30 subjects are evaluable (though additional futility looks are also controlled for if necessary). A subject is considered evaluable if they are in the all treated population and have had at least two post baseline disease assessments.

For the MM expansion cohort, response data will be reviewed once approximately 15, 22, and 30 subjects are evaluable and the number of overall responses (PR, VGPR, CR, and sCR) observed will be compared with the stopping rules provided in Table 17 below.

Table 17 Futility Stopping Region

	Number of Overall Responses												
Number of Evaluable Subjects	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**>11**
15	■	■	■										
16	■	■	■										
17	■	■	■										
18	■	■	■	■									
19	■	■	■	■									
20	■	■	■	■									
21	■	■	■	■									
22	■	■	■	■	■								
23	■	■	■	■	■								
24	■	■	■	■	■								
25	■	■	■	■	■	■							
26	■	■	■	■	■	■							
27	■	■	■	■	■	■							
28	■	■	■	■	■	■							
29	■	■	■	■	■	■	■						
30	■	■	■	■	■	■	■						
31	■	■	■	■	■	■	■						
32	■	■	■	■	■	■	■	■					
33	■	■	■	■	■	■	■	■					
34	■	■	■	■	■	■	■	■	■				
35	■	■	■	■	■	■	■	■	■				
36	■	■	■	■	■	■	■	■	■				
37	■	■	■	■	■	■	■	■	■	■			
38	■	■	■	■	■	■	■	■	■	■			
39	■	■	■	■	■	■	■	■	■	■	■		
40	■	■	■	■	■	■	■	■	■	■	■	■	

Note: The shaded regions are the specific regions for stopping the study for futility. For instance, if there are 4-5 or fewer responses in 25 subjects, then the predictive probability for success will be less than the futility criterion, 5.0%, and the study will be stopped.

In addition to the considering the recommendations of the futility analyses, final decisions on stopping enrolment in the MM cohort will depend on the totality of the data collected. Examples of consideration of the totality of the data include, further investigation of the clinical activity of subgroups of subjects based on their BCMA expression levels and evaluation of the quality of responses (including sCR, CR and Clinical Benefit Rate, as defined in Appendix 1). Should the recommendation to stop for futility be disregarded in favor of a decision to continue the trial based on the totality of the data, the overall type I error rate of the expansion phase will be inflated.

No interim analyses will be performed on the BCMA+ lymphomas cohort; though consideration would be given to closing the cohort should the enrollment be stopped in the MM cohort.

If necessary, a subject may be replaced if they are deemed to be Lost to Follow-Up (LTFU) or they have withdrawn due to a toxicity deemed to not have been related to GSK2857916.

Subjects will not be replaced when they discontinue the study due to: Progression (symptomatic or otherwise), toxicity related to GSK2857916, or lack of efficacy.

Other administrative interim analyses may be performed if needed.

Final analysis of MM population may be performed separately, before the NHL cohort completes the study.

13.7. Key Elements of Analysis Plan

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the Reporting and Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be information, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized.

13.7.1. Anti-Cancer Activity Analyses

The All Treated Population will be used for anti-cancer activity analyses. Since this is a Phase I study, anti-cancer activity will be evaluated based on clinical evidence and response criteria. If data warrant, the response data will be summarized by dose level. Correlation analysis will be conducted to explore any relationship between the tumor response based on either the International Myeloma Working Group Uniform Response Criteria (for subjects with MM; see Appendix 1) or the Response Criteria for Malignant Lymphoma (for subjects with lymphomas, refer to Appendix 2). Full details will be specified in the Reporting and Analysis Plan (RAP).

13.7.2. Safety Analyses

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g. laboratory tests, vital signs, electrocardiogram [ECGs]) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the Reporting and Analysis Plan (RAP).

13.7.2.1. Extent of Exposure

The number of subjects administered study treatment will be summarized according to the duration of therapy.

13.7.2.2. Adverse Events

Adverse events (AEs) will be coded using the standard MedDRA and grouped by system organ class. Adverse events (AEs) will be graded by the investigator according to the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), (version 4).

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, serious adverse events (SAEs) and AEs leading to discontinuation of study treatment. Adverse events (AEs), if listed in the NCI-CTCAE (version 4) will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

Characteristics (e.g. number of occurrences, action taken, grade, etc) of the following AEs of clinical interest will be summarized separately: corneal events, hematologic toxicities (including but not limited to thrombocytopenia and neutropenia), infusion related reaction etc. Details will be provided in the RAP.

The incidence of deaths and the primary cause of death will be summarized.

13.7.2.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) (Version 4.0). The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel.

Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit, as appropriate.

The worst-case- toxicity grade in hematology and chemistry result during the treatment will be summarized. Shift tables from baseline to the worst toxicity grade during treatment will be provided for each laboratory analyte.

Further details will be provided in the Reporting and Analysis Plan (RAP).

13.7.2.4. Immunogenicity Analyses

For each subject, the results and titers of anti-GSK2857916 binding antibodies will be listed for each assessment time point. The frequency and percentage of subjects with positive and negative results will be summarized for each assessment time and overall for each subject by dose cohort.

13.7.2.5. Other Safety Measures

Data for vital signs, electrocardiograms (ECGs), and echocardiograms (ECHOs) will be summarized based on predetermined criteria identified to be of potential clinical concern (PCI). For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. Further details will be provided in the Reporting and Analysis Plan (RAP).

13.7.3. Pharmacokinetic Analyses

13.7.3.1. Raw Plasma Concentrations

Linear and semi-logarithmic individual plasma concentration-time profiles and mean and median profiles (when applicable) by GSK2857916 dose and schedule will be plotted for both GSK2857916 (intact and total) and cys-mcMMAF in Part 1.

In Part 2, individual model-predicted GSK2857916 plasma concentration-time profiles, observed concentrations in individual subjects and population predicted plasma concentrations provided by NONMEM (non-linear mixed effects modelling), will be presented graphically by subject (semi-log plot) and by treatment (linear and semi-log plots).

Plasma concentrations of GSK2857916 (intact and total) and cys-mcMMAF will be listed for each subject and summarized by planned time point, dose cohort and schedule in Part 1and Part 2.

Derived Plasma Pharmacokinetic Parameters

Pharmacokinetic analysis will be the responsibility of the CPMS Department, QSci, GSK.

In Part 1 of the study, plasma GSK2857916 concentration-time data will be analyzed by non-compartmental methods using WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following GSK2857916 (intact and total) PK parameters will be determined as data permit, for each dose of GSK2857916, each schedule and for each subject: After single dose : area under the plasma concentration-time curve (AUC(0-t), AUC (0-tau) and/or AUC(0-∞)), maximum observed plasma concentration (Cmax),time to Cmax (tmax), last time point where the concentration is above the limit of quantification (tlast), systemic clearance (CL), Volume of distribution at steady state (Vss), terminal phase elimination rate constant (λz), terminal phase half-life (t½). After repeat dose: Cmax and Ctrough. For cys-mcMMAF, after single dose, Cmax and AUC(0-t) will be derived and after repeat dose Cmax and Ctrough.

In Part 2 of the study, plasma GSK2857916 concentration-time data together with data from part 1 will be analysed using a population approach. A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters and identify relevant covariates (e.g., age, weight, or disease related covariates). PK parameters will be listed and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval of log-transformed parameters) by dose cohort and schedule in Part 1 and Part 2. To assess the extent of accumulation following GSK2857916 repeat dosing, the observed accumulation ratio (Ro) for both GSK2857916 (intact and total) and cys-mcMMAF will be determined as Cmax and Ctrough at steady-state to Cmax and Ctrough after the first dose, respectively.

Raw urine Concentrations

Urine concentrations of cys-mcMMAF (part 1 only) will be listed and summarised by GSK2857916 dose, schedule and nominal time range. Plots may also be produced if deemed necessary.

Derived Urine Pharmacokinetic Parameters

If data permits, the following pharmacokinetic parameters will be determined for each GSK2857916 dose, each schedule and for each subject (Part 1 only):

Urinary recovery of unchanged cys-mcMMAF within the 24 h period collection (Ae(0-24)) will be calculated. It will be calculated as the product of the concentration in urine and the urine weight, thus assuming a urine density of 1 g/mL.

Fraction of total cys-mcMMAF dose excreted (Fe) in the 24-h interval will be estimated as Ae(0-24)/(cys-mcMMAF)Dose, in the Schedule 1only (i.e. every 3weeks).

Derived cys-mcMMAF urine pharmacokinetic parameters will be listed and summarised by GSK2857916 dose and schedule.

13.7.3.2. Statistical Analysis of Pharmacokinetic Data

Statistical analyses of the pharmacokinetic (PK) parameters data will be the responsibility of Discovery Biometrics, GSK.

GSK2857916 (intact and total) and cys-mcMMAF concentration-time data will be listed for each subject and summarized by descriptive statistics at each time point by cohort.

Dose Proportionality: In Part 1, if more than 2 dose cohorts are required to reach RP2 dose, exploration of dose proportionality for GSK2857916 (intact and total) and Cys-mcMMAFAUC(0-∞)/AUC(0-tau) and Cmax following single dose administration and GSK2857916 (intact and total) and cys-mcMMAF Cmax and Ctrough following repeat dose administration will be evaluated graphically and using the power model as described below:

$$\log(pharmacokinetic\ parameter) = a + b * \log(dose)$$

where *a* is the y-intercept and *b* is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope will be fitted as fixed effects. If there is sufficient data, the model may also be fit with the intercept and/or slope as random effects depending on the ability of the model to converge and on estimation of variance-covariance matrix. The mean slope and corresponding 90% confidence interval will be estimated from the power model.

13.7.4. Pharmacokinetic/Pharmacodynamic Analyses

Exploratory plots will be presented to examine potential relationships between individual and/or pooled plasma concentrations/exposure and relevant safety and PD endpoints. If deemed appropriate, further PK/PD modelling will be performed on the safety and PD endpoints selected based on the results of the exploratory graphical analysis showing obvious relationships or trends between the dose, concentration/exposure and the safety and PD endpoints. The choice of the structural PK/PD models will be dependent on the emerging data. More details of any exploratory PK/PD analyses will be provided in the RAP.

The exposure response relationship between GSK2857916 (dose, concentration, Cmax, or AUC) and clinical activity (e.g. ORR) will also be explored combining Part 1 and Part 2 data together if deemed appropriate.

13.7.4.1. Translational Research Analyses

The results of translational research investigations will be reported either within or separately from the main clinical study report (CSR). All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Further details on the translational research analyses will be addressed in the Reporting and Analysis Plan (RAP).

13.7.4.2. Novel Biomarker(s) Analyses

The results of these biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the novel biomarker.

13.7.5. Genetic Analyses

Further details on genetic analyses will be addressed in Appendix 7.

13.7.6. Pharmacodynamic Biomarkers and Exploratory Response Prediction Biomarkers

[redacted]

13.7.6.1. [redacted]

[redacted]

13.7.7. Clinical Activity Analyses

Overall Response Rate ORR) is one of the secondary endpoints to measure clinical activity of this study.

For multiple myeloma, ORR is defined as the percentage of subjects with a confirmed PR or better (i.e. PR, VGPR, CR and sCR), according to the IMWG Panel I (Appendix 1), as assessed by the investigator. In addition, Clinical Benefit rate (CBR) is defined as the percentage of subjects with a confirmed MR or better (i.e.MR, PR, VGPR, CR and sCR), according to the IMWG Panel I (Appendix 1), as assessed by the investigator.

The number and percentage of subjects in the following response categories will be presented sCR (stringent complete response), (complete response) CR, (very good partial response) VGPR, (partial response) PR, (minimal response) MR, stable disease (SD), progressive disease (PD), and not evaluable (NE)

sCR+CR+VGPR+PR for overall response (ORR)

sCR+CR+VGPR+PR+MR for Clinical Benefit rate (CBR)

The corresponding exact 95% CI for ORR and Clinical Benefit Rate (CBR) will also be provided. Subjects with unknown or missing response will be treated as non-responders, i.e., these subjects will be included in the denominator when calculating percentages of response.

For lymphoma, ORR is defined as the percentage of subjects with confirmed CR, or PR, as described in the Revised Response Criteria for Malignant Lymphoma (Appendix 2). ORR for lymphomas will be summarized in a similar way as multiple myeloma. The corresponding exact 95% CI for ORR will also be provided.

Other exploratory time-to-event (TTE) endpoints related to clinical activity for Part 2 (MM) of this study are TTP, DOR, TTR, and PFS.

Time to disease progression (TTP) is defined as the time from first dose until the earliest date of PD per IMWG, or death due to PD. Determination of dates of TTP event and dates for censoring will be described in the RAP. **Duration of response (DOR)** is defined as the time from first documented evidence of PR or better until disease progression (PD) per IMWG, or death due to PD among subjects who achieve a response

(i.e. confirmed PR or better). Responders without disease progression will be censored at the censoring time point for TTP.

Time to response (TTR) is defined as the time between the date of first dose and the first documented evidence of response (PR or better). Subjects without confirmed response (PR or better) will be censored at the censoring date for TTP.

Progression-free survival (PFS) is defined as the time from first dose until the earliest date of disease progression (PD) per IMWG, or death due to any cause. Determination of dates of PFS event and dates for censoring will be described in the RAP.

For all the TTE endpoints described above, median TTE with 95% CI will be estimated employing the Kaplan-Meier method as data permits. A Kaplan-Meier survival curve will be generated. The number and percentage of subjects who had the event or were censored will also be reported.

Exploratory subgroup analyses may be performed for all endpoints to measure clinical activity as appropriate.

Overall Survival: The protocol is amended to collect long-term survival data (i.e. up to 1 year after last subject completes or discontinues treatment). Subjects who have already completed the study will be contacted to request re-consent.

If all the patients (who were alive at the time of study completion) can be re-consented, OS landmark analysis may be performed at 9 and 12 months using Kaplan-Meier analysis as data permits.

Otherwise, only descriptive analysis (number and % of deaths and lost to follow-up) will be performed.

13.7.8. Health Outcome Analyses

Symptom impact and HRQoL will be assessed using the e-Diary. Change from baseline and change over time will be summarized.

The calculation of scores and methods to deal with missing data will be provided in the RAP.

Visual Functioning Questionnaire (NEI VFQ-25 and OSDI): Data will be collected from end of treatment (EOT) visit as baseline. Additional data will be collected in follow-up visits on a monthly basis for subjects with ongoing corneal events or signs at EOT for 1 year or until resolution, whichever occurs first. These data will not be collected for subjects who already completed the treatment. Methods for calculation of scores will be provided in the RAP. Due to limited number of on-treatment subjects at the time of protocol amendment, only individual subject data will be presented.

14. STUDY CONDUCT CONSIDERATIONS

14.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

14.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional review board (IRB)/ethics committee (EC) review and approval of study protocol and any subsequent amendments
- Subject informed consent
- Investigator reporting requirements

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

14.3. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the IP, and this new event is likely to affect the study of subjects, the Sponsor, and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard.

The Sponsor will work with the investigator to ensure the Institutional review board (IRB)/ethics committee (EC) is notified.

14.4. Quality Control (Study Monitoring)

In accordance with applicable regulations, Good Clinical Practice (GCP) and GSK procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the electronic case report form (eCRF) will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

14.5. Quality Assurance

To ensure compliance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and all applicable regulatory requirements, GSK may conduct quality assurance audits of the site. Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

14.6. Study and Site Closure

The end of the study will be defined as the date of the last visit of the last subject enrolled.

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, International Conference on Harmonization Good Clinical Practice (ICH GCP), and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/EC promptly and provide the reason(s) for the suspension/termination.

GSK may also close study sites which fail to recruit subjects within a predefined timeframe, as defined within the Study Procedures Manual (SPM).

14.7. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

14.8. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the GSK Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

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16. APPENDICES

16.1. Appendix 1: International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma

Response	IMWG Criteria
sCR	• CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4]
CR	• Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3]
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level <100 mg/24 h
PR	• ≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable,[5] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	• ≥25% but <49% reduction of serum M protein and reduction in 24 hour urine M protein by 50-89%, which still exceeds 200 mg per 24 hour • In addition to the above criteria, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
No change/Stable disease	• Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive Disease	• Increase of ≥ 25% from lowest response value in any one or more of the following: o Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[6] o Urine M-component and/or (the absolute increase must be ≥200 mg/24 h)

Response	IMWG Criteria
	• Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Bone marrow plasma cell percentage; the absolute percentage must be ≥ 10%[7] • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[6] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] • Decrease in haemoglobin of ≥ 2 g/dL [1.25 mmol/L] • Rise in serum creatinine by 2 mg/dL or more [177 mol/L or more]
Relapse from CR[5] (to be used only if the endpoint studied is DFS)[8]	Any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥ 5% plasma cells in the bone marrow7 • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

Overall Responders: PR, VGPR, CR, sCR
Clinical Benefit Rate: Overall responders + MR

Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; and Kyle RA, Rajkumar SV. Leukemia
2008;23:3-9.
Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable
disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in
addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference
between involved and uninvolved free light chain (FLC) levels.
3 Confirmation with repeat bone marrow biopsy not needed.

4 Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratioby immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells foranalysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.
5 All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression free survival
6 For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.
7 Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.
8 For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

16.2. Appendix 2: Revised Response Criteria for Malignant Lymphoma

Response Criteria for Malignant Lymphoma				
Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a). FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b). Variably FDG-avid or Pet negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a). FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b). Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a). FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b). Variably FDG-avid or PET negative; no change in size of previous lesions on CT		

Response Criteria for Malignant Lymphoma				
Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
Relapsed Disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET positive if FDG-avid lymphoma or Pet positive prior to therapy	>50% increase from nadir in the SPD or any previous lesions	New or recurrent involvement

Abbreviations: CR = complete remission; FDG = [^{18}F]fluorodeoxyglucose; PET = positron emission tomography; CT = computed tomography; PR = partial remission; SPD = sum of the product of the diameters; SD = stable disease; PD = progressive disease

16.3. Appendix 4: NYHA Functional Classification System

The **New York Heart Association (NYHA) Functional Classification: Class I, II, III or IV Heart Failure** [NYHA, 1994] provides a simple way of classifying the extent of heart failure. It places subjects in one of 4 categories based on the level of limitation experienced during physical activity:

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Reference:

The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994:253-256.

16.4. Appendix 5: Modified Diet in Renal Disease Formula

MDRD	eGFR = $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female$) \times (1.212$ if African American$)$ GFR is expressed in mL/min/1.73 m2, SCr is serum creatinine expressed in mg/dL, and age is expressed in years. The link below will auto-calculate the creatinine clearance: http://nephron.org/cgi-bin/MDRD_GFR/cgi

16.5. Appendix 6: ECOG Performance Status1

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

16.6. Appendix 7: Genetics

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including GSK2857916 or any concomitant medicines;
- Multiple myeloma and lymphomas expressing BCMA susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in part 2 (expansion cohort) of the clinical study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Subject participation in the genetic research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

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16.7. Appendix 8: Liver Safety Drug Restart Guidelines

Drug restart may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if there is favorable benefit: risk ratio and no alternative medicine available.

Background Information on Drug Restart/Rechallenge

Following drug-induced liver injury, **drug restart or rechallenge is associated with a 13% mortality across all drugs in prospective studies.**[1] Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered in one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality. Risk factors for a fatal drug restart/rechallenge outcome include: hypersensitivity[1] with initial liver injury (e.g. fever, rash, eosinophilia), jaundice or bilirubin ≥2xULN or INR>1.5 suggesting severe liver injury, prior IP-related severe or fatal drug restart/rechallenge[2,3] or evidence of drug-related preclinical liability / mitochondrial impairment[3].

Drug Restart/Rechallenge Process (also see Figure 1)

6. Principal Investigator (PI) requests consideration of drug restart for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment.

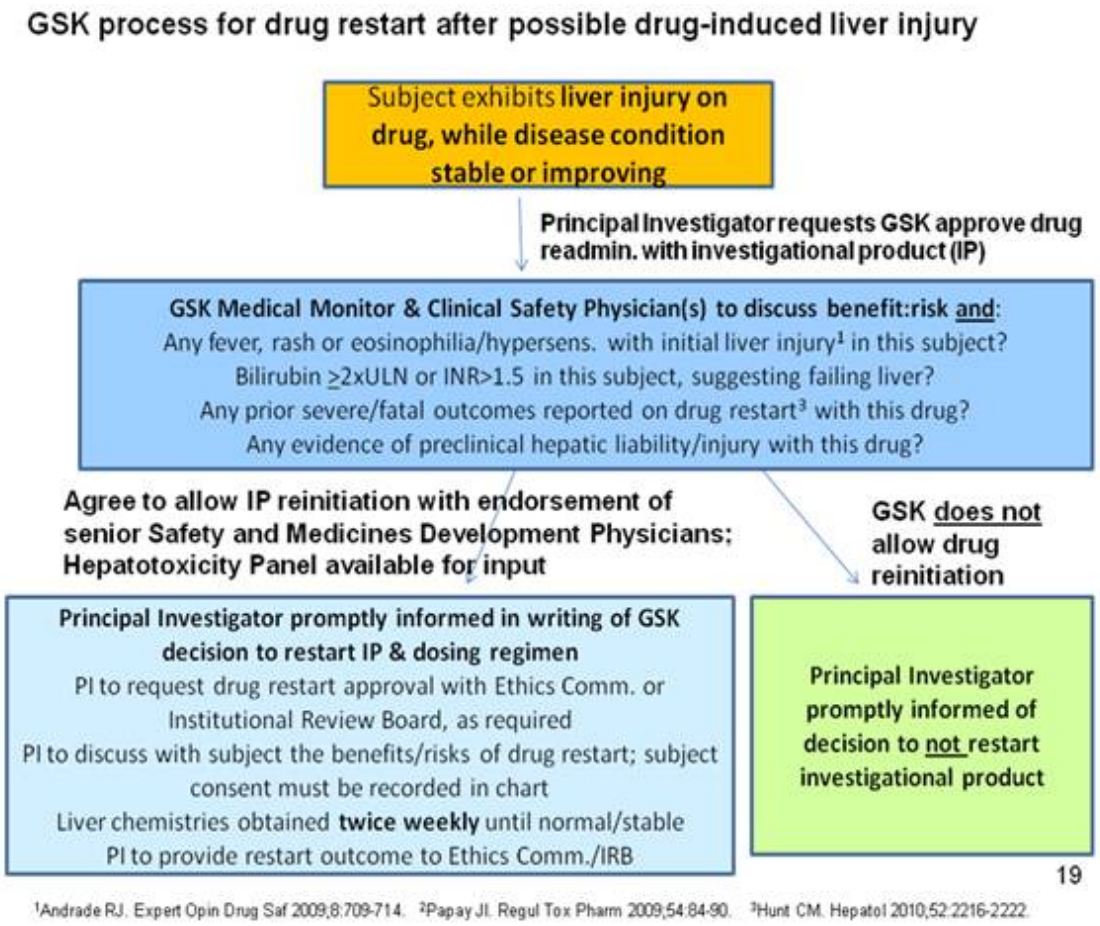
GSK Medical Monitor & Clinical Safety Physician.to review the subject's restart/rechallenge risk factors & complete checklist (Table 18).

Table 18 Checklist for drug restart/rechallenge for critical medicine

(Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)		
	Yes	**No**
Compelling benefit of the investigational product (IP) **for this subject and no alternative therapy**. **Provide brief explanation**:		
Relative benefit-risk favorable for drug restart/rechallenge, after considering the **following high risk factors**:		
• Initial liver injury event included:		
– fever, rash, eosinophilia, or hypersensitivity		
– or bilirubin ≥2xULN (direct bilirubin >35% of total)		
• Subject currently exhibits ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5		
• Severe or fatal restart/rechallenge has earlier been observed with IP **If yes, please provide brief explanation**:		
• IP associated with known preclinical hepatic liability/ injury		

If GSK provides written approval for restart/rechallenge following the above review, the Principal Investigator (PI) must ensure the following:

- The PI is to obtain Ethics Committee or Institutional Review Board review of drug re-initiation, as required.
- PI must discuss the possible benefits and risks of drug re-initiation with the subject.
- The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent specifically for the IP restart must be recorded in the study chart.
- The drug must be reinitiated at GSK approved dose(s).
- Subjects approved by GSK for restart of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.
- The Ethics Committee or Institutional Review Board is to be informed of the subject's outcome, as required.
- GSK is to be notified of any adverse events, as per Section 8.5.2.



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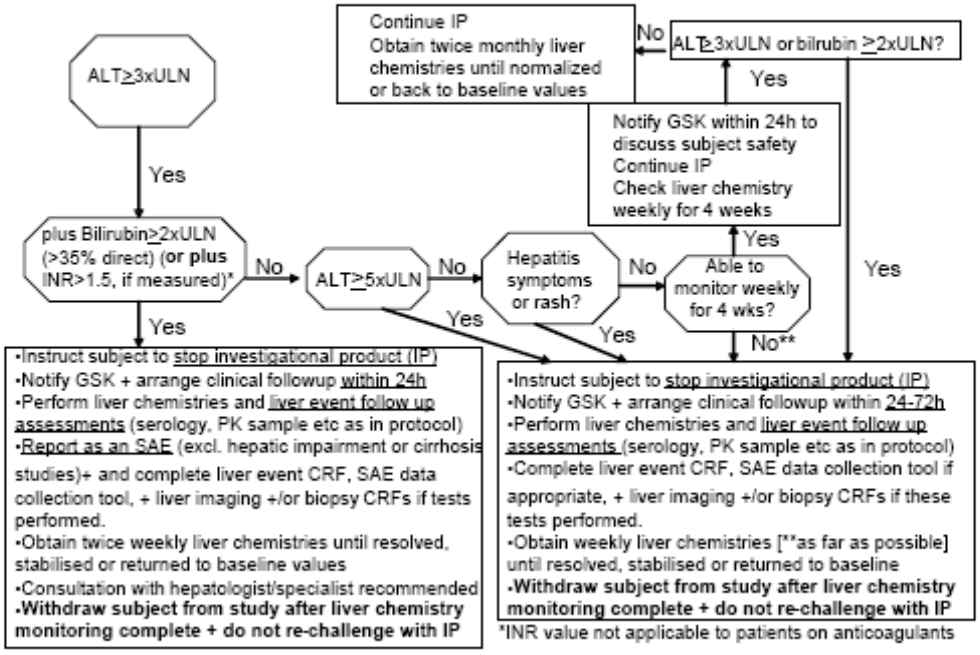
Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, et al. Drug-induced liver injury following positive drug rechallenge. Regul Toxicol Pharmacol 2009;54:84-90.

Phase I Liver Safety Algorithms



16.8. Appendix 9: Urine Protein Creatinine (UPC) Ratio Clinical meaning of UPC

There is a good correlation between the ratio of protein concentration to creatinine concentration in a random urine sample and the amount of protein excreted over 24 hours. Creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate.

Normal protein excretion is <150 mg/24 hours and is similar for men and women.

Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day.

Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day.

Calculating UPC

UPC ratio = Urine protein (mg/dL) / Urine creatinine (mg/dL).

UPC ratio ≈ equivalent to grams of protein excreted in urine over 24 hrs.

Example: Patient has a urine protein = 90 mg/dL and urine creatinine = 30 mg/dL.

UPC ratio= (90 mg/dL) / (30 mg/dL) = 3

The calculated UPC ratio is 3, which correlates to roughly 3 g protein excretion in a 24-hour period.

Units for UPC ratio

Note: To calculate UPC, protein and creatinine concentrations must be expressed in the same units (mg/dL, g/L, or µmol/L). If, for example, protein concentration is expressed in mg/dL and creatinine concentration is expressed in µmol/L, conversion of one of the concentration values is required. Conversion factors are:

From	To	Conversion Factor
Conventional Units: mg/dL	SI Units: µmol/L	Multiply by 88.4
SI Units: µmol/L	Conventional Units: mg/dL	Divide 88.4

References:

NKF: NKF KDOQI Guidelines [Internet]. National Kidney Foundation; nd. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Available from http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g5.htm

Xin G, Wang M, Jian L, Xu F, Wang H. Protein-to-creatinine ratio in spot urine samples as a predictor of quantitation of proteinuria 2004. Clinica Chimica Acta 350:35-39.

16.9. Appendix 10: Blood Requirements

16.9.1. Blood Requirements for All Lab Tests, Except PK

16.9.1.1. Dose Escalation: Every 3 Weeks for Multiple Myeloma

Test Sample	Sample Volume	Screening	Cycle 1	Each Subsequent Cycle
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	15-20 ml	5 ml
Coagulation	5 ml	5 ml	10-15 ml	5 ml
SPEP	6 ml	6 ml		6 ml
CRP	1 ml	1 ml		1 ml
B2 Microglobulin	1 ml	1 ml		1 ml
Kappa, lambda free LC, FLC	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml	10 ml		
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml	3 ml		0-3 ml
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	3 ml	3 ml		3 ml
sBCMA	1 ml		5 ml	1-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
Total		59.5 ml	51.5-66.5 ml	45.5-51.5 ml

1. Required for women of childbearing potential

16.9.1.2. Dose Escalation: Weekly for Multiple Myeloma

Test Sample	Sample Volume	Screening	Cycle 1	Each Subsequent Cycle
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	15-20 ml	5 ml
Coagulation	5 ml	5 ml	10-15 ml	5 ml
SPEP	6 ml	6 ml		6 ml
CRP	1 ml	1 ml	1 ml	1 ml
B2 Microglobulin	1 ml	1 ml	1 ml	1 ml
Kappa, lambda free LC, FLC	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml		10 ml	

Test Sample	**Sample Volume**	**Screening**	**Cycle 1**	**Each Subsequent Cycle**
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml		3 ml	0-3 ml
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	6 ml		6 ml	6 ml
sBCMA	1 ml		6 ml	1-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
Total		43.5 ml	73.5-88.5 ml	48.5-54.5 ml

1. Required for women of childbearing potential

16.9.1.3. Dose Expansion: Every 3 Weeks for Multiple Myeloma

Test Sample	**Sample Volume**	**Screening**	**Cycle 1**	**Each Subsequent Cycle**
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	10-15 ml	5 ml
Coagulation	5 ml	5 ml	10-15 ml	5 ml
SPEP	6 ml	6 ml		6 ml
CRP	1 ml	1 ml		1 ml
B2 Microglobulin	1 ml	1 ml		1 ml
Kappa, lambda free LC, FLC	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml		10 ml	
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml		3 ml	0-3 ml
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	6 ml		6 ml	6 ml
sBCMA	1 ml		2 ml	1-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
Genetics Sample	6 ml		6 ml	
Total		43.5 ml	68.5-83.5 ml	48.5-54.5 ml

1. Required for women of childbearing potential

16.9.1.4. Dose Expansion: Weekly for Multiple Myeloma

Test Sample	Sample Volume	Screening	Cycle 1	Each Subsequent Cycle
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	10-15 ml	5 ml
Coagulation	5 ml	5 ml	10-15 ml	5-10 ml
SPEP	6 ml	6 ml		6 ml
CRP	1 ml	1 ml		1 ml
B2 Microglobulin	1 ml	1 ml		1 ml
Kappa, lambda free LC, FLC	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml		10 ml	
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml		3 ml	0-3 ml
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	6 ml		6 ml	6 ml
sBCMA	1 ml		1 ml	1-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
Genetics Sample	6 ml		6 ml	
Total		43.5 ml	68.5-83.5 ml	48.5-59.5 ml

1. Required for women of childbearing potential

16.9.1.5. Dose Expansion: Every 3 Weeks for Lymphomas

Test Sample	Sample Volume	Screening	Cycle 1	Each Subsequent Cycle
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	10-15 ml	5 ml
Coagulation	5 ml	5 ml	10-15 ml	5 ml
CRP	1 ml	1 ml		1 ml
B2 Microglobulin	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml		10 ml	
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml		3 ml	0-3 ml
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	6 ml		6 ml	6 ml

Test Sample	Sample Volume	Screening	Cycle 1	Each Subsequent Cycle
sBCMA	1 ml		1 ml	0-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
Genetics Sample	6 ml		6 ml	
Total		36.5 ml	67.5-82.5 ml	40.5-47.5 ml

1. Required for women of childbearing potential

16.9.1.6. Dose Expansion: Weekly for Lymphomas

Test Sample	Sample Volume	Screening	Cycle 1	Each Subsequent Cycle
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	10-15 ml	5-10 ml
Coagulation	5 ml	5 ml	10-15 ml	5 ml
CRP	1 ml	1 ml		1 ml
B2 Microglobulin	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml		10 ml	
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml		3 ml	0-3 ml
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	6 ml		6 ml	6 ml
sBCMA	1 ml		5 ml	0-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
Genetics Sample	6 ml		6 ml	
Total		36.5 ml	74.5-89.5 ml	40.5-51.5 ml

1. Required for women of childbearing potential

16.9.2. Blood Requirements for PK

PK Schedule	Sample Volume	Cycle 1	Cycle 2	Cycle 3	Cycle 5	Total Volume
Escalation Every 3 Weeks	5 ml	60 ml	10 ml	10 ml		80 ml
Escalation Weekly	5 ml	80 ml	10ml	10 ml		100 ml
Expansion Every 3 Weeks MM	5 ml	20 ml	20 ml	20 ml	20 ml	80 ml
Expansion Weekly MM	5 ml	20 ml	10 ml	10 ml	10 ml	50 ml
Expansion Every 3 Weeks Lymphomas	5 ml	40 ml	20 ml	20 ml	10 ml	90 ml
Expansion Weekly Lymphomas	5 ml	40 ml	20 ml	20 ml	10 ml	90 ml

16.9.3. Total Blood Requirements

Schedule	Screening	Cycle 1	Each Subsequent Cycle
Escalation Every 3 Weeks MM	59.5 ml	51.5-66.5 ml	45.5-51.5 ml
Escalation Weekly MM	43.5 ml	73.5-88.5 ml	48.5-54.5 ml
Expansion Every 3 Weeks MM	43.5 ml	68.5-83.5 ml	48.5-54.5 ml
Expansion Weekly MM	43.5 ml	68.5-83.5 ml	48.5-59.5 ml
Expansion Every 3 Weeks Lymphomas	36.5 ml	67.5-82.5 ml	40.5-47.5 ml
Expansion Weekly Lymphomas	36.5 ml	74.5-89.5 ml	40.5-51.5 ml

The Study Procedures Manual will be updated with new information if changes in blood volumes are required.

16.10. Appendix 11: Pgp Inhibitors

Amiodarone
Atorvastatin
Azithromycin
Carvedilol
Clarithromycin
Dronedarone
Fluvoxamine
Indinavir
Indinavir and Ritonavir
Itraconazole
Ketonazole
Lapatinib
Lopinavir and Ritonavir
Nicardipine
Quinidine
Ranolazine
Ritonavir
Saquinavir and Ritonavir
Telaprevir
Verapamil
Valspodar

The Study Procedures Manual will be updated if changes to the Pgp inhibitor list is required.

16.11. Appendix 12: Protocol Amendment Changes

16.11.1. Amendment 1

Where the Amendment Applies

United Kingdom

Summary of Amendment Changes with Rationale

1. Regulatory Agency Identifying Number(s): Corrected EudraCT Number

    - Rationale: Typographical error corrected.

2. Protocol Synopsis, Exclusion Criteria, page 25; Section 5.2.2, Exclusion Criteria, page 85: Added #18

    - Rationale: MHRA requested the exclusion of subjects with current or history of corneal pathology given the corenal necrosis seen in rat studies.

3. Section 3.3, Part 1: Dose-Escalation Phase, page 47; Section 3.3.1.2.1, Planned Dose Levels, pages 50 and 51; Section 3.3.3, Dose-Limiting Toxicity – Part 1 only, page 54; Section 3.4, RP2 Dose and Administration Schedule Selection for Part 2, page 56: Added reference to new Section 12.1, Data Dissemination and Communication Plan.

    - Rationale: References to new section on data dissemination and communication to sites requested by MHRA added.

4. Section 3.9.2, QTc Stopping Criteria, page 67; Section 3.10.3, Dose Modifications Table 13, page 77.

    - Rationale: MHRA requested subjects with increase in QTc > 60 msec from baseline be withdrawn from study treatment.

5. Section 12.1, Data Dissemination and Communication Plan, page 132.

    - Rationale: MHRA requested a detailed communication plan be included in the protocol. This plan should address the assignment of subjects to a cohort with consideration of cohort size and number of sites, and should address how dissemination of safety data to all sites will be handled.

List of Specific Changes

Regulatory Agency Identifying Number(s):

OLD TEXT

Compound Number	IND Number	EudraCT Number
GSK2857916	119333	2003-004549-18

NEW TEXT

Compound Number	IND Number	EudraCT Number
GSK2857916	119333	~~2003~~2013-004549-18

Protocol Synopsis, Exclusion Criteria

NEW TEXT

18. Current corneal disease or a history of corneal disease.

Section 3.3 Part 1: Dose-Escalation Phase

NEW TEXT

Note: For details on data dissemination and communication with sites (dose escalation meetings and safety update meetings), refer to Section 12.1.

Section 3.3.1.2.1 Planned Dose Levels, 2nd Paragraph

PREVIOUS TEXT

Description of the New Continual Reassessment Method: After each cohort, a dosing recommendation for the next cohort will be made using the N-CRM [Neuenschwander, 2008]. All available data, including safety, PK and PD data from current and prior cohorts will be reviewed at the dose escalation meeting. Although the N-CRM will be used to recommend the next dosing level, clinical judgment by the Medical Monitor and internal dose-escalation committee in consultation with the investigators can halt enrolment into lower dose cohorts as deemed appropriate at any time during the trial.

REVISED TEXT

Description of the New Continual Reassessment Method: After each cohort, a dosing recommendation for the next cohort will be made using the N-CRM [Neuenschwander, 2008]. All available data, including safety, PK and PD data from current and prior cohorts will be reviewed at the dose escalation meeting **(see Section 12.1)**. Although the

N-CRM will be used to recommend the next dosing level, clinical judgment by the Medical Monitor and internal dose-escalation committee in consultation with the investigators can halt enrolment into lower dose cohorts as deemed appropriate at any time during the trial.

Section 3.3.1.2.1 Planned Dose Levels, 6th Paragraph

PREVIOUS TEXT

The recommended dose will be the dose with the highest posterior probability of lying in the target toxicity interval with the additional requirement that the sum of the posterior probabilities of the DLT rate lying in the excessive toxicity or unacceptable toxicity range is less than 25%. Selection of the next dose cohort to be enrolled is also subject to the constraint that the next dose level can be no more than two times that of the current dose level. An updated estimate of the toxicity curve will be provided at the time of each dose escalation meeting.

REVISED TEXT

The recommended dose will be the dose with the highest posterior probability of lying in the target toxicity interval with the additional requirement that the sum of the posterior probabilities of the DLT rate lying in the excessive toxicity or unacceptable toxicity range is less than 25%. Selection of the next dose cohort to be enrolled is also subject to the constraint that the next dose level can be no more than two times that of the current dose level. An updated estimate of the toxicity curve will be provided at the time of each dose escalation meeting **(see Section 12.1)**.

Section 3.3.3, Dose Limiting Toxicity – Part 1 Only

PREVIOUS TEXT

Any subject in Part 1 (Dose Escalation) who received at least one dose of the drug (regardless of schedule) will be evaluated for DLTs

REVISED TEXT

Any subject in Part 1 (Dose Escalation) who received at least one dose of the drug (regardless of schedule) will be evaluated for DLTs. **Safety data together with DLTs will be reviewed during the dose escalation meetings prior to opening enrollment into subsequent cohorts (see Section 12.1).**

Section 3.4, RP2 Dose and Administration Schedule Selection for Part 2

NEW TEXT

Note: For details on data dissemination and communication with sites (safety update meetings), refer to Section 12.1.

Section 3.9.2, QTc Stopping Criteria

PREVIOUS TEXT

If a subject that meets the corrected QT (QTc)[1] interval duration criteria below, study treatment(s) will be withheld.

- QT interval corrected for heart rate by Fridericia's formula (QTcF) >530 msec

[1]Based on average QTc value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

REVISED TEXT

Study treatment will be withheld in ~~If~~ a subject ~~that~~ who meets the corrected QT (QTc)[1] interval duration criteria below, ~~study treatment(s) will be withheld~~.

- QT interval corrected for heart rate by Fridericia's formula (QTcF) >~~530~~**500** msec

or

- **Increase in QTc of > 60 msec from baseline**

[1]Based on average QTc value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment withheld.

~~If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.~~

Section 3.10.3, Dose Modifications

PREVIOUS TEXT

Table 13 Dose Adjustment/Stopping Criteria

Toxicity Grade[a]	Dose Modification of GSK2857916
Grade 1	• Continue at current dose level. Consider supportive care recommendations
Grade 2	• If toxicity is considered not clinically relevant, continue with 100% scheduled dose • If toxicity is considered clinically relevant withhold the dose until toxicity resolves to Grade 1 or baseline. If resolved within 14 days, then restart at current dose level. Consider supportive care recommendations • If not resolved within 14 days, discuss with GSK Medical Monitor
Grade 3	• Withhold dose until toxicity resolves to Grade 1 or baseline, unless condition fits exceptions noted below. If resolved within 14 days, resume treatment at dose reduced by 25% (first dose reduction), or 50% (second dose reduction). Consider supportive care recommendations. If not resolved within 14 days, discuss with GSK Medical Monitor **Exceptions**: • Subjects who develop G3 toxicities which respond to standard treatment and resolve to ≤G1 within 48 hours may continue treatment at scheduled or reduced dose • Permanently discontinue for grade 3 or greater QTc prolongation ie, QTcF >530 msec • Troponin elevations: See Section 3.9.3 for troponin stopping criteria
Grade 4	• Permanently discontinue study medication **Exceptions:** • G4 thrombocytopenia with no sign of bleeding, if recovered within 14 days. For dose reductions see Section 3.10 • G4 lymphopenia (dose reductions by 25-50% may be considered

b. Considered related to investigational drug.

REVISED TEXT

Toxicity Grade[a]	Dose Modification of GSK2857916
Grade 1	• Continue at current dose level. Consider supportive care recommendations
Grade 2	• If toxicity is considered not clinically relevant, continue with 100% scheduled dose • If toxicity is considered clinically relevant withhold the dose until toxicity resolves to Grade 1 or baseline. If resolved within 14 days, then restart at current dose level. Consider supportive care recommendations • If not resolved within 14 days, discuss with GSK Medical Monitor
Grade 3	• Withhold dose until toxicity resolves to Grade 1 or baseline, unless condition fits exceptions noted below. If resolved within 14 days, resume treatment at dose reduced by 25% (first dose reduction), or 50% (second dose reduction). Consider supportive care recommendations. If not resolved within 14 days, discuss with GSK Medical Monitor **Exceptions**: • Subjects who develop G3 toxicities which respond to standard treatment and resolve to ≤G1 within 48 hours may continue treatment at scheduled or reduced dose • Permanently discontinue for grade 3 or greater QTc prolongation ie, QTcF > ~~500~~ **500 msec or QTcF increase by > 60 msec from baseline** • Troponin elevations: See Section 3.9.3 for troponin stopping criteria
Grade 4	• Permanently discontinue study medication **Exceptions:** • G4 thrombocytopenia with no sign of bleeding, if recovered within 14 days. For dose reductions see Section 3.10 • G4 lymphopenia (dose reductions by 25-50% may be considered

c. Considered related to investigational drug.

Section 5.2.2, Exclusion Criteria

NEW TEXT

18. Current corneal disease or a history of corneal disease.

Section 12.1, Data Dissemination and Communication Plan

NEW TEXT

The GSK Medical Monitor will review screening packets to ensure that subjects being considered for enrollment meet eligibility criteria prior to entering the study. Subjects will not be assigned a study number until their screening packet is reviewed and approved by the GSK Medical Monitor. GSK will remain in constant contact with the clinical sites during the enrolment period to ensure that cohort enrolment in Parts 1 and 2 of this study

are completed as per protocol. Investigators will be informed about available openings for enrolment on the trial and will be asked to pre-screen their subjects to determine potential eligibility, and to avoid over-enrolment. Enrolment will be offered to a given site for a limited period of time, and if the site chosen cannot successfully enrol a subject within a pre-specified time period then another site will be offered the opportunity to enrol a subject.

During Part 1 of the study, Study Team Safety Update Meetings will be held every three weeks to review relevant data with the Principal Investigators (or delegates) and site staff. These meetings will be held on an "as needed" basis (but no less frequent than once a month) during Part 2 (eg, to share safety experience and to communicate results of scheduled futility analyses). Safety, PK, PD, and clinical outcome data available for all subjects at the time of the scheduled Safety Update Meeting will be reviewed and summarized. In addition, Dose Escalation Meetings will be scheduled at the conclusion of the DLT assessment period for subjects enrolled in each cohort to review safety PK, and PD data and determine the next dose level appropriate for study. Dose escalation decisions will be made with team and investigator agreement after review of available safety data from at least one cycle of therapy with GSK2867916 (ie, 21 days for the once every 3 weeks schedule and 28 days for weekly schedule). All dose escalation or safety decisions will be documented in writing with copies maintained at each site and the Master Study Files at GSK. Available data will be provided to participants prior to each scheduled Safety or Dose Escalation Meeting.

Attendees of Safety Update and Dose Escalation Meetings will include but not limited to all clinical investigators (or designees) and site staff, the GSK Medical Monitor, Clinical Investigation Lead, Clinical Operations Study Lead (USA and Local Operating Company designees), Data Quality Leader, Global Clinical Safety and Pharmacovigilance Representative, Statistician, Pharmacokineticist, and Translational Medicine Lead.

16.11.2. Amendment 2

Where the Amendment Applies

Canada, United Kingdom, United States

Summary of Amendment Changes with Rationale

1. Page 1, Subject
   - Rationale: updated key words of subject
2. Page 2, Amendment 1 Rationale
   - Rationale: updated wording of Amendment 1 rationale for clarity
3. Page 12, List of Abbreviations
   - Rationale: removed abbreviations no longer being used in the protocol and made corrections to typographical errors
4. Page 18, Study Objectives, Endpoints and Hypotheses and Section 2
   - Rationale: corrected definition of MR from Minor Response to Minimal Response
5. Page 20, Protocol Synopsis Inclusion Criteria and Section 5.2.1 Inclusion Criteria
   - Rationale: updated Inclusion Criterion #2 to add minimum weight requirement to ensure subjects do not exceed maximum blood volume sampled for research tests within a month
6. Page 27, Clinical Activity Assessment
   - Rationale: corrected definition of MR from Minor Response to Minimal Response
7. Section 1.2.3.4.1 and Section 10
   - Rationale: added restriction for use of Pgp inhibitors per FDA request
8. Section 3.1, Table 3
   - Rationale: added “serial” to add clarity on PK samples required for subjects in Dose Escalation
   - Per FDA request, added text that maxmimum dose to be administered will not exceed 5mg/kg
9. Section 3.3.1.1
   - Rationale: Per FDA request, removed specification of “clinically significant” in reference to toxicities
10. Section 3.1, Section 3.3.1.2.1, and Section 3.8

- Rationale: Per FDA request, added the maximum dose of drug to be administered in the study

11. Section 3.3.3
    - Rationale: Per FDA request, removed specification of "clinically significant" in reference to toxicities. Clarified the DLT definitions of thrombocytopenia and skin reactions
12. Section 3.8
    - Rationale: Per FDA request, added text that maxmimum dose to be administered will not exceed 5mg/kg
13. Section 3.9.5
    - Rationale: Added clarification on use of premedication before the first dose if warranted. Added clarification on management of subjects with grade 3 allergic reactions or cytokine release syndrome
14. Section 3.9.6
    - Rationale: Added further clarification on management of subjects with allergic reactions per FDA request
15. Section 3.9.8
    - Rationale: Per FDA request, added stopping criteria for subjects with corneal toxicity
16. Section 3.10.2
    - Rationale: Clarifications added on dose adjustments and stopping criteria for serum creatinine, thrombocytopenia, INR prolongation, and ocular toxicity.
17. Section 4
    - Rationale: Added Lot # restrictions per FDA request. Updated storage conditions of prepared drug.
18. Section 6.3
    - Rationale: Per FDA request, added clarification on discontinuation from study
19. Section 7.1
    - Rationale: Updated all Time and Events tables for Dose Escalation and Dose Expansion to add Hepatitis B and C testing at Screening, removal of sBCMA and cytokine samples at Screening, and clarification on PD samples
20. Section 7.3.6, Table 15
    - Rationale: Updated clinical laboratory test table to remove tests not required in the study
21. Section 7.4.1
    - Rationale: Updated blood volume for PK samples
22. Appendix 10

- Rationale: updated blood volume tables

23. Appendix 11

- Rationale: New appendix added per FDA request to list Pgp Inhibitors

List of Specific Changes

Example heading is listed below, and should be modified as appropriate.

Title Page, Subject

PREVIOUS TEXT

Multiple Myeloma, BCMA expressing, Advanced Hematologic Malignancies

REVISED TEXT

Multiple Myeloma, BCMA ~~expressing~~, ~~Advanced~~ Hematologic Malignancies

Revision Chronology

PREVIOUS TEXT

2012N155299_01	2014-MAR-01	Amendment 01: Country specific Amendment for the United Kingdom to address required changes per MHRA. Updated Exclusion Criteria to exclude subjects with current or medical history of corneal pathology. Updated QTc withdrawal criterion to modify QTc withdrawal for QTc ≥ 500msec and to include > 60 msec increase from baseline. Updated Data Management Section 12 to include details on dissemination of data and communication plan.

REVISED TEXT

2012N155299_01	2014-MAR-01	Amendment 01: Country specific Amendment for the United Kingdom to address required changes per MHRA. Updated Exclusion Criteria to exclude subjects with current ~~or medical~~ corneal disease or history of corneal ~~pathology~~ disease. Updated QTc withdrawal criterion to modify QTc withdrawal for QTc ≥ 500msec and to include > 60 msec increase from baseline. Updated Data Management Section 12 to include details on dissemination of data and communication plan.

List of Abbreviations

PREVIOUS TEXT

CPK	Creatine Phosphokinase
CK	Creatinine kinase
CK-MB	Creatinine kinase MB-isoenzyme
MR	Minor response

REVISED TEXT

~~CPK~~	~~Creatine Phosphokinase~~
CK	Creatin~~in~~e kinase
CK-MB	Creatin~~in~~e kinase MB-isoenzyme
MR	~~Minor~~ Minimal response

Protocol Synopsis, Study Objectives

PREVIOUS TEXT

Secondary	
• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM and other BCMA expressing hematologic malignancies	• Clinical activity measured as Overall Response Rate (ORR) which is defined as follows: o For MM: the percentage of subjects achieving confirmed partial response or better (≥PR) o In addition, the percentage of subjects with minor response (MR) will be assessed for clinical benefit rate (CBR) (Appendix 1) o For Other Hematologic Malignancies: the percentage of subjects achieving PR or better (≥PR) (Appendix 2 and Appendix 3)

REVISED TEXT

Secondary	
• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM and other BCMA expressing hematologic malignancies	• Clinical activity measured as Overall Response Rate (ORR) which is defined as follows: o For MM: the percentage of subjects achieving confirmed partial response or better (≥PR) o In addition, the percentage of subjects with ~~minor~~ minimal response (MR) will be assessed for clinical benefit rate (CBR) (Appendix 1) o For Other Hematologic Malignancies: the percentage of subjects achieving PR or better (≥PR) (Appendix 2 and Appendix 3)

Protocol Synopsis, Inclusion Criteria

PREVIOUS TEXT

2. Male or female, 18 years or older (at the time consent is obtained).

REVISED TEXT

2. Male or female, 18 years or older (at the time consent is obtained) and must have a body weight of at least 45 kg (99 lb).

Protocol Synopsis, Clinical Activity Assessment

PREVIOUS TEXT

CLINICAL ACTIVITY ASSESSMENT	Clinical activity will be measured as Overall Response Rate (ORR) which is defined as follows: • For MM: the percentage of subjects with confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) as assessed by 2011 recommendation of the International Myeloma Working Group (IMWG) Panel I. Clinical benefit rate (CBR), including minor response (MR), may be considered in addition to ORR. (Appendix 1). • For Other Hematologic Malignancies: the percentage of subjects with confirmed CR, PR, as described in the Revised Response Criteria for Malignant Lymphoma (Appendix 2) and for CLL Appendix 3).

REVISED TEXT

CLINICAL ACTIVITY ASSESSMENT	Clinical activity will be measured as Overall Response Rate (ORR) which is defined as follows: • For MM: the percentage of subjects with confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) as assessed by 2011 recommendation of the International Myeloma Working Group (IMWG) Panel I. Clinical benefit rate (CBR), including ~~minor~~ minimal response (MR), may be considered in addition to ORR. (Appendix 1). • For Other Hematologic Malignancies: the percentage of subjects with confirmed CR, PR, as described in the Revised Response Criteria for Malignant Lymphoma (Appendix 2) and for CLL Appendix 3).

Section 1.2.3.4.1, Victim interaction potential

NEW TEXT

Concomitant dosing of GSK2857916 with strong Pgp inhibitors should be avoided unless considered medically necessary (See Appendix 11: Pgp Inhibitors for list of relevant Pgp inhibitors).

Section 2, Objective(s), Endpoint(s) and Hypothesis

PREVIOUS TEXT

Secondary	
Objective	**Endpoint**
• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM and other BCMA expressing hematologic malignancies	• Clinical activity measured as Overall Response Rate (ORR) which is defined as follows: o For MM: the percentage of subjects achieving confirmed partial response or better (≥PR) o In addition, the percentage of subjects with minor response (MR) will be assessed for clinical benefit rate (CBR) (Appendix 1) o For Other Hematologic Malignancies: the percentage of subjects achieving PR or better (≥PR) (Appendix 2 and Appendix 3)

REVISED TEXT

Secondary	
Objective	**Endpoint**
• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM and other BCMA expressing hematologic malignancies	• Clinical activity measured as Overall Response Rate (ORR) which is defined as follows: o For MM: the percentage of subjects achieving confirmed partial response or better (≥PR) o In addition, the percentage of subjects with ~~minor~~ minimal response (MR) will be assessed for clinical benefit rate (CBR) (Appendix 1) o For Other Hematologic Malignancies: the percentage of subjects achieving PR or better (≥PR) (Appendix 2 and Appendix 3)

Section 3.1, Discussion of Study Design, Table 3 Study Design

PREVIOUS TEXT

Part 1 Dose Escalation (n=up to 30 subjects) **Population: relapsed/refractory MM** Characterize safety, PK, PD, immunogenicity and establish RP2 dose of GSK2857916 Schedule 1: GSK2587916 once every 3 weeks (21-day cycle) (n=~20) Schedule 2: GSK2587916 once weekly for 3 consecutive weeks, 1-week rest (28-day cycle) (n=~9) PK samples will be collected from all subjects in Part 1

REVISED TEXT

Part 1 Dose Escalation (n=up to 30 subjects) **Population: relapsed/refractory MM** Characterize safety, PK, PD, immunogenicity and establish RP2 dose of GSK2857916 Schedule 1: GSK2587916 once every 3 weeks (21-day cycle) (n=~20) Schedule 2: GSK2587916 once weekly for 3 consecutive weeks, 1-week rest (28-day cycle) (n=~9) Serial PK samples will be collected from all subjects in Part 1

Section 3.1, Discussion of Study Design

PREVIOUS TEXT

This is a First Time in Human (FTIH), open-label, dose escalation trial consisting of two parts: a Part 1 dose escalation phase and a Part 2 expansion phase for safety, and clinical activity testing (Table 3 and Section 3.2). The study will enroll a total of approximately 80 subjects with relapsed/refractory MM or other BCMA-expressing hematologic malignancies.

REVISED TEXT

This is a First Time in Human (FTIH), open-label, dose escalation trial consisting of two parts: a Part 1 dose escalation phase and a Part 2 expansion phase for safety, and clinical activity testing (Table 3 and Section 3.2). The study will enroll a total of approximately

80 subjects with relapsed/refractory MM or other BCMA-expressing hematologic malignancies. The maximum dose to be administered in this trial will not exceed 5 mg/kg.

Section 3.3.1.1, Single Subject Cohort Run-in (Schedule 1 only)

PREVIOUS TEXT

- A single subject will be enrolled at each dose level as outlined in Table 4 until occurrence of a clinically significant ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out.
- Initially, GSK2857916 will be administered (IV) via 60 min infusion once every three weeks (21 days = 1 cycle) on Schedule 1. One subject or the sentinel subject ie, the very first subject on the study; will initially be enrolled at the starting dose of 0.03 mg/kg in Cohort 1 (Refer to Section 3.6.4 for starting dose rationale). The initial dose will be given to the sentinel subject. Serial blood samples will be collected for PK. The sentinel subject must remain under observation for at least 24 hours after dosing before discharge. GSK2857916 (intact and total [intact + unconjugated antibody]) and cys-mcMMAF plasma concentrations will be analyzed and reviewed together with the safety data (DLT period). If the first dose is considered tolerated, the sentinel subject will be allowed to stay on the study and receive subsequent doses at the same dose level (ie, 0.03 mg/kg) as scheduled, every three weeks (21 days interval) for up to 16 doses (or until disease progression, toxicity or withdrawal of consent).
- If the sentinel subject does not experience a ≥ clinically significant Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out during the first cycle (within 21 days), the next subject will be allowed to enroll in the next cohort at a dose increased by ≤100% of the starting dose. Dose escalation with increments up to 100% of the previous dose will continue with enrolment of 1 subject per cohort until the occurrence of the first clinically significant ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out. (run in procedure outlined in Table 4)
- The single subject (small cohort) run-in will be halted when the first clinically significant ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out occurs in one subject in Cycle 1 (21 days). At this point, the cohort will be expanded to 3 or more subjects at the same dose level and the escalation will continue to follow the N-CRM procedure as outlined in Table 4

Table 19 Single Subject (Small Cohort) Run-In Procedure for GSK2857916 given on Schedule 1 (once every 21 days)

Dose Level	Number of subjects with ≥G2 toxicity	Dose Escalation/Action
Dose Level 1/Cohort 1	0 out of 1 subject (Sentinel subject)	Predicted starting dose 0.03 mg/kg every 21 days
Dose Level 2/Cohort 2	0 out of 1 subject	Escalate to the next dose level with increase ≤100% of the starting dose
Dose Level 3 and beyond/Cohort 3 and beyond	0 out of 1 subject	Escalate to the next dose level with increase of ≤100% of the dose tested in the previous cohort
	1 out of 1 subject*	Switch to Cohort size of 3 or more subjects

*Increase of doses **up to** 100% of the previous dose may continue until the first clinically significant ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out occurs in one subject in Cycle 1 (21 days). At this point the single subject (small cohort) run-in is halted. Continue with N-CRM, with cohort sizes of 3 or more subjects. Increase of doses ≤100% will be considered for subsequent cohorts of 3 or more subjects.

REVISED TEXT

- A single subject will be enrolled at each dose level as outlined in Table 4 until occurrence of a ~~clinically significant~~ ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out.
- Initially, GSK2857916 will be administered (IV) via 60 min infusion once every three weeks (21 days = 1 cycle) on Schedule 1. One subject or the sentinel subject ie, the very first subject on the study; will initially be enrolled at the starting dose of 0.03 mg/kg in Cohort 1 (Refer to Section 3.6.4 for starting dose rationale). The initial dose will be given to the sentinel subject. Serial blood samples will be collected for PK. The sentinel subject must remain under observation for at least 24 hours after dosing before discharge. GSK2857916 (intact and total [intact + unconjugated antibody]) and cys-mcMMAF plasma concentrations will be analyzed and reviewed together with the safety data (DLT period). If the first dose is considered tolerated, the sentinel subject will be allowed to stay on the study and receive subsequent doses at the same dose level (ie, 0.03 mg/kg) as scheduled, every three weeks (21 days interval) for up to 16 doses (or until disease progression, toxicity or withdrawal of consent).
- If the sentinel subject does not experience a ≥ ~~clinically significant~~ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out during the first cycle (within 21 days), the next subject will be allowed to enroll in the next cohort at a dose increased by ≤100% of the starting dose. Dose escalation with increments up to 100% of the previous dose will continue with enrolment of 1 subject per cohort until the occurrence of the first ~~clinically significant~~ ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out. (run in procedure outlined in Table 4)

- The single subject (small cohort) run-in will be halted when the first ~~clinically significant~~ ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out occurs in one subject in Cycle 1 (21 days). At this point, the cohort will be expanded to 3 or more subjects at the same dose level and the escalation will continue to follow the N-CRM procedure as outlined in Table 4

Table 20 Single Subject (Small Cohort) Run-In Procedure for GSK2857916 given on Schedule 1 (once every 21 days)

Dose Level	Number of subjects with ≥G2 toxicity	Dose Escalation/Action
Dose Level 1/Cohort 1	0 out of 1 subject (Sentinel subject)	Predicted starting dose 0.03 mg/kg every 21 days
Dose Level 2/Cohort 2	0 out of 1 subject	Escalate to the next dose level with increase ≤100% of the starting dose
Dose Level 3 and beyond/Cohort 3 and beyond	0 out of 1 subject	Escalate to the next dose level with increase of ≤100% of the dose tested in the previous cohort
	1 out of 1 subject*	Switch to Cohort size of 3 or more subjects

*Increase of doses **up to** 100% of the previous dose may continue until the first ~~clinically significant~~ ≥ Grade 2 toxicity for which relationship to the investigational agent cannot be ruled out occurs in one subject in Cycle 1 (21 days). At this point the single subject (small cohort) run-in is halted. Continue with N-CRM, with cohort sizes of 3 or more subjects. Increase of doses ≤100% will be considered for subsequent cohorts of 3 or more subjects.

Section 3.3.1.2.1, Planned Dose Levels

NEW TEXT

Prior to the start of the study, projected dose levels on Schedule 1 (in mg/kg) are 0.03, 0.06, 0.12, 0.24, 0.48, 0.96, 1.92, 2.88, 3.6, and 4.5 mg/kg. Additional doses and schedules may be explored based on emerging safety, PK, and PD data. <u>The maximum dose to be administered in this trial will not exceed 5 mg/kg.</u>

Section 3.3.3, Dose Limiting Toxicity – Part 1 only

PREVIOUS TEXT

Subjects who have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced.An event will be considered a DLT if it is clinically significant and its relationship to the investigational agent cannot be ruled out occurs within the DLT reporting period (first 21 days of treatment for schedule 1, and first 28 days for schedule 2) and meets one of the following criteria:

- Albuminuria ≥2000 mg/24 hr which has been confirmed by repeat test at least 7 days apart and is not considered to be related to disease progression based on consultation of investigator with GSK medical monitor
- Grade 4 neutropenia (without fever) lasting ≥7 days
- Febrile neutropenia lasting ≥72 hours
- Grade ≥3 thrombocytopenia associated with clinically significant bleeding or Grade 4 thrombocytopenia lasting >7 days and not responding to platelet transfusions
- Any Grade 3 or greater non-hematologic toxicity as described in Common National Cancer Institute-Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 [NCI, 2009] with the exception of the following Grade 3 events that can be controlled within 48 hours with routine supportive measures
    - Nausea and vomiting that can be controlled with anti-emetics
    - Diarrhea that can be controlled with anti-diarrheals
    - Rash or allergic reactions that can be controlled with antihistamines and steroids
    - Clinically asymptomatic electrolyte abnormalities which can be corrected within 48 hours)
- Liver toxicity meeting pre-specified GSK liver stopping criteria (see Liver in Section 3.9.1)

Tumor lysis syndrome does NOT constitute a DLT (Section 3.9.7).

REVISED TEXT

Subjects who have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced.An event will be considered a DLT if ~~it is clinically significant and~~ its relationship to the investigational agent cannot be ruled out occurs within the DLT reporting period (first 21 days of treatment for schedule 1, and first 28 days for schedule 2) and meets one of the following criteria:

- Albuminuria ≥2000 mg/24 hr which has been confirmed by repeat test at least 7 days apart and is not considered to be related to disease progression based on consultation of investigator with GSK medical monitor
- Grade 4 neutropenia (without fever) lasting ≥7 days
- Febrile neutropenia lasting ≥72 hours
- Grade ≥3 thrombocytopenia associated with ~~clinically significant~~ bleeding ~~or~~ <u>where estimated blood loss is > 10mL</u> or Grade 4 thrombocytopenia lasting >7 days and not responding to platelet transfusions
- Any Grade 3 or greater non-hematologic toxicity as described in Common National Cancer Institute-Terminology Criteria for Adverse Events (NCI-

CTCAE) version 4.0 [NCI, 2009] with the exception of the following Grade 3 events that can be controlled within 48 hours with routine supportive measures

- Nausea and vomiting that can be controlled with anti-emetics
- Diarrhea that can be controlled with anti-diarrheals
- Rash or ~~allergic~~ other skin reactions that can be controlled with antihistamines and steroids
- Clinically asymptomatic electrolyte abnormalities which can be corrected within 48 hours)

- Liver toxicity meeting pre-specified GSK liver stopping criteria (see Liver in Section 3.9.1)

Tumor lysis syndrome does NOT constitute a DLT (Section 3.9.7).

A subject who develops a DLT will be allowed to stay on study only if the toxicity did not meet stopping criteria and recovered to ≤ Grade 1 within 14 days, or after a longer recovery time if benefit to subject can be demonstrated and if the investigator and medical monitor agree that for a given subject the benefits may outweigh the risks.

Section 3.8, Dosage and Administration of Study Treatment(s)

NEW TEXT

The maximum dose to be administered to subjects in this trial is 5 mg/kg.

Section 3.9.5, Infusion-related Reactions and Cytokine Release Syndrome

PREVIOUS TEXT

Premedication is not allowed prior to first infusion. Premedication should be considered in any subject who experienced an infusion related reaction at first or any subsequent infusion with GSK2857916.

REVISED TEXT

Premedication is not allowed prior to first infusion unless deemed medically appropriate by the GSK Medical Monitor in consultation with investigators following evaluation of infusion related reactions across cohorts. Premedication should be considered in any subject who experienced an infusion related reaction at first or any subsequent infusion with GSK2857916.

Section 3.9.6, Allergic and Anaphylactic reaction

PREVIOUS TEXT

As GSK2857916 is a fully humanized ADC, it is considered unlikely for acute allergic reactions to occur in response to GSK2857916 exposure; however, all subjects will be monitored carefully for evidence of allergic response. A subject that exhibits signs or symptoms of severe hypersensitivity or anaphylaxis will receive appropriate medical

treatment and remain on study at the discretion of the investigator and after discussion with the GSK medical monitor.

- Further treatment with GSK2857916 needs to be discussed with MM prior to next dose administration.

REVISED TEXT

As GSK2857916 is a fully humanized ADC, it is considered unlikely for acute allergic reactions to occur in response to GSK2857916 exposure; however, all subjects will be monitored carefully for evidence of allergic response. A subject that exhibits signs or symptoms of severe hypersensitivity or anaphylaxis will receive appropriate medical treatment and ~~remain on study at the discretion of the investigator and after discussion with the GSK medical monitor.~~ be withdrawn from the study.

- Subjects who experience ≥ Grade 3 allergic reaction will be withdrawn from study

- Further treatment with GSK2857916 in subjects who experience a ≥ Grade 3 infusion related reaction needs to be discussed with MM prior to next dose administration. Those subjects will be allowed to continue on study after recovery of the reaction to ≤ Grade 1 but will have to receive pre-medication prior to each subsequent dose of GSK2857916, and their infusion time will be extended to 2-4 hours (depending on severity of the reaction).

Section 3.9.8, Ocular Toxicity

NEW TEXT

Section 3.9.8, Ocular Toxicity and Stopping Criteria

All subjects will be advised to use prednisolone phosphate 1% or dexamethasone 0.1% eye drop 4 times a day (QID) for 4 days starting 1 day prior to each dose. Additional use of lubrication eye drops (artificial tears) QID PRN throughout the trial is recommended, especially if subject develops any ocular symptoms. Subjects who develop ≥ Grade 3 ocular or corneal toxicity will be permanently removed from study.

Section 3.10.2, Predicted Toxicities and Proposed Dose Adjustments/Stopping Criteria

PREVIOUS TEXT

Thrombocytopenia	Grade 3: >25 and <50x10^9/L	• With clinically significant bleeding: Withhold the: • No clinically significant bleeding: continue treatment with 25% dose reduction

Ocular/corneal toxicity	Grade 2/Grade 3	• First occurrence: o Interrupt treatment with GSK2857916 o Consult ophthalmologist immediately o When recovered to G≤1 Re-start treatment with GSK2857916 at 25% dose reduction upon resolution to ≤G1 • Second occurrence: o Interrupt treatment with GSK2857916 o Consult ophthalmologist immediately o Once resolved to≤ G1 or less: Restart treatment with GSK2857916 at additional 25% dose reduction • Third occurrence: • Permanently discontinue treatment with GSK2857916 and withdraw subject from study
	Grade 4	• Consult ophthalmologist immediately • Permanently discontinue treatment with GSK2857916

REVISED TEXT

Thrombocytopenia	Grade 3: >25 and <50x10^9/L	• ~~With clinically significant bleeding~~ Where estimated blood loss is ≥ 10 mL: withhold the <u>treatment</u>: • No ~~clinically significant~~ bleeding: continue treatment with 25% dose reduction

Ocular/corneal toxicity	Grade 2~~/Grade 3~~	• First occurrence: o Interrupt treatment with GSK2857916 o Consult ophthalmologist immediately o When recovered to G≤1 Re-start treatment with GSK2857916 at 25% dose reduction upon resolution to ≤G1 • Second occurrence:

		○ Interrupt treatment with GSK2857916 ○ Consult ophthalmologist immediately ○ Once resolved to≤ G1 or less: Restart treatment with GSK2857916 at additional 25% dose reduction • Third occurrence: • Permanently discontinue treatment with GSK2857916 and withdraw subject from study
	Grade 3/Grade 4	• Consult ophthalmologist immediately • Permanently discontinue treatment with GSK2857916

NEW TEXT

Serum creatinine≥ Grade 3	>3.0mg/dL from baseline or 3.0-6.0xULN	• Provide appropriate medical treatment. • Withdraw permanently from trial

INR prolongation	≥2.5	• Evaluate and provide medical treatment if necessary • If INR prolongation is not related to use of anticoagulants withdraw subject from study

Section 3.10.3, Dose Modifications, Table 13 Dose Adjustment/Stopping Criteria

PREVIOUS TEXT

Toxicity Grade[a]	Dose Modification of GSK2857916
Grade 3	• Withhold dose until toxicity resolves to Grade 1 or baseline, unless condition fits exceptions noted below. If resolved within 14 days, resume treatment at dose reduced by 25% (first dose reduction), or 50% (second dose reduction). Consider supportive care recommendations. If not resolved within 14 days, discuss with Medical Monitor. **Exceptions**: • Subjects who develop G3 toxicities which respond to standard treatment and resolve to ≤G1 within 48 hours may continue treatment at scheduled or reduced dose • Permanently discontinue for grade 3 or greater QTc prolongation ie, QTcF >500 msec or QTcF increase by > 60 msec from baseline • Troponin elevations: See Section 3.9.3 for troponin stopping criteria

[a]Considered related to investigational drug.

REVISED TEXT

Toxicity Grade[a]	Dose Modification of GSK2857916
Grade 3	• Withhold dose until toxicity resolves to Grade 1 or baseline, unless condition fits exceptions noted below. If resolved within 14 days, resume treatment at dose reduced by 25% (first dose reduction), or 50% (second dose reduction). Consider supportive care recommendations. If ~~not~~ toxicity is resolved within period longer than 14 days, ~~discuss with Medical Monitor.~~ continuation of treatment may be considered on an individual basis if benefit to subject can be demonstrated and if the investigator and medical monitor agree that for a given subject the benefits may outweigh the risks **Exceptions**: • Subjects who develop G3 toxicities which respond to standard treatment and resolve to ≤G1 within 48 hours may continue treatment at scheduled or reduced dose • Permanently discontinue for grade 3 or greater QTc prolongation ie, QTcF >500 msec or QTcF increase by > 60 msec from baseline • Troponin elevations: See Section 3.9.3 for troponin stopping criteria

[a]~~Considered~~ Possibly related to investigational drug.

Section 4.1, Description of Investigational Product

NEW TEXT

Lot number	132373860

GSK2857916 will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements. **Only Lot#132373860 of drug product will be used for this trial.**

Section 4.2, Preparation/Handling/Storage of GSK2857916 Investigational Product

PREVIOUS TEXT

Preparation

GSK2857916 Solution for Infusion, 20 mg/mL is supplied as a frozen liquid. Before use, thaw each vial of GSK2857916 for Infusion, 20mg/mL, 1.5mL for up to 4 hours under refrigerated conditions, protected from light. Following thawing, gently swirl the vial to ensure uniformity. GSK2857916 should be diluted in normal saline (0.9%) to no more than 2 mg/mL and no less than 0.2 mg/mL.

The dosing solution of GSK2857916 can be held up to 8 hours at room temperature (diluted drug product in bag) from a stability perspective, but should be used as soon as possible as the product does not contain an antimicrobial preservative.

Administration

GSK2857916 is compatible with polyvinylchloride-lined or polyolefin-lined intravenous infusion administration sets, 0.2 micron polyethersulfone filters, or optionally a polyurethane catheter. Doses of GSK2857916 are to be administered as an IV infusion via an infusion pump that can ensure precision to the decimal point of a mL for the infusion rate at lower doses. It is recommended to prime the IV tubing with at least 15 mL prior to dosing.

Storage

GSK2857916 must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the GSK2857916 will be limited to the investigator and authorized site staff. GSK2857916 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

GSK2857916 is to be stored at a temperature range of -50°C to -15°C. Maintenance of a temperature log is required.

The expiry date, where required, is stated on the product label.

REVISED TEXT

Preparation

GSK2857916 Solution for Infusion, 20 mg/mL is supplied as a frozen liquid (Lot# 132373860). Before use, thaw each vial of GSK2857916 for Infusion, 20mg/mL, 1.5mL for up to 4 hours under refrigerated conditions, protected from light. Following thawing, gently swirl the vial to ensure uniformity. GSK2857916 should be diluted in normal saline (0.9%) to no more than 2 mg/mL and no less than 0.2 mg/mL.

The dosing solution of GSK2857916 can be held up to 24 hours under refrigerated conditions or 4 ~~8~~ hours at room temperature (diluted drug product in bag) from a stability perspective, but should be used as soon as possible as the product does not contain an antimicrobial preservative.

Administration

GSK2857916 is compatible with polyvinylchloride-lined or polyolefin-lined intravenous infusion administration sets, 0.2 micron polyethersulfone filters, or optionally a polyurethane catheter. Doses of GSK2857916 are to be administered as an IV infusion via an infusion pump that can ensure precision to the decimal point of a mL for the infusion rate at lower doses. It is recommended to prime the IV tubing with at least 15 mL prior to dosing.

Administration of drug product in this trial is restricted to Lot#132373869.

Storage

GSK2857916 must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the GSK2857916 will be limited to the investigator and authorized site staff. GSK2857916 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

GSK2857916 is to be stored at a temperature range of -50°C to -15°C. Maintenance of a temperature log is required.

The expiry date, where required, is stated on the product label. **Only Lot#132373860 of drug product is acceptable for use in this trial.**

Section 5.2.1, Inclusion Criteria

PREVIOUS TEXT

2. Male or female, 18 years or older (at the time consent is obtained).

REVISED TEXT

2. Male or female, 18 years or older (at the time consent is obtained) and must have a body weight of at least 45 kg (99 lb).

Section 6.3, Permanent Discontinuation fro Study Treatment

PREVIOUS TEXT

- a dose delay of >14 days unless the investigator or GSK Medical Monitor agree that further treatment may benefit the subject. Exceptions apply to nephrotoxicity as outlined in Section 3.10.2

REVISED TEXT

- a dose delay of >14 days unless the investigator or GSK Medical Monitor agree that subject derives benefit and that further treatment benefits will outweigh the risks ~~may benefit the subject~~. Exceptions apply to nephrotoxicity as outlined in Section 3.10.2

Section 7.1.1.1, Every 3 Weeks Dosing Schedule for Multiple Myeloma

PREVIOUS TEXT

Study Assessments1	Screen2	DAY 1 C1	**DAY 2 C1**	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
BCMA assessment (flow)	X[15]								

Study Assessments1	Screen2	DAY 1 C1	Day 2 C1	Day 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
PD	X			X					
Serum (soluble BCMA)	X[18]	X[18]	X[18]	X[18]	X[18]	X[18]	Predose at the start of each cycle	X[18]	
Serum (cytokines/chemokines)	X[19]	X[19]	X			X[19]	At predose and EOI on D1 of each cycle	X	

15. Sample(s) collected for analysis by central lab.
18. A single sample for sBCMA will be collected at screening,-C1D8, C1D15 and at the End of Study visit. sBCMA samples will also be collected on C1D1 at EOI (±5 minutes) and on C1D2 24h post SOI. On C2D1 sBCMA will be collected pre-dose (within 30 minutes prior to SOI) and at the EOI (±5 minutes)

REVISED TEXT

Study Assessments1	Screen2	DAY 1 C1	**DAY 2 C1**	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
BCMA assessment and PD (flow)	X[15]			X[15]					

Study Assessments1	Screen2	DAY 1 C1	Day 2 C1	Day 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
~~PD~~	~~X~~[15]			~~X~~					
Serum (soluble BCMA)	~~X~~[18]	X[18]	X[18]	X[18]	X[18]	X[18]	Predose at the start of each cycle	X[18]	
Serum (cytokines/chemokines)	~~X~~[19]	X[19]	X			X[19]	At predose and EOI on D1 of each cycle	X	

15. Sample(s) collected for analysis by central lab. The same sample will be used for BCMA (flow) and PD during Screening.
18. A single sample for sBCMA will be collected at ~~screening,~~ C1D8, C1D15 and at the End of Study visit. sBCMA samples will also be collected on C1D1 at predose (within 30 minutes prior to SOI), at EOI (±5 minutes) and on C1D2 24h post SOI. On C2D1 sBCMA will be collected pre-dose (within 30 minutes prior to SOI) and at the EOI (±5 minutes)

NEW TEXT

Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 2 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study**	**3-Month Off-study Follow-up**
HBV/HCV tests	X								

Section 7.1.1.2, Weekly Dosing Schedule (Dose Escalation) for Multiple Myeloma

PREVIOUS TEXT

Study Assessments1	Screen2	DAY 1 C1	**DAY 2 C1**	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
BCMA assessment (flow)	X[15]								

Study Assessments1	Screen2	**DAY 1 C1**	**DAY 2 C1**	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
PD	X			X[17]					
Serum (soluble BCMA)	X[19]	X[19]	X[19]	X[19]	X[19]	X[19]	Predose at the start of each cycle	X	
Serum (cytokines/chemokines)	X[20]	X[20]	X	X[20]	X[20]	X[20]	At predose and EOI on D1 of each cycle	X	

15. Sample(s) collected for analysis by central lab.
19. A single sample for sBCMA will be collected at screening and on C1D8 predose, and at the End of Study visit. sBCMA samples will also be collected on C1D1 at EOI (±5 minutes) and on C1D2 24h post SOI. On C1D15 and C2D1 collect at predose (within 30 minutes prior to SOI) and EOI (±5 minutes)

REVISED TEXT

Study Assessments1	Screen2	**DAY 1 C1**	**DAY 2 C1**	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
BCMA assessment and PD (flow)	X[15]			X[15, 17]					

Study Assessments1	Screen2	**DAY 1 C1**	**DAY 2 C1**	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
~~PD~~	~~X[15]~~			~~X[17]~~					
Serum (soluble BCMA)	~~X[19]~~	X[19]	X[19]	X[19]	X[19]	X[19]	Predose at the start of each cycle	X	
Serum (cytokines/chemokines)	~~X[20]~~	X[20]	X	X[20]	X[20]	X[20]	At predose and EOI on D1 of each cycle	X	

15. Sample(s) collected for analysis by central lab. The same sample will be used for BCMA (flow) and PD during Screening.
19. A single sample for sBCMA will be collected at ~~screening and on~~ C1D8 predose, and at the End of Study visit. sBCMA samples will also be collected on C1D1 at predose (within 30 minutes prior to SOI), at EOI (±5 minutes) and on C1D2 24h post SOI. On C1D15 and C2D1 collect at predose (within 30 minutes prior to SOI) and EOI (±5 minutes)

NEW TEXT

Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 2 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study**	**3-Month Off-study Follow-up**
HBV/HCV tests	X								

Section 7.1.2.1, Every 3 Weeks Dosing Schedule for Multiple Myeloma

PREVIOUS TEXT

Study Assessments1	Screen2	**DAY 1 C1**	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
BCMA assessment (flow)	X[16]							

Study Assessments1	Screen2	DAY 1 C1	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
PD	X		X[18]					
Serum (soluble BCMA)	X[20]	X[20]			X[20]	Predose at the start of each cycle	X	
Serum (cytokines/chemokines)	X[21]	X[21]			X[21]	Predose and EOI on D1 of each cycle	X	

16. Sample(s) collected for analysis at central lab.
20. Collect sBCMA at screening (single sample), C1D1 at EOI (±5 minutes), C2D1 at predose (within 30 minutes prior to SOI) and at EOI (+- 5 minutes).

REVISED TEXT

Study Assessments1	Screen2	**DAY 1 C1**	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
BCMA assessment and PD (flow)	X[16]		X[16, 18]					

Study Assessments1	Screen2	DAY 1 C1	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
~~PD~~	~~X[16]~~		~~X[18]~~					
Serum (soluble BCMA)	~~X[20]~~	X[20]			X[20]	Predose at the start of each cycle	X	
Serum (cytokines/chemokines)	~~X[21]~~	X[21]			X[21]	Predose and EOI on D1 of each cycle	X	

16. Sample(s) collected for analysis at central lab. The same sample will be used for BCMA (flow) and PD during Screening. On D8 only postdose PD assessment will be performed, if applicable (refer to footnote 18).
20. Collect sBCMA at ~~screening (single sample),~~ C1D1 predose (within 30 minutes prior to SOI) and at EOI (±5 minutes), C2D1 at predose (within 30 minutes prior to SOI) and at EOI (+- 5 minutes).

NEW TEXT

Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
HBV/HCV tests	X							

Section 7.1.2.2, Dose Expansion Weekly Dosing Schedule for Multiple Myeloma

PREVIOUS TEXT

Study Assessments1	Screen2	**DAY 1 C1**	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	Day 15 C2	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
BCMA assessment and PD (flow)	X[15]								

Study Assessments1	Screen2	DAY 1 C1	Day 8 C1	**DAY 15 C1**	**DAY 1 C2**	Day 15 C2	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
PD	X		X[17]						
Serum (soluble BCMA)	X[19]	X[19]	X[19]	X[19]	X[19]		Predose at the start of each cycle	X	
Serum (cytokines/chemokines)	X[20]	X[20]	X[20]	X[20]	X[20]		Predose and EOI on D1 of each cycle	X	

15. Sample(s) collected for analysis at central lab. The same sample will be used for BCMA (flow) and PD during Screening.
19. A single sBCMA sample will be collected at Screening or predose (within 30 minutes prior to SOI) unless otherwise specified. On C1D15 and C2D1 collect samples at predose (within 30 minutes prior to SOI) and at EOI (±5 minutes).

REVISED TEXT

Study Assessments1	Screen2	**DAY 1 C1**	DAY 8 C1	**DAY 15 C1**	**DAY 1 C2**	Day 15 C2	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
BCMA assessment and PD (flow)	X[15]		X[15, 17]						

Study Assessments1	Screen2	DAY 1 C1	Day 8 C1	**DAY 15 C1**	**DAY 1 C2**	Day 15 C2	D1 of C3-C16	**END OF STUDY**	**3-MONTH OFF-STUDY FOLLOW-UP**
~~PD~~	~~X~~[15]		~~X~~[17]						
Serum (soluble BCMA)	~~X~~[19]	X[19]	X[19]	X[19]	X[19]		Predose at the start of each cycle	X	
Serum (cytokines/chemokines)	~~X~~[20]	X[20]	X[20]	X[20]	X[20]		Predose and EOI on D1 of each cycle	X	

15. Sample(s) collected for analysis at central lab. The same sample will be used for BCMA (flow) and PD during Screening. On D8 only postdose PD assessment will be performed, if applicable (refer to footnote 17).
19. A single sBCMA sample will be collected at ~~Screening or~~ C1D1 predose (within 30 minutes prior to SOI) unless otherwise specified. On C1D15 and C2D1 collect samples at predose (within 30 minutes prior to SOI) and at EOI (±5 minutes).

NEW TEXT

Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	Day 15 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
HBV/HCV tests	X								

Section 7.1.2.3, Dose Expansion Every 3 Weeks Dosing Schedule for Other Hematologic Malignancies

PREVIOUS TEXT

Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
Serum (soluble BCMA)	X[14]				X[14]			
Serum (cytokines/chemokines)	X[15]	X[15]			X[15]	Predose and EOI on D1 of each cycle	X	

Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
Survival Status								X[24]
Subsequent Treatment								X[24]

14. A single sBCMA sample will be collected at screening. On C2D1 sBCMA will be collected at predose (within 30 minutes prior to SOI) and at EOI (±5 minutes).

REVISED TEXT

Study Assessments1	Screen[2]	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
Serum (soluble BCMA)	~~X~~[14]	X[14]			X[14]			
Serum (cytokines/chemokines)	~~X~~[15]	X[15]			X[15]	Predose and EOI on D1 of each cycle	X	

Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
Survival Status								X[25]
Subsequent Treatment								X[25]

14. A single sBCMA sample will be collected ~~at screening.~~ C1D1 predose (within 30 minutes prior to SOI). On C2D1 sBCMA will be collected at predose (within 30 minutes prior to SOI) and at EOI (±5 minutes).

NEW TEXT

Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
HBV/HCV tests	X							

Tumor biopsy for BCMA expression	X[24]							

24. Archival or fresh tissue required for BCMA testing. Refer to Section 5.2.1 Inclusion Criterion #4 for eligibility criteria.

Section 7.1.2.4, Dose Expansion Weekly Dosing Schedule for Other Hematologic Malignancies

PREVIOUS TEXT

Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	Day 15 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
Serum (soluble BCMA)	X[13]	X[13]	X[13]	X[13]	X[13]			X[13]	
Serum (cytokines/chemokines)	X[14]	X[14]	X[14]	X[14]	X[14]		Predose and EOI on D1 of each cycle	X	

Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	Day 15 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
Survival Status									X[23]
Subsequent Treatment									X[23]

13. A single sample for sBCMA will be collected at screening, on C1D8 predose, and at the End of Study visit. sBCMA samples will also be collected on C1D1 at EOI (±5 minutes). On C1D15 and C2D1 collect at predose (within 30 minutes prior to SOI) and EOI (±5 minutes)

REVISED TEXT

Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	Day 15 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
Serum (soluble BCMA)	~~X[13]~~	X[13]	X[13]	X[13]	X[13]			X[13]	
Serum (cytokines/chemokines)	~~X[14]~~	X[14]	X[14]	X[14]	X[14]		Predose and EOI on D1 of each cycle	X	

Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	Day 15 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
Survival Status									X~~23~~25
Subsequent Treatment									X~~23~~25

13. A single sample for sBCMA will be collected ~~at screening,~~ on C1D8 predose, and at the End of Study visit. sBCMA samples will also be collected on C1D1 at predose (within 30 minutes prior to SOI) and EOI (±5 minutes). On C1D15 and C2D1 collect at predose (within 30 minutes prior to SOI) and EOI (±5 minutes)

NEW TEXT

Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	Day 15 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
HBV/HCV tests	X								
Study Assessments1	Screen2	Day 1 C1	Day 8 C1	Day 15 C1	Day 1 C2	Day 15 C2	D1 of C3-C16	End of Study	3-Month Off-study Follow-up
Tumor biopsy for BCMA expression	X[23]								

23. Arcived or fresh tissue required for BCMA testing. Refer to Section 5.2.1 Inclusion Criterion #4 for eligibility criteria.

Section 7.3.6, Laboratory Assessments, Table 15, List of Clinical Laboratory Tests

PREVIOUS TEXT

Glucose, fasting	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin

Magnesium	Phosphorous	Creatinine kinase (CK)	LDH

Serum Creatine Phosphokinase (CPK)

Human Immunodeficiency virus (HIV)

REVISED TEXT

Glucose~~, fasting~~	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Magnesium	Phosphorous	Creatini~~ne~~ kinase (CK)	LDH

~~Serum Creatine Phosphokinase (CPK)~~

~~Human Immunodeficiency virus (HIV)~~

Section 7.4.1, Blood Sample Collection for Pharmacokinetics

PREVIOUS TEXT

Blood samples of approximately 1 mL for pharmacokinetic (PK) analysis of GSK2857916 (ADC and total antibody) and cys-mcMMAF will be collected at the time points indicated in the Time and Events Tables (Section 7.1). Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded.

Details on PK blood sample collection, processing, storage and shipping procedures are provided in the Study Procedures Manual (SPM).

REVISED TEXT

Blood samples of approximately ~~1~~ 5 mL for pharmacokinetic (PK) analysis of GSK2857916 (ADC and total antibody) and cys-mcMMAF will be collected at the time points indicated in the Time and Events Tables (Section 7.1). Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded.

Details on PK blood sample collection, processing, storage and shipping procedures are provided in the Study Procedures Manual (SPM). Blood volumes for PK samples are outlined in Appendix 10 (Section 17.10).

Section 10, Concomitant Medications and Non-Drug Therapies

NEW TEXT

Concomitant dosing of GSK2857916 with strong Pgp inhibitors should be avoided unless considered medically necessary (See Appendix 11 for list of relevant Pgp inhibitors).

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. The SPM will be updated to include this information. Any such changes will be communicated to the investigative sites in the form of a letter.

Section 17.10, Appendix 10: Blood Requirements

PREVIOUS TEXT

Blood Requirements in Dose Escalation and Dose Expansion Cohorts for All Lab Tests, Except PK

Test Sample	Sample Volume	Requirements for Screening – Cycle 1	Requirements for Subsequent Cycles
Hematology	5 ml	10-25 ml	5 ml
Chemistry	5 ml	15-20 ml	5 ml
Coagulation	5 ml	10-20 ml	5 ml
Hgb A1c	5 ml	5 ml	
SPEP/UPEP	6 ml	6 ml	6 ml
CRP	1 ml	1-2 ml	1 ml
B2 microglobulin	1 ml	1-2 ml	1 ml
Kappa, lambda free LC, FLC	1 ml	1 ml	1 ml
Immunoglobulin levels (IgG, IgA, IgM)	6 ml	6 ml	6 ml
Plasma collection for [redacted] and circulating cytokines	5 ml	5 ml	5 ml
Hepatitis B, Hepatitis C	3 ml	3 ml	
HIV	5 ml	5 ml	
CK-MB	3 ml	6 ml	3 ml
Anti-Drug Antibody	3 ml	3 ml	3 ml
BNP	3 ml	3 ml	
Troponin	2.5 ml	5 ml	2.5 ml
TBNK	3 ml	3 ml	3 ml
sBCMA[1]	1 ml	6 ml	6 ml
PGx[2]	6 ml	6 ml	
	Total Volume	**100-132 ml**	**52.5 ml**

[1]Calculation reflects blood drawn for sBCMA measurement in a MM subject

[2] Dose expansion only

Blood Requirements for PK

PK Schedule	Sample Volume	Cycle 1	Cycle 2	Cycle 3	Cycle 5	Total Volume
Escalation Every 3 Weeks	3 ml	27 ml	6 ml	6 ml		39 ml
Escalation Weekly	3 ml	33 ml	6 ml	6 ml		45 ml
Expansion Every 3 Weeks MM	3 ml	6 ml	6 ml	6 ml	6 ml	24 ml
Expansion Every 3 Weeks Other Hematologic Malignancies	3 ml	12 ml	6 ml	6 ml	6 ml	30 ml
Expansion Weekly MM	3 ml	24 ml	12 ml	12 ml	6 ml	54 ml
Expansion Weekly Other Hematologic Malignancies	3 ml	24 ml	12 ml	12 ml	6 ml	54 ml

Total Blood Requirements

Schedule	Screening + Cycle 1	Subsequent Cycles
Escalation Every 3 Weeks	127-159 ml	58.5 ml
Escalation Weekly	133-165 ml	58.5 ml
Expansion Every 3 Weeks	106-144 ml	58.5 ml
Expansion Weekly	124-156 ml	58.5-64.5 ml

REVISED TEXT

~~Blood Requirements in Dose Escalation and Dose Expansion Cohorts for All Lab Tests, Except PK~~

~~Test Sample~~	~~Sample Volume~~	~~Requirements for Screening – Cycle 1~~	~~Requirements for Subsequent Cycles~~
~~Hematology~~	~~5 ml~~	~~10-25 ml~~	~~5 ml~~
~~Chemistry~~	~~5 ml~~	~~15-20 ml~~	~~5 ml~~
~~Coagulation~~	~~5 ml~~	~~10-20 ml~~	~~5 ml~~
~~Hgb-A1c~~	~~5 ml~~	~~5 ml~~	
~~SPEP/UPEP~~	~~6 ml~~	~~6 ml~~	~~6 ml~~
~~CRP~~	~~1 ml~~	~~1-2 ml~~	~~1 ml~~
~~B2 microglobulin~~	~~1 ml~~	~~1-2 ml~~	~~1 ml~~
~~Kappa, lambda free LC, FLC~~	~~1 ml~~	~~1 ml~~	~~1 ml~~
~~Immunoglobulin levels (IgG, IgA, IgM)~~	~~6 ml~~	~~6 ml~~	~~6 ml~~
~~Plasma collection for [redacted] and circulating cytokines~~	~~5 ml~~	~~5 ml~~	~~5 ml~~

Test Sample	**Sample Volume**	**Requirements for Screening – Cycle 1**	**Requirements for Subsequent Cycles**
Hepatitis B, Hepatitis C	3 ml	3 ml	
HIV	5 ml	5 ml	
CK-MB	3 ml	6 ml	3 ml
Anti-Drug Antibody	3 ml	3 ml	3 ml
BNP	3 ml	3 ml	
Troponin	2.5 ml	5 ml	2.5 ml
TBNK	3 ml	3 ml	3 ml
sBCMA[1]	1 ml	6 ml	6 ml
PGx[2]	6 ml	6 ml	
	Total Volume	**100-132 ml**	**52.5 ml**

[1]Calculation reflects blood drawn for sBCMA measurement in a MM subject

[2] Dose expansion only

Blood Requirements for PK

PK Schedule	**Sample Volume**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 5**	**Total Volume**
Escalation Every 3 Weeks	3 ml	27 ml	6 ml	6 ml		39 ml
Escalation Weekly	3 ml	33 ml	6 ml	6 ml		45 ml
Expansion Every 3 Weeks MM	3 ml	6 ml	6 ml	6 ml	6 ml	24 ml
Expansion Every 3 Weeks Other Hematologic Malignancies	3 ml	12 ml	6 ml	6 ml	6 ml	30 ml
Expansion Weekly MM	3 ml	24 ml	12 ml	12 ml	6 ml	54 ml
Expansion Weekly Other Hematologic Malignancies	3 ml	24 ml	12 ml	12 ml	6 ml	54 ml

Total Blood Requirements

Schedule	**Screening + Cycle 1**	**Subsequent Cycles**
Escalation Every 3 Weeks	127-159 ml	58.5 ml
Escalation Weekly	133-165 ml	58.5 ml
Expansion Every 3 Weeks	106-144 ml	58.5 ml
Expansion Weekly	124-156 ml	58.5-64.5 ml

Blood Requirements for All Lab Tests, Except PK

Test Sample	Sample Volume	Screening	Cycle 1	Each Subsequent Cycle
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	15-20 ml	5 ml
Coagulation	5 ml	5 ml	10-15 ml	5 ml
SPEP	6 ml	6 ml		6 ml
CRP	1 ml	1 ml		1 ml
B2 Microglobulin	1 ml	1 ml		1 ml
Kappa, lambda free LC, FLC	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml	10 ml		
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml	3 ml		0-3 ml
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	3 ml	3 ml		3 ml
sBCMA	1 ml		5 ml	1-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
Total		59.5 ml	51.5-66.5 ml	45.5-51.5 ml

1. Required for women of childbearing potential

Dose Escalation: Weekly for Multiple Myeloma

Test Sample	Sample Volume	Screening	Cycle 1	Each Subsequent Cycle
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	15-20 ml	5 ml
Coagulation	5 ml	5 ml	10-15 ml	5 ml
SPEP	6 ml	6 ml		6 ml
CRP	1 ml	1 ml	1 ml	1 ml
B2 Microglobulin	1 ml	1 ml	1 ml	1 ml
Kappa, lambda free LC, FLC	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml	10 ml		
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml	3 ml	3 ml	0-3 ml

Test Sample	**Sample Volume**	**Screening**	**Cycle 1**	**Each Subsequent Cycle**
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	3 ml	3 ml		3 ml
sBCMA	1 ml		6 ml	1-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
Total		59.5 ml	57.5-72.5 ml	45.5-51.5 ml

1. Required for women of childbearing potential

Dose Expansion: Every 3 Weeks for Multiple Myeloma

Test Sample	**Sample Volume**	**Screening**	**Cycle 1**	**Each Subsequent Cycle**
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	10-15 ml	5 ml
Coagulation	5 ml	5 ml	10-15 ml	5 ml
SPEP	6 ml	6 ml		6 ml
CRP	1 ml	1 ml		1 ml
B2 Microglobulin	1 ml	1 ml		1 ml
Kappa, lambda free LC, FLC	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml	10 ml		
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml	3 ml		0-3 ml
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	3 ml	3 ml		3 ml
sBCMA	1 ml		2 ml	1-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
PgX	6 ml		6 ml	
Total		59.5 ml	49.5-64.5 ml	45.5-51.5 ml

1. Required for women of childbearing potential

Dose Expansion: Weekly for Multiple Myeloma

Test Sample	Sample Volume	Screening	Cycle 1	Each Subsequent Cycle
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	10-15 ml	5 ml
Coagulation	5 ml	5 ml	10-15 ml	5-10 ml
SPEP	6 ml	6 ml		6 ml
CRP	1 ml	1 ml		1 ml
B2 Microglobulin	1 ml	1 ml		1 ml
Kappa, lambda free LC, FLC	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml	10 ml		
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml	3 ml		0-3 ml
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	3 ml	3 ml		3 ml
sBCMA	1 ml		1 ml	1-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
PgX	6 ml		6 ml	
Total		59.5 ml	49.5-64.5 ml	45.5-56.5 ml

1. Required for women of childbearing potential

Dose Expansion: Every 3 Weeks for Other Hematologic Malignancies

Test Sample	Sample Volume	Screening	Cycle 1	Each Subsequent Cycle
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	10-15 ml	5 ml
Coagulation	5 ml	5 ml	10-15 ml	5 ml
CRP	1 ml	1 ml		1 ml
B2 Microglobulin	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml	10 ml		
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml	3 ml		0-3 ml
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	3 ml	3 ml		3 ml

Test Sample	**Sample Volume**	**Screening**	**Cycle 1**	**Each Subsequent Cycle**
sBCMA	1 ml		1 ml	0-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
PgX	6 ml		6 ml	
Total		52.5 ml	48.5-63.5 ml	37.5-44.5 ml

1. Required for women of childbearing potential

Dose Expansion: Weekly for Other Hematologic Malignancies

Test Sample	**Sample Volume**	**Screening**	**Cycle 1**	**Each Subsequent Cycle**
Hematology	5 ml	5 ml	10-15 ml	5 ml
Chemistry	5 ml	5 ml	10-15 ml	5-10 ml
Coagulation	5 ml	5 ml	10-15 ml	5 ml
CRP	1 ml	1 ml		1 ml
B2 Microglobulin	1 ml	1 ml		1 ml
IgG, IgA, IgM	6 ml	6 ml		6 ml
[redacted]	10 ml	10 ml		
Cytokines	3 ml		6 ml	6 ml
HBV/HCV	3 ml	3 ml		
CK-MB	3 ml	3 ml	3 ml	3 ml
ADA	3 ml	3 ml	3 ml	0-3 ml
BNP	3 ml	3 ml		
Troponin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
TBNK	3 ml	3 ml		3 ml
sBCMA	1 ml		5 ml	0-2 ml
Pregnancy Test[1]	2 ml	2 ml		0-2 ml
PgX	6 ml		6 ml	
Total		52.5 ml	55.5-70.5 ml	37.5-49.5 ml

1. Required for women of childbearing potential

Blood Requirements for PK

PK Schedule	Sample Volume	Cycle 1	Cycle 2	Cycle 3	Cycle 5	Total Volume
Escalation Every 3 Weeks	5 ml	60 ml	10 ml	10 ml		80 ml
Escalation Weekly	5 ml	80 ml	10ml	10 ml		100 ml
Expansion Every 3 Weeks MM	5 ml	20 ml	20 ml	20 ml	20 ml	80 ml
Expansion Weekly MM	5 ml	20 ml	10 ml	10 ml	10 ml	50 ml
Expansion Every 3 Weeks Other Hematologic Malignancies	5 ml	40 ml	20 ml	20 ml	10 ml	90 ml
Expansion Weekly Other Hematologic Malignancies	5 ml	40 ml	20 ml	20 ml	10 ml	90 ml

Total Blood Requirements

Schedule	Screening	Cycle 1	Each Subsequent Cycle
Escalation Every 3 Weeks MM	59.5 ml	111.5-126.5 ml	45.5-61.5 ml
Escalation Weekly MM	59.5 ml	137.5-152.5 ml	45.5-61.5 ml
Expansion Every 3 Weeks MM	59.5 ml	69.5-84.5 ml	45.5-61.5 ml
Expansion Weekly MM	59.5 ml	69.5-84.5 ml	45.5-66.5 ml
Expansion Every 3 Weeks Other Hematologic Malignancies	52.5 ml	88.5-103.5 ml	37.5-64.5 ml
Expansion Weekly Other Hematologic Malignancies	52.5 ml	95.5-110.5 ml	37.5-69.5 ml

The Study Procedures Manual will be updated with new information if changes in blood volumes are required.

Section 17.11, Appendix 11: Pgp Inhibitors

NEW TEXT

Amiodarone
Atorvastatin
Azithromycin
Carvedilol
Clarithromycin
Dronedarone
Fluvoxamine
Indinavir
Indinavir and Ritonavir
Itraconazole
Ketonazole
Lapatinib
Lopinavir and Ritonavir
Nicardipine
Quinidine
Ranolazine
Ritonavir
Saquinavir and Ritonavir
Telaprevir
Verapamil
Valspodar

The Study Procedures Manual will be updated if changes to the Pgp inhibitor list is required.

16.11.3. Amendment 3

Where the Amendment Applies

Canada

Summary of Amendment Changes with Rationale

1. Section 4.2, Preparation/Handling/Storage of GSK2867916 Investigational Product

    - Rationale: Health Canada requested change to the amount of time prepared product can be kept under refrigerated conditions from 24 hours to 8 hours as the product does not contain an antimicrobial preservative

List of Specific Changes

Section 4.2, Preparation/Handing/Storage of GSK2857916 Investigational Product

PREVIOUS TEXT

Preparation

GSK2857916 Solution for Infusion, 20 mg/mL is supplied as a frozen liquid (Lot# 132373860). Before use, thaw each vial of GSK2857916 for Infusion, 20mg/mL, 1.5mL for up to 4 hours under refrigerated conditions, protected from light. Following thawing, gently swirl the vial to ensure uniformity. GSK2857916 should be diluted in normal saline (0.9%) to no more than 2 mg/mL and no less than 0.2 mg/mL.

The dosing solution of GSK2857916 can be held up to 24 hours under refrigerated conditions or 4 hours at room temperature (diluted drug product in bag) from a stability perspective, but should be used as soon as possible as the product does not contain an antimicrobial preservative.

REVISED TEXT

Preparation

GSK2857916 Solution for Infusion, 20 mg/mL is supplied as a frozen liquid (Lot# 132373860). Before use, thaw each vial of GSK2857916 for Infusion, 20mg/mL, 1.5mL for up to 4 hours under refrigerated conditions, protected from light. Following thawing, gently swirl the vial to ensure uniformity. GSK2857916 should be diluted in normal saline (0.9%) to no more than 2 mg/mL and no less than 0.2 mg/mL.

The dosing solution of GSK2857916 can be held up to ~~24~~ 8 hours under refrigerated conditions or 4 hours at room temperature (diluted drug product in bag) from a stability perspective, but should be used as soon as possible as the product does not contain an antimicrobial preservative.

16.11.4. Amendment 4

Where the Amendment Applies

Amendment 4 applies to all sites in Canada, United Kingdom, and United States

Amendment Changes with Rationale

The protocol Amendment 2 dated 20 March 2014 (applied to all sites) and protocol Amendment 3 dated 05 May 2014 (applied to sites in Canada) are replaced by Amendment 4 with the effective date of 05 MAY 2016.

The following protocol changes have been implemented to include patient reported outcome instruments in the Part 2 multiple myeloma cohort and refine the lymphoma histologies eligible in Part 2 BCMA-expressing lymphoma cohort (the prior cohort name of "other hematologic malignancies" will be replaced with "lymphomas"; this revision will be referenced throughout the protocol. Additionally the requirement for 60% of tumor cells staining positive for BCMA expression was removed. The total number of subjects that may be enrolled is presented by a range of 80 to 95 to provide an updated estimate based on the number of subjects who enrolled at the time of the amendment. Additional modifications include: changing the time-point specific blood specimens are collected for baseline/pre-treatment immunogenicity and biomarker measurements, and the visit window for certain assessments. The primary and secondary medical monitors were updated and study treatment dose modification revisions were made for Grade 3 ocular toxicities.

Original text displayed as strikethrough indicates replaced or removed text. New text is displayed as underline. Revisions within tables will either be presented with the entire table or displayed as text (i.e., for larger tables). Revisions to figures will be displayed first by the old figure and then followed by the new figure. Typos or minor word changes will not be presented.

Summary of Changes

1. Medical Monitor/Sponsor Contact Information

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	GSK Address
Primary Medical Monitor	PPD MD	PPD		GlaxoSmithKline 1250 South Collegeville Road Mailstop ~~UP1450~~ UP-4300 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD ~~MD~~ PPD MD			GlaxoSmithKline 1250 South Collegeville Road Mailstop UP4315UP4300 Collegeville, PA 19436, USA PPD

2. Protocol Synposis

RATIONALE: This is a FTIH study that will assess the safety, pharmacokinetics (PK), pharmacodynamics (PD) and therapeutic potential of GSK2857916 in multiple myeloma (MM) and ~~other hematologic malignancies~~ lymphomas that express BCMA.

The hypothesis is that GSK2857916 can be safely administered to subjects with BCMA positive malignancies at doses where target engagement can be demonstrated. This study will determine if adequate target engagement of BCMA receptors translates into clinical benefit for subjects with MM and ~~other~~ BCMA positive ~~hematologic malignancies~~ lymphomas.

OBJECTIVES:

Secondary

• To evaluate the pharmacokinetic (PK) profile of GSK2857916 and the breakdown product cys-mcMMAF) after intravenous (IV) single and repeat dose administration in subjects with relapsed/refractory MM and ~~other~~ BCMA expressing ~~hematologic malignancies~~ lymphomas	• GSK2857916 and cys-mcMMAF PK parameters following IV single and repeat dose administration during dose escalation as data permit (e.g., AUCs Cmax, tmax, CL, V_{SS}, t½ [single dose], Cmax and Ctrough [repeat dose]). GSK2857916 population PK parameters in expansion cohorts at the RP2 dose (e.g. clearance (CL), volume of distribution (Vd)), and relevant covariates which may influence exposure (e.g. age, weight, or disease-related covariates e.g. BCMA expression)
• To assess anti-drug antibody (ADA)formation after IV single and repeat dose administration of GSK2857916	• ADA incidence and titers after single and repeat IV dosing of GSK2857916
• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM and ~~other~~ BCMA expressing ~~hematologic malignancies~~ lymphomas	• Clinical activity measured as Overall Response Rate (ORR) which is defined as follows: o For MM: the percentage of subjects achieving confirmed partial response or better (≥PR) o In addition, the percentage of subjects with minimal response (MR) will be assessed for clinical benefit rate (CBR) (Appendix 1) o For ~~Other Hematologic Malignancies~~ Lymphomas: the percentage of subjects achieving PR or better (≥PR) (Appendix

	2Appendix 2) ~~(Appendix 3)~~
Exploratory	
• To evaluate PD markers in MM after treatment with GSK2857916	• sBCMA levels, BCMA receptor occupancy and cell death markers in subjects with MM.
• To explore relationships of GSK2857916 plasma concentrations/exposure with pharmacodynamics (PD), safety and clinical activity	• Relationship between receptor occupancy, tumor cell death markers, sBCMA and GSK2857916 plasma PK parameters; • Relationship between safety/clinical activity (e.g. ORR) and GSK2857916 PK parameters
• To characterize the relationship between clinical response and other biologic tumor characteristics (DNA, protein analysis)	• [redacted]
• To investigate the relationship between genetic variants in the host and response to ~~GSK2867916~~ study medicine, or susceptibility, severity and progression of disease.	• Relationship between host genetic variation and response to ~~GSK2867916~~ study medicine or susceptibility, severity and progression of disease
• To explore the effect of GSK2857916 on bone pain/fatigue and HRQoL in subjects with relapsed/refractory MM (Part 2)	• Changes from baseline in bone pain/fatigue and analgesic use as measured by the eDiary • Interviews with subjects to further characterize changes in bone pain/fatigue and impacts on HRQoL

Rationale for Change: update the objectives and endpoints to align with the other hematologic malignancies to be restricted to lymphomas and the inclusion of fatigue and bone pain quality of life instruments in Part 2 multiple myeloma cohort. Also allow for genetic research to include analyses of genetic variants with disease susceptibility, severity, and progression of disease.

STUDY DESIGN: This study is an open-label, dose escalation Phase I FTIH study to determine the RP2 dosing regimen of GSK2857916. The recommended dose and schedule will be selected based on the safety, pharmacokinetic (PK), and pharmacodynamic (PD) profiles observed after administering the study drug to subjects with multiple myeloma (MM). The study will consist of two parts and will enroll approximately 80-95 subjects. The Part 1 dose escalation phase will characterize the safety and tolerability of respective dosing regimen for GSK2857916 utilizing the model based on the Neuenschwander continual reassessment method (N-CRM). Initially, GSK2857916 will be administered via 60 min intravenous (IV) infusion once every three weeks (21 days = 1 cycle). After a MTD or recommended phase 2 dose (RP2D) has been established on the once every three weeks schedule, the safety, tolerability, and PK of once-weekly dosing of GSK2857916 for three consecutive weeks with 1 week rest (28 days = 1 cycle) may be explored in an additional cohort(s). Part 2 will explore the safety, tolerability, PK, PD, and clinical activity of the RP2 dose of GSK2857916 identified in Part 1. Subjects with MM (n=40) and lymphomas expressing BCMA (n=10) will be enrolled inexpansion cohort in Part 2. Futility analyses will be performed on the MM cohort after approximately 15, 22, 30 subjects have been enrolled. Sparse PK sampling will be collected to further characterize GSK2857916 exposures for the selected dose schedule. Although not required for MM, subjects with ~~other BCMA-positive hematologic malignancies~~ lymphomas will be enrolled in Part 2 based upon the detection of positive BCMA staining of tumor cells in a prospective immunohistochemistry screening assay performed at a central laboratory.

NUMBER OF SUBJECTS: Approximately 80-95 subjects will be enrolled.

Up to 30 subjects with relapsed/refractory MM will be enrolled in Part 1, Schedule 1; Schedule 2, if explored, will enroll up to 15 additional subjects in Part 1.

Up to 40 subjects with relapsed/refractory MM and up to 10 subjects with ~~other hematologic malignancies~~ lymphomas expressing BCMA will be enrolled in Part 2.

INCLUSION CRITERIA

2. Male or female, 18 years or older (at the time consent is obtained) ~~and must have a body weight of at least 45 kg (99 lb).~~

4. **Part 2/Other BCMA positive Hematologic Malignancies cohort:**

   a. Subject with one of the following ~~hematologic malignancies~~ lymphomas: ~~Waldenstrom's Macroglobulinemia (WM),~~ Diffuse Large B-cell Lymphoma (DLBCL), or ~~and chronic lymphocytic leukemia (CLL)~~ follicular lymphoma (FL) that exhibits positive BCMA expression on tumor cells as determined by a central laboratory using a validated IHC assay. ~~The BCMA positivity is defined as having approximately 60% of tumor cells staining positive for BCMA, and the staining intensity must be ≥2 on IHC scale 0-3.~~

Eligible subjects with BCMA positive malignancies lymphomas must also fulfill the prior treatment requirements as follows:

b. DLBCL ~~and WM~~: at least 2 prior lines of systemic therapy containing at least one line of chemo-immunotherapy with anti-CD20 antibody, and either has undergone stem cell transplant or is considered transplant ineligible.

c. FL: at least 2 prior lines of systemic therapy ~~CLL: at least 2 prior lines of systemic therapies, and who are refractory to fludarabine, and failed (or are ineligible) for rituximab, ofatumumab and bendamustine.~~

6. Adequate organ system functions as defined in Table below:

~~General~~	
~~Ca~~	~~≤1.1xULN~~

Exclusion Criteria:

1. Systemic anti-~~myeloma~~ tumor therapy within 14 days, or plasmapheresis within 7 days prior to the first dose of study drug.

17. Subjects with positive test for hepatitis C (HCV) infection are excluded regardless of viral load. If hepatitis C antibody test is positive, a confirmatory polymerase chain reaction (PCR) or recombinant immunoblot assay (RIBA) test should be performed. If the PCR or RIBA test is negative, subject is eligible for this trial.

Rationale for Changes: removed the minimum weight in Inclusion criterion 2 as that was required for the lowest doses administered during dose escalation. The Part 2 hematologic malignancies were refined to include DLBCL and FL only based on the frequency of BCMA expression and the intensity of expression observed.

PHARMACOKINETIC/ PHARMACODYNAMIC ASSESSMENT(S):

In the Part 2 dose expansion phase in subjects with other BCMA positive lymphomas ~~hematologic malignancies~~ PK samples will be taken for both GSK2587916 and cys-mcMMAF measurement according to the Time and Events Tables in Section 7.17.1.

CLINICAL ACTIVITY ASSESSMENT:

For ~~Other Hematologic Malignancies~~ Lymphomas: the percentage of subjects with confirmed CR, PR, as described in the Revised Response Criteria for Malignant Lymphoma (Appendix 2). ~~and for CLL Appendix 3).~~

TRANSLATIONAL RESEARCH

[redacted]

Leukocyte population will be characterized and may be correlated with clinical outcome.

~~Pharmacogenetic~~ A genetics samples will be collected in Part 2 and may be used to investigate variability in response that may be attributable to host genetic variation, if it emerges during this clinical study or a series of clinical studies of GSK2857916 (Appendix 7). Further, the genetic sample may be used to investigate the relationship between genetic variation and disease (susceptibility, severity or progression).

[redacted]

PATIENT REPORTED OUTCOMES

Part 2/MM cohort: changes in symptoms and health-related quality of life (HRQoL) will be assessed with the use of the Bone Pain/Fatigue diary.

Rationale for Change: inclusion of HRQoL assessments in Part 2 MM cohort will provide a preliminary assessement of patient report for affects of GSK2857916 on bone pain and fatigue.

3. Section 1.1 Background

BCMA is expressed in various B-cell malignancies, including MM. The expression levels in MM vary from patient to patient, but our studies demonstrate that all patients tested express detectable levels of BCMA protein on their tumor cells. BCMA expression varies between MM patients and GlaxoSmithKline (GSK) studies have shown that in samples taken from MM patients (N=45), 31% have low expression, 38% moderate expression and 31% high expression of BCMA as detected by immunohistochemistry (IHC). BCMA was also analyzed by flow cytometry in tumor cells from 48 MM patients which aligned well with IHC results. In addition, other B-cell malignancies including Follicular Lymphoma (FL) [Basso, 2005; GSKin-house data], Diffuse Large B-Cell Lymphoma (DLBCL), Large B-Cell Lymphoma (LBCL), Chronic Lymphocytic Leukemia (CLL) and Waldenstrom's Macroglobulinemia (WM) [Montes-Moreno, 2012] [Elsawa, 2006] [Endo, 2007] were reported to express BCMA at varying frequencies;DLBCL and FL were among the B-cell hematologic malignancies exhibiting the highest frequency of BCMA expression.

A soluble form of BCMA has also been reported [Sanchez, 2012]. Higher amounts of this soluble form were found in supernatants isolated from cultures of MM-containing peripheral blood and bone marrow mononuclear cells compared to normal cells. Moreover, soluble BCMA (sBCMA) was higher in the sera of MM patients (n=209) compared to sera from age-matched, healthy controls (n=40; $P < 0.0001$). Measurement of serum levels of BCMA was conducted by immunoassay to confirm the prevalence and level of sBCMA expression in MM. Soluble BCMA is present in serum at a median concentration of 9.28 ng/mL (range 6.10-14.09 ng/mL) in healthy volunteers (N=38) and is elevated in the serum of MM patients (N = 44) to median of 148.64 ng/mL (range 2.40-1062.48 ng/mL).

~~In addition, other B-cell malignancies including Diffuse Large B-Cell Lymphoma (DLBCL), Large B-Cell Lymphoma (LBCL), Chronic Lymphocytic Leukemia (CLL) and Waldenstrom's Macroglobulinemia (WM) [Montes-Moreno, 2012] [Elsawa, 2006] [Endo, 2007] have been reported to express BCMA at varying frequencies.~~

The restricted normal tissue expression profile of BCMA, along with its upregulation and survival function in MM and other BCMA-positive cancers makes it an attractive target for a therapeutic antibody with direct cell killing activity.

4. Section 1.3.2 Benefit Assessment

Currently there is no clinical evidence that treatment with GSK2857916 will result in any benefit to subjects. However, based on data from non clinical studies there is a possibility that GSK2857916 might reduce tumor burden in subjects with MM and ~~other~~ BCMA positive ~~hematologic malignancies~~ lymphomas.

5. Section 1.3.3 Overall Benefit:Risk Conclusion

Overall, due to ~~lack of any~~ limited clinical experience with GSK2857916 benefit/risk cannot be asseesesed at this time. The safety of subject is the primary objective of this study and adequate monitoring and guidance for dose reductions/stopping criteria are provided in the protocol to minimize risks associated with exposure to GSK2857916.

6. Objectives(s), Endpoint(s) and Hypothesis

Objective	Endpoint
Primary	
• To determine safety, tolerability, maximum tolerated dose (MTD), and recommended phase (RP2) dose and schedule of GSK2857916 administered	• Adverse events (AE) and changes in clinical signs and laboratory parameters
Secondary	
• To evaluate the pharmacokinetic (PK) profile of GSK2857916 and the breakdown product cys-mcMMAF) after intravenous (IV) single and repeat dose administration in subjects with relapsed/refractory MM and BCMA expressing lymphomas	• GSK2857916 and cys-mcMMAF PK parameters following IV single and repeat dose administration during dose escalation as data permit (e.g., AUCs Cmax, tmax, CL, V_{SS}, t½ [single dose], Cmax and Ctrough [repeat dose]). GSK2857916 population PK parameters in expansion cohorts at the RP2 dose (e.g. clearance (CL), volume of distribution (Vd)), and relevant covariates which may influence exposure (e.g. age, weight, or disease-related covariates e.g. BCMA expression)

Objective	Endpoint
• To assess anti-drug antibody (ADA)formation after IV single and repeat dose administration of GSK2857916	• ADA incidence and titers after single and repeat IV dosing of GSK2857916
• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM and BCMA expressing lymphomas	• Clinical activity measured as Overall Response Rate (ORR) which is defined as follows: o For MM: the percentage of subjects achieving confirmed partial response or better (≥PR) o In addition, the percentage of subjects with minimal response (MR) will be assessed for clinical benefit rate (CBR) (Appendix 1) o For ~~Other HematologicMalignancies~~ Lymphomas: the percentage of subjects achieving PR or better (≥PR) (Appendix 2 ~~and Appendix 3)~~
Exploratory	
• To evaluate PD markers in MM after treatment with GSK2857916	• sBCMA levels, BCMA receptor occupancy and cell death markers in subjects with MM.
• To explore relationships of GSK2857916 plasma concentrations/exposure with pharmacodynamics (PD), safety and clinical activity	• Relationship between receptor occupancy, tumor cell death markers, sBCMA and GSK2857916 plasma PK parameters; • Relationship between safety/clinical activity (e.g. ORR) and GSK2857916 PK parameters
• To characterize the relationship between clinical response and other biologic tumor characteristics (DNA, protein analysis)	• [redacted]
• To investigate the relationship between genetic variants in the host and response to ~~GSK2857916~~ study medicine or susceptibility, severity and	• Relationship between host genetic variation and response to ~~GSK2857916~~ study medicine or susceptibility, severity and progression of disease

Objective	Endpoint
progression of disease	
• To explore the effect of GSK2857916 on bone pain/fatigue and HRQoL in subjects with relapsed/refractory MM	• Changes from baseline in bone pain/fatigue and analgesic use as measured by the eDiary • Interviews with subjects to further characterize changes in bone pain/fatigue and impacts on HRQoL

7. Section 3.1 Discussion of Study Design

This is a First Time in Human (FTIH), open-label, dose escalation trial consisting of two parts: a Part 1 dose escalation phase and a Part 2 expansion phase for safety, and clinical activity testing (Table 3 and Section 3.2). The study will enroll a total of approximately 80-95 subjects with relapsed/refractory MM or other BCMA-expressing ~~hematologic malignancies~~lymphomas. The maximum dose to be administered in this trial will not exceed 5 mg/kg.

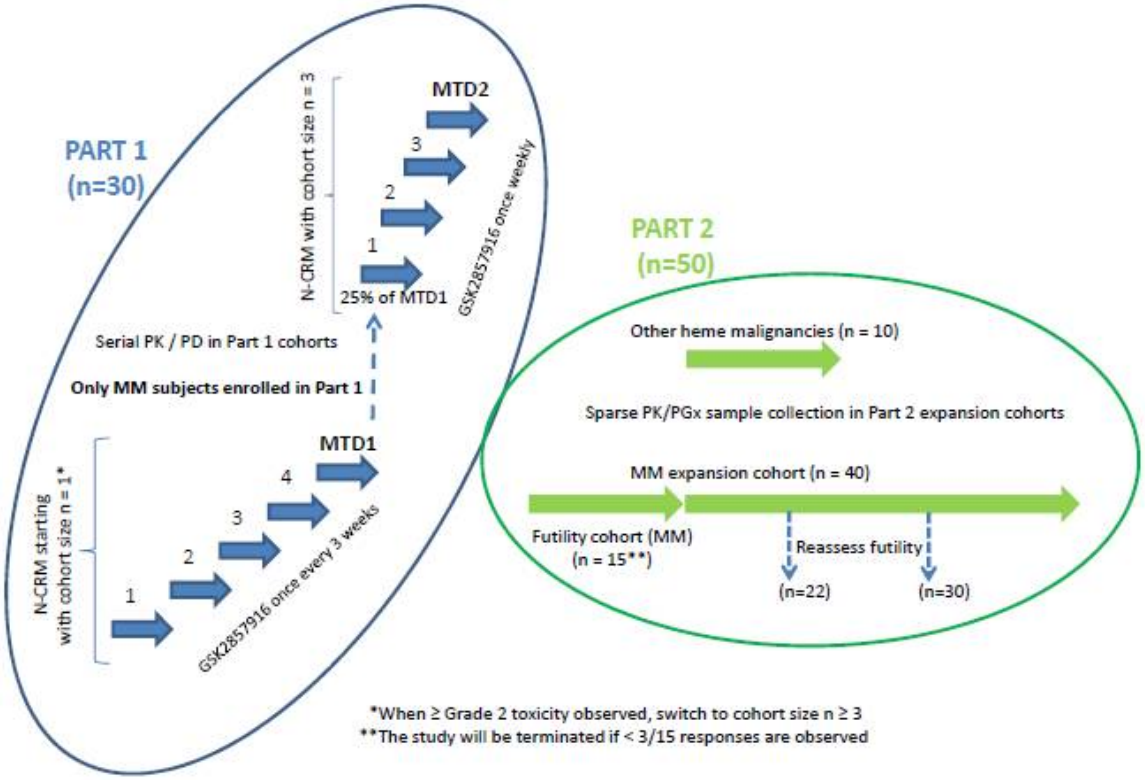
Part 1: Dose-escalation cohorts will characterize the safety, tolerability, PK, and PD of GSK2857916 given on a once every 21 days or a once weekly schedule. Only subjects with MM will be enrolled in Part 1 based on an N-CRM dose escalation model until MTD(s) or RP2D is/are established on an appropriate schedule(s).

Once an MTD1 or RP2D has been established on the once every 21-day (Schedule 1), the safety, tolerability, PK, and PD of once-weekly dosing (Schedule 2) of GSK2857916 may be explored as an additional cohort(s).

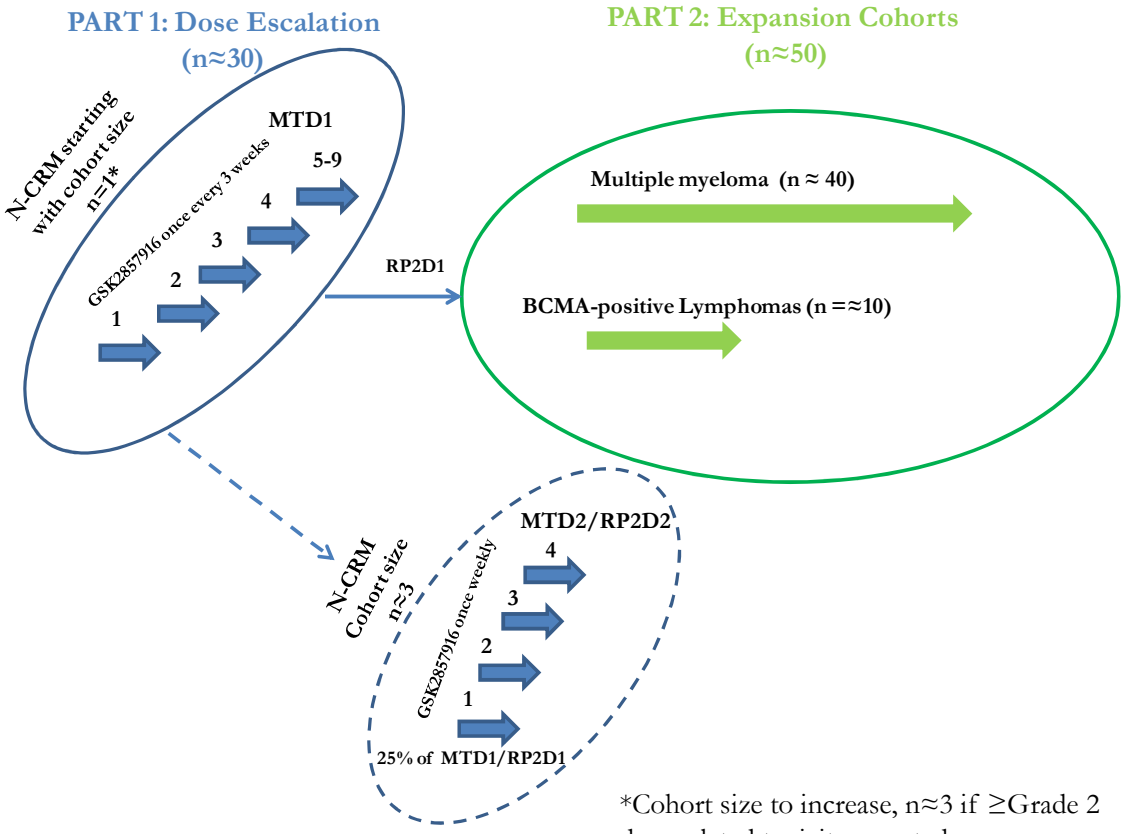
A smaller cohort of subjects with ~~other~~ BCMA positive ~~hematologic malignancies~~ lymphomas (up to 10 subjects) will be enrolled based upon prospective detection of positive BCMA tumor cell expression as determined by a central laboratory using a validated IHC ~~screening~~ assay. ~~BCMA staining intensity of ≥2 (on scale 0-3) in approximately ≥60% tumor cells vs. control slides will be assessed for study entry at a central laboratory). Enrollment into the cohort for other hematologic malignancies will be initiated once the safety of the selected dose and schedule have been confirmed in the MM expansion cohort (i.e. when at least >15 MM patients have enrolled and been evaluated for at least one cycle).~~

8. Section 3.2 Study Schematic

Old Figure



New Figure



*Cohort size to increase, n≈3 if ≥Grade 2 drug related toxicity reported

Abbreviations: MTD=maximum tolerated dose; N-CRM= Neuenschwander Continual Reassessment Method; RP2D=recommended phase 2 dose

1. Part 2 to initiate after once every 3 week recommended dose is determined
2. Dose escalation with once weekly schedule may commence in parallel to Part 2 expansion

Rationale for Changes: the figure was revised to illustrate that Part 2 will be initiated after a recommended dose for the once every three weeks schedule is determined. Dose escalation of the once weekly schedule if investigated may commence at any time during the conduct of the study.

9. Section 3.3 Part 1: Dose-Escalation Phase

After the MTD1 or RP2D is established for the once every three weeks Schedule 1, once weekly dosing of GSK2857916 (Schedule 2) may be evaluated prior to, or in parallel with the expansion phase as described in Section 3.3.2. A weekly dosing regimen may be chosen for further evaluation if toxicity is felt to be related to Cmax and that equivalent or greater exposures in terms of AUC can be safely achieved with weekly dosing compared with the once every 3weeks dosing regimen.

10. Section 3.3.1.2.1 Planned Dose Levels

Prior to the start of the study, projected dose levels on Schedule 1 (in mg/kg) are 0.03, 0.06, 0.12, 0.24, 0.48, 0.96, 1.92, 2.8, 3.6, and 4.5 mg/kg; actual dose levels will be determined by N-CRM (Neuenschwander-Continuous Reassessment Method). Additional doses and schedules may be explored based on emerging safety, PK, and PD data. The maximum dose to be administered in this trial will not exceed 5 mg/kg.

11. Section 3.3.1.2.3 Bayesian Prior

A graphical presentation of the initial prior is displayed in Figure 1. Doses are the projected doses. Actual doses used during the conduct of the trial may vary. An intermediate prior will be derived based on the initial prior by FACTS (Version 2.3 or higher) from Tessella. The final prior is determined based on the intermediate prior and all available data.

12. Section 3.3.2 Dose Escalation on Schedule 2 (GSK2857916 administered once weekly x3, 1 week rest; 28 days = 1 cycle)

- The once weekly dosing cohorts may be explored prior to, or in parallel with, enrollment to the expansion cohorts (Part 2).
- Depending on emerging safety signals, the proposed weekly starting dose will be 25% of MTD1 or RP2D1. If the initial dose of 25% of MTD1 or RP2D1 is not tolerated, dose escalation on the weekly schedule will be terminated and enrollment into Schedule 2 will be closed. If the starting dose is tolerated, escalation on the weekly schedule will continue at increments of ≤30% and will follow the N-CRM procedure until MTD2 or RP2D2 is reached.

13. Section 3.4 RP2 Dose and Administration Schedule Selection for Part 2

This lower dose level, or an intermediate dose considered the BED, may be tested as the RP2 dose for further evaluation in Part 2. Part 2 may start enrolling once Part 1 has completed enrollment of Schedule 1 (once every three weeks) and after the preliminary

PK and relevant PD data have been analyzed. ~~The schedule selection for Part 2 (weekly vs. once every 3 weeks vs. an intermediate schedule) will be based on the information collected following administration of GSK2857916 on the respective schedules evaluated in Part 1~~. The once weekly schedule may be explored prior to or in parallel with the expansion cohorts. Data considered will include, but not be limited to, relationships between safety and exposure, the PK profiles, as well as any emerging PD information, and early signs of clinical activity observed for each schedule evaluated in Part 1. If the once weekly schedule is explored prior to initiating Part 2, the chosen dosing regimen would need to provide evidence of the following in order to be the preferred schedule in Part 2: a better safety and tolerability profile at an equivalent or higher dose, or greater clinical activity, or a more desirable PK profile (i.e. no evidence of target-mediated disposition observed over the dosing interval). A preference might be given to the weekly schedule if at MTD1, the receptor occupancy levels are considered sub-optimal and/or saturation of soluble sBCMA is not maintained long enough on the every 3 weeks dosing schedule.

Part 2: Expansion Cohort:

(Note: For details on scheduled procedures in subjects given GSK2857916 in Part 2, refer to Time and Events Tables Section 7.1.2. The Time and Events Table for GSK2857916 administered to MM subjects on Schedule 1 is represented in Section 7.1.2.1, and the Time and Events Table for GSK2857916 administered to MM subjects on Schedule 2 is represented in Section 7.1.2.2. Refer to Time and Events Tables Section 7.1.2.3 and Section 7.1.2.4 for GSK2857916 administered to subjects with ~~other hematologic malignancies~~ lymphomas on Schedule 1 or Schedule 2, respectively).

Once the RP2 dose and schedule have been selected, expansion cohorts will be enrolled in order to better characterize the safety profile of the selected dose and schedule.

- The Part 2 expansion will enroll up to 50 subjects as summarized below:
    - Multiple Myeloma cohort (up to 40 subjects)- no prospective screening of BCMA is required for enrollment
        - Futility analyses based on ORR will take place after approximately 15, 22 and 30 subjects have been evaluated for response. Full details can be found in Section 13.6.2
        - BCMA expression data and retrospective analysis will be performed on samples collected in the MM population
        - PRO will be collected via eDiary in the MM population in Part 2 only
        - ~~Other~~BCMA positive lymphomas (defined as BCMA positive staining by IHC) ~~hematologic malignancies~~ (up to 10 subjects) – prospective screening of BCMA expression is required for enrollment

14. Section 3.6.1 Rationale for Study; Section 3.6.2 Rationale for Populations

This study will assess the safety, PK, PD and the therapeutic potential of GSK2857916 in subjects with MM and ~~other hematologic malignancies~~ lymphomas that express BCMA.

This study will determine if adequate target engagement of BCMA receptors translates into clinical benefit for subjects with MM and ~~other~~BCMA positive ~~hematologic malignancies~~lymphomas.

Subjects with lymphomas that exhibit BCMA expression have been selected as an exploratory cohort in this FTIH study; the frequency of BCMA expression in lymphomas is lower than that observed in MM, therefore prospective selection is required.

The target population for this study includes subjects with relapsed/refractory MM to establish the dose and characterize safety, PK and PD of GSK2857916. Subjects with ~~other~~BCMA expressing ~~hematologic malignancies~~ lymphomas will also be allowed on study after prospective screening by IHC demonstrates that BCMA is expressed on tumor cells. Potential subjects with ~~other~~ B-cell ~~malignancies~~lymphomas who will be tested for BCMA expression prior to study entry include, subjects with the following diseases: Diffuse Large B-Cell Lymphoma (DLBCL), , Folicullar Lymphoma (FL), ~~Chronic Lymphocytic Leukemia (CLL) and Waldenstrom's Macroglobulinemia who have~~ that have ~~failed~~progressed after 2 prior lines of systemic therapy for a given disease.

15. Section 3.6.4 Rationale for Endpoints

Markers showing significant correlation between baseline levels and clinical outcome may have predictive value and maybe further explored for utility in patient selection in future trials.

Anti-tumor activity will be explored to evaluate the potential for clinical benefit from GSK2857916 treatment. In addition, patient report outcomes will also be studied in Part 2 (MM subjects only)

Rationale for Changes: QoL measurements were included as exploratory endpoints In Part 2 multiple myeloma cohort in order to provide preliminary analyses of affects of treatment on fatigue and bone pain. Additionally, biomarker analyses in the BMA117159 may uncover markers that may be implemented for patient selection in future trials.

16. Section 3.9.8. Ocular Toxicity and Stopping Criteria
All subjects will be advised to use prednisolone phosphate 1% or dexamethasone 0.1% eye drop 4 times a day (QID) for 4 days starting 1 day prior to each dose. Additional use of lubrication eye drops (artificial tears) QID PRN throughout the trial is recommended, especially if subject develops any ocular symptoms. Subjects who develop Grade 3 ocular or corneal toxicity will be allowed to continue study

treatment after resolution to ≤ Grade 1; each case will be discussed individually between the investigator and the Medical Monitor. Subjects who develop ≥ Grade ~~3~~ 4 ocular or corneal toxicity will be permanently removed from study. Refer to Section 3.10.2 for futher guidance.

Rationale for Change: The requirement to permanently discontinue GSK2857916 for Grade 3 ocular toxicity was revised to require study treatment to be interrupted and to allow for these events to be discussed with regard to type of event and the duration of time for the event to resolve to Grade 1 or to baseline. If study treatment resumes, the dose will be reduced by at least 25% of the dose that was administered when event occurred.

17. Section 3.10.2 Predicted Toxicities and Proposed Dose Adjustments/Stopping Criteria

Grade 2 Ocular Toxicity: Further treatment ~~Permanently discontinue treatment~~ with GSK2857916 only allowed after discussion and in agreement with medical monitor ~~and withdraw subject from study~~

Grade 3

- First occurrence
  - Consult ophthalmologist immediately
  - Interrupt treatment with GSK2857916
  - Once resolved to ≤ G1: Restart treatment with GSK2857916 at 25% -50% dose reduction if the investigator and Medical Monitor agree that the potential benefits outweigh the risks
- Second occurrence
  - Consult ophthalmologist immediately

Permanently discontinue treatment with GSK2857916

~~Grade 3/~~ Grade 4

Rationale for Changes: The requirement to permanently discontinue GSK2857916 for Grade 3 ocular toxicity was revised to require study treatment to be interrupted and to allow for these events to be discussed with regard to type of event and the duration of time for the event to resolve to Grade 1 or to baseline. If study treatment resumes, the dose will be reduced by at least 25% of the dose that was administered when event occurred.

18. Section 4.1 Description of Investigation Product; Section 4.2

The lot number indicated on the label refers to labelled lot number; the batch Lot#132373860 may not be provided on the label.

Before use, thaw each vial of GSK2857916 for Infusion, 20mg/mL, 1.5mL for up to 4 hours under refrigerated conditions (2-8°C), protected from light. Following thawing, gently swirl the vial to ensure uniformity. GSK2857916 should be diluted in normal saline (0.9%) to no more than 2 mg/mL and no less than 0.2 mg/mL. Refer to the Study Procedures Manual (SPM) for further details on preparation of GSK2857916.

The dosing solution of GSK2857916 can be held under refrigerated conditions (2-8°C), for up to 24 hours (**NOTE**: For centers in Canada up to 8 hours only) or 4 hours at ambient temperature (diluted drug product in bag) from a stability perspective, but should be used as soon as possible as the product does not contain an antimicrobial preservative.

Rationale for Change: Clarify that lot number 132373860 refers to manufacturer batch lot number.

19. Section 5.1 Number of Subjects

An adequate number of subjects will be enrolled into the study to establish the recommended dose(s) for further study. It is estimated that approximately 30 subjects will be enrolled into Part 1, Schedule 1 (dose-escalation) of the study. Up to 40 subjects with MM and up to 10 subjects with ~~other~~ BCMA positive ~~hematologic malignancies~~ lymphomas (~50 subjects total) will be enrolled in Part 2 (expansion cohort). The number of subjects in the expansion cohort has been estimated based on expected variable expression of BCMA in those subjects (about 1/3 low, 1/3 medium, 1/3 high expression; approximately 13 subjects/group). The level of BCMA expression in a given subject is expected to impact target-mediated clearance, which as a consequence might be reflected in the PK/PD variability and safety profile of individual subjects. In addition, the sample size of 40 subjects in the MM cohort will allow for assessment of early signals of clinical activity and its relationship (if any) to variable target expression levels. A total of approximately 80 subjects will be enrolled in the study.If Part 1, Schedule 2 (once weekly schedule) is explored, up to 15 additional subjects will be enrolled; then a total of approximately 95 subjects will be enrolled in the study.

Rationale for Change: The number of subjects in dose escalation is increased to allow for the weekly dosing schedule to be investigated as the estimated 30 subjects in dose escalation were allocated to the Q3week schedule.

20. Section 5.2.1 Inclusion Criteria

2. Male or female, 18 years or older (at the time consent is obtained) ~~and must have a body weight of at least 45 kg (99 lb).~~

4. **Part 2/Other BCMA positive Hematologic Malignancies cohort:**

   d. Subject with one of the following ~~hematologic malignancies~~ lymphomas: ~~Waldenstrom's Macroglobulinemia (WM),~~ Diffuse Large B-cell Lymphoma (DLBCL), or ~~and chronic lymphocytic leukemia (CLL)~~ follicular lymphoma (FL) that exhibits positive BCMA expression on tumor cells as determined by a central laboratory using a validated IHC assay. ~~The BCMA positivity is defined as having approximately 60% of tumor cells staining positive for BCMA, and the staining intensity must be ≥2 on IHC scale 0-3.~~

Eligible subjects with BCMA positive malignancies lymphomas must also fulfill the prior treatment requirements as follows:

   e.DLBCL ~~and WM~~: at least 2 prior lines of systemic therapy containing at least one line of chemo-immunotherapy with anti-CD20 antibody, and either has undergone stem cell transplant or is considered transplant ineligible.

f. FL: at least 2 prior lines of systemic therapy ~~CLL: at least 2 prior lines of systemic therapies, and who are refractory to fludarabine, and failed (or are ineligible) for rituximab, ofatumumab and bendamustine.~~

6. Adequate organ system functions as defined in Table below:

~~General~~	
~~Ca~~	~~≤1.1xULN~~

21. Section 5.2.2 Exclusion Criteria

1. Systemic anti-~~myeloma~~ tumor therapy within 14 days, or plasmapheresis within 7 days prior to the first dose of study drug.

17. Subjects with positive test for hepatitis C (HCV) infection are excluded regardless of viral load. If hepatitis C antibody test is positive, a confirmatory polymerase chain reaction (PCR) or recombinant immunoblot assay (RIBA) test should be performed. If the PCR or RIBA test is negative, subject is eligible for this trial.

Rationale for Changes: removed the minimum weight in Inclusion criterion 2 as that was required for the lowest doses administered during dose escalation. The Part 2 hematologic malignancies were refined to include DLBCL and FL only based on the frequency of BCMA expression and the intensity of expression observed.

22. Section 7 Study Assessments and Procedures and Time and Events Tables

The maximum amount of blood collected in Screening and during the first Cycle 1 from each subject for the Dose Escalation and for the Dose Expansion is no more than ~~158~~ 162 ml of blood (See Appendix 10).

The following changes were made to all Time and Events Tables in Section 7.1.1.2, and all Tables in Section 7.1.2; selected changes made to Table in Section 7.1.1.1 are indicated in parentheses:

- End of Study visit was clarified as End of Study Treatment visit (also Section 7.1.1.1)
- Study Assessment: CK-MB ~~(local),~~ Troponin; BM biopsy for disease assessment ~~and BCMA expression (IHC)~~; Peripheral blood (flow for TBNK and intracellular cytokine testing). For Tables referring to Part 2 study assessment: ~~PGx~~Genetics sample. For Part 2 MM cohort study assessments: e-Diary and Exit Interview and all associated visits.
- Serum for ADA, Plasma for [redacted] and whole blood for TBNK analysis at screening was moved to Day 1 cycle 1 pre-dose.
- C1 D8 visit added for whole blood for TBNK/intracellular cytokine analyses
- Footnotes (note footnote number provided as the number may not be consistent across all tables:
    - Screening examination to include BCVA (best-corrected visual acuity), slit lamp examination (with special focus on cornea), intraocular pressure,

dilated fundoscopic examination may be performed within 21 days prior to first dose. (also Section 7.1.1.1)
- On-study exams to include BCVA (best-corrected visual acuity) and slit lamp examination (with special focus on cornea); window for exams is up to 3 days prior to dosing. (also Section 7.1.1.1)
- Description of change: BNP and CK-MB can be measured by central or local lab. (also Section 7.1.1.1)
- On days where ECG timepoints align with PK sampling timepoints, ECGs should be performed prior to PK samples being drawn (PK sample should be taken at the exact nominal time). (also Section 7.1.1.1)
- At Screening, LVEF may be performed within 30 days prior to first dose. All ECHOs indicated on dosing days may be performed up to 5 days before dosing. All ECHOs to be done locally and sent to GSK for central imaging storage. (also Section 7.1.1.1)
- Description of change for TBNK blood sample: no longer collected at Screening but collected C1D1 predose.
- For Part 2 Tables: 26. Informed consent for optional ~~PGx (pharmacogenetics)~~ genetics research should be obtained before collecting a sample.
- For Part 2 MM: e-Diary to be completed at screening, then Days 1-7, 8, 15 of each treatment cycle. Upon implementation of the e-Diary, these assessments will be required. Exit interview to be performed within 14 days of end of study visit.

Rationale for Changes: Ocular and ECHOs assessments window increased at Screening for ocular and on dosing days to allow flexibility for scheduling of these assessments prior to dosing. Baseline blood samples for ADA and biomarker tests moved to C1D1 to only collect those samples from eligible subjects who receive study treatment. Allow for BNP and CK-MB testing by central laboratory as not all site local laboratories perform these tests.

23. Section 7.2 Baseline Assessments

Baseline (Screening) assessments obtained will include:

- Imaging studies (extramedullary disease for MM if indicated,or CT/PET scan for ~~other hematologic malignancies~~lymphomas)
- For MM: [redacted]
- ~~Peripheral blood (flow for TBNK)~~
- For MM: BM biopsy for disease assessment ~~and BCMA expression (IHC)~~
- For ~~other hematologic malignancies~~ Lymphomas: archival or fresh tissue evaluation for BCMA expression

24. Section 7.3.6 Laboratory Assessments

Table 15:

Hepatitis C (Hep C antibody -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay or a validated HCV PCR viral test should be reflexively performed **on the same sample** to confirm the result)

25. Section 7.3.8 Immunogenicity

Serum samples for determination of anti-GSK2857916 antibodies will be taken from all subjects in this study at the time-points specified in the Time and Events Tables in Section 7.1. Timing of the assessments may be adjusted based on emerging data. Details of sample preparation, storage and analysis will be provided in the SPM.

Samples will be analyzed for the presence of anti-GSK2857916 antibodies by a validated electrochemiluminescent immunoassay. All samples will be tested in ascreening assay, and positive samples will be further characterized for specificity and antibody titers.

Rationale for Change: Included section to describe specifics on the immunogenicity assessments.

26. Section 7.5 Translation Research

Section 7.5.1:

Whole blood count of mononuclear cells (PBMC) and their activation status and intracellular cytokine profile.

Section 7.5.1.4:

Clusters of markers circulating in the ~~plasma~~blood have been found to correlate with tumor pathway activation. A broad panel of cytokines/chemokines will be evaluated at various timepoints as outlined in the Time and Events table (Section 7.1) and correlated with clinical outcome to treatment with GSK2857916. In addition to measuring total cytokine levels in serum, activated lymphocytes and monocytes producing involved in the cytokine production will be determined via intracellular cytokine assay.

Section 7.5.2:

[redacted]

27. Section 7.6 ~~Pharmacogenetics~~ Genetics

An important exploratory objective of the clinical study is ~~pharmacogenetic (PGx)~~ genetic research. Participation in PGx is optional but all subjects who are eligible for the clinical study and are enrolled into part 2 (expansion cohort) will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for ~~PGx~~ genetic research.

~~Subjects who provide consent will have a blood sample taken for analysis. The presence/absence of genetic variations in host DNA will be analyzed to determine their relationship with response (safety, tolerability, pharmacokinetics (PK) and efficacy) to treatment with GSK2857916.~~

Information regarding ~~PGx research~~ genetic research is included in Appendix 7. In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the ~~PGx~~ genetic research described in Appendix 7 unless otherwise indicated. Where required by regulatory authorities, approval of the ~~PGx~~genetic assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the ~~PGx~~ genetic assessments is being deferred and the study, except for ~~PGx~~genetic assessments, can be initiated. When ~~PGx~~genetic assessments will not be approved, then the approval for the rest of the study will clearly.

Rationale for Change: Also allow for genetic research to include analyses of genetic variants with disease susceptibility, severity, and progression of disease.

28. Section 7.8 Health Outcomes:Quality of Life

Health Outcomes Endpoints

The patient reported outcome (PRO) instruments that will be used are the Bone Pain/Fatigue Assessment via an e-Diary. In the Part 2 multiple myeloma cohort, the implementation of this assessment will occur upon availability of the instruments.

Bone Pain/Fatigue Assessment: Bone pain burden will be measured by e-Diary consisting of certain modified questions from Brief Pain Inventory-Short Form (BPI-SF) which assesses pain intensity and the interference of pain with daily life [Atkinson, 2010; Cleeland, 1994] and Brief Fatigue Inventory (BFI) [Cleeland, 2010]. The BPI-SF is one of the most frequently used pain assessments [Cleeland, 2009] and has been used in various disease areas, including cancer pain and neuropathic pain [Daut, 1982; McDowell 1996]. The questionnaire has demonstrated both reliability and validity across cultures and languages [Cleeland, 1994]. The BFI has also been used in cancer patients to measure fatigue [Mendoza, 1999].

Bone pain and fatigue burden will be measured by an e-Diary consisting of 7 short questions, including 4 questions to assess pain intensity (severity) and one question to assess the interference of pain with daily life activities. The items ask about pain experienced within the last 24 hours. It also includes 2 questions on use of pain medication. Fatigue will be measured by 2 short questions – one to assess the level of fatigue in the past 24 hours and the second to assess the interference of fatigue with general activity. Data from this e-Diary will be used to understand and characterize pain/fatigue experience and explore time to potential pain relief while controlling for the use of pain medication.

It is expected that the improvement in intensity of bone pain/fatigue and the impact of bone pain/fatigue on general activity will take place within the first 8 cycles of treatment and the self-completion of the e-Diary during this period will accurately capture the changes in bone pain/fatigue.

Upon availability of the Bone Pain/Fatigue Assessment e-Diary, MM subjects will self-complete the assessments at the following times:

- Starting 2-4 days prior to Cycle 1 Day 1
- Daily from Day 1 through Day 8 for each Cycle to time of study treatment discontinuation
- Day 15 of each Cycle to time of study treatment discontinuation
- Study Treatment Discontinuation visit

Samples of the paper versions of the PRO questionnaires are included in SPM.

29. Section 13. 7.2.3 Immunogenicity Analyses (Section 14 deleted)

For each subject, the results and titers of anti-GSK2857916 binding antibodies will be listed for each assessment time point. The frequency and percentage of subjects with positive and negative results will be summarized for each assessment time and overall for each subject by dose cohort.

Rationale for Change: Section was placed in Safety Analyes sections.

30. Section 13.7.8 Health Outcome Analyses

Symptom imact and HRQoL will be assessed using the e-Diary. Chage from baseline and change over time will be summarized.

31. The calculation of scores and methods to deal with missing data will be provided in the RAP. **Section 16.3 Appenidx 3: Response Definition after Treatment for Patients with CLL**

Entire section deleted as CLL is no longer a hematologic malignancy under investigator in Part 2.

32. Section 16.6 Appendix 7 ~~Pharmacogenetics (PGx)~~ Genetics

Updated with current template language which allows for analyses of genetic variants with disease susceptibility, severity, and progression of disease.

16.11.5. Amendment 5

Amendment 5 applies to all sites in Canada, United Kingdom, and United States

The protocol Amendment 4 dated 05 May 2016 (applied to all sites) is replaced by Amendment 5 with the effective date of DD MMM YYYY.

Summary of Changes

The following protocol changes have been implemented to include additional follow up of multiple myeloma subjects for ocular exams (for those whose corneal signs or symptoms have not resolved), additional patient reported outcome instruments, addition of time-to-event endpoints as exploratory objectives. Subjects who have completed treatment or the 3 month follow up visit (end of study) prior to amendment 5 will be reconsented for further follow up and survival status. Other administrative changes are also included

Original text displayed as strikethrough indicates replaced or removed text. New text is displayed as underline. Revisions within tables is either presented with the entire table or displayed as text (i.e., for larger tables). Typos or minor word changes are not presented.

List of Changes

1. List of Abbreviations

CI	Confidence interval
DOR	Duration of response
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire - 25
OSDI	Ocular Surface Disease Index
PFS	Progression-free survival
SD	Stable disease
TTP	Time to progression

Rationale for Change: Updated to include new abbreviations used within the amendment.

2. Protocol Synopsis
STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES

Objective	Endpoint
Exploratory	
• To explore the effect of GSK2857916 on ~~bone pain~~ symptoms (including bone pain, fatigue and visual symptoms) and impacts on ~~and~~ HRQoL in subjects with relapsed/refractory MM (Part 2)	• Changes from baseline in bone pain/fatigue and analgesic use as measured by the eDiary • Interviews with subjects to further characterize changes in ~~bone pain~~ symptoms (including bone pain, fatigue and visual symptoms) and impacts on HRQoL
• To explore changes in visual symptoms and function following discontinuation of treatment with GSK2857916	• Changes in visual symptoms and impacts as measured by the OSDI and NEI-VFQ-25 following treatment discontinuation • Follow-up telephone interviews conducted to further understand subjects experience with visual symptoms and changes in symptoms and related impacts following treatment discontinuation
• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM in terms of time-to-event (TTE) endpoints (Part 2 MM)	• Time to progression (TTP), defined as: the time from first dose until the earliest date of PD per International Multiple Myeloma Working Group (IMWG), or death due to PD. • Duration of response (DOR), defined as: the time from first documented evidence of PR or better; until the time when disease progression (PD) is documented per IMWG; or death due to PD occurs in participants who achieve a response, i.e. confirmed PR or better. • Time to response (TTR), defined as: the time between the date of first dose and the first documented evidence of response (PR or better). • Progression-free survival (PFS), defined as: the time from first dose until the earliest date of disease progression (PD) per IMWG, or death due to any cause.

Rationale for Change: To align with changes made in the main Objectives and Endpoints table.

PATIENT REPORTED OUTCOMES

Part 2/MM cohort: changes in symptoms and health-related quality of life (HRQoL) will be assessed with the use of the Bone Pain/Fatigue diary.

Changes in visual symptoms and impacts with the use of the OSDI and NEI-VFQ-25

Rationale for Change: Questionnaires added to obtain additional patient information on the resolution of corneal events after the treatment period.

STATISTICAL METHODS

Part1: After each dosing cohort, the N-CRM will be used to recommend the next dose level based on observed dose-limiting toxicities (DLTs). The dose escalation decisions will be based on this recommendation as well as the totality of the safety, pharmacokinetic, and pharmacodynamic data.

Part 2: Futility analyses will be performed on the MM cohort after approximately 15, 22, and 30 evaluable subjects have been enrolled. The methodology utilized is based on the predictive probability of success if enrollment continues to 40 subjects [Lee, 2008].

Clinical Activity

The exact 95% confidence interval (CI) for overall response rate (ORR) and clinical benefit rate (CBR) will be provided. Subjects with unknown or missing response will be treated as non-responders, i.e., these subjects will be included in the denominator when calculating percentages of response.

For the Part 2 MM population, additional exploratory time-to-event (TTE) endpoint will include TTP, DOR, TTR, and PFS, as data permits. For all the TTE endpoints listed above, median TTE with 95% CI will be estimated employing the Kaplan-Meier method as data permits. A Kaplan-Meier survival curve will be generated. The number and percentage of subjects who had the event or were censored will also be reported.

Adverse Events: Adverse events will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment.

The incidence of deaths and the primary cause of death will be summarized.

Clinical Laboratory Evaluation: The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel.

Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit or worst-case post baseline, as appropriate.

The worst-case- toxicity grade in hematology and chemistry result during the treatment will be summarized. Shift tables from baseline to the worst toxicity grade during treatment will be provided for each laboratory analyte.

Other Safety Measures: Data for vital signs, electrocardiograms (ECGs), and echocardiograms (ECHOs) will be summarized. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and

maximum. For categorical variables, the summaries will include frequencies and corresponding percentages.

Rationale for Change: To further clarify and define statistical analyses.

3. Section 2.0 Objective(S), Endpoint(S) And Hypothesis

Objective	Endpoint
Exploratory	
• To explore the effect of GSK2857916 on ~~bone pain/fatigue~~symptoms (including bone pain, fatigue and visual symptoms) and impacts on ~~and~~ HRQoL in subjects with relapsed/refractory MM (Part 2)	• Changes from baseline in bone pain/fatigue and analgesic use as measured by the eDiary • Interviews with subjects to further characterize changes in ~~bone pain~~ symptoms (including bone pain, fatigue and visual symptoms) and impacts on HRQoL
• To explore changes in visual symptoms and function following discontinuation of treatment with GSK2857916 (Part 2 MM)	• Changes in visual symptoms and impacts as measured by the OSDI and NEI-VFQ-25 following treatment discontinuation • Follow-up telephone interviews conducted to further understand subjects experience with visual symptoms and changes in symptoms and related impacts following treatment discontinuation
• To explore the initial anti-tumor activity of GSK2857916 in subjects with relapsed/refractory MM in terms of time-to-event (TTE) endpoints (Part 2 MM)	• Time to progression (TTP), defined as: the time from first dose until the earliest date of PD per International Multiple Myeloma Working Group (IMWG), or death due to PD. • Duration of response (DOR), defined as: the time from first documented evidence of PR or better; until the time when disease progression (PD) is documented per IMWG; or death due to PD occurs in subjects who achieve a response, i.e. confirmed PR or better. • Time to response (TTR), defined as: the time between the date of first dose and the first documented evidence of response (PR or better). • Progression-free survival (PFS), defined as: the time from first dose until the earliest date of disease progression (PD) per IMWG, or death due to any cause.

Rationale for Change: To further define and clarify the objectives of the QoL questionnaire and interviews; to implement follow up questionnaires for patients experiencing ocular symptoms post dosing; to further define and clarify statistical endpoints.

4. Section 5.2.1. Inclusion Criteria

Table 14 Adequate Organ System Function

System	Laboratory Values
Total bilirubin	≤1.5~~25~~ X ULN (isolated bilirubin ~~>~~≤1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

Rationale for Change: Clarification as per Note to file submitted to all sites.

5. Section 6.2 Subject Completion Criteria

For Part 1 (dose-escalation phase), a completed subject is one who has completed at least 1 cycle of study treatment and an End of Study Visit without events causing them to withdraw or discontinue from the study for reasons listed in Section 6.3 For Part 2 (expansion cohort), a completed subject is one who has received at least one dose of study treatment without events causing them to withdraw or discontinue study treatment for reasons listed in Section 6.3 and completed an End of Study Visit.

A participant will be considered to have completed the study if he or she has received at least one dose of the study treatment and, has died before the end of the study, has not been lost to follow-up, or has not withdrawn consent from study participation.

Rationale for Change: To clarify subject study completion criteria.

6. Section 7.1.2.1. Every 3 Weeks Dosing Schedule for Multiple Myeloma

	Time and Events Table for Full Study (Cycle = 21 days)								
Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment[34]**	**Monthly Follow up[35]**	~~**3-Month Off-study Follow-up**~~
Ocular Exam	X[3]				X[4]	At the start of each cycle[4]	X[4]	X[35]	
Pregnancy Test	X[10]					At the start of cycles 5[10], 9[10], 13[10]	X[10]	X[11]	~~X[11]~~
OSDI							X[31]	X[31]	
NEI-VFQ-25[31]							X[31]	X[31]	
Exit Interview							X[3132]		
Follow-up Interview								X[33]	
Survival Status								X[29]	~~X[29]~~
Subsequent Treatment								X[29]	~~X[29]~~

4. On-study exams, to include BCVA (best-corrected visual acuity) and slit lamp examination (with special focus on cornea); window for exams is up to 3 days prior to dosing. In the event that a subject has a dose delay due to a non-ocular toxicity and an ocular exam has been performed for that cycle, a repeat ocular exam 3 days prior to dosing may be omitted if the participant did not have corneal signs on the previous exam and does not have any new corneal symptoms.

5. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +10 minutes, +30 minutes (±~~5~~15 min) after SOI, EOI, and 1 hour post EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +30 minutes after SOI, and EOI. **On days where vital sign timepoints align with PK sampling timepoints, vital signs should be assessed prior to PK samples being drawn.**

29. All participants should be followed for survival for 1 year from last subject last dose. ~~Record subject's survival status~~ and whether subsequent treatment for disease was given. Subject does not need to come in for visit. Participants who have completed treatment or the 3 month follow up visit (end of study) prior to amendment 5 will be reconsented for further follow up and survival status.

31. OSDI and NEI-VFQ-25 to be administered during end of study treatment visit. Additional assessments for subjects who are experiencing corneal symptoms to be completed via telephone on a monthly basis for up to 1 year, or until resolution of symptoms (whichever comes first) during the follow-up period.

32. Exit interview to be performed within ~~14~~ 21 days of end of study visit

33. Optional follow-up telephone interview interview to explore visual symptoms and changes in symptoms and related impacts following treatment discontinuation be performed at least 6 months following the End of Study Treatment visit. This interview would only be for those subjects who experienced corneal symptoms during treatment and consent to participate.

34. End of treatment visit should be performed within 30 days (+7 days) after the last dose or prior to the start of new anti-cancer treatment, whichever is earlier. In cases where more than 30 days (+7 days) have elapsed from the date of the subject's last dose due to dosing delays and a subsequent decision to take the subject off treatment, the end of study treatment visit should be scheduled as soon as possible to allow the final assessments to be performed at the earliest date.

35. Participants with corneal signs or symptoms at the end of study treatment visit should be monitored by ophthalmic exam once a every month after the last study dose until deemed clinically stable by an eye care professional complete resolution or for 12 months (whichever comes first). Corneal exams to include BCVA and slit lamp examination (with

special focus on cornea). Participants who have completed treatment or the 3 month follow up visit (end of study) will be reconsented for further additional ophthalmology follow up.

~~36. The 3-month off study follow up visit should be performed within 3 months (90 days) (±7 days) after the last dose. The subject is not required to come to the clinic for this visit (except when a pregnancy test is required). The assessments can be performed by phone calls, email or other means of communication.~~

Rationale for Change: To implement monthly follow ups and clarify administrative inconsistencies in the Time and Events Table. Increase the window for performing the Exit Interview in order to allow additional flexibility in scheduling.

7. Section 7.1.2.3. Dose Expansion Every 3 Weeks Dosing Schedule for Lymphomas

Study Assessments[1]	**Screen[2]**	**Day 1 C1**	**Day 8 C1**	**Day 15 C1**	**Day 1 C2**	**D1 of C3-C16**	**End of Study Treatment[26]**	**Monthly Follow up[27]**	~~**3-Month Off-study Follow-up**~~
Ocular Exam	X[3]				X[4]	At the start of each cycle[4]	X[4]	X[27]	
Pregnancy Test	X[10]					At the start of cycles 5[10], 9[10], 13[10]	X[10]	X[11]	~~X[11]~~
Survival Status								X[25]	~~X[25]~~
Subsequent Treatment								X[25]	~~X[25]~~

4. On-study exams to include BCVA (best-corrected visual acuity) and slit lamp examination (with special focus on cornea); window for exams is up to 3 days prior to dosing. In the event that a subject has a dose delay due to a non-ocular toxicity and an ocular exam has been performed for that cycle, a repeat ocular exam 3 days prior to dosing may be omitted if the participant did not have corneal signs on the previous exam and does not have any new corneal symptoms. ~~investigator determines that it is not medically necessary and the subject does not have any new ocular symptoms.~~

5. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +10 minutes, +30 minutes (± ~~5~~15 min) after SOI, EOI, and 1 hour post EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +30 minutes after SOI, and EOI. **On days where vital sign timepoints align with PK sampling timepoints, vital signs should be assessed prior to PK samples being drawn.**

21. CT/PET or CT scans from within 21 days prior to first dose are acceptable. CT scans are acceptable at all restaging assessments unless CR is suspected, in which case a PET/CT scan will be obtained to confirm CR.

25. Record subject's survival status until last subject completes or discontinues treatment and whether subsequent treatment for disease was given. Subject does not need to come in for visit.

26. End of treatment visit should be performed within 30 days (+7 days) after the last dose or prior to the start of new anti-cancer treatment, whichever is earlier. In cases where more than 30 days (+7 days) have elapsed from the date of the subject's last dose due to dosing delays and a subsequent decision to take the subject off treatment, the end of study treatment visit should be scheduled as soon as possible to allow the final assessments to be performed at the earliest date.

27. All participants should be followed for survival for 1 year from last dose. Participants with corneal signs or symptoms at the end of study treatment visit should be monitored by ophthalmic exam every month after the last study

dose until deemed clinically stable by an eye care professional or for 12 months (whichever comes first). Corneal exams to include BCVA and slit lamp examination (with special focus on cornea).

Rationale for Change: To align with additional follow ups implemented in the MM cohort.

8. Section 7.1.2.4. Dose Expansion Weekly Dosing Schedule for Lymphomas

4. On-study exams, to include BCVA (best-corrected visual acuity) and slit lamp examination (with special focus on cornea); window for exams is up to 3 days prior to dosing. In the event that a subject has a dose delay due to a non-ocular toxicity and an ocular exam has been performed for that cycle, a repeat ocular exam 3 days prior to dosing may be omitted if the participant did not have corneal signs on the previous exam and does not have any new corneal symptoms.

Rationale for Change: To clarify that ocular exams do not need to occur if already completed in that cycle if there are no corneal signs and symptoms after the treatment period.

9. Section 7.3 Safety Evaluations

Section 7.3.6. Ocular Exam
An ocular exam to include BCVA (best-corrected visual acquity), slit lamp examination (with special focus on the cornea), intraocular pressure, and dilated funduscopic examination will be conducted for all subjects at screening. Additional exams will be performed as specified in the Time and Events Tables (Section 7.1) during the treatment period and at monthly follow-up visits as clinically indicated.

Rationale for Change: To add further follow up visits to assess corneal signs and symptoms after the treatment period.

Section 7.3.10. Visual Functioning Questionnaires
The impact of potential ocular toxicity on function and health-related quality of life will be assessed with the use of 2 visual function questionnaires: the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), and the Ocular Surface Disease Index (OSDI). Subjects will complete the self-administered versions of these two assessments during their End of Study Treatment visit. Subjects who are unable to complete the questionnaire on their own due to blurry vision, and require assistance can have the questionnaire read to them by an interviewer. If the questionnaires are administrated by an Interviewer, then the questionnaire should be read to the subjects verbatim, and subject responses should be recorded directly without any interpretation.

Subjects who continue to experience visual symptoms after discontinuation of study treatment will complete additional interviewer-administered assessments via telephone on a monthly basis for up to 1 year during the Follow-up period or until the resolution of their visual symptoms, whichever comes first.

Section 7.3.10. 1. National Eye Institute Visual Functioning Questionnaire-25
The NEI-VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question [Mangione., 2001]. The NEIVFQ-25 generates the following vision-targeted sub-scales: global vision rating difficulty with near vision activities; difficulty with distance vision activities; limitations in social functioning due to vision; role limitations due to vision; dependency on others due to vision; mental health symptoms due to vision; driving difficulties; limitations with peripheral vision, limitations with color vision; and corneal pain. In addition to the core items from the NEI-VFQ-25, select questions from the Appendix of Optional Additional Questions will be administered to further assess the impact of corneal events on visual function.

Section 7.3.10. 2. Ocular Surface Disease Index Questionnaire
The Ocular Surface Disease Index (OSDI) is a 12-item questionnaire designed to assess both the frequency of dry eye symptoms and their impact on vision-related functioning [Schiffman, 2000]. The OSDI has demonstrated good reliability, validity, sensitivity, and specificity, and can be used as a complement to other clinical and subjective measures of dry eye disease by providing a quantifiable assessment of dry eye symptom frequency and the impact of these symptoms on vision-related functioning.

Rationale for Change: To implement questionnaires at the end of study treatment visit and during follow-up for patients experiencing ocular symptoms, in order to assess changes in visual symptoms and function following discontinuation of treatment with GSK2857916.

10. Section 7.8. Health Outcomes: Quality of Life
~~**Health Outcomes Endpoints**~~**Section 7.8.1. Bone Pain/Fatigue Assessment (eDiary)**

Section 7.8.2. Exit Interview and Follow-up Interview

To further evaluate disease and treatment related symptoms (including bone pain and fatigue, and visual symptoms) and associated impacts on function and health-related quality-of-life, participants in the Part 2 multiple myeloma cohort will complete an optional Exit Interview conducted via telephone. The interview will be conducted by a trained interviewer and will be audio recorded for transcription and analysis. The telephone interview should be conducted within 21 days following completion of the End of Study Treatment visit.

Subjects who have experienced ocular symptoms during the treatment period will have the option to also consent to participate in an optional Follow-up interview. The Follow-up interview will be conducted by a trained interview via telephone at least 6 months following the End of Study Treatment visit. The Follow-up interview will focus on visual symptoms experienced by the subject, impacts on function and health-related quality-of-life and management and resolution of their visual symptoms following discontinuation of study treatment.

Both the Exit Interview and Follow-Up interview are optional, and the failure to complete either interview will not constitute a protocol deviation.

Rationale for Change: To implement follow up interviews for patients who experienced corneal symptoms to further understand changes in visual symptoms and function experienced during the study and following discontinuation of treatment with GSK2857916.

11. Section 13.4.1 Analysis Populations
The '**All Treated**' population is defined as all eligible subjects who receive at least 1dose of study treatment. An incorrect treatment schedule or drug administration or an early termination of treatment will not result in exclusion of subjects from this population. Subjects with major deviations from the eligibility criteria affecting safety or from the treatment schedule at the DLT evaluation period (1 cycle: 21 days for once every 3 weeks schedule or 28 days for once weekly schedule) for reasons other than toxicity may be presented in separate tables/listings.

The 'All Treated' population will further be classified in the following sub-populations.

- Part 1: all Part 1 subjects of All Treated population. Note, subjects in Part 1 are exclusively multiple myeloma patients.
- Part 2 MM: all Part 2 MM subjects of All Treated population
- All Treated MM: comprise of subjects in Part 1 and Part 2 MM.
- Part 2 NHL: all Part 2 lymphoma subjects of All Treated population.

The '**DLT Evaluable**' population in Part 1 enables an appropriate evaluation of study DLTs. It is defined as those subjects fulfilling the 'All Treated' population criteria, and having met the following adequate exposure criteria:

- For Schedule 1 (once every 3 weeks dosing) subjects received a complete infusion in cycle 1.

- For Schedule 2 (once weekly dosing for 3 consecutive weeks, 1 week rest) subjects receive three infusions, two of which must be complete infusions, in cycle 1. (as increases up to ≤30% are implemented between cohorts, less than 2 complete infusions would result in a total dose closer to the previous dose investigated).

Any subject in the "All Treated" population who experiences a DLT, as defined in Section 3.3.3 will also be included in the DLT evaluable population regardless of exposure.

The ~~'PK'~~'**All Evaluable (MM)'** population is a subset of the 'All Treated' population, who were initially treated at RP2D in the expansion cohort and have at least two post-baseline disease assessments or they have progressed or died or permanently discontinued treatment. This population will be used for the futility analysis of the MM expansion cohort.

The '**Pharmacokinetic (PK) Population**' is defined as those subjects in the "All Treated" population from whom at least one PK sample was obtained, analyzed, and was measurable.

The '**Pharmacodynamic (PD) Population**' is defined as those subjects in the "All Treated" population from whom at least one PD sample was obtained, analyzed, and was measurable.

Rationale for Change: To further clarify and define statistical populations.

12. Section 13.6 Interim Analysis, Section 13.6.2 Part 2

Subjects will not be replaced when they discontinue the study due to: Progression (symptomatic or otherwise), toxicity related to GSK2857916, or lack of efficacy.

Other administrative interim analyses may be performed if needed.

Final analysis of MM population may be performed separately, before the NHL cohort completes the study.

Rationale for Change: To further define timeframe for MM population in relation to NHL cohort.

13. Section 13.7.2.2 Adverse Events

Characteristics (e.g. number of occurrences, action taken, grade, etc) of the following AEs of ~~special~~ clinical interest will be summarized separately: corneal events, hematologic toxicities (including but not limited to thrombocytopenia and neutropenia), infusion related reaction etc. Details will be provided in the RAP.

The incidence of deaths and the primary cause of death will be summarized.

Rationale for Change: To further define AEs of clinical interest.

14. Section 13.7.2.3 Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) (Version 4.0). The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel. ~~Laboratory test results outside the reference ranges that do not have associated NCI-CTCAE criteria will be summarized using proportions.~~

Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit or worst-case post baseline, as appropriate.

The worst-case- toxicity grade in hematology and chemistry result during the treatment will be summarized. Shift tables from baseline to the worst toxicity grade during treatment will be provided for each laboratory analyte.

Further details will be provided in the Reporting and Analysis Plan (RAP).

Rationale for Change: To further define analysis of clinical laboratory evaluations.

15. Section 13.7.2.5 Other Safety Measures

Data for vital signs, electrocardiograms (ECGs), and echocardiograms (ECHOs) will be summarized based on predetermined criteria identified to be of potential clinical concern (PCI). For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. Further details will be provided in the Reporting and Analysis Plan (RAP).

Rationale for Change: To further define analysis of ECGs and ECHOs.

16. Section 13.7.7 Clinical Activity Analyses

~~Clinical activity will be calculated based on Overall Response Rate (ORR), which is defined as the percentage of subjects with confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) as assessed by 2011 recommendation of the International Myeloma Working Group (IMWG) Panel I (Appendix 1). Clinical benefit rate may be considered in addition to ORR.~~

Overall Response Rate (ORR) is one of the secondary endpoints to measure clinical activity of this study.

For multiple myeloma, ORR is defined as the percentage of subjects with a confirmed PR or better (i.e. PR, VGPR, CR and sCR), according to the IMWG Panel I (Appendix 1), as assessed by the investigator. In addition, Clinical Benefit rate (CBR) is defined as the percentage of subjects with a confirmed MR or better (i.e.MR, PR, VGPR, CR and sCR), according to the IMWG Panel I (Appendix 1), as assessed by the investigator.

The number and percentage of subjects in the following response categories will be presented sCR (stringent complete response), (complete response) CR, (very good partial response) VGPR, (partial response) PR, (minimal response) MR, stable disease (SD), progressive disease (PD), and not evaluable (NE)

sCR+CR+VGPR+PR for overall response (ORR)

sCR+CR+VGPR+PR+MR for Clinical Benefit rate (CBR)

The corresponding exact 95% CI for ORR and Clinical Benefit Rate (CBR) will also be provided. Subjects with unknown or missing response will be treated as non-responders, i.e., these subjects will be included in the denominator when calculating percentages of response.

For lymphomas, ORR is ~~Clinical activity for lymphomas will be calculated based on ORR~~ defined as the percentage of subjects with confirmed CR, or PR, as described in the Revised Response Criteria for Malignant Lymphoma (Appendix 2). ORR for lymphomas will be summarized in a similar way as multiple myeloma. The corresponding exact 95% CI for ORR will also be provided.

Other exploratory time-to-event (TTE) endpoints related to clinical activity for Part 2 (MM) of this study are TTP, DOR, TTR, and PFS.

Time to disease progression (TTP) is defined as the time from first dose until the earliest date of PD per IMWG, or death due to PD. Determination of dates of TTP event and dates for censoring will be described in the RAP. **Duration of response (DOR)** is defined as the time from first documented evidence of PR or better until disease progression (PD) per IMWG, or death due to PD among subjects who achieve a response

(i.e. confirmed PR or better). Responders without disease progression will be censored at the censoring time point for TTP.

Time to response (TTR) is defined as the time between the date of first dose and the first documented evidence of response (PR or better). Subjects without confirmed response (PR or better) will be censored at the censoring date for TTP.

Progression-free survival (PFS) is defined as the time from first dose until the earliest date of disease progression (PD) per IMWG, or death due to any cause. Determination of dates of PFS event and dates for censoring will be described in the RAP.

For all the TTE endpoints described above, median TTE with 95% CI will be estimated employing the Kaplan-Meier method as data permits. A Kaplan-Meier survival curve will be generated. The number and percentage of subjects who had the event or were censored will also be reported.

Exploratory subgroup analyses may be performed for all endpoints to measure clinical activity as appropriate.

Overall Survival: The protocol is amended to collect long-term survival data (i.e. up to 1 year after last subject completes or discontinues treatment). Subjects who are already completed the study will be contacted to request re-consent.

If all the patients (who were alive at the time of study completion) can be re-consented, OS landmark analysis may be performed at 9 and 12 months using Kaplan-Meier analysis as data permits.

Otherwise, only descriptive analysis (number and % of deaths and lost to follow-up) will be performed.

Rationale for Change: To further define efficacy analysis and add analysis of time-to-event endpoints.

17. Section 13.7.8. Health Outcome Analyses

Symptom impact and HRQoL will be assessed using the e-Diary. Change from baseline and change over time will be summarized.

The calculation of scores and methods to deal with missing data will be provided in the RAP.

Visual Functioning Questionnaire (NEI VFQ-25 and OSDI): Data will be collected from end of treatment (EOT) visit as baseline. Additional data will be collected in follow-up visits on a monthly basis for subjects with ongoing corneal events or signs at EOT for 1 year or until resolution, whichever occurs first. These data will not be collected for subjects who already completed the treatment. Calculation of scores will be provided in the RAP. Due to limited number of on-treatment subjects at the time of protocol amendment, only a listing by subject will be generated.

Rationale for Change: To further clarify how the NEI-VFQ-25 and OSDI will be reported.

18. Section 15. References

Mangione, C. M., P. P. Lee, P. R. Gutierrez, K. Spritzer, S. Berry, R. D. Hays and I. National Eye Institute Visual Function Questionnaire Field Test. "Development of the 25-item National Eye Institute Visual Function Questionnaire." Arch Ophthalmol 2001; 119(7): 1050-1058.

Schiffman, R. M., M. D. Christianson, G. Jacobsen, J. D. Hirsch and B. L. Reis. "Reliability and validity of the Ocular Surface Disease Index." Arch Ophthalmol 2000; 118(5): 615-621.

Rationale for Change: References added to align with updates to questionnaires.