5. SINGLE DOSE TOXICITY

Table 5.1 Belantamab mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period

Study Type: Single-Dose Toxicity

Report Title: GSK2857916A: Single-dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period

Test Article: Belantamab mafodotin
Batch No.: [redacted]

Species/Strain: Rat/Crl:WI(Han)

Duration of Dosing: 1 day
Duration of Off-dose: 14 days

Study No.: R29778

Initial Age: 10 weeks

Route/Frequency: Bolus intravenous injection via tail vein, single dose

Date of First Dose: 25 January 2012

Vehicle/Formulation: Phosphate buffered saline pH7.4/Solution

Study in Compliance with GLP: No

GSK Document Number: 2012N134122

Data Collected: Toxicokinetics, immunogenicity, clinical observations, body weight, food consumption, hematology, clinical chemistry, urinalysis, liver weights, macroscopic and microscopic pathology, electron microscopy

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Numbers of Animals: Main	4	4	4	4	4	4	4	4
Off-dose	4	0	4	4	4	0	4	4
Toxicokinetic	0	3	3	3	0	3	3	3
GSK2857916 (ADC concentration)								
AUC(0-t) (µg.h/mL)	NA	19300	48300	88800	NA	19100	49900	117000
Cmax (µg/mL)	NA	242	626	2160	NA	249	695	2150
Noteworthy Findings								
Unscheduled Deaths	0	0	0	2	0	0	0	0
	One off-dose male previously given 100 mg/kg was killed on Day 9R due to adverse clinical observations (limited use of hindlimbs, swollen left hindlimb, unsteady gait, subdued behaviour, pinched flanks and piloerect coat). A further off-dose male previously given 100 mg/kg was killed on Day 10R due to poor condition (multiple small wet/open wounds over whole body, bruising on the right ear and scabs over the whole body; plus subdued behaviour, irregular/laboured breathing, swollen right hindlimb, hyperreactivity to sound and piloerect coat). After clinical observations of swollen hindlimbs were noted in further males previously given 100 mg/kg, all the remaining males previously given 100mg/kg (off-dose and toxicokinetic animals) were killed on Day 11R.							
Clinical Observations	Scabs were noted on Day 8 in 2 terminal males given 100 mg/kg; from Day 10R in 2 off-dose males previously given 100 mg/kg; from Day 12R in all off-dose females previously given 100 mg/kg; and from Day 19R in one off-dose male previously given 30 mg/kg. Piloerect coat was noted from Day 7 onwards in males given 100 mg/kg. One off-dose female previously given 100 mg/kg showed reddening of the skin on the tail from Day 10R, a raised area on the skin in the lumbar region on Days 12 to 15R and 21R, and thinning hair on the dorsal abdomen from Day 17R.							

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Immunogenicity	One rat given 30 mg/kg and 7 rats given 100 mg/kg were potentially positive for anti-GSK2857916 antibodies.							
Body Weight Change (g)								
Days 1 to 4	7.60	7.20	8.70	-13.29	1.93	4.70	5.33	-6.97
Days 4 to 7	6.10	7.70	7.26	-4.05	1.44	0.00	0.21	5.72
Days 1 to 7	13.70	14.90	15.96	-17.34	3.37	4.70	5.54	-1.25
Days 8R to 21R	41.15	-	29.80	-	15.08	-	11.33	30.47
Food Consumption (g/rat/day)								
Days 1 to 7	24.6	24.1	24.9	13.4	15.0	15.2	15.6	12.8
Days 8R to 11R	25.0	-	24.5	14.1	-	-	-	-
Days 8R to 21R	24.6	-	22.4	-	15.9	-	16.3	15.8
Hematology								
Total reticulocyte count ($x10^9$/L)								
Day 8	188.10	174.45	209.40	8.48	228.60	268.03	227.50	3.90
Day 11R	-	-	-	48.85	-	-	-	-
Day 22R	210.20	-	471.75	-	195.05	-	316.33	567.60
High reticulocyte count ($x10^9$/L)								
Day 8	26.3	22.8	41.5	3.5	63.0	52.7	65.8	0.5
Day 11R	-	-	-	8.5	-	-	-	-
Day 22R	41.7	-	176.5	-	42.8	-	90.0	285.3
Medium reticulocyte count ($x10^9$/L)								
Day 8	69.0	67.3	87.0	1.5	77.7	102.7	82.0	1.3
Day 11R	-	-	-	13.5	-	-	-	-
Day 22R	81.0	-	150.5	-	63.3	-	107.7	131.5
Low reticulocyte count ($x10^9$/L)								
Day 8	93.0	84.5	81.0	3.5	88.0	113.3	79.8	2.0
Day 11R	-	-	-	26.5	-	-	-	-
Day 22R	87.7	-	144.5	-	89.0	-	118.3	150.8

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Platelets (x10^9/L)								
Day 8	902.3	1042.8	1823.8	945.5	1035.3	1052.0	1665.5	1310.8
Day 11R	-	-	-	1032.5	-	-	-	-
Day 22R	926.7	-	922.8	-	886.8	-	836.3	932.8
Hemoglobin (g/L)								
Day 8	148.3	145.5	139.3	135.3	134.7	142.0	133.0	123.5
Day 11R	-	-	-	124.0	-	-	-	-
Day 22R	141.3	-	140.5	-	142.5	-	137.7	109.8
Hematocrit (L/L)								
Day 8	0.445	0.430	0.415	0.400	0.407	0.420	0.398	0.372
Day 11R	-	-	-	0.365	-	-	-	-
Day 22R	0.437	-	0.433	-	0.440	-	0.423	0.338
Red cell count (x10^{12}/L)								
Day 8	8.593	8.480	8.148	8.010	7.637	8.320	7.785	7.248
Day 11R	-	-	-	7.720	-	-	-	-
Day 22R	8.673	-	9.008	-	8.250	-	8.323	6.260
Red cell distribution width (%)								
Day 8	10.65	10.60	11.60	12.83	10.90	10.97	11.88	12.00
Day 11R	-	-	-	13.90	-	-	-	-
Day 22R	11.90	-	13.90	-	10.70	-	11.47	16.95
White blood cell count (x10^9/L)								
Day 8	5.940	6.115	5.750	3.578	4.280	4.587	4.955	2.190
Day 11R	-	-	-	7.435	-	-	-	-
Day 22R	7.077	-	11.295	-	4.735	-	7.547	4.423
Neutrophil count (x10^9/L)								
Day 8	0.945	1.733	1.338	0.583	0.660	1.183	1.040	0.113
Day 11R	-	-	-	4.290	-	-	-	-
Day 22R	1.190	-	2.060	-	0.585	-	1.443	1.428

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Lymphocyte count (x10⁹/L)								
Day 8	4.692	4.063	4.118	2.868	3.423	3.127	3.688	2.013
Day 11R	-	-	-	3.040	-	-	-	-
Day 22R	5.510	-	8.618	-	3.905	-	5.750	2.688
Monocyte count (x10⁹/L)								
Day 8	0.165	0.200	0.123	0.040	0.100	0.177	0.100	0.015
Day 11R	-	-	-	0.115	-	-	-	-
Day 22R	0.240	-	0.393	-	0.148	-	0.203	0.198
Eosinophil count (x10⁹/L)								
Day 8	0.083	0.078	0.115	0.035	0.063	0.063	0.080	0.023
Day 11R	-	-	-	0.000	-	-	-	-
Day 22R	0.083	-	0.118	-	0.063	-	0.080	0.073
Basophil count (x10⁹/L)								
Day 8	0.028	0.023	0.020	0.028	0.017	0.023	0.020	0.008
Day 11R	-	-	-	0.000	-	-	-	-
Day 22R	0.020	-	0.063	-	0.018	-	0.033	0.013
Myeloid:erythroid ratio								
Day 8	-	-	-	11.350	-	-	-	6.145
Day 11R	-	-	-	11.180	-	-	-	-
Day 22R	0.998	-	1.308	-	1.200	-	1.130	1.210
Megakaryocyte count								
Day 8	-	-	-	8.25	-	-	-	8.50
Day 11R	-	-	-	5.50	-	-	-	-
Day 22R	6.00	-	5.50	-	5.00	-	3.00	10.50

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Clinical Chemistry								
Plasma alanine aminotransferase (U/L)								
Day 8	26.8	32.0	33.0	139.5	22.3	41.0	38.0	87.5
Day 11R	-	-	-	112.0	-	-	-	-
Day 22R	36.8	-	51.5	-	24.0	-	29.5	59.5
Plasma glutamate dehydrogenase (U/L)								
Day 8	5.53	8.35	10.58	47.25	4.63	10.70	6.95	27.48
Day 11R	-	-	-	41.35	-	-	-	-
Day 22R	16.10	-	24.10	-	5.95	-	5.98	11.40
Plasma aspartate aminotransferase (U/L)								
Day 8	73.8	78.5	118.8	755.8	61.5	62.5	100.5	689.3
Day 11R	-	-	-	646.0	-	-	-	-
Day 22R	70.8	-	124.8	-	63.8	-	95.8	215.3
Plasma alkaline phosphatase (U/L)								
Day 8	254.5	272.0	335.8	1337.0	120.8	112.8	173.8	479.5
Day 11R	-	-	-	1559.0	-	-	-	-
Day 22R	231.8	-	274.8	-	88.0	-	128.5	199.8
Plasma total bilirubin (µmol/L)								
Day 8	0.58	0.50	0.40	0.30	0.88	0.75	0.60	0.35
Day 11R	-	-	-	0.30	-	-	-	-
Day 22R	0.80	-	0.95	-	0.83	-	0.93	0.38
Plasma albumin (g/L)								
Day 8	34.8	34.5	35.3	31.8	38.8	39.5	37.3	35.5
Day 11R	-	-	-	32.5	-	-	-	-
Day 22R	34.0	-	37.3	-	40.3	-	41.0	39.5

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Plasma total protein (g/L)								
Day 8	57.8	58.0	62.5	69.5	61.5	62.3	62.8	71.5
Day 11R	-	-	-	71.0	-	-	-	-
Day 22R	57.5	-	65.0	-	63.3	-	66.3	72.3
Plasma urea (mmol/L)								
Day 8	6.43	6.00	6.13	6.23	6.73	6.65	7.20	8.28
Day 11R	-	-	-	4.25	-	-	-	-
Day 22R	5.93	-	5.88	-	7.90	-	7.20	8.23
Plasma creatinine (µmol/L)								
Day 8	29.0	23.5	27.0	39.5	31.5	28.5	31.3	40.5
Day 11R	-	-	-	32.5	-	-	-	-
Day 22R	28.3	-	27.0	-	31.8	-	33.0	34.8
Plasma calcium (mmol/L)								
Day 8	2.505	2.490	2.618	2.750	2.480	2.528	2.530	2.743
Day 11R	-	-	-	2.790	-	-	-	-
Day 22R	2.463	-	2.625	-	2.520	-	2.545	2.595
Plasma cholesterol (mmol/L)								
Day 8	1.413	1.248	1.588	1.680	0.893	0.793	0.845	2.190
Day 11R	-	-	-	1.805	-	-	-	-
Day 22R	1.145	-	1.593	-	1.133	-	1.338	2.178
Plasma triglycerides (mmol/L)								
Day 8	0.560	0.575	0.498	1.018	0.480	0.285	0.325	0.393
Day 11R	-	-	-	1.210	-	-	-	-
Day 22R	0.583	-	0.485	-	0.345	-	0.330	0.328
Plasma potassium (mmol/L)								
Day 8	3.65	3.38	3.60	3.63	3.03	3.13	3.35	3.28
Day 11R	-	-	-	3.75	-	-	-	-
Day 22R	3.35	-	3.95	-	2.78	-	3.00	3.55

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Serum total immunoglobulin G1 and 2 subclasses (g/L)								
Day 8	0.68	0.68	0.58	0.75	0.88	0.55	0.93	1.03
Day 11R	-	-	-	1.60	-	-	-	-
Day 22R	0.55	-	1.35	-	1.28	-	1.18	1.48
Serum immunoglobulin G1 (mg/L)								
Day 8	70.5	80.5	54.3	100.0	102.3	61.3	93.8	150.0
Day 11R	-	-	-	299.0	-	-	-	-
Day 22R	108.8	-	425.8	-	191.0	-	225.5	321.0
Serum immunoglobulin G2a (mg/L)								
Day 8	146.3	150.8	117.3	195.5	272.5	160.3	302.3	277.8
Day 11R	-	-	-	496.0	-	-	-	-
Day 22R	133.3	-	260.3	-	403.3	-	446.0	515.5
Serum immunoglobulin G2b (mg/L)								
Day 8	100.3	125.5	108.0	178.5	147.0	102.0	141.0	176.3
Day 11R	-	-	-	183.0	-	-	-	-
Day 22R	126.8	-	262.3	-	370.8	-	251.3	244.3
Serum immunoglobulin G2c (mg/L)								
Day 8	358.3	305.0	292.0	283.0	337.0	249.0	406.5	419.8
Day 11R	-	-	-	608.0	-	-	-	-
Day 22R	183.0	-	428.0	-	279.0	-	247.0	371.8
Serum immunoglobulin A (mg/L)								
Day 8	8.3	8.8	10.8	62.0	8.0	7.0	9.8	34.0
Day 11R	-	-	-	40.0	-	-	-	-
Day 22R	9.5	-	20.0	-	11.8	-	12.5	15.0

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Serum immunoglobulin M (g/L)								
Day 8	0.693	1.035	1.575	6.688	0.730	0.610	1.415	4.508
Day 11R	-	-	-	5.455	-	-	-	-
Day 22R	0.690	-	2.008	-	0.915	-	1.453	2.760
Serum immunoglobulin E (mg/L)								
Day 8	0.648	0.733	0.733	1.530	0.728	0.695	0.793	1.118
Day 11R	-	-	-	8.330	-	-	-	-
Day 22R	0.743	-	1.370	-	0.938	-	0.863	1.090
Plasma creatine kinase (U/L)								
Day 8	236.0	162.3	233.0	440.5	123.3	112.3	139.5	376.0
Day 11R	-	-	-	364.0	-	-	-	-
Day 22R	153.0	-	163.3	-	97.8	-	249.3	191.8
Plasma aldolase (U/L)								
Day 8	21.0	18.3	27.8	91.8	12.5	13.8	18.8	47.3
Day 11R	-	-	-	72.5	-	-	-	-
Day 22R	17.5	-	26.0	-	12.0	-	17.5	27.0
Plasma gamma glutamyltransferase (U/L)								
Day 8	1.0	1.0	1.0	12.0	1.0	1.0	1.0	4.3
Day 11R	-	-	-	11.0	-	-	-	-
Day 22R	1.0	-	1.0	-	1.0	-	1.0	1.0
Serum tissue inhibitor of metalloproteinase-1 (µg/L)								
Day 8	3.5	3.8	6.5	52.5	3.0	3.0	3.8	18.8
Day 11R	-	-	-	31.0	-	-	-	-
Day 22R	4.0	-	7.0	-	2.8	-	4.8	5.3

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Serum monocyte chemoattractant protein-1 (µg/L)								
Day 8	6.3	6.3	12.8	42.5	4.0	4.3	6.5	18.5
Day 11R	-	-	-	22.0	-	-	-	-
Day 22R	5.0	-	6.0	-	3.3	-	4.0	9.5
Serum alpha-1 acid glycoprotein (mg/L)								
Day 8	52.0	62.5	212.8	1323.3	77.0	88.5	296.0	1355.3
Day 11R	-	-	-	1222.5	-	-	-	-
Day 22R	53.0	-	128.8	-	31.3	-	49.3	280.5
Serum alpha-2 macroglobulin (mg/L)								
Day 8	21.5	13.5	21.3	110.3	27.3	21.3	23.0	72.8
Day 11R	-	-	-	139.0	-	-	-	-
Day 22R	10.3	-	18.5	-	15.3	-	19.8	32.5
Serum lipocalin (µg/L)								
Day 8	52.0	75.5	144.5	6082.0	32.0	62.8	105.3	1540.8
Day 11R	-	-	-	5397.0	-	-	-	-
Day 22R	48.8	-	196.8	-	28.0	-	125.3	123.3
Serum skeletal troponin I (ng/mL)								
Day 8	1.2003	1.5323	0.6518	7.1143	0.6995	0.4055	0.8125	1.7605
Day 11R	-	-	-	2.1315	-	-	-	-
Day 22R	1.7493	-	0.8913	-	0.6658	-	7.1160	0.7480
Serum interleukin-6 (pg/mL)								
Day 8	205.5	235.3	347.0	599.8	187.0	292.0	425.8	619.8
Day 11R	-	-	-	196.0	-	-	-	-
Day 22R	236.8	-	226.3	-	212.8	-	370.8	288.8

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Serum interleukin-1 alpha (pg/mL)								
Day 8	16.8	14.3	13.3	40.8	20.5	19.8	16.3	28.8
Day 11R	-	-	-	31.0	-	-	-	-
Day 22R	17.5	-	13.5	-	17.3	-	19.0	20.0
Serum interleukin-1 beta (pg/mL)								
Day 8	95.0	82.0	113.8	188.0	81.8	86.3	129.5	161.0
Day 11R	-	-	-	121.0	-	-	-	-
Day 22R	79.3	-	73.5	-	56.3	-	83.0	106.3
Serum tumour necrosis factor alpha (pg/mL)								
Day 8	247.5	338.0	863.0	2370.5	301.0	469.8	777.0	1358.0
Day 11R	-	-	-	73.5	-	-	-	-
Day 22R	232.5	-	242.8	-	182.5	-	493.0	218.8
Serum chemokine (C-X-C motif) ligand 1 (pg/mL)								
Day 8	269.3	301.5	403.8	872.3	231.0	361.5	604.0	738.5
Day 11R	-	-	-	202.5	-	-	-	-
Day 22R	249.0	-	292.3	-	260.8	-	394.3	394.3
Urinalysis								
Urine total protein:volume (mg/cp)								
Day 8	6.24	7.18	7.89	119.61	0.73	0.75	0.79	25.90
Day 22R	6.70	-	5.58	-	0.60	-	0.65	4.65
Urine albumin:volume (mg/cp)								
Day 8	0.15	0.08	0.24	59.01	0.09	0.10	0.10	17.14
Day 22R	0.28	-	0.18	-	0.05	-	0.10	2.50

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Urine N-acetyl glucosaminidase:volume (µM/cp)								
Day 8	128.4	145.0	162.5	471.1	74.6	73.0	74.1	130.5
Day 22R	154.5	-	142.0	-	69.8	-	61.0	115.5
Urine lipocalin-2:volume (µg/cp)								
Day 8	1.095	1.793	3.025	5506.138	0.605	1.480	3.523	1104.446
Day 22R	1.380	-	4.728	-	0.610	-	2.553	11.620
Urine alpha-glutathione S-transferase:volume (µg/cp)								
Day 8	0.918	0.890	1.069	3.265	0.079	0.080	0.119	0.761
Day 22R	0.828	-	0.623	-	0.068	-	0.058	0.175
Urine clusterin:volume (µg/cp)								
Day 8	0.0579	0.0473	0.0594	0.2866	0.0109	0.0113	0.0136	0.0560
Day 22R	0.0585	-	0.0470	-	0.0110	-	0.0115	0.0378
Urine mu-glutathione S-transferase:volume (µg/cp)								
Day 8	0.093	0.090	0.121	0.374	0.013	0.015	0.015	0.068
Day 22R	0.095	-	0.095	-	0.015	-	0.013	0.025
Urine kidney injury molecule-1:volume (µg/cp)								
Day 8	0.009	0.010	0.010	0.048	0.004	0.005	0.004	0.048
Day 22R	0.010	-	0.010	-	0.000	-	0.000	0.015
Organ Weights[b]								
Liver weight								
Day 8	8.2595g	1.02X	1.07X	1.32X	5.1258g	1.01X	1.05X	1.35X
Day 11R	-	-	-	1.46X	-	-	-	-
Day 22R	9.1680g	-	1.00X	-	5.1598g	-	1.08X (1.18X[c])	1.36X

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Liver relative to body weight								
Day 8	2.770%	0.99X	0.99X	1.19X	2.753%	1.01X	1.02X	1.27X
Day 11R	-	-	-	1.43X[d]	-	-	-	-
Day 22R	2.623%	-	1.01X	-	2.685%	-	1.09X (1.17X[c])	1.19X
Terminal Kill (Day 8)								
Macroscopic Examination (number of animals)	4	4	4	4	4	4	4	4
Brown adipose tissue								
Discolouration, dark	0	0	0	1	0	0	0	1
Liver								
Discolouration, dark	0	0	0	1	0	0	0	1
Discolouration, pale	0	0	0	1	0	0	0	1
Spleen								
Increased size	0	0	0	3	0	0	0	1
Testes								
Flaccid	0	0	0	4	0	0	0	0
Reduced size	0	0	0	4	0	0	0	0
Thymus								
Reduced size	0	0	0	3	0	0	0	2
Microscopic Examination (number of animals)	4	4	4	4	4	4	4	4
Brown adipose tissue								
Microvesiculation; decreased								
Moderate	0	0	0	1	0	0	0	2

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Eyes								
Single cell necrosis; cornea; bilateral								
Minimal	0	0	4	4	0	0	4	4
Heart								
Inflammatory cell infiltrate; epicardium; atrium; mixed cell								
Minimal	0	0	0	2	0	1	1	0
Injection Site								
Degeneration/necrosis; skeletal muscle								
Mild	0	0	1	0	0	0	0	0
Hemorrhage; perivascular								
Minimal	0	0	0	0	1	1	1	0
Mild	0	0	0	2	0	0	0	2
Hyperplasia; epidermis; localised								
Minimal	0	0	0	0	0	0	1	0
Mild	0	0	0	4	0	0	0	0
Inflammation; vascular; perivascular								
Minimal	0	0	0	0	0	0	1	0
Mild	0	0	1	0	0	0	0	0
Inflammatory cell infiltrate; perivascular								
Minimal	0	1	0	0	0	1	1	0

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Kidneys								
Basophilia; tubular								
Minimal	1	1	3	0	0	0	0	0
Mild	0	0	1	0	0	0	0	0
Degeneration; tubular								
Minimal	0	0	0	2	0	0	0	2
Mild	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	1
Glomerulopathy								
Minimal	0	0	0	3	0	0	0	0
Mild	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	1
Liver								
Degeneration/regeneration; kupffer cell; diffuse								
Minimal	0	0	0	0	0	0	0	4
Mild	0	0	0	2	0	0	0	0
Moderate	0	0	0	2	0	0	0	0
Lung								
Alveolar macrophages, prominent	0	3	4	4	0	2	4	3
Lymph node - Mandibular								
Inflammatory cell infiltrate; perivascular; mixed cell								
Minimal	0	0	0	4	0	0	0	1
Lymph node - Mesenteric								
Cellularity increased; medulla								
Minimal	0	0	0	3	0	0	0	0

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Inflammatory cell infiltrate; perivascular; mixed cell								
Minimal	0	0	0	0	0	0	0	1
Mild	0	0	0	2	0	0	0	0
Ovaries								
Degeneration; corpus luteum								
Minimal	-	-	-	-	0	0	3	0
Mild	-	-	-	-	0	0	0	1
Moderate	-	-	-	-	0	1	0	2
Marked	-	-	-	-	0	0	0	1
Degeneration; follicle								
Minimal	-	-	-	-	0	0	1	1
Mild	-	-	-	-	0	0	1	3
Retained oocyte; focal	-	-	-	-	0	0	0	1
Retained oocyte; multifocal	-	-	-	-	0	0	0	3
Spleen								
Extramedullary hematopoiesis								
Minimal	0	0	0	0	0	1	0	0
Moderate	0	0	0	0	0	1	0	0
Congestion								
Minimal	0	0	0	0	0	0	4	0
Mild	0	0	0	4	0	0	0	3
Fibrosis; red pulp								
Minimal	0	0	0	0	0	0	0	2
Mild	0	0	0	1	0	0	0	2
Moderate	0	0	0	3	0	0	0	0

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Lymphocytolysis; white pulp; red pulp								
Minimal	0	0	4	0	0	0	0	1
Mild	0	0	0	0	0	0	0	1
Moderate	0	0	0	4	0	0	0	2
Pigmented macrophages; red pulp; increased								
Minimal	0	0	0	0	0	0	4	1
Sternum – Bone Marrow								
Cellularity decreased								
Mild	0	0	0	0	0	0	0	4
Cellularity increased								
Minimal	0	0	1	0	0	0	0	0
Mild	0	0	0	1	0	0	0	0
Moderate	0	0	0	2	0	0	0	0
Fibrosis; multifocal								
Minimal	0	0	0	1	0	0	0	0
Mild	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	0
Testes								
Degeneration; seminiferous tubule; diffuse								
Moderate	0	0	3	0	-	-	-	-
Marked	0	0	0	4	-	-	-	-
Degeneration; seminiferous tubule; multifocal								
Mild	0	0	1	0	-	-	-	-

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Spermatid retention								
Minimal	0	1	0	0	-	-	-	-
Thymus								
Cellularity decreased								
Minimal	0	0	2	0	0	0	0	0
Mild	0	0	1	0	0	0	2	0
Moderate	0	0	0	1	0	0	0	0
Marked	0	0	0	3	0	0	0	4
White adipose tissue								
Inflammation; perivascular; adipocyte; mixed cell; multifocal								
Minimal	0	0	0	1	0	0	0	1
Mild	0	0	0	1	0	0	0	1
Brachial Nerve								
Inflammatory cell infiltrate; perivascular; mixed cell								
Minimal	0	0	0	2	0	0	0	2
Electron Microscopy (number of animals)	1	0	0	1	0	0	0	1
Kidney								
Numerous spherical inclusion bodies within podocyte cytoplasm	0	-	-	1	-	-	-	1
Enlarged podocytes with effacement of the foot processes with associated attenuation of podocyte cytoplasm	0	-	-	1	-	-	-	1

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

		Male				Female			
Daily Dose (mg/kg)[a]		0	10	30	100	0	10	30	100
Mortalities/Early Termination Kill (Day 9R to 11R)									
Macroscopic Examination (number of animals)		0	0	0	4	0	0	0	0
Epididymides									
Reduced size		-	-	-	3	-	-	-	-
Skin									
Neck, scabs		-	-	-	1	-	-	-	-
Spleen									
Increased size		-	-	-	4	-	-	-	-
Testes									
Flaccid		-	-	-	3	-	-	-	-
Reduced size		-	-	-	4	-	-	-	-
Thymus									
Reduced size		-	-	-	4	-	-	-	-
Microscopic Examination (number of animals)		0	0	0	4	0	0	0	0
Adrenals									
Inflammatory cell infiltrate; mixed cell	cortex;								
	Minimal	-	-	-	3	-	-	-	-
Brown adipose tissue									
Microvesiculation; decreased									
	Moderate	-	-	-	3	-	-	-	-
Epididymides									
Degenerate germ cells; lumen									
	Marked	-	-	-	1	-	-	-	-
Hypospermia									
	Marked	-	-	-	1	-	-	-	-

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Eyes								
Single cell necrosis; cornea; bilateral								
Minimal	-	-	-	4	-	-	-	-
Heart								
Inflammatory cell infiltrate; epicardium; atrium; mixed cell								
Minimal	-	-	-	1	-	-	-	-
Injection Site								
Degeneration/necrosis; skeletal muscle								
Mild	-	-	-	1	-	-	-	-
Hyperplasia; epidermis; localised								
Mild	-	-	-	2	-	-	-	-
Kidneys								
Degeneration; tubular								
Minimal	-	-	-	2	-	-	-	-
Moderate	-	-	-	2	-	-	-	-
Glomerulopathy								
Minimal	-	-	-	2	-	-	-	-
Liver								
Cellularity increased; sinusoid; diffuse								
Mild	-	-	-	1	-	-	-	-
Cellularity increased; sinusoid								
Minimal	-	-	-	1	-	-	-	-
Mild	-	-	-	1	-	-	-	-
Degeneration/regeneration; Kupffer cell; diffuse								
Minimal	-	-	-	1	-	-	-	-

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Lung								
Alveolar macrophages, prominent	-	-	-	4	-	-	-	-
Lymph node - Mandibular								
Inflammatory cell infiltrate; perivascular; mixed cell								
Minimal	-	-	-	2	-	-	-	-
Mild	-	-	-	1	-	-	-	-
Moderate	-	-	-	1	-	-	-	-
Lymph node - Mesenteric								
Cellularity increased; medulla								
Minimal	-	-	-	4	-	-	-	-
Sciatic Nerve								
Inflammatory cell infiltrate; perivascular								
Minimal	-	-	-	2	-	-	-	-
Skin								
Necrosis; epidermis; localised								
Marked	-	-	-	1	-	-	-	-
Spleen								
Congestion								
Mild	-	-	-	4	-	-	-	-
Extramedullary hematopoiesis								
Mild	-	-	-	2	-	-	-	-
Fibrosis; red pulp								
Mild	-	-	-	4	-	-	-	-

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Lymphocytolysis; white pulp; red pulp								
Mild	-	-	-	1	-	-	-	-
Moderate	-	-	-	3	-	-	-	-
Sternum – Bone Marrow								
Cellularity increased								
Mild	-	-	-	4	-	-	-	-
Fibrosis; multifocal								
Mild	-	-	-	1	-	-	-	-
Minimal	-	-	-	2	-	-	-	-
Moderate	-	-	-	1	-	-	-	-
Testes								
Degeneration; seminiferous tubule; diffuse								
Marked	-	-	-	4	-	-	-	-
Thymus								
Cellularity decreased								
Moderate	-	-	-	2	-	-	-	-
Marked	-	-	-	2	-	-	-	-
Brachial Nerve								
Inflammatory cell infiltrate; perivascular; mixed cell								
Minimal	-	-	-	2	-	-	-	-

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Off-dose Kill (Day 22R)								
Macroscopic Examination (number of animals)	4	0	4	0	4	0	4	4
Epididymides								
Reduced size	0	-	2	-	0	-	0	0
Liver								
Discolouration, dark	0	-	1	-	0	-	0	1
Skin								
Neck, scabs	0	-	0	-	0	-	0	1
Spleen								
Increased size	0	-	1	-	0	-	0	1
Testes								
Flaccid	0	-	4	-	0	-	0	0
Reduced size	0	-	4	-	0	-	0	0
Thymus								
Reduced size	0	-	0	-	0	-	0	0
Microscopic Examination (number of animals)	4	0	4	0	4	0	4	4
Brown adipose tissue								
Microvesiculation; decreased								
Moderate	0	-	0	-	0	-	0	1
Epididymides								
Hypospermia								
Marked	0	-	2	-	-	-	-	-
Eyes								
Single cell necrosis; cornea; bilateral								
Minimal	0	-	4	-	0	-	4	4

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Heart								
Inflammatory cell infiltrate; epicardium; atrium; mixed cell								
Minimal	0	-	0	-	0	-	2	0
Injection Site								
Hemorrhage; perivascular								
Mild	0	-	1	-	0	-	0	1
Hyperplasia; epidermis; diffuse								
Mild	0	-	0	-	0	-	0	1
Hyperplasia; epidermis; localised								
Minimal	0	-	0	-	0	-	0	1
Inflammatory cell infiltrate; perivascular								
Minimal	0	-	0	-	0	-	2	2
Kidneys								
Degeneration/regeneration; tubular								
Minimal	0	-	0	-	0	-	0	1
Mild	0	-	0	-	0	-	0	3
Liver								
Cellularity increased; sinusoid								
Minimal	0	-	1	-	0	-	0	4
Mild	0	-	0	-	0	-	0	0
Lung								
Alveolar macrophages, prominent	0	-	4	-	0	-	4	4

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Inflammation; perivascular; mixed cell								
Minimal	0	-	0	-	0	-	0	0
Mild	0	-	1	-	0	-	0	0
Moderate	0	-	1	-	0	-	0	0
Lymph node - Mandibular								
Cellularity increased; medulla								
Minimal	0	-	0	-	0	-	0	1
Inflammatory cell infiltrate; perivascular; mixed cell								
Minimal	0	-	0	-	0	-	0	2
Moderate	0	-	0	-	0	-	0	0
Lymph node - Mesenteric								
Cellularity increased; medulla								
Minimal	0	-	0	-	0	-	0	1
Inflammatory cell infiltrate; perivascular; mixed cell								
Minimal	0	-	0	-	0	-	0	1
Ovaries								
Degeneration; corpus luteum								
Minimal	-	-	-	-	0	-	0	1
Mild	-	-	-	-	0	-	2	2
Moderate	-	-	-	-	1	-	2	0
Skin								
Hyperplasia; epidermis; localised								
Mild	0	-	0	-	0	-	0	1

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Spleen								
Extramedullary hematopoiesis								
Mild	0	-	0	-	0	-	0	1
Moderate	0	-	1	-	0	-	0	0
Marked	0	-	1	-	0	-	0	3
Fibrosis; red pulp								
Minimal	0	-	0	-	0	-	0	2
Pigmented macrophages; red pulp; increased								
Mild	0	-	2	-	0	-	4	0
Sternum – Bone Marrow								
Cellularity increased								
Minimal	0	-	1	-	0	-	0	4
Mild	0	-	0	-	0	-	0	0
Adipocytes, increased								
Minimal	0	-	1	-	0	-	2	0
Testes								
Atrophy; seminiferous tubule; multifocal								
Moderate	0	-	1	-	-	-	-	-
Marked	0	-	3	-	-	-	-	-
Degeneration; seminiferous tubule; multifocal								
Mild	0	-	3	-	-	-	-	-
Moderate	0	-	1	-	-	-	-	-

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Crl:WI(Han) Rats Followed by a 14-Day Off-Dose Period (Continued)

Study Type: Single Dose Toxicity **Study No:** R29778

	Male				Female			
Daily Dose (mg/kg)[a]	0	10	30	100	0	10	30	100
Thymus								
Cellularity decreased								
Minimal	0	-	0	-	0	-	0	4
Moderate	0	-	0	-	0	-	0	0
White adipose tissue								
Inflammation; perivascular; adipocyte; mixed cell; multifocal								
Minimal	0	-	0	-	0	-	0	1

Key:

a = Doses are expressed in terms of the parent compound.b = For controls, group means are shown for absolute and/or relative weights. For test article-treated groups, change from control is shown (on Day 11R, change from D22R control is shown).
c = Mean change for Animals 49 and 51 compared to group mean control is shown.
d = Mean change from group mean control on Day 8 is shown.
Belantamab mafodotin = GSK2857916.
- = Not examined.
NA = Not applicable; R= Recovery.

Table 5.2 Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Monkeys Followed by a 2-Week Off-Treatment Period

Species/ Strain	Route (Vehicle/ Formulation/ Form and batch)	Doses (mg/kg) (Form Tested)	Number of Animals/Sex	Noteworthy Findings[c]	Report No. (Study No.)
Monkey (cynomolgus)	IV (bolus) / (PBS/Solution) (Belantamab mafodotin batch [redacted])[c]	0 (vehicle) 3[a] 10 30	2M/2F[b] 1M/1F 2M/2F[b] 2M/2F[b]	Slight body weight loss was noted at all doses, with most monkeys gaining weight in the off-treatment period. Clinical observations included reduced eating and abnormal feces (≥3 mg/kg), emesis (30 mg/kg) and discoloration of the skin at the injection or non-injection sites (3 and 30 mg/kg), the majority of which was associated with microscopic hemorrhage and/or increased melanin pigment in both terminal and off-treatment animals. Microscopic changes noted in the kidney at 30 mg/kg in the dosing and off-dose phases included granules or casts in the glomeruli or renal tubules, renal tubular degeneration / regeneration, single cell necrosis with subepithelial inflammation and hypertrophy of the collecting duct, hemorrhage, and degeneration/regeneration with necrosis in the proximal tubules. Eosinophilic granules seen in the glomeruli were determined to be lysosomes located in podocytes and parietal epithelial cells. Increased urine NAG excretion was noted at 30 mg/kg on Day 7 and at 3 mg/kg on Day 21. Increased urine total protein and albumin excretion values were also noted on Day 7 at 30 mg/kg, which persisted for the male and were comparable to or approaching baseline for the female on Day 21. Hemorrhage was seen microscopically in the heart, skin and stomach at 30 mg/kg and was associated with mild PT and APTT prolongation and decreases in red cell mass and platelet counts. Additional microscopic findings in the dosing and off-treatment periods were noted in the spleen (pigmented macrophages, mitotic figures in cells of marginal zone, periarterial lymphoid sheath and red pulp, prominent reticular and endothelial cells in red pulp, ≥10 mg/kg; extramedullary hematopoiesis, 30 mg/kg), liver (mitotic figure increase in hepatocytes and hypertrophic sinusoidal cells, 30 mg/kg), bone marrow (decreased hematopoietic cells, 30 mg/kg; increased pigmented macrophages, ≥3 mg/kg), lymph nodes (inguinal,	2012N133495 (D11146)

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Monkeys Followed by a 2-Week Off-Treatment Period (Continued)

Species/ Strain	Route (Vehicle/ Formulation/ Form and batch)	Doses (mg/kg) (Form Tested)	Number of Animals/Sex	Noteworthy Findings[c]	Report No. (Study No.)
				mandibular and mesenteric: increased mitotic figures in medulla, ≥3 mg/kg) and thymus (decreased cellularity, ≥10 mg/kg; necrosis, 30 mg/kg). At 30 mg/kg, increased monocytes and CRP and decreased serum total protein and albumin were noted. Increased serum AST, total bilirubin and skeletal muscle troponin I were noted at ≥3 mg/kg, increased GLDH and ALT were noted at ≥10 mg/kg, and increased ALP and cholesterol were noted at 30 mg/kg. Values for most clinical pathology parameters were comparable to or approaching baseline in the off-treatment period. The percentage and absolute numbers of CD20+ B cells were mildly decreased in the peripheral blood in animals given ≥3 mg/kg, with reversibility noted in the off-treatment period. AUC0-t (mean) data for belantamab mafodotin (ADC) at 3, 10 and 30 mg/kg were 4.15, 15.0 and 60.7 mg.h/mL (males) and 3.55, 10.5 and 53.4 mg.h/mL (females). Mean Cmax values at 3, 10 and 30 mg/kg were 0.0750, 0.388 and 1.49 mg/mL (males) and 0.0891, 0.210 and 0.742 mg/mL (females). AUC0-t (mean) data for belantamab mafodotin (total mAb) at 3, 10 and 30 mg/kg were 4.20, 14.9 and 52.8 mg.h/mL (males) and 3.90, 10.3 and 49.6 mg.h/mL (females). Mean Cmax values at 3, 10 and 30 mg/kg were 0.0726, 0.346 and 0.958 mg/mL (males) and 0.0812, 0.201 and 1.16 mg/mL(females)	

Belantamab Mafodotin: Single-Dose Intravenous Dose Range Toxicity Study in Monkeys Followed by a 2-Week Off-Treatment Period (Continued)

Species/ Strain	Route (Vehicle/ Formulation/ Form and batch)	Doses (mg/kg) (Form Tested)	Number of Animals/Sex	Noteworthy Findings[c]	Report No. (Study No.)
				AUC0-t (mean) data for cys-mcMMAF (following administration of belantamab mafodotin at 3, 10 and 30 mg/kg) were 52.8, 166 and 762 ng.h/mL (males) and 52.9, 145 and 544 ng.h/mL (females). Mean Cmax values at 3, 10 and 30 mg/kg were 1.07, 2.79 and 11.1 ng/mL (males) and 0.919, 2.68 and 7.76 ng/mL (females). ADA antibodies were not detected in monkeys given belantamab mafodotin.	

Key:

a = The dose level of 3 mg/kg was determined based on preliminary data for clinical observations and clinical pathology obtained up to approximately 1 week after dosing of Groups 1 through 3. Subsequently, the dosing day for the 3 mg/kg group occurred approximately 8 days after the dosing day for Groups 1 through 3. The dosing day was designated as Day 1 for all groups in the data collection system.

b = The first male and female given 0, 3 and 30 mg/kg were designated as main study animals; the second male and female in each of these groups were designated as off-dose.

c = For bioanalytical purposes, belantamab mafodotin is quantified as belantamab mafodotin (ADC) and belantamab mafodotin (total mAb). Belantamab mafodotin (ADC) is defined as GSK2857914 conjugated to one or more mcMMAF groups (DAR >0) and belantamab mafodotin (total mAb) is defined as GSK2857914 with or without conjugated mcMMAF (DAR≥0).

ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; APTT = Activated partial thromboplastin time; AST = Aspartate aminotransferase.

AUC0-t = Area under the plasma concentration-time curve from Time 0 to the last quantifiable concentration during the whole sampling period.

Belantamab mafodotin = GSK2857916.

Cmax = Highest plasma concentration observed; CRP = C-reactive protein;

cys-mcMMAF = Microtubule inhibitor MMAF conjugated to cysteine via a protease resistant maleimidocaproyl (mc) linker [The active cytotoxic moiety released from belantamab mafodotin].

GLDH = Glutamate dehydrogenase; IV = Intravenous; NAG = N-Acetyl-β-D-glucosaminidase; NOEL = No observed effect level.

PBS = Phosphate buffered saline; PT = Prothrombin time.

Table 5.3 Exploratory Non-GLP Single-Dose Range-Finding Toxicity Study of SGD-1362 (cys-mcMMAF) in Female Rats with a 14-Day Recovery Phase

Species/ Strain	Route (Vehicle/ Formulation/ Form and batch)	Doses (mg/kg) (Form Tested)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Rat (SD)	IV (bolus) (PBS/Solution) (cys-mcMMAF Batch [redacted])	2.5, 10 17.5, 25	3F ($3F^R$)	Treatment related findings were limited to mild to moderate reductions in reticulocyte counts at dose levels ≥17.5 mg/kg. The HNSTD and MTD were considered to be the highest dose tested of 25 mg/kg. The NOEL was considered to be 10 mg/kg due to the absence of any findings at this dose level. Mean plasma concentrations of cys-mcMMAF one hour postdose at 2.5, 10, 17.5 and 25 mg/kg were 10490, 123500, 164500 and 284000 ng/mL.	2013N177526 (R-TOX-44)

Key:

cys-mcMMAF = Microtubule inhibitor MMAF conjugated to cysteine via a protease resistant maleimidocaproyl (mc) linker [The active cytotoxic moiety released from belantamab mafodotin].

HNSTD = Highest non-severely toxic dose; IV = Intravenous; MTD = Maximum tolerated dose; NOEL = No observed effect level.

PBS = Phosphate buffered saline; R = Recovery; SD = Sprague-Dawley.

Table 5.4 GLP Single-Dose Intravenous Range-Finding Toxicity Study of SGD-1362 (cys-mcMMAF) in Cynomolgus Monkeys

Species/ Strain	Route (Vehicle/ Formulation/ Form and batch)	Doses (mg/kg) (Form Tested)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Monkey (cynomolgus)	IV (bolus) (PBS/Solution) (cys-mcMMAF Batch [redacted])	1, 3, 6,10	1M/1F	A single IV (bolus) injection of cys-mcMMAF to male and female cynomolgus monkeys was well-tolerated at doses up to 10 mg/kg. The HNSTD and NOAEL were considered to be the highest dose of 10 mg/kg. The NOEL was 3 mg/kg due to minimal and transient increases in AST and/or total bilirubin in both sexes at dose levels of 6 and 10 mg/kg. Individual AUC0-last data for cys mcMMAF at 1, 3, 6 or 10 mg/kg in males were 1300, 6980, 12500 or 38200 ng.h/mL respectively, and in females were 1450, 7090, 9200 or 10400 ng.h/mL respectively. Individual Cmax data for cys mcMMAF at 1, 3, 6 or 10 mg/kg in males were 10500, 26700, 142000 or 971000 ng/mL respectively, in females were 10900, 25400, 58800 or 38400 ng/mL respectively.	2013N177529(1019-008)

Key:

AUC0-last = Area under the plasma concentration-time curve from Time 0 to the last quantifiable concentration during the whole sampling period.
AST = Aspartate aminotransferase. Cmax = Highest plasma concentration observed.
cys-mcMMAF = Microtubule inhibitor MMAF conjugated to cysteine via a protease resistant maleimidocaproyl (mc) linker [The active cytotoxic moiety released from belantamab mafodotin].
HNSTD = Highest non-severely toxic dose; IV = Intravenous; NOAEL = No observed adverse effect level; NOEL = No observed effect level.
PBS = Phosphate buffered saline.

6. REPEAT DOSE TOXICITY: NON-PIVOTAL STUDIES

No studies of this type were conducted.

7. REPEAT DOSE TOXICITY: DEFINITIVE STUDIES

Table 7.1 Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period

Study Type: Repeat-Dose Toxicity	**Report Title:** GSK2857916: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period	**Test Article:** Belantamab mafodotin **Batch No.:** [redacted]
Species/Strain: Rat/Wistar Han	**Duration of Dosing:** 3 weeks **Duration of Off-dose:** 12 weeks	**Study No.:** R30467G **GSK Document Number:** 2013N174857
Initial Age: 9 to 11 weeks	**Route/Frequency:** Intravenous infusion for 10 minutes via tail vein, once weekly	**Location in CTD:** m4.2.3.2
Date of First Dose: 21 January 2013	**Vehicle/Formulation:** 25 mM aqueous Citrate Buffer containing 0.05mM EDTA, 200mM Trehalose and 0.02% Polysorbate 80 (pH6)	**Study in Compliance with GLP:** Yes

Data Collected: Toxicokinetics, clinical observations, body weight, food consumption, ophthalmoscopy, body temperature measurements hematology, coagulation, clinical chemistry, urinalysis, cytokine measurements, organ weights, macroscopic and microscopic pathology, electron microscopy (lung only).

Conclusion: Belantamab mafodotin (vehicle, 3, 10 or 30 mg/kg) was given intravenously to male and female rats for 3 weeks (once weekly, total of 3 doses) by infusion, followed by a 12-week off-dose period (0, 3 and 30 mg/kg groups only).

Adverse microscopic changes in the testes were noted at ≥10 mg/kg (degeneration and atrophy of seminiferous tubules). At 30 mg/kg adverse microscopic changes were also noted in the kidney (tubular degeneration) and sternum/bone marrow (decreased cellularity) at the end of the treatment period, and in the lung (macrophage aggregates, inflammatory cell infiltration and alveolar wall thickening) at the end of the off-dose period.

Non adverse microscopic changes were noted in the mandibular and mesenteric lymph nodes, femur/femorotibial joint (males), and male mammary gland at 30 mg/kg; the epididymides, ovaries, spleen, sternum/bone marrow, liver, injection site, and thymus at ≥10 mg/kg; and the eyes and lung at all doses.

Following the 12 week off-dose period, in animals previously given 30 mg/kg there was recovery of the changes in all tissues except the lungs and testes/epididymides together with additional microscopic changes in incisor teeth.

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 AUC0-168 6100 μg.h/mL, range 5960 to 6240 μg.h/mL, and mean Cmax 103 μg/mL, range 101 to 105 μg/mL (based on gender averaged Day 15 values for Belantamab mafodotin ADC)]. Based on the current study findings, the severely toxic dose 10 (STD10) was considered to be 10 mg/kg].

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

	Male				Female			
Daily Dose (mg/kg)[a]	0	3	10	30	0	3	10	30
Numbers of Animals: Main	10	10	10	10	10	10	10	10
Off-dose	12	6	0	6	12	6	0	6
Toxicokinetic	6	6	6	6	6	6	6	6
Plasma GSK2857916 ADC								
AUC(0-168) (μg.h/mL) Day 1	NA	3800	12600	34800	NA	3430	11300	31600
Day 15	NA	5960	26000	51300	NA	6240	17500	45900
Cmax (μg/mL) Day 1	NA	78.9	291	945	NA	75.6	241	727
Day 15	NA	105	327	767	NA	101	278	761
Plasma GSK2857916 Total								
AUC(0-168) (μg.h/mL) Day 1	NA	3800	12800	33600	NA	3660	10800	30300
Day 15	NA	7170	30500	60000	NA	7150	21000	54000
Cmax (μg/mL) Day 1	NA	69.8	244	834	NA	76.5	207	602
Day 15	NA	107	335	798	NA	103	265	743
Plasma cys-mcMMAF								
AUC(0-t) (ng.h/mL) Day 1	NA	NC	259	807	NA	NC	286	1150
Day 15	NA	252	1130	2900	NA	263	1360	2670
Cmax (ng/mL) Day 1	NA	1.54	5.31	22.0	NA	0.936	2.84	11.0
Day 15	NA	4.26	14.9	62.7	NA	3.54	18.2	44.1
Urine cys-mcMMAF (ng)								
Day 7	NA	114	347	1250	NA	53.9	202	492
Day 14	NA	137	438	1530	NA	53.0	257	971
Day 22	NA	117	358	1770	NA	50.9	204	1130
Day 42R	NA	1.24	-	49.5	NA	NQ	-	20.7
Day 64R	NA	NQ	-	8.43	NA	NQ	-	2.81
Day 85R	NA	NQ	-	2.81	NA	NQ	-	NQ
Day 106R	NA	NQ	-	NQ	NA	NQ	-	NQ

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

	Male				Female			
Daily Dose (mg/kg)[a]	0	3	10	30	0	3	10	30
Noteworthy Findings								
Unscheduled Deaths	1	0	0	0	0	0	0	1
	One control male died immediately after removal from the restraint tube on completion of dosing on Day 1. Clinical observations of gasping breathing, pale eyes, prostrate and no righting reflex were seen prior to death.							
	One female given 30 mg/kg died in the restraint tube prior to dosing on Day 8.							
Clinical Observations	Teeth abnormalities were noted from Day 56R onwards in males and females previously given 30 mg/kg. Findings comprised teeth (upper, lower or both sets of incisors) white in appearance, upper and lower incisors appeared to be unevenly/abnormally worn, upper incisors appeared longer, and thicker, and lower incisors appeared shorter. Generally, these observations were noted in all animals throughout the remainder of the off–dose period, although there was evidence of recovery from Day 71R onwards.							
Clinical Examination	Findings of upper incisor teeth white in appearance were noted on Day 104R in 4/6 males and 5/6 females previously given 30 mg/kg. In addition, upper incisor teeth appeared longer, thicker, and/or unevenly worn in 3 males and 5 females, and lower incisor teeth appeared abnormally worn and shorter in 1 male.							
Body Weight Change[b]								
Days 1 to 18	30.05 g	1.06X	0.96X	0.53X	14.29 g	0.95X	1.04X	0.55X
Days 22R to 39R	54.97 g	0.94X	-	1.21X	33.52 g	1.12X	-	1.14X
Days 39R to 102R	53.35 g	1.21X	-	0.82X	21.06 g	1.13X	-	0.86X
Food Consumption[b]								
Days 1 to 22	22.9 g/ animal/day	0.97X	0.95X	0.91X	17.1 g/ animal/day	0.97X	0.99X	0.91X
Days 22R to 106R	23.7 g/ animal/day	0.97X	-	0.94X	18.4 g/ animal/day	1.03X	-	1.01X

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

		Male				Female			
Daily Dose (mg/kg)[a]		0	3	10	30	0	3	10	30
Hematology									
Hematocrit (L/L)	Day 22	0.458	0.480	0.465	0.362**	0.431	0.421	0.414*	0.324**
Hemoglobin concentration (g/L)									
	Day 22	145.1	151.2	146.2	114.6**	141.3	139.7	136.6*	106.3**
Red cell count (x10E12/L)	Day 22	8.316	8.543	8.457	6.817**	7.573	7.531	7.531	6.108**
Mean cell volume (fL)	Day 22	56.34	56.81	55.47	51.98**	58.33	57.54	56.42**	54.47**
Mean cell hemoglobin (pg)	Day 22	17.58	17.61	17.15	16.19**	18.77	18.59	18.10*	17.41**
Red cell distribution width (%)									
	Day 22	12.31	12.22	13.40*	15.28**	11.21	11.10	11.86**	15.40**
	Day 106R	12.25	12.77	-	13.97**	10.31	10.18	-	10.92**
Low absorption reticulocyte absolute count (x10E9L)	Day 22	93.1	102.1	94.8	42.3**	104.8	97.7	82.8	77.6
	Day 106R	84.5	86.5	-	98.8*	89.3	96.0	-	98.0
Medium absorption reticulocyte absolute count (x10E9L)	Day 22	81.8	88.6	88.9	43.8**	78.2	78.4	76.5	67.9
	Day 106R	66.5	74.0	-	75.3	72.3	79.8	-	77.0
High absorption reticulocyte absolute count (x10E9L)	Day 22	112.5	120.9	191.8**	184.6**	117.5	99.3	133.8	231.0**
	Day 106R	61.4	72.8	-	121.7**	62.8	66.5	-	72.2
Platelet count (x10E9/L)	Day 22	879.4	1005.4	1142.0*	1877.2**	907.3	945.8	1166.5**	1857.7**
White cell count (x10E9/L)	Day 22	7.459	7.978	10.372	3.526**	5.389	4.390	5.007	2.578**
	Day 106R	4.456	4.795	-	6.188*	3.807	3.953	-	5.230*
Neutrophil count (x10E9/L)	Day 22	1.013	1.378	2.574	0.332**	0.639	0.847	1.035	0.439
Lymphocyte count (x10E9/L)	Day 22	6.194	6.271	7.379	3.060**	4.557	3.379	3.783	2.059**
	Day 106R	3.257	3.565	-	5.067**	3.048	3.133	-	4.437**

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

		Male				Female			
Daily Dose (mg/kg)[a]		0	3	10	30	0	3	10	30
Monocyte count (x10E9/L)	Day 22	0.129	0.170	0.218	0.031**	0.098	0.080	0.101	0.022**
Eosinophil count (x10E9/L)	Day 22	0.0750	0.1067	0.1260	0.0711	0.0630	0.0711	0.0640	0.0389*
Basophil count (x10E9/L)	Day 22	0.016	0.026	0.040*	0.009	0.011	0.007	0.008	0.003**
Clinical Chemistry									
Alanine aminotransferase (U/L)									
	Day 22	42.3	41.8	52.1**	136.2**	28.3	33.0*	40.2**	99.6**
Glutamate dehydrogenase (U/L)									
	Day 22	5.48	6.37	9.77*	35.05**	3.53	6.87	5.64**	30.32**
Aspartate aminotransferase (U/L)	Day 22								
		75.6	79.0	122.1**	514.1**	59.6	65.9	89.0**	373.3**
Alkaline phosphatase (U/L)	Day 22	231.8	242.6	293.1**	690.1**	121.9	110.0	132.7	313.4**
Total bilirubin (umol/L)	Day 22	0.58	0.48	0.46	0.34**	0.62	0.81	0.72	0.37**
Albumin (g/L)	Day 22	34.7	36.8**	36.0**	37.9**	37.0	40.6**	39.9**	41.7**
Total protein (g/L)	Day 22	58.3	61.6*	62.8**	71.3**	58.6	63.9**	64.9**	75.4**
Urea (mmol/L)	Day 22	7.86	8.08	7.81	9.55**	9.26	9.08	8.85	10.51*
Calcium (mmol/L)	Day 22	2.439	2.504*	2.507*	2.593**	2.473	2.549*	2.571*	2.618**
	Day 106R	2.377	2.393	-	2.455*	2.472	2.438	-	2.557**
Cholesterol (mmol/L)	Day 22	1.644	1.747	1.688	1.411	1.618	1.754	1.940*	2.383**
	Day 106R	1.622	1.552	-	1.782	1.624	1.478	-	2.070*
Triglycerides (mmol/L)	Day 22	0.727	0.948	0.772	0.467**	0.366	0.457	0.362	0.410
	Day 106R	0.856	0.950	-	1.267*	0.478	0.502	-	0.450
Potassium (mmol/L)	Day 22	4.05	4.25	4.27	4.20	3.20	3.42	3.28	3.70
Aldolase (U/L)	Day 22	20.0	20.5	28.5**	58.4**	11.7	11.1	17.1**	40.3**
Creatine kinase (U/L)	Day 22	245.6	253.1	289.6	482.9**	102.7	121.2	148.8**	289.6**
Immunoglobulin A (mg/L)	Day 22	13.3	17.2	15.6	23.7**	16.3	12.0	14.4	26.3*
Immunoglobulin M (g/L)	Day 22	0.342	0.450*	0.611**	0.869**	0.452	0.390	0.609*	1.051**
Serum lipocalin (ug/L)	Day 22	44.4	74.0**	136.0**	133.8**	22.4	37.5**	77.3**	167.0**
	Day 106R	44.5	34.3	-	49.2	22.9	23.8	-	40.7**

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

		Male				Female			
Daily Dose (mg/kg)[a]		0	3	10	30	0	3	10	30
Alpha-1 acid glycoprotein (mg/L)									
	Day 22	52.5	59.9*	168.7**	639.7**	37.3	37.5	65.4**	604.6**
	Day 106R	55.7	47.3	-	55.2	27.1	41.7*	-	30.2*
Alpha-2 macroglobulin (mg/L)									
	Day 22	12.4	11.4	17.1	21.8**	10.7	14.9*	12.9*	18.6**
	Day 106R	7.8	6.3	-	8.8	12.3	10.2	-	9.8
Alpha 1 electrophoresis (g/L)	Day 22	14.07	-	-	17.52**	13.47	-	-	18.61**
Beta electrophoresis (g/L)	Day 22	8.23	-	-	16.89**	7.51	-	-	14.88**
Cytokines									
Monocyte chemoattractant protein-1 (pg/mL)									
	Day 1: Predose	1992.0	2011.9	2001.0	2073.4	2116.6	2148.6	2357.4	2169.6
	Day 2: 24 hours	2090.8	2274.3	2544.7*	6394.4**	2439.8	2772.9*	3570.8**	8085.3**
	Day 15: Predose	2723.1	2815.7	3487.5**	7002.2**	2656.7	2617.5	2956.3	5323.8**
	Day 16: 24 hours	2451.5	2864.7**	3689.1**	9118.7**	2574.2	2536.9	3780.4**	8478.1**
Interleukin-1 beta (pg/mL)									
	Day 1: Predose	50.2	38.7	41.3	42.6	53.2	41.9	41.3	40.9
	Day 2: 24 hours	43.7	36.2	49.7	78.1**	63.4	45.2	60.4	95.5**
	Day 15: Predose	50.3	49.6	56.1	86.3**	74.6	52.0	65.7	88.3**
	Day 16: 24 hours	56.5	49.9	58.1	93.3**	56.5	58.3	55.7	109.3**
Interleukin-6 (pg/mL)									
	Day 1: Predose	116.5	126.9	97.2	149.4	99.8	94.8	87.9	147.4
	Day 2: 24 hours	93.5	58.3	124.2	355.3**	167.7	185.5	321.4**	525.8**
	Day 15: Predose	144.4	146.0	195.6	347.9**	118.9	115.7	194.9	231.6*
	Day 16: 24 hours	77.1	91.5	115.3	298.6**	188.2	219.0	326.6**	399.5**

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

		Male				Female			
Daily Dose (mg/kg)[a]		0	3	10	30	0	3	10	30
Tumor Necrosis Factor Alpha (pg/mL)									
	Day 1: Predose	63.9	38.2	49.4	66.2	47.9	33.1	49.6	54.8
	Day 2: 24 hours	39.6	28.6	40.6	122.8**	70.2	69.6	97.1**	158.3**
	Day 15: Predose	70.9	65.1	65.6	133.5**	40.6	53.7	92.5**	77.3**
	Day 16: 24 hours	50.6	53.5	82.2**	132.0**	77.1	100.6*	120.9**	165.3**
Urinalysis									
Urine total protein:volume (mg/cp)									
	Day 14	6.27	6.77	6.32	8.67**	0.78	0.68	0.83	1.17**
	Day 22	5.88	6.69	7.35*	17.14**	0.76	0.74	0.83	10.43**
	Day 43R	5.81	5.55	-	9.43**	0.76	0.78	-	1.75**
	Day 64R	6.81	6.72	-	6.92	0.80	0.70	-	1.22*
Urine NAG:volume (mU/cp)	Day 14	109.9	122.9	107.3	145.9**	70.9	66.1	83.0*	65.3
Urine albumin:volume (mg/cp)									
	Day 14	0.00	0.01	0.01	0.32**	0.04	0.01	0.02	0.26**
	Day 22	0.01	0.02	0.04	5.49**	0.06	0.01	0.05	8.33**
	Day 43R	0.01	0.05	-	1.03**	0.04	0.02	-	0.83**
	Day 64R	0.03	0.02	-	0.38**	0.07	0.00	-	0.33*
	Day 85R	0.03	0.02	-	0.20**	0.03	0.05	-	0.57**
	Day 106R	0.00	0.03*	-	0.17**	0.03	0.00	-	0.30**
Urine alpha GST:volume (ug/cp)									
	Day 22	0.797	1.074	1.048	1.221*	0.058	0.066	0.055	0.315**
Urine KIM-1:volume (ug/cp)	Day 7	0.0070	0.0074	0.0083*	0.0105**	0.0043	0.0046	0.0049	0.0058**
	Day 14	0.0061	0.0069	0.0074	0.0145**	0.0043	0.0039	0.0047	0.0069**
	Day 22	0.0064	0.0073	0.0080*	0.0213**	0.0043	0.0045	0.0049	0.0147**
	Day 43R	0.0062	0.0053	-	0.0088*	0.0047	0.0052	-	0.0055

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

		Male				Female			
Daily Dose (mg/kg)[a]		0	3	10	30	0	3	10	30
Urine lipocalin-2:volume (ug/cp)									
	Day 7	2.986	3.554	4.804**	9.787**	1.245	1.748*	2.882**	12.814**
	Day 14	2.554	3.501**	5.690**	63.098**	1.354	2.301**	4.235**	79.130**
	Day 22	2.620	4.522**	8.327**	56.835**	1.361	2.877**	6.057**	39.102**
	Day 43R	2.775	2.967	-	9.955**	1.423	2.883**	-	10.253**
	Day 64R	3.125	2.833	-	9.614**	1.490	1.983	-	8.542**
	Day 85R	2.932	2.320	-	4.210*	1.566	1.468	-	6.302*
Urine RPA-1:volume (U/cp)	Day 14	9.76	10.14	10.07	19.60**	11.63	11.03	11.11	13.88
	Day 22	8.48	11.85*	11.44*	20.68**	11.73	10.46	11.84	18.87**
	Day 43R	9.59	10.05	-	23.62**	14.34	15.82	-	13.18
Organ Weights[c]									
Liver									
Absolute	Day 22	8.1839 g	1.06X	1.01X	1.10X	6.0267 g	0.96X	1.01X	1.22X**
	Day 106R	9.2550 g	1.00X	-	1.14X	6.4981 g	0.99X	-	1.09X
Relative to body weight	Day 22	2.635 %	1.05X	1.05X	1.17X**	3.002 %	0.99X	1.01X	1.28X**
	Day 106R	2.310 %	0.99X	-	1.11X	2.681 %	0.98X	-	1.10X
Relative to brain weight	Day 22	399.2 %	1.20X*	1.06X*	1.15X*	323.1 %	0.98X	1.00X	1.23X**
	Day 106R	443.2 %	1.00X	-	1.14X	336.8 %	0.96X	-	1.08X
Spleen									
Absolute	Day 22	0.5885 g	0.99X	1.10X	1.61X**	0.4972 g	0.87X	0.96X	1.42X**
	Day 106R	0.6275 g	1.01X	-	1.22X	0.5007 g	1.03X	-	1.04X
Relative to body weight	Day 22	0.190 %	0.98X	1.13X*	1.71X**	0.247 %	0.91X	0.98X	1.50X**
	Day 106R	0.158 %	1.00X	-	1.18X	0.207 %	1.01X	-	1.05X
Relative to brain weight	Day 22	28.74 %	1.12X	1.15X	1.69X**	26.61 %	0.89X	0.96X	1.44X**
	Day 106R	29.91 %	1.02X	-	1.23X	25.91 %	0.99X	-	1.03X

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

		Male				Female			
Daily Dose (mg/kg)[a]		0	3	10	30	0	3	10	30
Testes									
Absolute	Day 22	3.4848 g	1.11X	0.76X*	0.50X**	NA	NA	NA	NA
	Day 106R	3.9006 g	1.03X	-	0.70X	NA	NA	NA	NA
Relative to body weight	Day 22	1.128 %	1.09X	0.78X**	0.53X**	NA	NA	NA	NA
	Day 106R	0.975 %	1.03X	-	0.68X	NA	NA	NA	NA
Relative to brain weight	Day 22	171.05 %	1.23X	0.79X**	0.52X**	NA	NA	NA	NA
	Day 106R	186.50 %	1.04X	-	0.70X	NA	NA	NA	NA
Thymus									
Absolute	Day 22	0.5251 g	0.94X	0.78X*	0.49X**	0.4553 g	0.91X	0.83X*	0.46X**
	Day 106R	0.4014 g	0.98X	-	0.87X	0.3728 g	0.88X	-	0.79X
Relative to body weight	Day 22	0.167 %	0.95X	0.82X*	0.54X**	0.226 %	0.95X	0.84X*	0.49X**
	Day 106R	0.100 %	0.97X	-	0.85X	0.155 %	0.87X	-	0.79X
Relative to brain weight	Day 22	25.645 %	1.08X	0.82X	0.52X**	24.417 %	0.93X	0.83X*	0.47X**
	Day 106R	19.261 %	0.98X	-	0.87X	19.344 %	0.85X	-	0.78X
Macroscopic Examination									
Terminal Kill									
(number of animals)		10	10	10	10	10	10	10	9
Epididymides									
Reduced size		0	0	0	4	NA	NA	NA	NA
Spleen									
Increased size		0	0	0	3	0	0	0	0
Testes									
Flaccid		0	0	4	7	NA	NA	NA	NA
Reduced size		0	0	1	9	NA	NA	NA	NA
Thymus									
Reduced size		0	0	0	1	0	0	0	2

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

	Male				Female			
Daily Dose (mg/kg)[a]	0	3	10	30	0	3	10	30
Off-Dose Kill								
(number of animals)	11	6	0	6	12	6	0	6
Epididymides								
Flaccid	0	-	-	1	NA	NA	NA	NA
Reduced size	0	-	-	1	NA	NA	NA	NA
Lung								
Areas, pale, many	0	0	-	4	0	0	-	6
Teeth								
Incisors, discolouration, pale/white	0	0	-	2	0	0	-	3
Testes								
Flaccid	0	0	-	2	NA	NA	NA	NA
Reduced size	0	0	-	4	NA	NA	NA	NA
Microscopic Examination								
Mortalities								
Eyes (number of animals)	1	0	0	0	0	0	0	1
Single cell necrosis; cornea; bilateral								
Minimal	0	-	-	-	-	-	-	1
Lung (number of animals)	1	0	0	0	0	0	0	1
Alveolar macrophages prominent	0	-	-	-	-	-	-	1
Eosinophilic material; alveolus								
Minimal	0	-	-	-	-	-	-	1

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

	Male				Female			
Daily Dose (mg/kg)[a]	0	3	10	30	0	3	10	30
Terminal Kill								
Brown Adipose Tissue (number of animals)	10	10	10	10	10	10	10	9
Vacuolation; decreased; diffuse								
Moderate	0	0	0	0	0	0	0	1
Epididymides (number of animals)	10	10	10	10	0	0	0	0
Aspermia; bilateral	1	0	0	10	NA	NA	NA	NA
Hypospermia								
Moderate	0	0	10	0	NA	NA	NA	NA
Inflammatory cell infiltrate; interstitium; mixed cell								
Mild	0	0	4	5	NA	NA	NA	NA
Eyes (number of animals)	10	10	10	10	10	10	10	9
Single cell necrosis; cornea; bilateral								
Minimal	0	0	8	10	0	2	10	9
Single cell necrosis; cornea; unilateral								
Minimal	0	0	1	0	0	0	0	0
Femur – Femoro-Tibial Joint (number of animals)	10	10	10	10	10	10	10	9
Bone remodelling								
Minimal	0	0	0	5	0	0	0	0
Mild	0	0	0	3	0	0	0	0
Injection Site (number of animals)	10	10	10	10	10	10	10	9

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

	Male				Female			
Daily Dose (mg/kg)[a]	0	3	10	30	0	3	10	30
Degeneration/necrosis; skeletal muscle; focal								
Minimal	0	0	0	1	0	0	0	0
Hyperplasia; epidermis; localised								
Mild	0	0	1	2	0	0	0	1
Inflammation; perivascular								
Minimal	2	3	5	5	1	1	2	3
Mild	0	0	1	1	3	7	5	4
Kidney (number of animals)	10	10	10	10	10	10	10	9
Degeneration; tubular, bilateral								
Minimal	0	0	0	1	0	0	0	4
Mild	0	0	0	1	0	0	0	1
Liver (number of animals)	10	10	10	10	10	10	10	9
Extramedullary hematopoiesis								
Minimal	0	0	1	3	0	0	0	1
Lung (number of animals)	10	10	10	10	10	10	10	9
Alveolar macrophages prominent	0	10	10	10	0	4	10	9
Eosinophilic material; alveolus								
Minimal	0	9	0	0	0	4	0	0
Mild	0	1	10	10	0	0	10	9
Lymph Node - Mandibular (number of animals)	10	10	10	10	10	10	10	9
Multinucleate giant cells; medulla; sinus								
Minimal	0	0	0	2	0	0	0	0

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

	Male				Female			
Daily Dose (mg/kg)[a]	0	3	10	30	0	3	10	30
Lymph Node - Mesenteric (number of animals)	10	10	10	10	10	10	10	9
Multinucleate giant cells; medulla; sinus								
Minimal	0	0	0	3	0	0	0	5
Mild	0	0	0	2	0	0	0	0
Mammary Gland (number of animals)	5	8	6	6	10	0	0	9
Single cell necrosis; epithelium								
Minimal	0	0	0	4	0	-	-	0
Mild	0	0	0	1	0	-	-	0
Ovaries (number of animals)	0	0	0	0	10	10	10	9
Luteinised nonovulatory follicle; unilateral, multifocal								
Minimal	NA	NA	NA	NA	0	0	0	2
Luteinised nonovulatory follicle; focal								
Minimal	NA	NA	NA	NA	0	0	1	2
Spleen (number of animals)	10	10	10	10	10	10	10	9
Congestion								
Minimal	0	0	1	0	0	0	0	3
Mild	0	0	0	8	0	0	0	6
Extramedullary hematopoiesis								
Minimal	5	7	2	2	4	5	1	0
Mild	0	1	0	0	2	3	0	0
Moderate	0	0	0	0	1	1	0	0
Lymphocytolysis; red pulp;white pulp								
Minimal	0	0	2	0	0	0	0	4
Mild	0	0	0	10	0	0	0	5

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

	Male				Female			
Daily Dose (mg/kg)[a]	0	3	10	30	0	3	10	30
Pigmented macrophages; red pulp; increased								
Minimal	0	0	5	0	0	0	6	0
Mild	0	0	0	0	0	0	4	0
Sternum – Bone Marrow (number of animals)	10	10	10	10	10	10	10	9
Cellularity decreased								
Minimal	0	0	0	5	0	0	0	1
Mild	0	0	0	2	0	0	0	0
Moderate	0	0	0	3	0	0	0	0
Single cell necrosis								
Minimal	0	0	0	9	0	0	0	8
Bone remodelling								
Minimal	0	0	1	5	0	0	0	0
Mild	0	0	0	1	0	0	0	0
Moderate	0	0	0	3	0	0	0	0
Testes (number of animals)	10	10	10	10	0	0	0	0
Atrophy; seminiferous tubule								
Minimal	1	0	0	0	NA	NA	NA	NA
Mild	1	0	0	0	NA	NA	NA	NA
Marked	0	0	0	1	NA	NA	NA	NA
Degeneration; seminiferous tubule								
Mild	1	0	2	0	NA	NA	NA	NA
Degeneration/ atrophy; seminiferous tubule								
Moderate	0	0	5	0	NA	NA	NA	NA
Marked	0	0	3	9	NA	NA	NA	NA

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

	Male				Female			
Daily Dose (mg/kg)[a]	0	3	10	30	0	3	10	30
Thymus (number of animals)	10	10	10	10	10	10	10	9
Cellularity decreased								
Mild	0	0	0	2	0	0	0	3
Inflammatory cell infiltrate; mixed cell								
Minimal	0	0	0	3	0	0	0	0
Mild	0	0	0	5	0	0	0	1
Lymphocytolysis								
Minimal	0	0	0	3	0	0	0	4
Mild	0	0	0	4	0	0	0	2
Moderate	0	0	0	3	0	0	0	3
Off-Dose Kill								
Epididymides (number of animals)	11	6	-	6	0	0	-	0
Aspermia; bilateral	0	0	-	6	NA	NA	-	NA
Kidneys (number of animals)	11	6	-	6	12	6	-	6
Casts; hyaline								
Minimal	1	0	-	3	2	0	-	3
Lung (number of animals)	11	6	-	6	12	6	-	6
Alveolar macrophages aggregate; multifocal								
Minimal	0	0	-	1	0	0	-	0
Mild	0	0	-	4	0	0	-	6
Testes (number of animals)	11	6	-	6	0	0	-	0
Atrophy; seminiferous tubule								
Marked	0	0	-	6	NA	NA	-	NA
Teeth (number of animals)	11	6	-	6	12	6	-	6

Belantamab Mafodotin: 3-Week Intravenous Toxicity Study in Wistar Han Rats, Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** R30467G

	Male				Female			
Daily Dose (mg/kg)[a]	0	3	10	30	0	3	10	30
Degeneration; ameloblast; incisor; bilateral								
Mild	0	0	-	1	0	0	-	2
Degeneration; ameloblast; incisor; unilateral								
Mild	0	0	-	1	0	0	-	0
Electron Microscopy								
Terminal Kill	Large amounts of tubular-myelin (pulmonary surfactant) were seen within the alveolar spaces of animals given 30 mg/kg.							

Key:

a = Doses are expressed in terms of the parent compound.

b = For controls, group means are shown; and for test article-treated groups, change from control is shown.

c = For controls, group means are shown for absolute and/or relative weights. For test article-treated groups, change from control is shown. Statistical significance is based on actual data not change from control data.

* $p < 0.05$

** $p < 0.01$

Belantamab mafodotin = GSK2857916.

- = Not examined

NA = Not applicable; NC = Not calculated (due to insufficient data); NQ = Not quantifiable.

Table 7.2 Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period

Study Type: Repeat Dose Toxicity	**Report Title:** GSK2857916: 3-Month (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period.	**Test Item:** Belantamab mafodotin **Batch No.:** [redacted]
Species/Strain: Wistar Han IGS rats	**Duration of Dosing:** Once every 3 weeks for 3 months at Weeks 1, 4, 7 and 10 **Duration of Off-dose:** 12 weeks	**GSK Reference No.:** R32025G
Initial Age: Approximately 14 weeks old	**Route/Frequency:** 10-minute intravenous infusion into the tail vein, once every 3 weeks for 3 months	**GSK Document Number:** 2018N374327
Date of First Dose: 23 January 2018	**Vehicle/Formulation:** 25 mM aqueous citrate buffer containing 0.05 mM EDTA, 200 mM Trehalose and 0.02% polysorbate 80 (pH 6.2 ± 0.3)	**Study in Compliance with GLP:** Yes

Data Collected: Dose concentration, toxicokinetics, clinical observations, body weight, food consumption, ophthalmoscopy (including fluorescein staining), hematology (including bone marrow counts), coagulation, clinical chemistry, urinalysis and urinary renal biomarker analysis, skeletal troponin I and aldolase measurements, anti-drug antibodies analysis, cytokine analysis, organ weights, macroscopic and microscopic pathology.

Conclusion: Belantamab mafodotin was given to Wistar Han rats at 0, 3, 10 or 30 mg/kg/dose, once every 3 weeks for 3 months (Weeks 1, 4, 7 and 10) by 10-minute intravenous infusion into the tail vein. Followed by a 12-week off-dose period (0, 10 and 30 mg/kg/dose groups only).

There was 1 unscheduled death in a vehicle-treated animal during the dosing period which was not test item-related.

Adverse microscopic findings were seen in the lung at all doses (increase in alveolar macrophages with eosinophilic material and perivascular inflammatory cell infiltrates in animals given > 3 mg/kg/dose, and neutrophilic alveolar inflammation around terminal airways with type 2 pneumocyte hypertrophy/hyperplasia in one female given 10 mg/kg/dose); teeth/incisors (degeneration) and testes (tubular degeneration/atrophy) at > 10 mg/kg/dose; and kidney (tubular degeneration/regeneration) at 30 mg/kg/dose.

Non adverse microscopic findings were seen in the eye/cornea (increased mitoses at all doses and single cell necrosis at ≥10 mg/kg/dose) at > 3 mg/kg/dose; male mammary gland (lobular atrophy) and spleen (congestion) at ≥10 mg/kg/dose; and liver (extramedullary hematopoiesis, males only) at 30 mg/kg/dose. There were hematology and coagulation parameter changes at > 10 mg/kg/dose; increases in cytokines TNF- α and KC/GRO levels at ≥10 mg/kg/dose; and urinary renal biomarkers and clinical chemistry changes at 30 mg/kg/dose.

Changes considered to be secondary to the testes changes were seen in the epididymides (aspermia) and male pituitary (increased cytoplasmic vacuolation).

Following the 12-week off-dose period, there was evidence of progression of the microscopic changes in the lungs at ≥10 mg/kg/dose and testes at 30 mg/kg/dose, and changes were still present in the testes/epididymides and male pituitary gland at > 10 mg/kg/dose. Microscopic changes in the eye/cornea, teeth/incisors, spleen, kidney, liver and male mammary gland were fully reversible.

Based on the adverse microscopic changes in the lung at all doses, a no observed adverse effect level (NOAEL) was not established but it is less than 3 mg/kg/dose. At 3 mg/kg/dose, AUC0-504 and Cmax for belantamab mafodotin (ADC) was 10500 μg.hr/mL and 131 μg/mL, respectively, and AUC0-504 and Cmax for belantamab mafodotin (mAb) was 12700 μg.hr/mL and 133 μg/mL, respectively (based on gender averaged Week 10 values).

Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity — Study No. R32025G

		Male				Female			
Daily Dose (mg/kg/dose[a])		0	3	10	30	0	3	10	30
Numbers of Animals:	Main	12	12	12	12	12	12	12	12
	Off-dose	6	0	6	6	6	0	6	6
	Toxicokinetic	6	6	6	6	6	6	6	6
Toxicokinetics									
GSK2857916 (ADC)									
AUC(0-504) (µg•h/mL)	Week 4	-	11100	39000	99700[b]	-	8900	28900	71300
	Week 10	-	12700	45500	106000	-	8350	29100	74100
C_{max} (µg/mL)	Week 4	-	120	428	1100[b]	-	118	424	1070
	Week 10	-	144	501	1310	-	118	402	1190
Mean (µg/mL)	Off-dose Week 4	f	NA	9.20[h]	30.6	-	NA	6.03	17.5
	Off-dose Week 8	-	NA	1.74	7.86	-	NA	0.985	2.48
	Off-dose Week 12/13	-	NA	NQ[i]	1.38	-	NA	NQ	NQ
GSK2857916 (mAb)									
AUC(0-504) (µg•h/mL)	Week 4	-	13200	45700	114000[b]	-	11100	33600	81700
	Week 10	-	15100	50900	125000	-	10400	34000	89400
C_{max} (µg/mL)	Week 4	-	111	427	1080[b]	-	118	401	1070
	Week 10	-	135	481	1180	-	130	331	1150
Mean (µg/mL)	Off-dose Week 4	g	NA	11.3[h]	38.8	-	NA	7.38	22.0
	Off-dose Week 8	-	NA	2.34	8.57	-	NA	1.23	2.94
	Off-dose Week 12/13	-	NA	NQ[i]	1.59	-	NA	NQ	NQ

Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity — Study No. R32025G

		Male				Female			
Daily Dose (mg/kg/dose)[a]		0	3	10	30	0	3	10	30
cys-mcMMAF									
AUC(0-504) (ng•h/mL)	Week 4	-	NC	42.5	288	-	NC	42.4	196
	Week 10	-	NC	50.0	413	-	NC	81.9	370
C_{max} (ng/mL)	Week 4	-	NQ	0.933	2.61	-	NQ	1.68	3.41
	Week 10	-	NQ	1.92	4.92	-	NQ	1.49	8.69
Mean (ng/mL)	Off-dose Week 4	-	NA	NQ	NQ	-	NA	NQ	NQ
	Off-dose Week 8	-	NA	NQ	NQ	-	NA	NQ	NQ
	Off-dose Week 12/13	-	NA	NQ	NQ	-	NA	NQ	NQ
Noteworthy Findings									
Anti-GSK2857916 Antibodies		Two toxicokinetic males given 30 mg/kg/dose were screened and confirmed positive for anti- belantamab mafodotin-antibodies in Weeks 4 and 12. Samples exhibited an increase in titer with repeated dosing. During the off-dose phase, one male previously given 30 mg/kg/dose was screened and confirmed positive for anti- belantamab mafodotin antibodies at Off-dose Week 8.							
Unscheduled Deaths		1[d]	0	0	0	0	0	0	0
Body Weight Change (grams)									
	Day Ran1 to 7	18	21	16	19	7	7	8	5
	Day 21 to 28	3	8	0*	-2**	3	5	2	3
	Day 42 to 49	5	7	5	4	1	-1	-1	1
	Day 63 to 77	11	10	-3	-1	-2	0	1	-3
Food Consumption (g/animal/day)									
	Week 1	21.8	22.7	21.3	20.9	14.5	14.6	14.4	13.9
	Week 4	21.3	22.4	20.3	19.0	14.2	13.7	14.1	13.7
	Week 7	20.7	21.8	19.7	18.9	13.7	13.6	13.4	13.5
	Week 10	20.6	20.9	19.1	18.4	13.6	13.8	13.3	13.2
	Week 12	21.2	21.6	19.2	21.5	14.5	14.0	14.4	14.2

Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **Study No. R32025G**

	Male				Female			
Daily Dose (mg/kg/dose)[a]	0	3	10	30	0	3	10	30
Hematology								
Absolute Neutrophils (10^9/L)								
Week 4	1.31	1.30	1.47	1.60	0.58	0.77	0.82**	1.16**
Week 12/13	1.21	1.58	2.01**	2.14**	0.67	0.79	1.20**	1.85**
Hemoglobin Concentration (g/L)								
Week 4	165.9	161.3	165.4	158.1**	157.8	158.8	157.6	153.5*
Week 12/13	164.2	164.1	163.1	140.6**	156.6	155.8	150.6	140.3**
Hematocrit (%)								
Week 4	52.9	51.9	53.2	50.6**	51.1	50.3	50.5	49.1**
Week 12/13	51.1	51.7	50.1	45.5**	49.1	48.4	47.1*	44.7**
Reticulocytes (10^9/L)								
Week 4	192.7	174.1	192.1	262.0**	152.5	145.1	146.8	190.5**
Week 12/13	158.8	157.4	185.0**	279.3**	172.8	159.8	175.1	272.8**
Red Blood Cell Distribution Width (%)								
Week 4	12.3	12.1	12.5	13.2**	10.9	10.8	11.1	11.7**
Week 12/13	12.5	12.2	13.5**	15.8**	11.1	11.0	12.0**	14.3**
Off-dose Week 12/13	12.7	NA	13.0	13.4*	10.9	NA	10.7	11.4
Mean Corpuscular Volume (fL)								
Week 4	53.4	53.8	53.2	51.3**	55.4	56.8*	55.0	53.9**
Week 12/13	51.2	51.6	49.4**	45.7**	53.3	53.7	52.1*	48.9**
Mean Corpuscular Hemoglobin (pg)								
Week 4	16.7	16.7	16.5	16.0**	17.1	18.0**	17.2	16.9
Week 12/13	16.4	16.4	16.1	14.1**	17.0	17.3	16.7	15.4**
White Blood Cell Count (10^9/L)								
Week 4	6.17	6.11	5.94	7.21	3.18	3.08	3.59	4.66**
Week 12/13	5.39	6.50*	7.07**	7.18**	3.41	3.04	3.92	5.58**

Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **Study No. R32025G**

	Male				Female			
Daily Dose (mg/kg/dose)[a]	0	3	10	30	0	3	10	30
Absolute Lymphocytes (10^9/L)								
Week 4	4.49	4.40	4.16	5.25	2.42	2.13	2.58	3.27**
Week 12/13	3.75	4.42	4.56*	4.51*	2.50	2.02	2.47	3.27*
Absolute Monocytes (10^9/L)								
Week 12/13	0.21	0.24	0.24	0.28**	0.11	0.10	0.13	0.24**
Absolute LUC (10^9/L)								
Week 12/13	0.11	0.13	0.13	0.14*	0.07	0.06	0.07	0.14*
Bone Marrow Counts								
(number of animals)	12	12	12	12	6	6	6	6
Total Nucleated Cells								
Week 12/13	224.2	247.7	230.8	227.2	222.5	242.0	219.0	218.2
Myeloid Cells								
Week 12/13	134.8	149.0	115.8*	119.1*	122.2	132.7	117.7	110.5
Myeloid %								
Week 12/13	0.599	0.603	0.500**	0.523**	0.549	0.549	0.539	0.506
Erythroid Cells								
Week 12/13	89.4	98.7	115.1**	108.1**	100.3	109.3	101.3	107.7
Erythroid %								
Week 12/13	0.401	0.397	0.500**	0.477**	0.451	0.451	0.461	0.494
M/E ratio								
Week 12/13	1.521	1.548	1.022**	1.154**	1.237	1.232	1.183	1.033
Coagulation								
Fibrinogen (mg/dL)								
Week 12/13	288	298	338**	412**	203	197	232	293**
Clinical Chemistry								
Aspartate Aminotransferase (U/L)								
Week 4	110	115	113	123	93	94	84	107*
Week 12/13	101	97	105	160**	92	89	94	145**

Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity						Study No. R32025G			
		Male				Female			
Daily Dose (mg/kg/dose)[a]		0	3	10	30	0	3	10	30
Alanine Aminotransferase (U/L)									
	Week 4	38	37	38	45**	24	25	27	33**
	Week 12/13	35	33	37	62**	28	26	29	45**
Total Protein (g/L)									
	Week 12/13	64.0	60.8	66.3	69.9**	69.2	64.3	69.5	75.4**
Albumin (g/L)									
	Week 12/13	39.3	37.6	40.2	41.7**	43.0	40.7	43.8	46.8**
Calcium (mmol/L)									
	Week 12/13	2.50	2.46	2.55	2.58*	2.55	2.50	2.61	2.64*
Cholesterol mmol/L)									
	Week 12/13	2.03	1.81	2.15	2.08	1.55	1.25	1.63	2.01**
Triglycerides (mmol/L)									
	Week 12/13	1.44	1.15	1.25	0.90**	0.81	0.73	0.61	0.50
Urinary Renal Biomarkers		At Week 12, there were increases in urinary albumin excretion (UABV) values (115X and 35X for males and females, respectively) and urinary total protein excretion (UTPV) values (up to 5.4X) in males and females given 30 mg/kg/dose and increases in urinary kidney injury molecule-1 (KM1V) excretion value (3.3X) in males given 30 mg/kg/dose.							
		Following a 12/13 Week Off-dose period, increases in UABV values were still apparent in males and females previously given 30 mg/kg/dose; but, showed partial recovery (14X and 23X for males and females, respectively).							
Cytokines Evaluations									
TNF-α (pg/mL)	Week 13	2.731	2.734	3.687	6.836***	2.500	2.500	2.958	4.763**
	Off-dose Week 12/13	2.500	NA	2.500	3.465	2.500	NA	2.500	2.500
KC/GRO (pg/mL)	Week 13	210.375	227.767	421.596**	376.948*	368.560	257.150	505.730	633.088*
	Off-dose Week 12/13	279.720	NA	253.710	238.902	594.183	NA	285.483	462.223
Organ Weights[c] Xcontrol									
Spleen									
	Absolute Weight (g)	0.7778	1.03X	0.96X	1.30X**	0.5086	1.06X	1.03X	1.21X**
	Organ/Body Weight Ratio (%)	0.177	1.00X	0.99X	1.33X**	0.211	1.09X	1.05X	1.23X**
	Organ/Brain Weight Ratio (%)	37.0	1.02X	0.97X	1.35X**	26.7	1.07X	1.03X	1.21X**

Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **Study No. R32025G**

	Male				Female			
Daily Dose (mg/kg/dose)[a]	0	3	10	30	0	3	10	30
Testes (Terminal)								
Absolute Weight (g)	4.0904	0.93X	0.44X**	0.61X**	NA	NA	NA	NA
Organ/Body Weight Ratio (%)	0.933	0.91X	0.45X**	0.62X**	NA	NA	NA	NA
Organ/Brain Weight Ratio (%)	194	0.92X	0.44X**	0.63X**	NA	NA	NA	NA
Testes (Off-dose)								
Absolute Weight (g)	4.1425	NA	0.37X**	0.55X**	NA	NA	NA	NA
Organ/Body Weight Ratio (%)	0.846	NA	0.37X**	0.55X**	NA	NA	NA	NA
Organ/Brain Weight Ratio (%)	200	NA	0.38X**	0.53X**	NA	NA	NA	NA
Liver								
Absolute Weight (g)	9.1239	1.02X	1.01X	1.13X*	5.4208	0.99X	1.03X	1.09X
Organ/Body Weight Ratio (%)	2.07	1.00X	1.05X	1.16X**	2.25	1.02X	1.05X	1.11X**
Organ/Brain Weight Ratio (%)	433	1.02X	1.02X	1.17X**	284	1.00X	1.04X	1.10X
Macroscopic Examination - Terminal (number of animals)	12	12	12	12	12	12	12	12
Lung								
Pale Area(s)	0	1	11	4	0	0	12	10
Testes								
Abnormal Color	0	1	8	10	NA	NA	NA	NA
Dark Area(s)	0	0	0	1	NA	NA	NA	NA
Pale Area(s)	0	0	0	1	NA	NA	NA	NA
Small	0	2	9	8	NA	NA	NA	NA
Soft	0	1	11	7	NA	NA	NA	NA
Epididymides								
Dark Area(s)	0	0	3	1	NA	NA	NA	NA
Small	0	1	6	7	NA	NA	NA	NA
Soft	0	0	2	1	NA	NA	NA	NA
Spleen								
Enlarged	0	0	0	1	0	0	0	0

Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity — Study No. R32025G

	Male				Female			
Daily Dose (mg/kg/dose)[a]	0	3	10	30	0	3	10	30
Macroscopic Examination - Off-dose (number of animals)	6	0	6	6	6	0	6	6
Lung								
Pale Area(s)	0	NA	4	3	0	NA	4	6
Testes								
Abnormal Color	0	NA	4	5	NA	NA	NA	NA
Small	0	NA	6	1	NA	NA	NA	NA
Soft	0	NA	6	4	NA	NA	NA	NA
Epididymides								
Small	0	NA	0	1	NA	NA	NA	NA
Microscopic Examination (Terminal)								
Lung and Bronchi								
(number of animals)	12	12	12	12	12	12	12	12
Alveolar Macrophages, Increased, Diffuse								
Minimal	0	2	1	6	0	2	8	4
Slight	0	1	10	6	0	0	3	8
Moderate	0	0	1	0	0	0	1	0
Eosinophilic Material, Alveoli								
Minimal	0	1	7	5	0	0	5	5
Slight	0	0	2	7	0	0	0	7
Infiltrate, Inflammatory Cell, Perivascular								
Minimal	0	0	4	7	0	0	10	6
Slight	0	1	8	5	0	0	2	6
Inflammation, Alveoli								
Slight	0	0	0	0	0	0	1	0
Eye Left								
(number of animals)	12	12	12	12	12	12	12	12

Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity — Study No. R32025G

	Male				Female			
Daily Dose (mg/kg/dose)[a]	0	3	10	30	0	3	10	30
Necrosis, Single Cell, Cornea								
Minimal	0	0	8	11	0	0	1	9
Increased Mitoses, Cornea	0	0	10	12	0	1	10	11
Eye Right								
(number of animals)	12	12	12	12	12	12	12	12
Necrosis, Single Cell, Cornea								
Minimal	0	0	4	9	0	0	2	8
Increased Mitoses, Cornea	0	1	9	12	0	2	10	11
Spleen								
(number of animals)	12	12	12	12	12	12	12	12
Congestion								
Minimal	0	0	9	11	0	0	7	11
Slight	0	0	0	1	0	0	0	0
Teeth								
(number of animals)	12	12	12	12	12	12	12	12
Degeneration, Incisors								
Minimal	0	0	11	0	0	0	7	3
Slight	0	0	0	10	0	0	0	9
Moderate	0	0	0	2	0	0	0	0
Testes								
(number of animals)	12	12	12	12	0	0	0	0
Degeneration, Atrophy, Tubular								
Slight	1	0	0	0	NA	NA	NA	NA
Marked	0	1[e]	12	12	NA	NA	NA	NA

Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **Study No. R32025G**

	Male				Female			
Daily Dose (mg/kg/dose)[a]	0	3	10	30	0	3	10	30
Epididymides								
(number of animals)	12	12	12	12	0	0	0	0
Aspermia	0	1[e]	12	12	NA	NA	NA	NA
Kidneys								
(number of animals)	12	12	12	12	12	12	12	12
Degeneration/Regeneration, Tubular								
Minimal	0	0	0	6	0	0	0	3
Slight	0	0	0	3	0	0	0	0
Liver								
(number of animals)	12	12	12	12	12	12	12	12
Extramedullary Hemopoiesis								
Minimal	0	0	0	5	0	0	0	0
Mammary Gland								
(number of animals)	12	12	12	12	12	0	0	12
Atrophy, Lobule								
Minimal	0	0	6	1	0	NA	NA	0
Slight	0	0	0	10	0	NA	NA	0
Pituitary Gland								
(number of animals)	12	12	12	12	12	0	0	12
Increased Vacuolation, Pars Distalis								
Minimal	0	1	12	12	0	NA	NA	0

Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity — Study No. R32025G

	Male				Female			
Daily Dose (mg/kg/dose)[a]	0	3	10	30	0	3	10	30
Microscopic Examination (Off-dose)								
Lung and Bronchi								
(number of animals)	6	0	6	6	6	0	6	6
Alveolar Macrophages, Increased, Diffuse								
Minimal	0	NA	2	2	0	NA	2	0
Slight	0	NA	3	3	0	NA	4	4
Moderate	0	NA	1	1	0	NA	0	2
Eosinophilic Material, Alveoli								
Minimal	0	NA	0	0	0	NA	0	2
Slight	0	NA	0	0	0	NA	0	1
Infiltrate, Inflammatory Cell, Perivascular								
Minimal	0	NA	2	2	0	NA	3	2
Slight	0	NA	4	4	0	NA	2	4
Inflammation, Alveoli								
Slight	0	NA	2	0	0	NA	1	1
Testes								
(number of animals)	6	0	6	6	0	0	0	0
Degeneration, Atrophy, Tubular								
Moderate	0	NA	1	0	NA	NA	NA	NA
Marked	0	NA	4	1	NA	NA	NA	NA
Severe	0	NA	1	5	NA	NA	NA	NA

Belantamab Mafodotin: 13-Week (Once Every 3-Weeks) Intravenous Infusion Toxicity Study in Rats Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **Study No. R32025G**

	Male				Female			
Daily Dose (mg/kg/dose)[a]	0	3	10	30	0	3	10	30
Epididymides								
(number of animals)	6	0	6	6	0	0	0	0
Aspermia	0	NA	5	6	NA	NA	NA	NA
Hypospermia	0	NA	1	0	NA	NA	NA	NA
Pituitary Gland								
(number of animals)	6	0	6	6	0	0	0	0
Increased Vacuolation, Pars Distalis								
Minimal	0	NA	6	6	NA	NA	NA	NA

Key:

- Not examined; LUC = Large Unstained Cells; NA = Not applicable; NC = Not calculated (due to insufficient data); NQ = Not quantifiable (cys-mcMMAF <0.5 ng/mL; GSK2857916 (ADC) < 250 ng/mL; GSK2857916 (mAb) <250 ng/mL).

* - p<0.05 ** - p<0.01 *** p≤0.001
Belantamab mafodotin = GSK2857916.

a = Doses expressed in terms of the antibody-drug conjugate, GSK2857916.

b = Due to data exclusions, the concentration at 0.25, 24, 96 and 336 hour timepoints were based on a single animal.

c = For controls, group means are shown for absolute and/or relative weights. For belantamab mafodotin-treated groups, fold-change from control is shown. Statistical significance is based on actual data not fold change.

d = A control TK male rat was found dead on Day 50. There was dark discoloration/congestion of multiple organs/tissues. The cause of death was undetermined.

e = These findings were considered not to be test item-related because of the single incidence in this group and frequent occurrence of degeneration/atrophy in the testes as a background finding.

f = Anomalously high concentration of 10900 ng/mL for animal 1018 confirmed by repeat analysis.

g = Anomalously high concentration of 13300 ng/mL for animal 1018 confirmed by repeat analysis.

h = Anomalously non-quantifiable concentration for animal 3060 excluded from the mean concentration calculation.

i = Non-quantifiable concentrations for animals 3055, 3056, and 3057 assigned as zero for the mean concentration calculation.

Table 7.3 Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period

Study Type: Repeat-Dose Toxicity

Report Title: GSK2857916: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period

Test Article: Belantamab mafodotin
Batch No.: [redacted]

Species/Strain: Monkey/Cynomolgus

Duration of Dosing: 3 Weeks
Duration of Recovery: 12 Weeks

Study No.: P70260G

Initial Age: 2.7 to 3.3 years

Route/Frequency: Intravenous (bolus, slow push; single and/or repeat administration into saphenous and/or brachial vein)/ Once weekly

Location in CTD: m4.2.3.2

Date of First Dose: 04-February-2013

Vehicle/Formulation: 25mM Citrate, 0.05mM EDTA, 200mM Trehalose, 0.02% Polysorbate 80, pH 6±0.3

Study in Compliance with GLP: Yes

GSK Document Number: 2013N158643

Data Collected: Clinical observations; body weights; food consumption measurements; hematology, coagulation, clinical chemistry (including C-reactive protein, IgG, IgM and skeletal troponin I analysis), and urinalysis results [including albumin:creatinine, N-acetyl-β-D glucosaminidase (NAG):creatinine, and kidney injury molecule-1 (kim-1):creatinine ratios]; ophthalmoscopic observations; electrocardiographic measurements (including 24-hour qualitative and quantitative assessment in males); immunophenotyping in peripheral blood [B cells, T cells (including $CD4^+$ and $CD8^+$ subsets), natural killer (NK) cells, and NK T cells]; organ weights; and macroscopic and microscopic observations (stage dependent evaluation of spermatogenesis was not performed due to sexual immaturity). Toxicokinetic evaluation (serial sampling) was performed on samples collected from all monkeys on Days 1 and 15 (Weeks 1 and 3, respectively). Single samples were collected from off-dose monkeys during Weeks 5, 6, 7, 8, 10, 12, 14, and 16 for toxicokinetic evaluation during the off-dose period. Blood samples were also collected (prior to dosing and during Weeks 4 and 16) for possible analysis of anti- belantamab mafodotin antibodies; however, as there were no changes in toxicokinetics parameters following repeat dosing and there was evidence of pharmacodynamic activity throughout the study, these samples were not analyzed.

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Conclusion: Test article-related microscopic findings consistent with a systemic inflammatory response were noted at doses ≥3 mg/kg/week and included findings in the spleen (increased macrophages in red pulp) and bone marrow (increased macrophages; 10 mg/kg/week only) with correlating clinical pathology changes including increased mean C-reactive protein and decreased serum albumin concentrations at ≥3 mg/kg/week and increases in total white blood cells (neutrophils, monocytes and large unstained cells) at 10 mg/kg/week. This response was also associated with decreased red cell mass and platelet counts, with evidence of regenerative responses in individual monkeys given 10 mg/kg/week. Increased mitotic figures were observed in Kupffer cells in the liver and mesangial cell in the kidney of monkeys given 10 mg/kg/week. Glomerulopathy and degeneration/regeneration of the distal nephron with increased urine protein and albumin excretion values were noted in 1 monkey given 10 mg/kg/week. In the thymic cortex, increased tingible body macrophages were noted at ≥3 mg/kg/week with, in some individual animals at 10 mg/kg/week, additionally associated decreased cellularity. Decreases in mean serum IgM were noted at doses ≥1 mg/kg/week and in serum IgG at 10 mg/kg/week and were consistent with expected pharmacology of belantamab mafodotin. Decreased absolute number and percentage of natural killer (NK cells) at doses ≥3 mg/kg/week and minimally increased absolute number and percentage of activated B cells at 10 mg/kg/week were observed. Additional clinical pathology changes at 10 mg/kg/week included increased mean aspartate aminotransferase, glutamate dehydrogenase, gamma glutamyltransferase, alanine aminotransferase, total bilirubin, cholesterol and triglyceride concentrations. Decreased food consumption was noted in monkeys at 10 mg/kg/week. Decreased body weight was noted in 1 monkey/group at doses ≥1 mg/kg/week following the last dose, and was rebounding by the time of necropsy in the monkey given 1 mg/kg/week. With the exception of decreased serum IgM concentrations, all findings were resolved by the end of the off-dose period.

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): AUC0-167 1240 μg.h/mL, range 893 to 1470 μg.h/mL; Cmax 27.5 μg\mL, range 22.7 to 32.9 μg/mL; GSK2857916 (Total) AUC0-167 1520 μg.h/mL, range 1210 to 1700 μg.h/mL; Cmax 27.3 μg\mL, range 22.4 to 31.7 μg/mL; cys-mcMMAF: AUC0-167 12.1 ng.h/mL, range 6.01 to 23.1 ng.h/mL; Cmax 0.499 ng\mL, range 0.341 to 1.03 ng/mL (gender-averaged based on Week 3 values)].

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70260G

		Male				Female			
Daily Dose (mg/kg/week)[a]		0	1	3	10	0	1	3	10
Numbers of Animals:	**Main**	3	3	3	3	3	3	3	3
	Off-Dose	2	0	2	0	2	0	2	0
GSK2857916 (ADC)									
AUC(0-167) (μg.h/mL)	Week 1	NC	882	2330	11300	NC	847	2340	11100
	Week 3	NC	1180	3590	20500	NC	1290	3922	22500
Cmax (μg/mL)	Week 1	ND	22.2	63.4	251	ND	22.4	54.0	247
	Week 3	ND	26.7	66.8	292	ND	28.2	59.8	292
t1/2 (h)	Week 3	NC	NA	113[b]	NA	NC	NA	97.2[b]	NA
GSK2857916 Total									
AUC(0-167) (μg.h/mL)	Week 1	NC	975	2650	11900	NC	918	2690	13300
	Week 3	NC	1500	4402	24200	NC	1540	4844	27400
Cmax (μg/mL)	Week 1	ND	21.9	62.1	238	ND	20.2	53.3	233
	Week 3	ND	26.3	70.5	292	ND	28.2	65.8	321
t1/2 (h)	Week 3	NC	NA	102[b]	NA	NC	NA	96.7[b]	NA
Cys-mcMMAF									
AUC(0-t[p]) (ng.h/mL)	Week 1	NC	11.8	62.5	248	NC	20.0	69.5	167
	Week 3	NC	12.2	85.6	416	NC	12.1	61.5	285
Cmax (ng/mL)	Week 1	ND	0.821	1.57	4.78	ND	0.625	2.36	4.70
	Week 3	ND	0.422	2.26	5.97	ND	0.577	1.67	4.83
t1/2 (h)	Week 3	NC	NA	ND[n]	NA	NC	NA	ND[n]	NA

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70260G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10	0	1	3	10
Noteworthy Findings								
Body Weight (kg)[c]								
Day 1	2.904	2.883	2.782	2.860	2.764	2.797 (2.32)[e]	2.544 (2.47)[f]	2.903 (2.83)[g]
Day 8	1.03X	1.03X	1.02X	1.01X	1.02X	1.03X (1.04X)[e]	1.01X (0.99X)[f]	0.99X (0.96X)[g]
Day 15	1.03X	1.03X	1.02X	1.00X	1.03X	1.03X (1.09X)[e]	1.01X (0.98X)[f]	1.00X (0.98X)[g]
Day 19	1.02X	1.03X	1.01X	1.00X	1.03X	0.99X (0.95X)[e,d]	0.99X (0.93X)[f]	0.99X (0.94X)[g,d]
Day 29	1.10X	NA	1.06X	NA	1.02X	NA	0.94X (0.91X)[f]	NA
Day 50	1.07X	NA	1.04X	NA	0.99X	NA	0.97X (0.95X)[f]	NA
Day 78	1.12X	NA	1.08X	NA	1.01X	NA	0.98X (0.98X)[f]	NA
Day 103	1.18X	NA	1.13X	NA	1.04X	NA	1.00X (1.00X)[f]	NA
Food Consumption (qualitative)	Greater than half the daily allotment of food was remaining in the cage on 4 to 7 days throughout the dosing phase in monkeys given 10 mg/kg/week. Additionally, there was a decrease in the consumption of citrus fruit in females given ≥3 mg/kg/week.							

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70260G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10	0	1	3	10
Hematology								
Neutrophil Count (x10E9/L)								
Day -5	5.588	3.673	3.824	3.890	5.942	6.290	4.472	5.300
Day 22	4.690	4.933	5.660	7.187	5.182	4.400	5.710	8.877
Day 106	6.355	NA	5.425	NA	4.530	NA	8.355	NA
Monocyte Count (x10E9/L)								
Day -5	0.306	0.240	0.204	0.330	0.336	0.217	0.182	0.207
Day 22	0.252	0.347	0.480	1.640	0.278	0.240	0.472	1.210
Day 106	0.150	NA	0.275	NA	0.155	NA	0.160	NA
Large Unstained Cell Count (x10E9/L)								
Day -5	0.048	0.047	0.042	0.053	0.034	0.023	0.030	0.037
Day 22	0.052	0.033	0.040	0.400	0.040	0.027	0.034	0.180
Day 106	0.030	NA	0.055	NA	0.020	NA	0.025	NA
Total White Blood Cell Count (x10E9/L)								
Day -5	10.686	9.077	8.416	10.437	10.400	8.870	7.648	7.930
Day 22	9.324	9.433	9.904	14.967	9.446	7.640	9.188	13.303
Day 106	9.890	NA	11.680	NA	8.245	NA	11.67	NA
Hemoglobin (g/L)								
Day -5	130.8	122.3	127.4	134.7 (132)[h]	123.2	124.7	122.6	125.0
Day 22	124.8	119.3	126.8	128.3 (108)[h]	120.2	120.7	116.2	104.0
Day 106	123.5	NA	130.0	NA	128.0	NA	119.0	NA

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70260G

		Male				Female			
Daily Dose (mg/kg/week)[a]		0	1	3	10	0	1	3	10
Total Red Blood Cell (x10E12/L)									
	Day -5	5.758	5.5	5.604	5.937 (6.09)[h]	5.118	5.497	5.438	5.380
	Day 22	5.406	5.290	5.642	5.833 (5.23)[h]	4.994	5.303	5.216	4.633
	Day 106	5.505	NA	5.935	NA	5.285	NA	5.265	NA
Hematocrit (L/L)									
	Day -5	0.438	0.410	0.428	0.457 (0.45)[h]	0.412	0.417	0.416	0.423
	Day 22	0.410	0.400	0.424	0.427 (0.37)[h]	0.408	0.413	0.388	0.360
	Day 106	0.415	NA	0.430	NA	0.415	NA	0.395	NA
Red Cell Distribution Width (%)									
	Day -5	12.48	12.17	12.60	12.23	12.36	12.47	12.16	11.90
	Day 22	12.80	12.67	12.82	14.50	12.48	12.97	12.48	15.43
	Day 106	12.65	NA	12.90	NA	11.90	NA	12.35	NA
Reticulocyte Count (x10E9/L)									
	Day -5	92.28	79.67	89.58	86.73	109.72	79.27	95.24	87.60 (69.9)[i]
	Day 22	97.48	95.13	85.88	113.47	112.68	84.00	84.96	194.50 (396.4)[i]
	Day 106	44.10	NA	55.85	NA	52.50	NA	41.95	NA
Platelet Count (x10E9/L)									
	Day -5	490.8	372.7	462.0	558.7	424.0	564.0	447.6	517.7
	Day 22	426.4	381.7	394.2	390.7	390.2	550.0	369.4	383.3
	Day 106	422.0	NA	336.0	NA	339.5	NA	446.5	NA

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70260G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10	0	1	3	10
Coagulation								
Activated Partial Thromboplastin Time (seconds)								
Day -5	19.64	19.97	19.3	21.33	19.82	19.43	19.98	21.57
Day 22	20.72	20.10	19.74	24.90	20.44	20.67	20.30	28.20
Day 106	24.60	NA	20.95	NA	20.30	NA	23.20	NA
Clinical Chemistry								
Aspartate Aminotransferase (U/L)								
Day -5	70.2	47.7	55.6	65.0	49.8	31.0	43.8	48.0
Day 22	49.2	58.7	91.2	459.3	48.4	34.7	86.4	624.0
Day 106	51.0	NA	41.5	NA	46.0	NA	49.5	NA
Glutamate Dehydrogenase (U/L)								
Day -5	22.72	16.70	18.26	25.80	16.50	14.97	11.56	16.03
Day 22	18.18	18.90	18.42	51.13	16.80	13.17	19.38	53.27
Day 106	23.70	NA	19.55	NA	22.50	NA	12.50	NA
Gamma Glutamyltransferase (U/L)								
Day -5	57.4	61.3	60.8	53.3	42.8	48.3	37.8	51.7
Day 22	61.8	55.7	72.0	97.7	40.2	46.7	38.6	105.3
Day 106	76.5	NA	93.0	NA	51.0	NA	38.5	NA
Alanine Aminotransferase (μg/L)								
Day -5	63.8	49.0	67.0	66.3	39.2	28.0	30.0	41.7
Day 22	47.4	49.0	62.2	93.0	41.0	34.0	38.0	91.0
Day 106	44.5	NA	51.5	NA	48.0	NA	31.0	NA

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70260G

		Male				Female			
Daily Dose (mg/kg/week)[a]		0	1	3	10	0	1	3	10
Total Bilirubin (μmol/L)									
	Day -5	3.34	3.37	2.62	3.43	2.58	4.60	3.36	3.50
	Day 22	2.68	3.20	2.66	5.97	2.56	2.53	2.76	5.80
	Day 106	4.15	NA	3.30	NA	2.20	NA	2.35	NA
Albumin (g/L)									
	Day -5	44.0	46.0	42.0	46.0 (46)[i]	43.0	42.7	42.8 (38)[f]	42.7
	Day 22	41.4	44.0	42.6	40.0 (37)[i]	42.0	44.3	42.2 (33)[f]	39.7
	Day 106	45.0	NA	42.0	NA	43.5	NA	42.0 (39)[f]	NA
C-Reactive Protein (mg/L)									
	Day -5	4.130	1.843	1.520	3.123	3.234	1.530	1.172	0.917
	Day 22	4.732	2.950	4.184	28.730	3.468	1.347	2.706	33.240
	Day 106	6.350	NA	2.535	NA	0.665	NA	0.645	NA
Cholesterol (mmol/L)									
	Day -5	4.062	3.580	3.488	3.407	3.438	3.797	3.514	3.977
	Day 22	3.626	3.443	3.818	5.193	3.268	3.710	3.790	4.730
	Day 106	3.415	NA	3.120	NA	3.510	NA	3.560	NA
Triglycerides (mmol/L)									
	Day -5	0.546	0.337	0.380	0.360	0.562	0.630	0.504	0.430
	Day 22	0.438	0.353	0.530	0.500	0.656	0.410	0.604	0.947
	Day 106	0.410	NA	0.605	NA	0.525	NA	0.550	NA
Immunoglobulin M (g/L)									
	Day -5	0.730	0.563	0.758	0.660	0.876	1.230	1.114	1.537
	Day 22	0.674	0.460	0.586	0.430	0.918	0.733	0.716	0.733
	Day 106	0.565	NA	0.410	NA	0.680	NA	0.735	NA

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70260G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10	0	1	3	10
Immunoglobulin G (g/L)								
Day -5	7.564	7.030	8.010	7.527	8.932	7.730	8.102	6.350 (7.07)[g], (4.66)[i]
Day 22	7.148	7.660	9.090	7.870	9.320	7.820	8.548	5.500 (5.50)[g], (3.69)[i]
Day 106	6.020	NA	7.475	NA	10.130	NA	8.655	NA
Urinalysis								
Urine Albumin:Creatinine (mg/mmol)								
Day -5	1.12	2.50	0.20	1.37 (0.1)[j]	0.70	1.57	0.58	1.50
Day 22	0.38	0.43	0.06	117.7 (347.9)[j]	1.10	19.40	3.56	3.90
Day 51	1.00	NA	0.40	NA	1.50	NA	1.80	NA
Day 79	0.45	NA	0.20	NA	0.10	NA	4.80	NA
Day 106	0.45	NA	0.40	NA	1.20	NA	1.05	NA
Total Protein:Creatinine (ratio)								
Day -5	85.8	127.7	112.8	104.7 (85)[j]	147.3	95.0 (94)[e]	118.5	117.3
Day 22	75.4	65.0	94.4	1355.0 (3852)[j]	121.0	892.7 (2240)[e]	236.8	167.3
Day 51	163.5	NA	175.0	NA	207.0	NA	157.0	NA
Day 79	113.5	NA	91.5	NA	93.0	NA	360.0	NA
Day 106	82.5	NA	105.5	NA	137.5	NA	159.0	NA

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70260G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10	0	1	3	10
Flow Cytometry								
NK Cells ($CD14^-/CD159a^+/CD3^-$) ($x10^6/mL$)[c]								
Day -5	0.54	0.29	0.57	0.64	0.39	0.22	0.28	0.14
Day 22	0.61X	0.48X	(2.03)[k] 0.23X (0.08X)[k]	0.17X	0.85X	1.05X	(0.34)[l],(0.49)[f] 0.39X (0.21X)[l],(0.12X)[f]	0.36X
Day 106	0.61X	NA	0.54X	NA	0.67X	NA	0.93X (0.82X)[l],(0.49X)[f]	NA
NK Cells ($CD14^-/CD159a^+/CD3^-$) (%)[c,o]								
Day -5	11.6	5.6	10.6	9.7	9.4	9.6	9.2	5.8
Day 22	0.67X	0.63X	(27.1)[k] 0.36X (0.15X)[k]	0.21X	0.97X	0.89X	(10.5)[l],(15.4)[f] 0.38X (0.31X)[l],(0.16X)[f]	0.34X
Day 106	0.79X	NA	0.51X	NA	0.76X	NA	0.93X (0.75X)[l],(0.60X)[f]	NA
Activated B Cells ($CD14^-/CD20^+/CD3^-/CD69^+$) ($x10^6/mL$)[c]								
Day -5	0.006	0.007	0.004	0.006	0.003	0.002	0.003	0.004
Day 22	0.67X	0.71X	1.25X	2.83X	1.33X	2.00X	1.00X	2.25X
Day 106	1.33X	NA	1.75X	NA	1.00X	NA	1.33X	NA
Activated B Cells ($CD14^-/CD20^+/CD3^-/CD69^+$) (%)[c]								
Day -5	0.6	0.5	0.5	0.6	0.5	0.7	0.8	1.1
Day 22	0.67X	0.80X	1.40X	3.33X	1.20X	1.29X	1.13X	3.18X
Day 106	2.50X	NA	1.20X	NA	1.40X	NA	1.13X	NA

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70260G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10	0	1	3	10
Microscopic Findings								
Numbers of Animals:								
Terminal Necropsy	3	3	3	3	3	3	3	3
Off-Dose Necropsy	2	0	2	0	2	0	2	0
Organ Weights								
Thymus[m]								
Terminal Necropsy								
absolute (g)	3.2480	1.04X	1.13X	0.75X	2.5097	0.49X	1.09X	0.42X
relative to body weight (%)	0.113	1.04X	1.15X	0.77X	0.093	0.46X	1.15X	0.40X
Recovery Necropsy								
absolute (g)	6.1800	NA	1.10X	NA	3.622	NA	0.94X	NA
relative to body weight (%)	0.185	NA	1.16X	NA	0.12	NA	1.17X	NA
Terminal Necropsy								
Spleen								
red pulp; increased macrophages								
minimal	0	0	2	2	0	0	1	3
mild	0	0	0	1	0	0	0	0
Bone Marrow (sternum)								
increased macrophages								
mild	0	0	0	2	0	0	0	0
moderate	0	0	0	0	0	0	0	3
Liver								
Kupffer Cell; mitotic increase; sinusoid; multifocal								
minimal	0	0	1	3	0	0	0	1

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70260G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10	0	1	3	10
Kidney								
mesangium; mitotic increase; glomerulus; multifocal								
minimal	0	0	0	2	0	0	0	1
glomerulopathy; multifocal								
mild	0	0	0	1[j]	0	0	0	0
distal nephron; degeneration/regeneration; multifocal;								
mild	0	0	0	1[j]	0	0	0	0

Belantamab Mafodotin: 3-Week (Once Weekly) Intravenous Dose Toxicity Study in Monkeys Followed by a 12-Week Off-Dose Period (Continued)

Study Type: Repeat-Dose Toxicity					**Study No.:** P70260G			
	Male				**Female**			
Daily Dose (mg/kg/week)[a]	0	1	3	10	0	1	3	10
Thymus								
cortex;tingible body macrophages;increased								
minimal	0	0	2	3	0	0	2	3
cellularity decreased; cortex								
minimal	0	0	0	2	0	0	0	0
moderate	0	0	0	0	0	0	0	2
Recovery Necropsy	There were no test article-related microscopic findings in monkeys euthanized at the end of the off-dose period.							

Key: NA=not applicable; NC=not calculable; ND=not determined

Belantamab mafodotin = GSK2857916.

a = Doses are expressed in terms of the antibody-drug conjugate (ADC), GSK2857916.

b = n=2

c = Group means (or individual values where indicated) are shown for baseline values (Day -5); X baseline values are shown for subsequent time points.

d = Terminal body weights obtained following overnight fasting showed a slight increase (0.97X baseline) in the weight of the female given 1 mg/kg/week while that for the female given 10 mg/kg/week remained unchanged.

e = Animal 251

f = Animal 354

g = Animal 451

h = Animal 400

i = Animal 452; increased reticulocyte counts in this female were associated with increased numbers of nucleated red blood cells and Howell-Jolly bodies on peripheral blood smear examination.

j = Animal 401

k = Animal 302

l = Animal 353

m = Absolute values are shown for control means for all time points while X control values are shown for groups given test article.

n = Cys-mcMMAF concentrations from samples collected during the off-dose period (3 mg/kg/week) were all below the LLQ (0.15 ng/mL) of the analytical method.

o = Percentage NK cells was determined from total lymphocytes which excluded $CD14^+$ monocytes.

p = During Weeks 1 and 3, plasma concentrations of cys-mcMMAF were quantifiable for up to at least 24 and 72 hours post dose for monkeys given 1 and 3 mg/kg/week, respectively, and for the entire 167-hour post dose sampling period for monkeys given 10 mg/kg/week.

Table 7.4 Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period

Study Type: Repeat Dose Toxicity	**Report Title:** GSK2857916: A 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period	**Test Item:** Belantamab mafodotin **Batch No.:** [redacted]
Species/Strain: Cynomolgus Monkey	**Duration of Dosing:** up to 13 weeks **Duration of Off-dose:** 12 weeks	**GSK Reference No.:** P71346G
Initial Age: 2 years	**Route/Frequency:** Intravenous injection / once weekly	**GSK Document Number:** 2018N375127
Date of First Dose: 09 Jan 2018	**Vehicle Formulation:** 25 mM aqueous Citrate buffer containing 0.05 mM EDTA, 200 mM Trehalose and 0.02% Polysorbate 80 (pH 6.2)	**Study in Compliance with GLP:** Yes

Data Collected: Toxicokinetics, clinical observations, body weight, food evaluation, veterinary physical examinations, ophthalmoscopy, electrocardiography, hematology, coagulation, clinical chemistry, urinalysis, urinary renal biomarker, acute phase protein (c-reactive protein), immunoglobulin (IgG and IgM), immunogenicity, cytokines, immunophenotyping, complement C3a, Bb and C5a (0 and 1 mg/kg/week only), immunohistochemistry, organ weights, and macroscopic and microscopic observations and pathology.

Conclusion: Belantamab mafodotin at 0 (vehicle), 1, 3 and 10 mg/kg/week was administered once weekly by intravenous injection to male and female cynomolgus monkeys for up to 13 weeks, followed by a 12-week off-dose period (0, 3 and 10 mg/kg/week). Belantamab mafodotin administration at 10 mg/kg/week resulted in a deteriorating condition that necessitated cessation of dosing after 5 doses (Week 5/Day 29), with the early euthanasia of one male on Day 33, and necropsy of the remaining main study monkeys given 10 mg/kg/week during Week 7. The 12-week off-dose phase for the high dose concluded in Week 17.

At 10 mg/kg/week, adverse pathological changes were noted in the kidneys (tubular degeneration/regeneration and/or membranoproliferative glomerulonephritis and necrosis of the kidney urothelium); in the esophagus and intestinal tract, mesenteric lymph node, and thymus (minimal to moderate fibrinoid necrosis, hemorrhage and/or thrombosis in one or several blood vessels), and in the spleen, various lymph nodes, and thymus (decreased lymphoid cellularity with or without lymphoid necrosis). Minimal hepatocellular necrosis was considered adverse based on its correlation with increases in liver enzymes. Microscopic changes at 10 mg/kg/week were no longer present following the 12-week off-dose period except for the evidence of minimal chronic vascular/perivascular inflammation in several blood vessels of the intestinal tract in one monkey that likely represents partial recovery.

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

The belantamab mafodotin-related microscopic finding at 3 mg/kg/week, which was considered adverse based on its correlation with the increases in liver enzymes, was limited to the minimal hepatocellular necrosis.

In addition to adverse findings noted above, non-adverse inflammatory microscopic findings included reversible increases in macrophages (with occasional increase in mitoses) in the bone marrow, red pulp of the spleen, thymus and brain (in choroid plexus only); Kupffer cell hypertrophy/hyperplasia (with occasional mitoses and/or single cell necrosis) and extramedullary hematopoiesis in the liver; increase in mitoses in the kidney interstitial tissue and/or mesangium (10 mg/kg/week only); increased myeloid cellularity in the bone marrow; and an increase in mitoses in the medulla and extramedullary hematopoiesis in various lymph nodes, were seen at ≥ 3 mg/kg/week. Systemic inflammation at ≥ 3 mg/kg/week was characterized by increased MCP-1 concentrations (≥1 mg/kg/week), increased neutrophil, monocyte and large unstained cell counts (10 mg/kg/week only) and C-reactive protein (10 mg/kg/week only) and fibrinogen concentrations, with decreased red cell mass parameters (10 mg/kg/week only), including platelet and reticulocyte counts. In addition, mild increases were noted for complement components Bb and C3a (no effect for C5a) at 1 mg/kg/week (only dose evaluated). At 10 mg/kg/week, red blood smear morphological changes, suggestive of red blood cell membrane damage, were related, 2 weeks after the last dose, to decreases in red blood cell mass, with evidence of regeneration including increases in red blood cell distribution width and mild increases in reticulocyte counts. Hematology changes were no longer observed at the end of the off-dose period. Associated with the bone marrow changes were minimal increases in M:E ratio, with a slight increase in the number of active macrophages, a slight left shift in the maturation sequence of the erythroid cell line and a slight increase in the number of metarubricytes with irregular nuclear shapes in one male at 10 mg/kg/week and in all females dosed at ≥ 3 mg/kg/week. Following the 12-week dose off period, a slight increase in the number of metarubricytes with binucleation and mitotic figures was observed at 10 mg/kg/week, with a minimal increase in the proportion of early precursors (mainly rubricytes) in one of the affected females. At 3 mg/kg/week, a minimal decrease in the M: E ratio was still present.

A belantamab mafodotin-related decrease in NK cell absolute counts and relative percentage was observed in males at 10 mg/kg/week in Weeks 4 and 7, in one male at 3 mg/kg/week in Week 13, and in females at ≥ 3 mg/kg/week in Weeks 4, 7 and 13. Following a 12-week off-dose period, these changes were not fully recovered.

In addition, seminiferous tubule degeneration noted in the testis at 10 mg/kg/week was fully reversible after 12-week off-dose.

One male given 1 mg/kg/week, experienced a robust and specific antibody response to belantamab mafodotin with evidence of circulating immune complex (CIC), decreased systemic exposure and pharmacodynamic activity (IgM concentrations), clinical signs of excessive salivation at the time of injection, elevated MCP-1 serum levels and increased Bb and C3a concentrations. During the dosing phase, low titer ADA were also detected in all monkeys given ≥3 mg/kg/week, without evidence of reduced exposure. Circulating immune complex (CIC), was detected in 2 animals given 1 mg/kg/week and 3 animals given 3 mg/kg/week at varying timepoints. Findings consistent with immune complex disease, including glomerulonephritis, vasculitis, immune complex deposition by IHC, changes in red blood cell morphology, and subsequent deteriorating clinical condition in several high dose monkeys and infusion reactions observed in one low dose male were likely associated with ADA.

As adverse microscopic findings were noted in the liver (hepatocellular necrosis with correlating increases in liver enzymes) in monkeys given 3 mg/kg/week, the no observed adverse effect level (NOAEL) for this study was considered to be 1 mg/kg/week (mean AUC(0-t) 1130 µg.h/mL, range 882 to 1370 and mean Cmax 27.3 µg/mL, range 25.0 to 30.4 [gender averaged, based on Week 13 values]).

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity — **GSK Reference No.:** P71346G

Daily Dose (mg/kg/week)[a]		Male				Female			
		0	1	3	10 [b]	0	1	3	10 [b]
Numbers of Animals:	**Main**	3	3	3	3	3	3	3	3
	Off-dose	2	0	2	2	2	0	2	2
Toxicokinetic[c]									
GSK2857916 (ADC)									
AUC(0-t) (µg.h/mL)	Week 4 (**Day** 22)	NC	1360 (1020) [d]	5200	21600	NC	1050	5260	21400
	Week 13 (**Day** 85)	NC	1280 (1050)[d]	6570	NA	NC	1030	6870	NA
C_{max} (µg/mL)	**Day** 22	NC	27.2 (26.5) [d]	81.8	302	NC	26.7	85.6	320
	Day 85	NC	27.7 (27.4) [d]	94.6	NA	NC	27.0	93.2	NA
GSK2857916 (mAb)									
AUC(0-t) (µg.h/mL)	**Day** 22	NC	1640 (1210) [d]	5960	30200	NC	1200	6010	28600
	Day 85	NC	1700 (1140) [d]	8140	NA	NC	1370	7930	NA
C_{max} (µg/mL)	**Day** 22	NC	27.1 (26.7) [d]	88.5	380	NC	26.2	94.1	356
	Day 85	NC	28.2 (22.4) [d]	103	NA	NC	29.5	104	N/A
cys-mcMMAF									
AUC(0-t) (ng.h/mL)	**Day** 22	NC	5.12	23.1	NR	NC	NC [g]	31.2	NR
	Day 85	NC	NA [e]	25.1	NA	NC	NC [g]	25.5	NA
C_{max} (ng/mL)	**Day** 22	NC	0.129	0.388	NR	NC	0.232	0.437	NR
	Day 85	NC	NQ[f]	0.396	NA	NC	0.196	0.433	NA

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Noteworthy Findings								
Unscheduled Deaths								
Main	0	0	0	3	0	0	0	3
Off-dose	0	0	0	0	0	0	0	0
Mortality	On Day 33 (Week 5; 4 days after the 5[ti] dose), one male, Animal No. 4004, given 10 mg/kg/week, was euthanized *in extremis* due to its moribund state. In consideration of the early termination of Animal No. 4004, dosing at 10 mg/kg/week was discontinued (last dose given on Day 29/Week 5) and, based on the deteriorating condition and the severity of the changes following review of preliminary data (including red cell mass/morphology changes) collected during Week 6/5 of the surviving animals given 10 mg/kg/week, animals were euthanized (scheduled euthanasia) on Day 45 (males)/43 (females) (Week 7). Severe tubular degeneration/regeneration and marked glomerulonephritis in the kidneys was considered the primary histopathological change leading to early euthanasia of Animal No. 4004. However, the acute presentation of the vascular changes in the gastro-intestinal tract (fibrinoid vascular necrosis) with secondary hemorrhages and fluid accumulation in the abdominal cavity (ascites seen grossly) likely contributed to the severe deteriorating condition of the animal in the hours prior to its euthanasia. Since renal tubular changes were aggravated by glomerulonephritis and vascular changes were also considered related to immune complexes, the ultimate cause of moribundity leading to euthanasia in this monkey was likely associated with immune complex formation. Additional belantamab mafodotin-related findings noted in monkeys given 10 mg/kg/week are outlined below.							
Clinical Observations	Additionally, when compared to control and lower-dosed animals, an increased incidence (in the frequency and/or number of affected animals) and severity (slight to severe) of firm swelling/mass in the inguinal region (in proximity to the area of blood collection), occasionally with discharge either unilaterally or bilaterally, was noted transiently from Day 31 until necropsy in males and females given ≥3 mg/kg/week. These observation, often accompanied by blue/red discolored skin, correlated with the moderate to marked hemorrhages (consistent with encapsulated hematomas) in the skeletal muscle of the inguinal region(s) (with clot or masses seen grossly). During the first 6 weeks of the off-dose period, observations of firm swelling (inguinal) were made in females previously given 10 mg/kg/week but completely resolved toward Week 12. One male given 1 mg/kg/week, No. 2002, had moderate salivation immediately after dose administration in Weeks 11 and 12 (Day 71 and 78). These observations were considered a possible systemic reaction to the administration of belantamab mafodotin, as evidenced by the findings noted in the immunogenicity endpoint for this animal.							

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Food Evaluation	Consistent with the clinical observations of thinness/prominent backbone noted at 10 mg/kg/week, there was an increased incidence in the frequency and/or number of affected animals of reduced appetite in males and females given 10 mg/kg/week only during Week 5 of dose administration (Days 30 to 34), when compared to controls and lower-dosed animals. There was no effect on appetence noted during the12-week off-dose period.							
Electrocardiography (Quantitative data analysis)	At 10mg/kg/week, no belantamab mafodotin-related effects in electrocardiographic parameters (PR, QRS, QT and QTc) were observed in males and females at Week 5. An increase in heart rate was noted during Week 5 in males alone from 4 to 18 hours post dose. Over this time period, an average increase of 19.6 beats per minute (16%), relative to the pretreatment values, was noted in males administered 10mg/kg/week compared to an average decrease of 13.2 beats per minute (9%), relative to the pretreatment values, in control animals. No changes in heart rate were noted in female animals.							
Hematology								
Neutrophil count (10^9/L)								
Baseline (Week -1)	5.940	6.250	6.268	6.986	5.660	8.190	3.592	6.826
Week 4	5.514	7.413	7.604	5.010	4.630	5.310	7.940	10.156
Week 6/5 (Day 36/34)	3.154	-	-	4.563	4.256	-	-	6.648
Week 7 (Day 45/43)	-	-	-	5.675	-	-	-	7.984
Week 13	6.888	8.683	9.386	-	5.488	4.217	4.964	-
Week 17	-	-	-	5.025	-	-	-	5.430
Week 25	7.855	-	5.455	-	2.845	-	4.740	-
Monocyte count (10^9/L)								
Baseline (Week -1)	0.168	0.180	0.188	0.172	0.214	0.257	0.136	0.210
Week 4	0.174	0.287	0.396	1.008	0.260	0.267	0.312	1.440
Week 6/5 (Day 36/34)	0.424	-	-	0.573	0.402	-	-	0.908
Week 7 (Day 45/43)	-	-	-	0.673	-	-	-	0.914
Week 13	0.248	0.230	0.620	-	0.214	0.317	0.450	-
Week 17	-	-	-	0.215	-	-	-	0.315
Week 25	0.240	-	0.330	-	0.300	-	0.165	-
Large unstained cells count (10^9/L)								
Baseline (Week -1)	0.056	0.053	0.050	0.044	0.034	0.090	0.038	0.042

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Week 4	0.062	0.043	0.064	0.225	0.036	0.060	0.044	0.253
Week 6/5 (Day 36/34)	0.106	-	-	0.195	0.054	-	-	0.372
Week 7 (Day 45/43)	-	-	-	0.200	-	-	-	0.402
Week 13	0.068	0.070	0.120	-	0.040	0.083	0.078	-
Week 17	-	-	-	0.055	-	-	-	0.055
Week 25	0.055	-	0.070	-	0.060	-	0.045	-
Platelet count (10^9/L)								
Baseline (Week -1)	387.0	437.3	533.8	418.6	418.2	539.0	377.4	488.4
Week 4	365.2	423.3	461.0	235.8	385.4	497.7	353.0	352.4
Week 6/5 (Day 36/34)	394.0	-	-	341.3	425.0	-	-	348.8
Week 7 (Day 45/43)	-	-	-	374.8	-	-	-	346.0
Week 13	377.8	433.7	408.8	-	407.8	526.7	368.8	-
Week 17	-	-	-	430.0	-	-	-	507.5
Week 25	445.5	-	542.0	-	512.5	-	363.5	-
Red blood cells count (10^{12}/L)								
Baseline (Week -1)	5.416	5.280	5.042	5.272	5.136	5.013	4.972	5.194
Week 4	5.530	5.553	5.212	5.644	5.394	5.350	5.520	5.822
Week 6/5 (Day 36/34)	5.272	-	-	4.148	5.028	-	-	5.000
Week 7 (Day 45/43)	-	-	-	4.873	-	-	-	4.890
Week 13	5.542	5.727	4.886	-	5.454	5.493	5.368	-
Week 17	-	-	-	5.570	-	-	-	5.725
Week 25	5.915	-	5.820	-	5.480	-	5.430	-
Reticulocyte count (absolute; 10^9/L)								
Baseline (Week -1)	67.68	82.07	141.58	86.98	90.80	78.53	77.84	87.88
Week 4	61.38	77.33	136.68	87.22	66.10	50.47	47.10	64.18
Week 6/5 (Day 36/34)	133.40	-	-	162.4	110.82	-	-	110.38
Week 7 (Day 45/43)	-	-	-	217.23	-	-	-	191.32
Week 13	49.24	46.70	147.72	-	38.92	44.17	31.42	-
Week 17	-	-	-	56.55	-	-	-	50.25
Week 25	72.20	-	58.20	-	77.25	-	56.05	-

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Hemoglobin (g/L)								
Baseline (Week -1)	133.4	129.7	125.0	133.2	130.8	124.3	126.4	130.0
Week 4	136.8	137.7	128.4	137.4	139.4	133.7	138.6	140.6
Week 6/5 (Day 36/34)	129.4	-	-	97.0	126.2	-	-	115.8
Week 7 (Day 45/43)	-	-	-	114.5	-	-	-	114.6
Week 13	133.6	135.0	117.2	-	135.4	131.7	129.8	-
Week 17	-	-	-	132.5	-	-	-	135.5
Week 25	137.5	-	132.0	-	138.0	-	131.0	-
Hematocrit (%)								
Baseline (Week -1)	40.14	38.83	38.16	39.20	38.54	38.33	38.60	38.64
Week 4	41.46	41.37	39.20	41.16	41.02	41.00	42.54	41.84
Week 6/5 (Day 36/34)	41.50	-	-	31.43	39.54	-	-	37.12
Week 7 (Day 45/43)	-	-	-	37.73	-	-	-	36.60
Week 13	41.96	42.93	37.72	-	41.26	42.07	41.02	-
Week 17	-	-	-	42.50	-	-	-	42.45
Week 25	43.85	-	44.05	-	42.70	-	41.75	-
Red blood cell distribution width (%)								
Baseline (Week -1)	12.74	12.33	13.14	13.10	12.94	12.37	12.78	12.80
Week 4	12.88	12.30	13.00	14.48	12.90	12.43	12.92	13.56
Week 6/5 (Day 36/34)	13.00	-	-	18.58	13.00	-	-	14.96
Week 7 (Day 45/43)	-	-	-	18.93	-	-	-	16.32
Week 13	12.32	12.03	13.14	-	12.24	12.00	12.76	-
Week 17	-	-	-	14.20	-	-	-	13.45
Week 25	13.25	-	12.95	-	12.85	-	12.65	-

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity — **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Blood Smear	On Week 4, red blood smear morphological examination revealed the presence of minimal to mild degree of schistocytes and/or spherocytes and/or central pallor in males and females at 10mg/kg/week and were suggestive of red blood cell membrane damage, with occasional nucleated redblood cells. In addition, other morphological changes, such as anisocytosis and/or polychromasia were observed in both, control and GSK3857916-treated animals but were sometimes of greater severity in animals at 10mg/kg/week. Occasional red blood cell morphological changes observed in Week 4 were still present in Week 7 in few males and females at 10mg/kg/week.							
Myeloid:Erythroid Ratio	There were minimal increases in the M:E ratio in 3/3 females at 3 mg/kg/week and in 1/2males at 10mg/kg/week. In addition, there was a slight increase in the number of active macrophages on bone marrow smears of 1/2 males and in 3/3 females at 10mg/kg/week, with a slight left shift in the maturation sequence of the erythroid cell line, due to a slight increase in the proportion of prorubricytes and rubricytes and associated with a slight increase in the number of metarubricytes with irregular nuclear shapes, including binucleation, presence of nuclear blebs and/or mitotic figures. Following the 12-week off-dose period, a slight increase in the number of metarubricytes with binucleation and mitotic figures was observed at Week 17 in 1 female at 10mg/kg/week, and a minimal increase in the proportion of early precursors (mainly rubricytes) in the other female at 10 mg/kg/week. At Week 25, a minimal decreasein the M: E ratio was still present in 1/2 males and in 2/2 females at 3 mg/kg/week.The changes in erythroid cell lineage were indicative of increased erythropoiesis.							
C-Reactive Protein								
Week -1	28.294	-	-	23.902	15.034	-	-	13.390
Week 4	21.950	-	-	112.038	9.210	-	-	23.760
Week 6/5 (Day 36/34)	18.294	-	-	208.198	8.614	-	-	23.162
Week 7 (Day 45/43)	-	-	-	41.870	-	-	-	30.954
Week 17	-	-	-	16.265	-	-	-	10.415
Renal Biomarkers								
UABC (mg/mmol)								
Week -1	0.30	-	-	0.62	1.34	-	1.32	0.68
Week 4	0.28	-	-	71.59	0.60	-	0.83	5.60
Week 6/5 (Day 36/34)	0.35	-	-	43.64	1.41	-	-	24.59
Week 7 (Day 45/43)	-	-	-	13.99	-	-	-	27.37
Week 13	0.34	-	-	-	0.59	-	3.91	-
Week 17	-	-	-	0.26	-	-	-	0.56
Week 25	0.49	-	3.90	-	2.19	-	2.24	-

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
UTPC (ratio)								
Week -1	0.063	-	-	0.080	0.119	-	0.082	0.067
Week 4	0.066	-	-	1.316	0.093	-	0.066	0.178
Week 6/5 (Day 36/34)	0.049	-	-	1.048	0.079	-	-	0.519
Week 7 (Day 45/43)	-	-	-	0.377	-	-	-	0.500
Week 13	0.050	-	-	-	0.064	-	0.348	-
Week 17	-	-	-	0.062	-	-	-	0.038
Week 25	0.048	-	4.530	-	0.073	-	0.090	-
Immunogenicity	The observations of concomitant changes seen in three immunogenicity methods (2 anti- belantamab mafodotin antibody assays and a circulating immune complex assay) indicate one male, Animal No.2002 given 1mg/kg/week, experienced a robust and specific antibody response to belantamab mafodotin; anti- belantamab mafodotin antibody (ADA) with increasing titer (up to 12800) over time and evidence of circulating immune complex (CIC). Decreased systemic belantamab mafodotin plasma concentrations were noted in this animal beginning Week 4, concurrent with emergence of ADA, and, by Week 13, had IgM values similar to those noted pre-study for the animal suggesting loss of belantamab mafodotin activity. This male, at Weeks 11 and 12, also showed clinical signs of excessive salivation at the time of injection and had elevated MCP-1 serum levels (4.2X upper limits of normal), and increased Bb and C3a concentrations (1.6X and 1.8X upper limits of normal, respectively) at one-hour post dose in Week 13. ADA were also detected in all monkeys in 3 or 10 mg/kg/week groups, and CIC was detected in 2 animals given 1mg/kg/week and 3 males, given 3mg/kg/week at varying timepoints during the dosing phase (ADA titer 200; near sensitivity limit of the ADA method). With the exception of Animal No. 2002, the presence of ADA did not lead to decreased exposures during the dosing phase therefore, the toxicity assessment in this study was considered to be valid. During the off-dose phase, 2 monkeys each given 3 and 10mg/kg/week confirmed positive for ADA at Weeks 17 and/or 25. One male and one female given 3mg/kg/week, had positive results with titers less than the cut point (the male at Week 17) and 800 (male and female at Week 25). Two male monkeys, given 10mg/kg/week, each had confirmed positive result at Week 17, with titers of 8000 and 4000, respectively. During the dosing phase, the highest reported titer for animals testing positive during the off-dose phase was less than the cut point or 200. The increase in titer in positive samples during the off-dose phase may be attributed to a decline in the amount of drug-ADA complex as drug is cleared and the presence of free ADA detected using the CIC method during the wash out period.							

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Immunophenotyping								
Natural-killer Cells								
Absolute count (cells/µL)								
Week -1	414.902	227.290	552.316	376.876	353.808	510.217	255.710	345.618
Week 4	305.888	237.573	322.566	122.370	352.822	559.873	159.498	136.982
Week 7 (Day 45/43)	-	-	-	153.905	-	-	-	209.984
Week 13	435.246	247.447	343.528	-	294.226	491.267	123.820	-
Week 17	-	-	-	444.890	-	-	-	447.465
Week 25	391.865	-	113.740	-	478.605	-	148.140	-
Relative percentage (%)								
Week -1	11.220	5.503	13.560	9.834	13.192	14.433	9.742	11.344
Week 4	8.844	7.233	8.182	2.368	12.134	13.630	6.454	3.954
Week 7 (Day 45/43)	-	-	-	2.873	-	-	-	4.598
Week 13	8.510	5.307	5.894	-	9.956	8.430	3.574	-
Week 17	-	-	-	6.465	-	-	-	8.635
Week 25	9.545	-	2.180	-	10.580	-	4.280	-
Cytokines								
MCP-1								
Week 1 predose	250.350	284.357	245.414	215.922	234.852	241.367	181.532	166.196
Week 4 predose	148.444	188.523	191.440	940.248	141.994	162.707	131.886	634.944
Day 22 predose	168.644	156.943	156.783	1132.587	<150.000	<150.000	<150.000	580.622
Day 22 0.25 hour post dose	<150.000	<150.000	<150.000	1152.146	<150.000	<150.000	<150.000	462.699
Day 22 3 hours post dose	184.338	795.376	204.320	1518.265	152.461	159.413	157.734	704.165
Day 22 24 hours post dose	186.266	256.511	390.600	2075.743	<150.000	182.577	314.269	1132.162

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Week 7 predose	-	-	-	560.788	-	-	-	693.024
Week 13 predose	193.396	214.327	367.012	-	126.436	142.357	194.184	-
Week 13 1 hour post dose	223.332	831.537	-	-	132.260	249.850	-	-
Week 17	-	-	-	243.710	-	-	-	155.935
Week 25	189.310	-	279.560	-	139.765	-	127.160	-
Complements								
C3a (pg/mL)								
Week 13 1 hour post dose	8438.358	16727.440	-	-	6361.976	11935.367	-	-
Bb (ng/mL)								
Week 13 1 hour post dose	1293.078	2271.160	-	-	1319.102	2733.093	-	-
Immunoglobulins								
IgM (g/L)								
Week -1	0.696	0.827	0.784	0.578	0.770	0.907	0.712	0.996
Week 4	0.616	0.587	0.386	0.374	0.800	0.627	0.442	0.768
Week 7	-	-	-	0.293	-	-	-	0.670
Week 13	0.542	0.570	0.262	-	0.692	0.377	0.318	-
Week 17	-	-	-	0.360	-	-	-	0.800
Week 25	0.605	-	0.670	-	0.830	-	0.450	-
IgG (g/L)								
Week -1	9.180	8.207	8.618	7.232	8.418	8.923	9.044	8.836
Week 4	9.306	9.643	9.040	8.272	8.858	9.150	10.564	10.214
Week 7	-	-	-	8.983	-	-	-	9.864
Week 13	8.668	9.957	10.298	-	8.326	8.610	12.204	-
Week 17	-	-	-	9.285	-	-	-	9.760
Week 25	9.375	-	7.890	-	7.150	-	7.960	-

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Coagulation								
Fibrinogen (g/L)								
Baseline (Week -1)	2.244	2.510	2.638	2.276	2.278	2.243	2.050	2.220
Week 6/5 (Day 36/34)	2.208	-	-	2.740	2.084	-	-	2.652
Week 7 (Day 45/43)	-	-	-	2.545	-	-	-	2.628
Week 13	2.192	2.890	2.524	-	2.336	2.230	2.692	-
Week 17	-	-	-	2.430	-	-	-	2.310
Week 25	2.630	-	2.275	-	2.020	-	1.915	-
Activated partial thromboplastin time (sec)								
Baseline (Week -1)	24.36	27.37	23.88	23.82	23.43	26.70	24.38	23.12
Week 6/5 (Day 36/34)	22.46	-	-	25.20	21.98	-	-	28.02
Week 7 (Day 45/43)	-	-	-	26.00	-	-	-	27.06
Week 13	23.66	24.30	22.62	-	22.66	24.33	22.24	-
Week 17	-	-	-	24.35	-	-	-	23.50
Week 25	23.30	-	23.80	-	22.25	-	23.75	-
Clinical Chemistry								
Aspartate aminotransferase (U/L)								
Baseline (Week -1)	47.2	49.0	46.2	41.8	36.4	35.3	42.4	38.6
Week 4	48.6	54.3	68.0	436.3	35.0	36.3	68.8	381.2
Week 6/5 (Day 36/34)	46.8	-	-	531.3	33.2	-	-	593.8
Week 7 (Day 45/43)	-	-	-	281.3	-	-	-	364.0
Week 13	48.0	56.3	108.2	-	29.4	40.0	106.6	-
Week 17	-	-	-	54.0	-	-	-	37.5
Week 25	40.0	-	42.0	-	25.0	-	36.0	-

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Alanine aminotransferase (U/L)								
Baseline (Week -1)	43.0	45.7	53.0	46.4	38.8	40.7	39.4	43.4
Week 4	34.6	47.3	56.6	97.6	35.0	35.7	42.2	84.8
Week 6/5 (Day 36/34)	36.8	-	-	89.5	29.8	-	-	95.2
Week 7 (Day 45/43)	-	-	-	86.5	-	-	-	82.8
Week 13	39.6	49.0	63.4	-	31.0	35.0	53.6	-
Week 17	-	-	-	61.0	-	-	-	32.5
Week 25	55.0	-	51.0	-	26.5	-	38.0	-
Gammaglutamyl transferase (U/L)								
Baseline (Week -1)	77.8	69.3	66.8	71.2	51.6	43.3	49.8	43.4
Week 4	90.2	82.7	83.4	131.8	58.4	54.3	64.4	89.2
Week 6/5 (Day 36/34)	89.2	-	-	134.5	53.2	-	-	105.0
Week 7 (Day 45/43)	-	-	-	104.0	-	-	-	96.6
Week 13	99.6	86.3	90.8	-	57.4	60.7	76.6	-
Week 17	-	-	-	90.5	-	-	-	55.0
Week 25	102.0	-	96.0	-	64.0	-	60.0	-
Glutamate dehydrogenase (U/L)								
Baseline (Week -1)	20.64	23.53	15.20	20.52	15.18	13.63	11.82	16.20
Week 4	20.06	26.80	19.18	65.32	14.26	14.20	13.12	58.78
Week 6/5 (Day 36/34)	26.88	-	-	65.00	14.92	-	-	90.30
Week 7 (Day 45/43)	-	-	-	44.43	-	-	-	58.58
Week 13	25.28	26.47	22.72	-	13.52	17.43	15.18	-
Week 17	-	-	-	51.15	-	-	-	22.50
Week 25	20.65	-	24.15	-	16.85	-	9.90	-

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Alkaline phosphatase (U/L)								
Baseline (Week -1)	611.0	611.7	581.2	629.0	375.2	450.0	455.6	477.8
Week 4	651.4	704.3	602.2	1008.6	421.2	483.0	581.8	568.6
Week 6/5 (Day 36/34)	588.0	-	-	843.3	372.2	-	-	587.6
Week 7 (Day 45/43)	-	-	-	632.8	-	-	-	527.2
Week 13	697.8	719.3	580.6	-	439.6	468.3	569.8	-
Week 17	-	-	-	725.5	-	-	-	471.0
Week 25	736.5	-	558.5	-	427.0	-	491.5	-
Cholesterol (mmol/L)								
Baseline (Week -1)	3.294	3.213	3.260	3.468	3.234	3.483	3.170	3.486
Week 4	3.248	3.463	3.872	4.028	3.560	3.940	3.542	4.696
Week 6/5 (Day 36/34)	3.040	-	-	4.305	3.080	-	-	3.838
Week 7 (Day 45/43)	-	-	-	4.275	-	-	-	4.110
Week 13	3.056	3.240	3.482	-	3.350	3.747	3.310	-
Week 17	-	-	-	3.050	-	-	-	2.970
Week 25	3.620	-	3.425	-	3.320	-	3.255	-
Phosphorus (mmol/L)								
Baseline (Week -1)	2.158	2.313	2.182	2.254	1.950	2.023	1.960	2.140
Week 4	2.220	2.420	2.098	2.095	2.000	1.990	1.958	1.944
Week 6/5 (Day 36/34)	1.838	-	-	1.228	1.576	-	-	1.684
Week 7 (Day 45/43)	-	-	-	2.308	-	-	-	2.100
Week 13	2.176	2.187	1.924	-	1.970	2.153	2.026	-
Week 17	-	-	-	2.245	-	-	-	2.050
Week 25	2.115	-	2.305	-	1.920	-	2.070	-

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Albumin (g/L)								
Baseline (Week -1)	43.6	45.3	43.2	44.8	44.0	43.7	49.6	46.4
Week 4	43.6	45.7	41.4	39.2	44.8	42.7	47.8	41.4
Week 6/5 (Day 36/34)	41.4	-	-	32.0	42.2	-	-	38.0
Week 7 (Day 45/43)	-	-	-	34.5	-	-	-	38.4
Week 13	40.0	41.0	37.4	-	40.2	40.7	45.2	-
Week 17	-	-	-	42.5	-	-	-	46.0
Week 25	42.0	-	46.0	-	45.5	-	47.0	-
Direct Bilirubin (µmol/L)								
Week 7 (Day 45/43)	-	-	-	0.78	-	-	-	0.94
Week 13	0.72	0.23	0.66	-	1.02	0.30	0.62	-
Week 17	-	-	-	1.40	-	-	-	1.10
Week 25	0.95	-	0.85	-	0.85	-	1.00	-
Indirect Bilirubin (µmol/L)								
Week 7 (Day 45/43)	-	-	-	1.48	-	-	-	2.10
Week 13	1.40	2.37	1.36	-	1.78	1.83	2.20	-
Week 17	-	-	-	2.50	-	-	-	2.40
Week 25	2.40	-	1.40	-	2.70	-	3.35	-
Organ Weights (X control)[i]								
Terminal Necropsy								
Thymus	5.1980	0.52	0.45	0.04	2.4410	1.15	0.43	0.16
Relative to brain weight	7.74066	0.50	0.48	0.05	3.47987	1.25	0.45	0.16
Relative to body weight	0.19594	0.55	0.47	0.05	0.09514	1.13	0.41	0.16
Kidney	11.0497	1.03	0.96	1.31	10.2857	1.09	1.20	1.29
Relative to brain weight	16.55749	0.99	1.04	1.35	14.73476	1.20	1.23	1.35
Relative to body weight	0.41582	1.09	1.04	1.40	0.40623	1.05	1.12	1.31

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Liver	49.2013	1.10	1.02	1.29	49.2887	1.15	1.13	1.21
Relative to brain weight	74.75219	1.04	1.08	1.31	71.02325	1.26	1.15	1.26
Relative to body weight	1.84464	1.17	1.10	1.39	1.94930	1.10	1.05	1.23
Macroscopic Examination Terminal Necropsy (number of animals)	3	3	3	3	3	3	3	3
Kidney								
Discoloration; dark	0	0	0	1	0	0	0	1
Discoloration; pale	0	0	0	1	0	0	0	0
Focus; dark	0	0	0	1	0	0	0	1
Thymus								
Small	0	0	1	3	1	0	2	3
Focus; dark	0	1	0	0	0	0	0	0
Liver								
Focus; dark	0	0	1	0	0	0	0	3
Focus; pale	2	1	1	0	1	2	0	1
Discoloration; mottled	0	0	0	0	0	0	0	1
Spleen								
Enlargement	0	0	1	3	0	0	0	3
Focus; pale	1	1	1	2	0	1	0	2
Focus; raised	0	0	0	0	0	1	0	0
Nodule	0	0	1	0	0	0	0	0
Adipose tissue								
Mass	0	0	1	0	0	0	0	0
Gland, adrenal								
Discoloration; mottled	0	0	0	1	0	0	0	0

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Focus; dark	0	0	0	0	1	0	0	0
Lymph node, Inguinal								
Focus; dark	0	0	0	2	0	0	0	3
Enlargement	0	0	0	1	0	0	0	0
Small intestine, Duodenum								
Focus; pale	0	0	0	0	0	0	0	1
Focus; raised	0	0	1	0	0	0	0	1
Small intestine, Ileum								
Focus; dark	0	0	0	1	0	0	0	0
Small intestine, Jejunum								
Abnormal content; dark	0	0	1	0	0	0	0	0
Large intestine, Cecum								
Focus; raised	0	0	0	1	0	0	0	0
Large intestine, Colon								
Focus; raised	0	0	0	1	0	0	0	0
Focus; dark	0	1	0	0	0	0	0	0
Large intestine, Rectum								
Focus; dark	0	0	0	1	0	0	0	0
Body Cavity, Abdominal								
Fluid accumulation; pale	0	0	0	1	0	0	0	0
Microscopic Examination Main Study Animals (number of animals)	3	3	3	3	3	3	3	3
Kidney [j]								
Examined	3	3	3	3	3	3	3	3
No visible lesions	0	2	1	0	1	1	0	0

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

		Male				Female			
Daily Dose (mg/kg/week)[a]		0	1	3	10 [b]	0	1	3	10 [b]
Necrosis; urothelial	Mild	0	0	0	1 [h]	0	0	0	0
Degeneration/regeneration; tubular		0	0	0	3	0	0	0	2
	Minimal	0	0	0	1	0	0	0	2
	Mild	0	0	0	1	0	0	0	0
	severe	0	0	0	1 [h]	0	0	0	0
Glomerulonephritis; membranoproliferative		0	0	0	3	0	0	0	2
	Minimal	0	0	0	1	0	0	0	2
	Mild	0	0	0	1	0	0	0	0
	Marked	0	0	0	1 [h]	0	0	0	0
Increased mitoses; interstitial Minimal		0	0	0	1	0	0	0	2
Increased mitoses; mesangial Minimal		0	0	0	0	0	0	0	2
Single cell necrosis; urothelial Minimal		0	0	1	1	0	0	0	0
Esophagus									
Hemorrhage	Mild	0	0	0	1 [h]	0	0	0	0
Thrombus	Minimal	0	0	0	1 [h]	0	0	0	0
Duodenum [j]									
Vascular necrosis	Mild	0	0	0	1 [h]	0	0	0	0
Ileum [j]									
Hemorrhage	Minimal	0	0	0	1 [h]	0	0	0	0
Necrosis; vascular	Mild	0	0	0	1 [h]	0	0	0	0
Thrombus	Minimal	0	0	0	1 [h]	0	0	0	0

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

		Male				Female			
Daily Dose (mg/kg/week)[a]		0	1	3	10 [b]	0	1	3	10 [b]
Jejunum [j]									
Hemorrhage	Mild	0	0	0	1 [h]	0	0	0	0
Necrosis; vascular	Moderate	0	0	0	1 [h]	0	0	0	0
Thrombus	Minimal	0	0	0	1 [h]	0	0	0	0
Cecum [j]									
Necrosis; vascular	Mild	0	0	0	1 [h]	0	0	0	0
Hemorrhage	Minimal	0	0	0	1 [h]	0	0	0	0
Colon [j]									
Hemorrhage	Mild	0	0	0	1 [h]	0	0	0	0
Necrosis; vascular	Mild	0	0	0	1 [h]	0	0	0	0
Rectum									
Hemorrhage	Mild	0	0	0	1 [h]	0	0	0	0
Necrosis; vascular	Moderate	0	0	0	1 [h]	0	0	0	0
Liver [j]									
Examined		3	3	3	3	3	3	3	3
No visible lesions		0	0	0	0	0	0	0	0
Necrosis; hepatocellular	Minimal	0	0	2	1	0	0	0	1
Increased mitoses; sinusoid		0	0	1	2	0	0	1	3
	Minimal	0	0	1	2	0	0	1	2
	Mild	0	0	0	0	0	0	0	1
Angiectasis	Mild	0	0	0	0	0	0	0	2
Single cell necrosis; sinusoid	Minimal	0	0	0	1	0	0	1	3

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Infiltration, mononuclear cell Minimal	1	0	2	0	1	0	2	1
Hypertrophy/hyperplasia; Kupffer cell	0	0	2	3	0	0	2	3
Minimal	0	0	2	1	0	0	2	2
Mild	0	0	0	2	0	0	0	1
Extramedullary hematopoiesis Minimal	0	0	0	1	0	0	0	2
Lung								
Thrombus Minimal	0	0	0	1 [h]	0	0	0	0
Heart								
Hemorrhage Minimal	0	0	0	1 [h]	0	0	0	0
Gland, adrenal								
Hemorrhage Mild	0	0	0	1 [h]	0	0	0	0
Urinary bladder								
Single cell necrosis; urothelial Minimal	0	0	2	1	0	0	0	1
Nerve, Sciatic								
Hemorrhage	0	0	0	2	0	0	0	0
Minimal	0	0	0	1	0	0	0	0
Mild	0	0	0	1	0	0	0	0
Brain (choroid plexus)								
Increased macrophages Minimal	0	0	0	1	0	0	0	0
Testis								
Degeneration; seminiferous tubules								
Minimal	0	0	0	1	-	-	-	-
Mild	0	0	0	1	-	-	-	-

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Muscle, skeletal								
Hemorrhage								
Moderate	0	0	0	0	0	0	0	1
Marked	0	0	0	1	0	0	0	0
Spleen								
Examined	3	3	3	3	3	3	3	3
No visible lesions	3	2	0	0	3	1	0	0
Increased macrophages; red pulp	0	0	3	3	0	0	3	3
Minimal	0	0	3	0	0	0	2	0
Mild	0	0	0	1	0	0	1	1
Moderate	0	0	0	2	0	0	0	2
Increased mitoses; red pulp	0	0	0	2	0	0	1	3
Minimal	0	0	0	2	0	0	1	0
Mild	0	0	0	0	0	0	0	3
Necrosis; lymphoid, germinal center	0	0	0	2	0	0	0	1
Minimal	0	0	0	1	0	0	0	0
Mild	0	0	0	1	0	0	0	1
Decreased cellularity; lymphoid, germinal center	0	0	1	1	0	0	0	2
Minimal	0	0	1	0	0	0	0	1
Mild	0	0	0	1	0	0	0	1

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Bone marrow								
Increased macrophages	0	0	0	3	0	0	1	3
Minimal	0	0	0	1	0	0	1	2
Mild	0	0	0	1	0	0	0	1
Moderate	0	0	0	1	0	0	0	0
Increased cellularity; myeloid Minimal	0	0	0	1	0	0	0	1
Increased mitoses Minimal	0	0	0	1	0	0	0	2
Thymus								
Examined	3	3	3	3	3	3	3	3
No visible lesions	3	2	2	0	3	3	0	0
Decreased cellularity; lymphoid	0	0	1	3	0	0	3	3
Minimal	0	0	1	0	0	0	3	1
Mild	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	1
Marked	0	0	0	1	0	0	0	1
Necrosis; vascular Minimal	0	0	0	1[h]	0	0	0	0
Increased macrophages Minimal	0	0	0	1	0	0	0	1
Lymph node, inguinal								
Examined	3	3	3	3	3	3	3	3
No visible lesions	2	3	1	0	1	0	1	0
Increased mitoses; medullary Minimal	0	0	1	1	0	0	1	1

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Decreased cellularity; lymphoid, germinal center	0	0	0	2	0	0	0	2
Minimal	0	0	0	2	0	0	0	1
Mild	0	0	0	0	0	0	0	1
Extramedullary hematopoiesis Minimal	0	0	0	2	0	0	0	0
Hemorrhage								
Minimal	0	0	0	0	0	1	0	0
Mild	0	0	0	1	0	0	0	1
Lymph node, mandibular								
Examined	3	3	3	3	3	3	3	3
No visible lesions	3	3	1	1	3	3	2	0
Increased mitoses; medullary Minimal	0	0	2	1	0	0	1	3
Extramedullary hematopoiesis	0	0	1	0	0	0	1	2
Minimal	0	0	0	0	0	0	1	2
Mild	0	0	1	0	0	0	0	0
Decreased cellularity; lymphoid, germinal center	0	0	0	2	0	0	0	2
Minimal	0	0	0	1	0	0	0	2
Mild	0	0	0	1	0	0	0	0
Necrosis; lymphoid, germinal center Minimal	0	0	0	0	0	0	0	1
Lymph node, mesenteric [j]								
Examined	3	3	3	3	3	3	3	3
No visible lesions	3	2	1	0	3	2	3	2
Extramedullary hematopoiesis Minimal	0	0	0	1	0	0	0	0

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Increased mitoses; medullary Minimal	0	0	1	1	0	0	0	1
Necrosis; vascular Minimal	0	0	0	1[h]	0	0	0	0
Decreased cellularity; lymphoid, germinal center Minimal	0	0	0	3	0	0	0	1
Adipose tissue								
Examined	0	0	1	0	NA	NA	NA	NA
Hemorrhage Mild	-	-	1	-	NA	NA	NA	NA
Immunohistochemistry Evaluation	Granular deposits containing IgM only were detected in glomerular tufts in the kidney and in the cytoplasm of Kupffer cells and/or sinusoidal lining cells in the liver from Animal No.4003. Additionally, granular deposits containing monkey IgG and/or IgM were detected in glomerular tufts in the kidney, within the tunica media of blood vessels in the GI tract, and in the cytoplasm of Kupffer cells and/or sinusoidal lining cells in the liver from Animal No. 4004. The monkey IgG and/or IgM staining in the glomerular tufts in the kidney from both Animal Nos. 4003 and 4004 was observed as granular and linear staining (suggestive of basement membrane localization) within some of the affected glomerular tufts. In the GI tract from Animal No. 4004, the granular deposits containing monkey IgG and IgM were typically located at branch points in affected arteries. In the liver from Animal No. 4003, the positive staining for human IgG (belantamab mafodotin) similarly correlated with the physiologic distribution of monkey IgG in this tissue. Specifically, belantamab mafodotin was detected in the cytoplasm of rare to occasional Kupffer cells and/or sinusoidal lining cells. Belantamab mafodotin was not detected in the kidney or GI tract from this animal nor in any of the tissues examined from Animal No. 4004. Belantamab mafodotin was also not detected in any of the tissues examined from the control (Group 1) animal, as expected.							
Organ Weight and Macroscopic Exam Off-dose Necropsy	Following a 12-week off-dose period, there were no belantamab mafodotin-related organ weight changes or macroscopic findings.							
Microscopic Examination Off-dose Necropsy (number of animals examined)	2	0	2	2	2	0	2	2
Duodenum								
Inflammation, vascular/perivascular, Chronic Minimal	0	0	0	1	0	0	0	0

Belantamab Mafodotin: 13-Week (Once Weekly) Intravenous Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-dose Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** P71346G

	Male				Female			
Daily Dose (mg/kg/week)[a]	0	1	3	10 [b]	0	1	3	10 [b]
Jejunum								
Inflammation, vascular/perivascular, chronic Minimal	0	0	0	1	0	0	0	0
Remaining tissues examined from off-dose necropsy animals	There were no test item-related findings noted in kidney, liver, spleen, thymus, lymph nodes (mandibular, mesenteric and inguinal), bone marrow (femur and sternum), brain, urinary bladder, testis and intestines (small and large; ileum, colon and cecum).							

Key:

Belantamab mafodotin = GSK2857916.

NA – Not applicable. NQ – Not quantifiable (<150 pg/mL). To calculate mean Cmax, the NQ value was assigned a zero value. NC – Not calculated.

NR – Not reportable. The concentrations are not reportable because of the potential of belantamab mafodotin to inflate cys-mcMMAF concentration when processed at ambient temperature.

- = Not examined / No Test Item-related effect.

a = Doses expressed in terms of the ADC, belantamab mafodotin.

b = The data outlined below is for the animals that were euthanized prior to scheduled necropsy (Day 33 for Animal No. 4004 and Day 45/43 for remaining main study males/females respectively), the last dose was administered on Day 29.

c = Belantamab mafodotin is a humanized B-cell maturation antigen (BCMA) monoclonal antibody (mAb) conjugated to monomethylauristatin F (MMAF). All plasma concentrations and toxicokinetic parameters are given in terms of the GSK2857916 (ADC), Antibody Drug Conjugate, (anti-BCMA conjugated to MMAF), GSK2857916 (mAb) (anti-BCMA mAb and anti-BCMA conjugated to MMAF) and cys-mcMMAF, as appropriate.

d = n=2. The parameter values from Animal No. 2002 was excluded from the mean/median and range calculations due to the sharp decrease in the plasma concentrations (non-quantifiable at later time points). The values in the parenthesis are the mean parameters calculated without data exclusion

e = No animal in this group had sufficient plasma concentration values to calculate AUC.

f = The mean value was below the LLQ (< 150 pg/mL) of this assay.

g = Not Calculated. AUC value could not be calculated in this group due to insufficient data.

h = Only Animal 4004.

i = Control values are expressed as absolutes in g.

j = For Animal 1001, 4003 and 4004, immunohistochemistry evaluation was performed on the kidneys, the GI sections (duodenum, jejunum, ileum, colon, and caecum) and the liver. Immunohistochemistry was performed to detect human IgG (indicative of belantamab mafodotin), endogenous monkey immunoglobulins (IgG and IgM), and complement component 3 (C3). Immunoperoxidase staining was used for demonstration of immune complex-related granular deposits.

Table 7.5 GLP Repeat-Dose (Once-Daily for 5 Days) Intravenous Toxicity Study of SGD-1362 (cys-mcMMAF) in Rats With a 2-Week Recovery Period

Study Type: Repeat Dose Toxicity

Report Title: GLP Repeat-dose (Once daily for 5 days) intravenous toxicity study of SGD-1362 (cys-mcMMAF) in rats with a 2-week recovery period

Test Article: cys-mcMMAF (SGD-1362)
Batch No.: [redacted]

Species/Strain: Rat/Sprague Dawley

Duration of Dosing: 5 days
Duration of Recovery: 2 weeks

Study No.: 1019-010

Initial Age: Approx. 6 weeks

Route/Frequency: Intravenous, once daily

Location in CTD: m4.2.3.2

Date of First Dose: 12 September 2011

Vehicle/Formulation: Phosphate Buffered Saline pH 7.2

Study in Compliance with GLP: Yes

GSK Document Number: 2013N177527

Data Collected: Toxicokinetics, clinical observations, body weight, food consumption, ophthalmoscopy, hematology, coagulation, clinical chemistry, urinalysis, organ weights, macroscopic and microscopic pathology.

Conclusion: Repeated intravenous administration of SGD-1362 to male and female rats was well-tolerated at doses up to 10 mg/kg/day. Corneal opacity in males at 5 and 10 mg/kg/day was considered possibly related to treatment. Minimal to mild increased alveolar histiocytosis at ≥1 mg/kg/day, still present after a 2 week recovery period at ≥5 mg/kg/day and minimal to mild increased subacute inflammation in males at ≥10 mg/kg/week and females at ≥5 mg/kg/day were observed in the lung. The HNSTD and NOAEL were considered to be the highest dose of 10 mg/kg/day in both sexes. The NOEL was considered to be <1 mg/kg/day due to increased alveolar histiocytosis in the lungs at all dose levels.

5-Day Intravenous Toxicity Study of SGD-1362 (cys-mcMMAF) in Rats With a 2-Week Recovery Period (Continued)

Study Number: 1019-010
Test Article: Linear cys-mcMMAF (SGD-1362)

Daily Dose (mg/kg/day)	0		1		5		10	
Number of Toxicokinetic Animals	M: 6	F: 6	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12
Toxicokinetics[a]								
AUC0-24 (hr•ng/mL)								
Day 1	NA	NA	4590	4830	40900	18500	126000	130000
Day 5	NA	NA	4100	3950	29300	23800	131000	122000
Cmax (ng/mL)								
Day 1	NA	NA	18200	96300	543000	490000	ALQ	812000
Day 5	NA	NA	77000	44000	521000	398000	ALQ	ALQ
T1/2 (hr)								
Day 1	NA	NA	NC	10.6	5.81	NC	6.10	NC
Day 5	NA	NA	NC	NC	8.71	8.13N	NC	6.80

5-Day Intravenous Toxicity Study of SGD-1362 (cys-mcMMAF) in Rats With a 2-Week Recovery Period (Continued)

Study Number: 1019-010
Test Article: Linear cys-mcMMAF (SGD-1362)

Daily Dose (mg/kg/day)	0		1		5		10	
Number of Main Study Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Number of Off-dose Animals	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Noteworthy Findings:								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Clinical Observations – Day minus 7 to Day 7[b]								
Material around eyes, Black	0/0	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Material around nose, Black	0/0	0/0	0/0	0/0	9/6	1/1	5/4	1/1
Material around nose, Brown	0/0	0/0	1/1	0/0	2/2	0/0	2/2	2/1
Material around nose, Red	0/0	0/0	0/0	1/1	3/2	0/0	5/4	1/1
Material around eyes, Red	0/0	0/0	0/0	0/0	0/0	0/0	0/0	1/1
Material around mouth, Black	0/0	0/0	0/0	0/0	0/0	1/1	0/0	0/0
Clinical Observations – Day 8 to Day 19[g]								
Material around mouth, Red	0/0	0/0	0/0	0/0	1/1	0/0	0/0	0/0
Material around nose, Black	3/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Material around nose, Red	0/0	5/2	1/1	0/0	1/1	1/1	1/1	0/0
Ophthalmology[c]	–	–	–	–	–	–	–	–
Day 5 Corneal opacity	0	0	0	0	2	0	3	0
Day 17 Corneal opacity	1	0	0	0	2[i]	0	2	1
Hematology[d]								
Number Examined (Main Study Animals)	10	10	10	10	10	10	10	10
Number Examined (Off-Dose Animals)	5	5	5	5	5	5	5	5
Platelet Distribution Width (%)								
Day 3	58.66	61.70	58.11	63.50	60.76	61.47	63.86*	63.69
Day 8	57.04	51.42	55.45	52.95	55.49	53.77	63.02**	58.79**

5-Day Intravenous Toxicity Study of SGD-1362 (cys-mcMMAF) in Rats With a 2-Week Recovery Period (Continued)

Study Number: 1019-010
Test Article: Linear cys-mcMMAF (SGD-1362)

Daily Dose (mg/kg/day)	0		1		5		10	
Number of Main Study Animals	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Number of Off-dose Animals	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Day 12[h]	63.64	69.90	60.30	68.22	68.48	69.38	65.24	66.58
Day 19[h]	55.74	51.32	57.08	52.46	52.90	49.98	55.28	52.42
Neutrophils ($10^3/\mu L$)								
Day 3	1.553	1.113	1.379	0.983	1.773	0.958	2.936**	1.350
Day 8	1.776	1.261	1.731	1.201	1.688	1.055	2.042	1.457
Day 12[h]	1.678	1.162	1.998	1.648	1.460	1.550	1.776	2.020
Day 19[h]	2.228	1.642	2.276	1.498	1.310	1.370	1.692	1.472
Clinical Chemistry[d]								
Number Examined (Main Study Animals)	10	10	10	10	10	10	10	10
Number Examined (Off-Dose Animals)	5	5	5	5	5	5	5	5
Aspartate Aminotransferase (U/L) – Day 8	84.2	71.1	81.7	81.2	100.6	86.2	127.6**	100.3**
Aspartate Aminotransferase (U/L) – Day 19[h]	80.0	70.8	64.4**	63.6	64.2**	71.6	73.4	68.6
Alanine Aminotransferase (U/L) - Day 8	36.0	27.8	33.6	30.3	38.6	29.7	46.8**	35.3*
Alanine Aminotransferase (U/L) - Day 19[h]	38.4	33.2	37.4	30.2	34.8	29.2	38.6	31.0
Organ Weights (%)[e] (Terminal Necropsy Day 8)								
Number Examined	10	10	10	10	10	10	10	10
Lung w/ bronchi (g)	1.326	1.082	-0	+1	+12	+9	+13*	+22**
Lung w/ bronchi/BWt (%)	0.5354	0.5789	-1	-0	+12	+9	+13*	+22**
Lung w/ bronchi/BrWt (ratio)	0.7127	0.5881	-1	+6	+13*	+10	+11	+26**
Organ Weights (%)[e] (Off-Dose Necropsy Day 19)	There were no increased lung weights at the off-dose necropsy							
Gross Pathology	–	–	–	–	–	–	–	–

5-Day Intravenous Toxicity Study of SGD-1362 (cys-mcMMAF) in Rats With a 2-Week Recovery Period (Continued)

Study Number: 1019-010
Test Article: Linear cys-mcMMAF (SGD-1362)

Daily Dose (mg/kg/day)	0		1		5		10	
Number of Main Study Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Number of Off-dose Animals	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Histopathology[f]								
Number Examined **(Terminal Necropsy Day 8)**	10	10	10	10	10	10	10	10
Lung (Terminal Necropsy Day 8)								
Histiocytosis, alveolar								
minimal	3	1	8	5	8	7	8	6
mild	0	0	0	0	2	2	2	4
Inflammation, subacute								
minimal	1	0	0	0	2	4	8	8
mild	1	0	0	0	1	0	1	0
Number Examined **(Off-dose Necropsy Day 19)**	5	5	5	5	5	5	5	5
Lung (Off-dose Necropsy Day 19)								
Histiocytosis, alveolar								
minimal	1	2	2	3	5	4	5	5
mild	1	0	0	0	0	0	0	0

Key:

– = No noteworthy findings; * = $p < 0.05$; ** = $p < 0.01$
ALQ = Two or more values were above the quantitation limit; BWt = Body weight; BrWt = Brain weight; NA = Not applicable; NC = Not calculated.
a = Lower limit of quantitation for SGD-1362: 0.0500 ng/mL. The control group was analyzed for plasma concentration; however, group means were not calculated.
b = Days -7 to 7. Reported as Number of Times Observed/Total Number of Animals Affected. Total number of animals observed during this period was 15M/15F (includes main test and off-dose animals).
c = Reported as number observed. Corneal opacity was observed in either or both eyes.
d = Group means are shown.
e = For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data not on the percent differences. All percent difference values are rounded to the nearest whole number.
f = Reported as number observed
g = Days 8 to 19. Reported as Number of Times Observed/Total Number of Animals Affected. Total number of animals observed 5M/5F (off-dose animals only)
h = Off-dose animals only; i = Different animals were affected on Days 5 and 7.

Table 7.6 GLP Repeat-Dose (Once-Daily for 5 Days) Intravenous Toxicity Study of SGD-1362 (cys-mcMMAF) in Cynomolgus Monkeys with a 2-Week Recovery Period

Study Type: Repeat Dose Toxicity

Report Title: GLP Repeat-dose (Once daily for 5 days) intravenous toxicity study of SGD-1362 (cys-mcMMAF) in cynomolgus monkeys with a 2-week recovery period

Test Article: cys-mcMMAF (SGD-1362)
Batch No.: [redacted]

Species/Strain: Monkey/Cynomolgus

Duration of Dosing: 5 days
Duration of Recovery: 2 weeks

Study No.: 1019-009

Initial Age: 2.3 to 4.1 years

Route/Frequency: Intravenous

Location in CTD: m4.2.3.2

Date of First Dose: 12 September 2011

Vehicle/Formulation: Phosphate Buffered Saline pH 7.2

Study in Compliance with GLP: Yes

GSK Document Number: 2013N177530

Data Collected: Toxicokinetics, clinical observations, body weight, food consumption, ophthalmoscopy, electrocardiography, respiratory rate, hematology, coagulation, clinical chemistry, urinalysis, organ weights, macroscopic and microscopic pathology.

Conclusion: Repeated intravenous administration of SGD-1362 (daily for 5 days) to male and female cynomolgus monkeys was well-tolerated at doses up to 5 mg/kg/day. The NOEL was <0.5 mg/kg/day due to non-adverse increases in monocytes in both sexes and lymphocytes in females at all dose levels. The highest dose level tested (5 mg/kg/day) was the HNSTD and NOAEL for this study.

5-Day Intravenous Toxicity Study of SGD-1362 (cys-mcMMAF) in Cynomolgus Monkeys with a 2-Week Recovery Period (Continued)

Study Number: 1019-009
Test Articles: Linear cys-mcMMAF (SGD-1362)

Daily Dose (mg/kg/day)	0		0.5		2		5	
Number of Animals	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Toxicokinetics[a]:								
AUC0-24hr (hr•ng/mL)								
Day 1	NA	NA	547	552	1890	2400	5720	5350
Day 5	NA	NA	476	447	2190	2550	6150	6240
Cmax (ng/mL)								
Day 1	NA	NA	3550	3620	12400	12800	33700	34600
Day 5	NA	NA	2530	2740	16100	15200	41600	44500
t1/2 (hr)								
Day 1	NA	NA	4.62	4.81	4.50	4.49	3.75	4.07
Day 5	NA	NA	5.93	7.45	9.14	10.7	11.4	10.8

5-Day Intravenous Toxicity Study of SGD-1362 (cys-mcMMAF) in Cynomolgus Monkeys with a 2-Week Recovery Period (Continued)

Study Number: 1019-009
Test Articles: Linear cys-mcMMAF (SGD-1362)

Daily Dose (mg/kg/day)	0		0.5		2		5	
Number of Main Study Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Number of Off-Dose Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Noteworthy Findings:								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Blood Pressure[b]								
Systolic Blood Pressure (mmHg)								
Day 1[c]	127.40	121.80	125.10	128.53	137.70	135.54	136.13	141.45
Day 7[c]	119.10	123.20	134.55	130.90	138.19	141.10	142.42	134.67
Day 18[d]	112.50	114.00	121.17	129.50	147.63	133.50	122.50	139.50
Diastolic Blood Pressure (mmHg)								
Day 1[c]	68.78	58.07	68.85	61.82	81.45	74.34	77.57	83.65
Day 7[c]	75.60	67.85	80.12	75.68	92.92	72.70	105.22	78.71
Day 18[d]	69.14	52.67	58.92	83.33	96.25	56.92	29.23	68.00
Mean Arterial Blood Pressure (mmHg)								
Day 1[c]	101.32	92.27	99.63	101.65	112.77	104.23	104.44	113.45
Day 7[c]	98.25	93.92	105.33	101.72	112.52	101.89	124.67	104.25
Day 18[d]	92.12	86.67	83.54	105.83	125.58	100.04	94.70	97.17
Hematology[b]								
Lymphocytes ($10^3/\mu L$)								
Day 3[c]	6.804	4.744	7.118	6.930	6.220	6.914	4.798	6.172
Day 8[c]	6.072	4.390	5.568	7.164*	5.586	7.422**	7.058	7.016*
Day 12[d]	7.325	4.640	10.16	10.40	6.720	7.510	9.055	8.515
Day 19[d]	5.735	3.490	8.225	6.935	4.520	5.045	6.940	5.545

5-Day Intravenous Toxicity Study of SGD-1362 (cys-mcMMAF) in Cynomolgus Monkeys with a 2-Week Recovery Period (Continued)

Study Number: 1019-009
Test Articles: Linear cys-mcMMAF (SGD-1362)

Daily Dose (mg/kg/day)	0		0.5		2		5	
Number of Main Study Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Number of Off-Dose Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Monocytes (10^3/µL)								
Day 3[c]	0.312	0.392	0.564	0.624	0.604*	0.816*	0.566	0.852*
Day 8[c]	0.270	0.326	0.526	0.560	0.640*	0.788*	0.702*	1.040**
Day 12[d]	0.310	0.640	0.580	0.785	0.505	0.600	0.415	0.705
Day 19[d]	0.405	0.455	0.340	0.585	0.280	0.305	0.340	0.320
Other Cells (10^3/µL)								
Day 3[c]	0.098	0.076	0.102	0.130	0.130	0.134	0.094	0.162
Day 8[c]	0.130	0.100	0.160	0.196	0.304	0.250	0.322	0.438**
Day 12[d]	0.140	0.180	0.210	0.275	0.135	0.185	0.220	0.195
Day 19[d]	0.155	0.080	0.120	0.185	0.075	0.125	0.115	0.125
Clinical Chemistry[b]								
Creatine Kinase (U/L)								
Day 3[c]	213.4	163.2	160.6	369.0	167.6	175.2	140.8	154.6
Day 8[c]	134.0	191.6	282.8	391.4	230.8	498.6	796.2	646.4
Day 12[d]	163.0	181.5	110.0	171.5	143.0	728.5	194.0	526.5
Day 19[d]	1437.0	119.0	376.0	288.5	193.5	231.0	341.5	176.5

Key:
– = No noteworthy findings; * = $p < 0.05$; ** = $p < 0.01$; NA = Not applicable
a = Geometric means are shown for treated groups; the control group was only analyzed for plasma concentration. Lower limit of quantitation = 0.0500 ng/mL.
b = Group means are shown.
c = Includes main test and off-dose animals; d = Off-dose animals only.

Table 7.7 GSK2857914: 4-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys

Study Type: Repeat-Dose Toxicity

Report Title: GSK2857914: 4-Week (Once Weekly) Intravenous Toxicity Study in Monkeys

Test Article: GSK2857914
Batch No.: [redacted]

Species/Strain: Monkey/Cynomolgus

Duration of Dosing: 4 weeks

Study No.: P70204G

Initial Age: 2.9 to 5.84 years

Route/Frequency: Intravenous (IV) bolus / weekly

Location in CTD: m4.2.3.2

Date of First Dose: 19-Nov-2012

Vehicle/Formulation: 50 mM sodium acetate trihydrate, 0.05 mM edetate disodium dihydrate (EDTA), 1% (w/v) L-arginine, 51 mM sodium chloride, 0.02% polysorbate 80 in Water for Injection USP, pH 5.5 ± 0.2

Study in Compliance with GLP: Yes

GSK Document Number: 2012N150466

Data Collected: Toxicokinetics, clinical observations, body weight, body temperature, ophthalmoscopy, electrocardiography, hematology, coagulation, clinical chemistry, urinalysis, anti-GSK2857914 antibodies, cytokines, immunophenotyping, organ weights, macroscopic and microscopic pathology.

Conclusion: Elevated cytokines and C-reactive protein (CRP) associated with the first dose of GSK2857914 were observed in monkeys given ≥10 mg/kg/week. Skin observations were noted in a few monkeys after the fourth weekly dose of ≥10 mg/kg/week and were associated with microscopic inflammatory changes in the dermis and epidermis with secondary changes in the regional lymph nodes. Microscopic findings considered consistent with a systemic inflammatory response were present in the spleen, bone marrow, kidney (100 mg/kg/week) and liver of monkeys given ≥10 mg/kg/week. Associated increases in CRP concentrations, changes in leukocyte counts and elevated inflammatory cytokine levels and/or serum immunoglobulin G (IgG) concentrations in individual monkeys were also noted at ≥10 mg/kg/week during Week 5. Additional changes included decreased mean serum albumin at ≥10 mg/kg/week and associated decreased mean serum total protein concentration at 100 mg/kg/week. There were decreases in red cell parameters at 10 and 100 mg/kg/week, increased reticulocytes at 30 mg/kg/week, and decreased platelets at ≥30 mg/kg/week. Decreased lymphoid cellularity of the marginal zone was noted in the spleen of monkeys given ≥10 mg/kg/week, a decrease in serum immunoglobulin M (IgM) concentrations was noted at ≥10 mg/kg/week, and a decrease in mean absolute numbers of B cells was seen at 10 or 100 mg/kg/week on Day 29. A decrease in mean absolute numbers of natural killer (NK) cells was noted in monkeys given ≥30 mg/kg/week. Sporadic instances of reduced eating and slight body weight loss were noted in monkeys given ≥30 mg/kg/week. Since the combination of skin findings, microscopic changes in multiple tissues, inflammatory cytokine and CRP changes and additional effects on clinical pathology parameters consistent with a systemic inflammatory response at all dose levels were considered adverse, a no-observed adverse effect level (NOAEL) could not be determined for this study [10 mg/kg/week: Week 4 gender-averaged mean AUC0-t 20.8 mg.h/mL, range 14.4 to 28.5 mg.h/mL; mean Cmax 0.362 mg/mL, range 0.289 to 0.393 mg/mL].

GSK2857914: 4-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70204G

	Male				Female			
Daily Dose (mg/kg/week)[1]	0	10	30	100	0	10	30	100
Numbers of Animals: Main	3	3	3	3	3	3	3	3
AUC(0-t) mg.h/mL Day 1 (Week 1)	NQ	16.3	57.1	158	NQ	17.0	46.1	150
Day 22 (Week 4)	NQ	20.6	84.4	193	NQ	21.0	46.3	207
Cmax mg/mL Day 1 (Week 1)	NQ	0.339	0.873	2.95	NQ	0.353	0.864	2.84
Day 22 (Week 4)	NQ	0.351	1.13	3.20	NQ	0.374	1.01	3.44
Noteworthy Findings								
Clinical Observations								
Skin-reddening[2]	0	0	0	1	0	0	0	1
Scabs[2]	0	0	1	1	0	1	0	0
Reduced eating	Reduced eating (>half portion remaining) was noted sporadically in females given 30 mg/kg/week from Day 14 to 28, and in males given 100 mg/kg/week on Day 23 only.							
Body Weight	On Day 26, body weight loss was noted in 1 female (9950) given 30 mg/kg/week and in 2 males (400 and 402) given 100 mg/kg/week (0.95X, 0.96X and 0.96X Day 1 values, respectively).							
Hematology[3]								
Hemoglobin (g/L)								
Week -1	127.0	124.3	125.0	130.3	118.0	119.7	116.0	119.0
Week 5	123.3	116.3 (100)[4]	124.3	116.3 (104)[5]	114.7	119.0	110.0	115.7
Hematocrit (L/L)								
Week -1	0.427	0.420	0.420	0.437	0.407	0.410	0.410	0.407
Week 5	0.413	0.400 (0.36)[4]	0.437	0.393 (0.35)[5]	0.400	0.413	0.387	0.403

GSK2857914: 4-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70204G

		Male				Female			
Daily Dose (mg/kg/week)[1]		0	10	30	100	0	10	30	100
Reticulocytes (x10^9/L)									
	Week -1	83.00	83.47	86.27	60.77	97.93	120.87	81.43	84.03
	Week 5	78.10	81.17	120.03	84.80	120.97	123.97	180.63 (208.7)[8], (239.2)[12]	139.00
Red blood cell distribution width (%)									
	Week -1	12.67	12.60	12.90	12.13	12.33	12.67	12.80	11.83
	Week 5	13.00	12.93	13.03	13.77	12.63	12.60	15.00 (15.8)[8], (17.2)[12]	12.10
Red blood cell count (x10^{12}/L)									
	Week -1	5.543	5.370	5.347	5.740	5.200	5.370	5.160	5.403
	Week 5	5.283	5.077 (4.62)[4]	5.413	5.200 (4.72)[5]	4.977	5.343	4.987	5.300
Platelets (x10^9/L)									
	Week -1	447.3	434.7	486.3	505.7	445.0	543.3	517.7	603.3
	Week 5	397.3	434.7	424.0 (298)[6]	342.0 (318)[7], (243)[5]	386.3	501.0	309.0 (187)[8]	662.3
White blood cell count (x10^9/L)									
	Week -1	10.527	11.393	11.607	11.897	11.397	14.560	16.700	12.630
	Week 5	12.757	13.210	8.223	6.230 (3.06)[7]	12.547	13.213	10.127 (12.97)[8]	11.340
Neutrophil absolute (x10^9/L)									
	Week -1	5.867	5.093	7.527	8.027	6.157	9.953	12.173	9.253
	Week 5	9.437	5.773	3.790 (1.17)[6]	3.280 (0.63)[7]	7.087	8.923	4.627 (2.98)[8]	8.573
Monocyte absolute (x10^9/L)									
	Week -1	0.300	0.367	0.233	0.257	0.463	0.257	0.307	0.303
	Week 5	0.267	1.060 (2.58)[4]	0.363	0.223 (0.11)[7]	0.483	0.360	0.557	0.293

GSK2857914: 4-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70204G

	Male				Female			
Daily Dose (mg/kg/week)[1]	0	10	30	100	0	10	30	100
Large unstained cells absolute ($x10^9$/L)								
Week -1	0.037	0.070	0.047	0.053	0.070	0.047	0.050	0.050
Week 5	0.023	0.307 (0.86)[4]	0.123 (0.29)[6]	0.070	0.057	0.113	0.077	0.053
Clinical Chemistry[3]								
Albumin (g/L)								
Week -1	46.0	45.0	47.3	46.0	45.3	47.3	47.0	44.0
Week 5	45.0	39.7	42.0	37.3	43.0	45.7	35.7	42.7
Total protein (g/L)								
Week -1	73.0	75.3	73.7	75.0	74.3	76.7	78.3	74.3
Week 5	71.7	72.7	67.7	67.7 (54)[5]	70.3	75.7	67.0	69.0
Immunoglobulin G (g/L)								
Week -1	7.873	10.083	6.960	8.403	8.330	8.597	9.873	10.130
Week 5	7.683	12.783 (16.79)[4]	6.613	10.843 (20.10)[7]	8.053	9.327	10.870	7.987
Immunoglobulin M (g/L)								
Week -1	0.667	0.593	0.880	0.777	1.073	1.043	1.643	1.243
Week 5	0.620	0.473 (0.47)[9]	0.333	0.473	1.020	0.617 (0.44)[10], (0.56)[11]	0.803	0.407
C-reactive protein (mg/L)								
Week -1	2.690	1.643	1.793	2.080	0.827	1.937	1.563	5.710
Week 1 (Day 1, 24 hours post dose)	5.273	5.307	10.427	4.457	3.170	4.627	10.643	12.137
Week 2 (Day 8, pre-dose)	3.490	1.627	2.873	2.167	1.007	2.240	1.780	5.117
Week 5	3.430	4.823	20.400	16.083	0.773	47.173 (138.69)[10]	23.833	7.240

GSK2857914: 4-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70204G

	Male				Female			
Daily Dose (mg/kg/week)[1]	0	10	30	100	0	10	30	100
Cytokines	Elevated plasma levels of IL-6, IL-8 and/or MCP-1 were noted at ≥10 mg/kg/week on Day 1 at 6 hours post dose in several animals, although cytokine induction was not consistently dose dependent or consistently observed in both males and females. On Day 15 (pre-dose) or Day 29 (Day 22, 168 hours post dose), IL-6, IL-8 and/or MCP-1 plasma levels were elevated in individual animals given ≥10 mg/kg/week.							
Immunophenotyping	In males given 30 or 100 mg/kg/week GSK2857914, there were decreases in the mean absolute NK (CD159a+/CD3-) cell counts on Day 29 (0.38X and 0.38X baseline, respectively), compared to 0.71X mean baseline in vehicle control males. Similar test article-related changes were observed in percent NK cells. On Day 29, absolute B cells were decreased to 0.44X baseline in 1 male given 100 mg/kg/week (402). In females given 100 mg/kg/week, mean absolute B cell counts on Day 29 were 0.53X baseline values compared to 1.33X in vehicle control females. Additionally, 1 female (252) given 10 mg/kg/week had a decrease in absolute B cells to 0.17X baseline on Day 29. Similar test article-related changes were observed in percent B cells.							
Anti-GSK2857914 antibodies	Anti-GSK2857914 antibodies were not detected in monkeys given GSK2857914.							
Macroscopic Examination (number of animals)	3	3	3	3	3	3	3	3
Lymph Node - Inguinal								
Increased size, bilateral	0	0	1	0	0	0	0	0
Lymph Node - Axillary								
Increased size, bilateral	0	0	0	1	0	0	0	0
Lymph Node - Subcutaneous								
Increased size, chest	0	0	0	1	0	0	0	0
Lymph Node – Mandibular/cervical								
Increased size, bilateral	0	1	0	0	0	0	0	0

GSK2857914: 4-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70204G

	Male				Female			
Daily Dose (mg/kg/week)[1.]	0	10	30	100	0	10	30	100
Skin								
Focal red, raised area (forelimb and hindlimb)	0	0	0	1	0	0	0	0
Focal red, raised, crusted area (forelimb and hindlimb)	0	0	0	0	0	1	0	0
Multiple red, raised, crusted discoloration (inguinal or neck area)	0	0	1	0	0	0	0	0
Focal red, raised, crusted area (chest, face, forelimb and hindlimb)	0	0	0	1	0	0	0	0
Localized crust with red discoloration (inguinal)	0	0	0	0	0	0	0	1
Microscopic Examination (number of animals)	3	3	3	3	3	3	3	3
Kidney								
Inflammatory cell infiltrate; mononuclear cell, multifocal, interstitium								
Minimal	1	1	0	1	1	2	2	2
Mild	0	0	1	0	0	0	0	0
Moderate	0	0	0	1	0	0	0	0

GSK2857914: 4-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70204G

	Male				Female			
Daily Dose (mg/kg/week)[1]	0	10	30	100	0	10	30	100
Liver								
Extramedullary hematopoiesis								
Minimal	0	0	0	0	0	0	1	0
Hypertrophy/hyperplasia; diffuse, kupffer cell								
Minimal	0	0	0	0	0	0	1	0
Mild	0	0	1	0	0	1	1	0
Inflammatory cell infiltrate; mixed cell, multifocal								
Minimal	0	0	0	0	0	0	2	0
Lymph Node – inguinal								
Cellularity increased; diffuse, sinus								
Moderate	-	-	1	-	-	-	-	-
Lymph Node – mandibular/cervical								
Cellularity increased; lymphocytic, bilateral, diffuse,cortex								
Mild	-	1	-	-	-	-	-	-
Lymph Node – axillary/subcutaneous								
Cellularity increased; histiocyte; Sinusoid								
Moderate	-	-	-	1	-	-	-	-

GSK2857914: 4-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70204G

	Male				Female			
Daily Dose (mg/kg/week)[1]	0	10	30	100	0	10	30	100
Skin								
Degeneration/necrosis; localized, epidermis								
Mild	0	0	1	1	0	1	0	0
Moderate	0	0	0	1	0	0	0	0
Hyperplasia; localized, epidermis								
Minimal	0	0	1	0	0	1	0	1
Mild	0	0	0	2	0	0	0	0
Inflammation; lymphohistiocytic, localized, perivascular; dermis								
Minimal	0	0	0	1	0	0	0	1
Mild	0	0	1	2	0	1	0	0
Spleen								
Cellularity decreased; lymphoid; marginal zone								
Minimal	0	3	0	1	0	2	1	1
Mild	0	0	0	2	0	1	2	2
Moderate	0	0	3	0	0	0	0	0
Cellularity increased; mononuclear cell, diffuse, red pulp								
Minimal	0	2	1	0	0	1	2	0
Mild	0	0	1	2	0	0	0	0

GSK2857914: 4-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys (Continued)

Study Type: Repeat-Dose Toxicity **Study No.:** P70204G

	Male				Female			
Daily Dose (mg/kg/week)[1]	0	10	30	100	0	10	30	100
Cellularity increased; neutrophilic, diffuse, red pulp								
Mild	0	0	1	0	0	0	0	0
Sternum – bone marrow								
Cellularity increased; myeloid								
Minimal	0	1	1	2	0	0	1	1

Key:

-Not examined
NQ=not quantifiable; below assay LLQ of 0.5 µg/mL
1 = Doses are expressed in terms of the monoclonal antibody.
2 = For clinical observations in skin, number of animals affected are presented.
3 = Group means are shown. Values in parentheses correspond to individual animal values (see footnotes 4 through 12).
4 = Animal 201, 5 = Animal 402,
6 = Animal 302, 7 = Animal 400,
8 = Animal 352, 9 = Animal 202,
10 = Animal 250, 11= Animal 252
12 = Animal 9950.

Table 7.8 GSK2857914: 13-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys

Study Type: Repeat Dose Toxicity	**Report Title**: GSK2857914A: 13-Week (Once Weekly) Intravenous or Subcutaneous Injection Toxicity Study in Cynomolgus Monkeys	**Test Item**: GSK2857914A **Lot No.**: [redacted]
Species/Strain: Non-human primate/Cynomolgus monkey	**Duration of Dosing**: 13 weeks	**GSK Reference No.**: P73042G
	Duration of Recovery: Not applicable	**Location in CTD**: m4.2.3.2
Initial Age: 28 to 34 months	**Route/Frequency**: Group 1 and 4: Intravenous (IV) injection, once weekly Group 1, 2 and 3: Subcutaneous injection, once weekly.	**GSK Document Number**: 2023N536587
Date of First Dose: 27 Sep 2023	**Vehicle/Formulation**: 50 mM sodium acetate, 57 mM L-arginine hydrochloride, 51 mM sodium chloride, 0.05 mM edetate disodium, 0.02% polysorbate 80, pH 5.5 +/- 0.2/Solution	**Study in Compliance with GLP**: Yes

Data Collected: Toxicokinetics, clinical observations, body weight, food evaluation, ophthalmoscopy, electrocardiography (qualitative and quantitative), hematology, clinical chemistry, C-reactive protein, urinalysis, urine chemistry, immunophenotyping, immunoglobin (IgG and IgM), cytokines analysis, anti-drug antibody analysis, organ weights, macroscopic and microscopic observations (stage-aware evaluation of spermatogenesis could not be conducted due to immaturity).

Conclusion: GSK2857914 was given weekly by subcutaneous (SC) injection for 3 months at 0 (vehicle), 2 or 10 mg/kg/dose or by intravenous (IV) bolus injection at 0 (vehicle) or 40 mg/kg/dose to cynomolgus monkeys (3 animals/sex/group with the exception of 4 animals/sex/group at 2 mg/kg/dose SC; animals given vehicle were administered both IV and SC injections). ADA responses were observed in the majority of animals and was considered to have affected the ability to assess toxicity of GSK2857914 in females given 2 mg/kg/dose SC as exposure was significantly reduced beginning Week 4. The toxicity assessment of GSK2857914 in the other groups was not affected as there was a sufficient number animals/sex/group with exposure throughout the study for evaluation. Overall, administration of GSK2857914 was well tolerated in cynomolgus monkeys at all doses and via both dose routes. GSK2857914-related inflammatory effects were noted in clinical pathology parameters (transient increases in monocyte counts, increased fibrinogen and C-reactive protein concentrations and/or decreased albumin concentrations) for monkeys given 10 mg/kg/dose SC or 40 mg/kg/dose IV, with decreased neutrophil counts noted in monkeys given ≥2 mg/kg/dose SC or 40 mg/kg/dose IV, in Weeks 5 and/or 8 and in increased immunoglobulin G levels at all doses/routes in Weeks 5 and/or 8. All of these findings had resolved by Weeks 14. Additionally, decreased immunoglobulin M concentrations were noted at all doses and routes in Weeks 5 and 14. Microscopically, macrophage vacuolation and perivascular mononuclear cell infiltration was noted at SC injection sites at doses ≥2 mg/kg/dose and was consistent with local administration of test formulations. All GSK2857914-related findings on this study were considered non-adverse due to low severity, transient nature and/or lack of microscopic findings consistent with systemic inflammation. Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 10 mg/kg/dose SC and 40 mg/kg/dose IV. At 10 mg/kg/dose SC, the GSK2857914 gender averaged mean AUC0-t and Cmax values were 11.2 mg.h/mL and 0.0933 mg/mL, respectively, after 13 weeks of dosing. At 40 mg/kg/dose IV, the GSK2857914 gender averaged mean AUC0-t and Cmax values were 75.5 mg.h/mL and 1.17 mg/mL, respectively, after 13 weeks of dosing.

GSK2857914: 13-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys (Continued)

Study Type: Repeat Dose Toxicity					GSK Reference No.: P73042G			
	Male				Female			
Weekly Dose (mg/kg/dose)[a]	0[b]	2[c]	10[c]	40[d]	0[b]	2[c]	10[c]	40[d]
Numbers of Animals: Main	3	4	3	3	3	4	3	3
$AUC_{(0-t)}$ (mg.h/mL) Day 22	NA	3.07[e]	11.2	69.7	NA	NA	9.62	67.6
Day 85	NA	2.88[f]	11.5[g]	73.6	NA	NA	11.0	78.5
C_{max} (mg/mL) Day 22	NQ	0.0247[e]	0.0957	1.13	NQ	NA[h]	0.0869	1.12
Day 85	NQ	0.0243[f]	0.0923[g]	1.16	NQ	NA[h]	0.0940	1.18
Noteworthy Findings								
Unscheduled Deaths	0	0	0	0	0	0	0	0
Hematology								
Monocyte (10^9/L)								
Week -1	0.317	0.263	0.370	0.123	0.103	0.160	0.130 (0.12[j])	0.183
Week 5	0.160	0.155	0.170	0.263	0.123	0.128	0.713 (1.68[j])	0.263
Week 8	0.357	0.348	0.480	0.323	0.260	0.388	0.420 (0.47[j])	0.420
Week 14	0.220	0.190	0.173	0.143	0.177	0.160	0.193 (0.20[j])	0.267
Neutrophil (10^9/L)								
Week -1	4.050	2.813 (2.58[k])	4.277	3.900	4.573	5.728	2.530 (1.93[j])	3.683 (2.83[l])
Week 5	2.677	3.460 (3.11[k])	2.497	2.637	2.177	4.663	3.827 (0.27[j])	3.330 (1.01[l])
Week 8	3.853	1.483 (0.66[k])	1.870	1.367	2.100	3.575	1.877 (1.36[j])	2.683 (0.80[l])
Week 14	5.390	3.885 (2.38[k])	4.493	2.907	2.100	3.210	3.903 (4.00[j])	2.683 (3.63[l])
Coagulation								
Fibrinogen (g/L)								
Week -1	2.477	2.653	2.397	2.220 (2.21[m])	2.183	2.093	2.047 (2.13[j])	2.423 (2.01[n])
Week 5	2.560	2.868	2.413	2.840 (3.76[m])	2.053	2.298	2.807 (3.97[j])	3.253 (4.04[n])
Week 14	2.463	2.933	2.533	2.327 (2.40[m])	2.083	2.003	1.970 (2.14[j])	2.417 (2.27[n])

GSK2857914: 13-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys (Continued)

Clinical Chemistry								
Albumin (g/L)								
Week -1	45.3	45.0	43.0	46.0 (47[m])	44.3	47.5	47.3 (43[j])	45.0 (46[n])
Week 5	44.3	44.3	40.3	42.3 (42[m])	43.0	45.5	41.3 (31[j])	40.3 (30[n])
C-reactive protein (mg/L)								
Week -1	2.973	1.503	4.267	2.713 (1.37[m])	2.543	1.783	2.667 (4.29[j])	13.510 (1.38[n])
Week 5	3.320	2.710	2.820	22.073 (34.32[m])	2.120	1.595	10.650 (29.03[j])	11.343 (5.40[n])
Immunoglobin								
IgG antibodies (mg/mL)								
Prestudy 2 (baseline)	2.673	2.520	2.387	3.133	2.523	2.725	2.933	2.850
Week 5	2.897	3.678	3.147	4.963	3.040	4.323	4.777	5.037
Week 14	2.573	2.700	2.333	3.043	2.823	2.338	2.520	2.970
IgM antibodies (mg/mL)								
Prestudy 1 (baseline)	0.427	0.450	0.340	0.500	0.580	0.520	0.390	0.463
Prestudy 2 (baseline)	1.007	1.023	0.770	1.683	1.627	1.358	0.777	0.953
Week 5	0.873	0.333	0.137	0.387	0.993	1.198	0.200	0.347
Week 14	0.547	0.215	0.277	0.135	0.583	0.458	0.127	0.207
Anti-Drug Antibody (Incidence)[i]								
Prestudy	0/3	0/4	0/3	0/3	0/3	0/4	0/3	0/3
Week 5	0/3	3/4	1/3	3/3	0/3	4/4	2/3	1/3
Week 14	0/3	2/4	1/3	0/3	0/3	4/4	0/3	1/3

GSK2857914: 13-Week (Once-Weekly) Intravenous Toxicity Study in Monkeys (Continued)

Microscopic Examination (number of animals)	3	4	3	3	3	4	3	3
Site injection, subcutaneous								
Vacuolation, macrophage								
Minimal	0	2	3	NA	0	3	3	NA
Infiltration, mononuclear cell; perivascular								
Minimal	0	0	2	NA	0	2	0	NA
Mild	0	0	0	NA	0	1	0	NA

NA = Not applicable; NQ = not quantifiable (below the lower limit of quantification)

a Doses expressed in terms of GSK2857914 and were administered weekly

b For Group 1 animals, the IV injection was followed immediately with the SC injection.

c SC injection(s)

d IV injection(s)

e n = 3, Animal No. 2004 was excluded from the mean calculation due to the atypical concentration profile compared to other animals within the group.

f n = 2, all concentrations in the samples collected from Animal No. 2004 were not quantifiable, and Animal No. 2003 was excluded from the mean calculation due to the atypical concentration profile compared to the other two animals within the group.

g n = 2, Animal No. 3001 was excluded from the mean calculation due to the atypical concentration profile compared to the other two animals within the group.

h Not Applicable, Animal No. 2504 had an atypical concentration profile, all concentrations in the samples collected from the other animals at 2 mg/kg/dose were not quantifiable.

i Number of Anti-Drug-Antibody (ADA) positive animals/total number of animals.

j Female No. 3501

k Male No. 2003

l Male No. 4002

m Male No. 4003

n Female No. 4501