Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence

Chronological Listing Explanation Page

Abbreviation	Description
A	Accidental death
T	Terminal kill
U	Unscheduled death

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Dose Level [a] (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration [a] (mg/mL)	Animal No.[b]			
				Main Study		Toxicokinetic Study [e]	
				Males	Females	Males	Females
1/ Reference Item	0	10	0	1001 to 1070	1501 to 1570	1071 to 1076	1571 to 1576
2/ GSK1278863	0.02	2 [d]	0.01	2001 to 2070	2501 to 2570	2071 to 2073	2571 to 2573
3/ GSK1278863	0.1	10	0.01	3001 to 3070	3501 to 3570	3071 to 3076	3571 to 3576
4/ GSK1278863	0.8	10	0.08	4001 to 4070	4501 to 4570	4071 to 4073	4571 to 4573
5/ GSK1278863	4 (Males) 7 (Females)	10 10	0.4 (Males) 0.7 (Females)	5001 to 5070	5501 to 5570	5071 to 5079	5571 to 5579
6/ Health Screen [c]	-	-	-	6001 to 6010	6501 to 6510	-	-

- = Not applicable.

[a] Doses and concentrations were expressed in terms of the parent compound.

[b] Any animal number replaced or reassigned during the study was documented in the study record and was included in the Final Report.

[c] Data used for health assessment only and retained on file.

[d] Dose volume was generally administered at a precision of 2 decimals: from dosing initiation until the mean body weight per sex reaches ≥ 500g (except for individual with a body weight ≥ 500g, dose volume was individually rounded up at 1 decimal). Then, the dose volume was measured at 1 decimal.

[e] Additional TK rats were added to Groups 1, 3 and 5 to allow collection of tissues for transcriptomic analysis. Additional TK rats were added to Group 5 to ensure toxicokinetics could be assessed appropriately as elevated hematocrits in previous studies have led to difficulty obtaining adequate plasma volume.

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Males

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1M	122	170	1001	U	muscle, skeletal	hemangiosarcoma	Yes
	170	170	1001	U	bone, femur	hemangiosarcoma	Yes
	170	170	1001	U	lung	hemangiosarcoma	Yes
	174	174	1054	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	327	327	1029	U	brain	meningioma, malignant	Yes
	327	327	1029	U	gland, pituitary	adenoma	No
	339	666	1052	U	skin	keratoacanthoma	No
	341	341	1019	U	gland, pituitary	adenoma	No
	341	341	1019	U	hemolymphoreticular tissue	leukemia, large granular lymphocytic	Yes
	371	371	1049	U	gland, pituitary	carcinoma	Yes
	371	371	1049	U	kidney	adenoma	No
	378	378	1042	U	gland, pituitary	adenoma	No
	405	405	1057	U	gland, pituitary	adenoma	No
	405	405	1057	U	gland, thyroid	c-cell carcinoma	Yes
	409	462	1020	U	subcutis	lipoma	No
	442	442	1040	U	tail	papilloma	No
	454	454	1069	U	hemolymphoreticular tissue	leukemia, large granular lymphocytic	Yes
	456	456	1016	U	pancreas	adenoma	No
	472	548	1038	U	subcutis	fibroma	No
	474	474	1044	U	gland, pituitary	adenoma	No
	474	474	1044	U	tail	liposarcoma	Yes
	488	496	1067	U	gland, mammary	adenocarcinoma	Yes
	493	618	1056	U	subcutis	fibroma	No
	496	496	1062	U	gland, parathyroid	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1M	496	496	1067	U	gland, adrenal	pheochromocytoma, benign	No
	508	666	1046	U	skin	keratoacanthoma	No
	513	513	1005	U	gland, parathyroid	adenoma	No
	513	513	1005	U	pancreas	islet cell carcinoma	Yes
	521	580	1003	U	skin	keratoacanthoma	No
	528	686	1010	T	skin	keratoacanthoma	No
	535	618	1056	U	subcutis	lipoma	No
	535	593	1070	U	subcutis	fibroma	No
	548	548	1038	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	549	616	1021	U	skin	keratoacanthoma	No
	549	620	1030	U	subcutis	lipoma	No
	549	630	1031	U	skin	keratoacanthoma	No
	549	644	1036	U	skin	hair follicle tumor, benign	No
	549	562	1055	U	subcutis	fibroma	No
	562	562	1055	U	gland, pituitary	adenoma	No
	562	562	1055	U	gland, thyroid	c-cell carcinoma	Yes
	563	622	1035	U	subcutis	fibroma	No
	564	564	1028	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	564	564	1028	U	urinary bladder	papilloma	No
	570	616	1021	U	gland, mammary	adenocarcinoma	Yes
	577	578	1004	U	subcutis	fibroma	No
	578	578	1004	U	gland, mammary	adenoma	No
	580	580	1003	U	gland, pituitary	adenoma	No
	582	582	1009	U	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1M	587	587	1050	U	gland, adrenal	cortical adenoma	No
	587	587	1050	U	gland, pituitary	adenoma	No
	593	593	1070	U	gland, thyroid	c-cell adenoma	No
	593	593	1070	U	muscle, skeletal	fibrosarcoma	Yes
	616	616	1021	U	gland, pituitary	adenoma	No
	618	618	1056	U	gland, pituitary	adenoma	No
	618	618	1056	U	gland, thyroid	c-cell carcinoma	Yes
	620	620	1030	U	gland, pituitary	adenoma	No
	620	620	1030	U	pancreas	islet cell adenoma	No
	622	622	1035	U	gland, thyroid	c-cell carcinoma	Yes
	628	628	1047	U	gland, pituitary	adenoma	No
	630	630	1031	U	gland, pituitary	adenoma	No
	630	630	1031	U	gland, thyroid	c-cell carcinoma	Yes
	630	630	1031	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	630	630	1048	U	gland, pituitary	adenoma	No
	630	630	1048	U	pancreas	islet cell adenoma	No
	632	632	1024	U	gland, pituitary	adenoma	No
	632	632	1024	U	lymph node, mesenteric	hemangioma	No
	632	632	1024	U	skin	keratoacanthoma	No
	633	675	1064	U	skin	keratoacanthoma	No
	646	646	1014	U	liver	hepatocellular adenoma	No
	646	646	1014	U	skin	papilloma	No
	647	691	1007	T	subcutis	fibroma	No
	647	691	1013	T	subcutis	fibroma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1M	652	652	1059	U	gland, pituitary	adenoma	No
	652	652	1059	U	gland, thyroid	c-cell adenoma	No
	652	652	1059	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	652	652	1059	U	pancreas	islet cell adenoma	No
	654	692	1045	T	subcutis	fibroma	No
	654	692	1061	T	gland, mammary	fibroadenoma	No
	666	666	1046	U	gland, pituitary	adenoma	No
	668	685	1032	T	subcutis	sarcoma	Yes
	668	688	1033	T	skin	keratoacanthoma	No
	670	670	1027	U	gland, thyroid	c-cell adenoma	No
	670	670	1027	U	pancreas	islet cell carcinoma	Yes
	678	678	1023	U	gland, preputial	papilloma	No
	678	678	1023	U	testis	interstitial (leydig) cell adenoma	No
	679	679	1066	T	gland, pituitary	adenoma	No
	680	680	1008	T	pancreas	islet cell adenoma	No
	680	680	1008	T	skin	fibroma	No
	681	681	1026	T	adipose tissue	hibernoma, benign	No
	681	681	1026	T	liver	hepatocellular adenoma	No
	681	681	1026	T	pancreas	ductal cell adenocarcinoma	Yes
	685	685	1032	T	gland, adrenal	pheochromocytoma, benign	No
	685	685	1032	T	pancreas	islet cell adenoma	No
	685	685	1032	T	skin	basal cell tumor, benign	No
	686	686	1010	T	gland, adrenal	pheochromocytoma, benign	No
	686	686	1010	T	pancreas	islet cell carcinoma	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1M	687	687	1006	T	gland, adrenal	pheochromocytoma, benign	No
	687	687	1006	T	gland, pituitary	adenoma	No
	687	687	1006	T	gland, thyroid	c-cell carcinoma	Yes
	688	688	1033	T	skin	papilloma	No
	691	691	1007	T	gland, adrenal	pheochromocytoma, benign	No
	691	691	1007	T	gland, thyroid	follicular cell adenoma	No
	691	691	1007	T	lung	bronchioloalveolar adenoma	No
	691	691	1012	T	gland, adrenal	pheochromocytoma, benign	No
	691	691	1012	T	gland, pituitary	adenoma	No
	691	691	1013	T	pancreas	islet cell adenoma	No
	691	691	1017	T	gland, adrenal	pheochromocytoma, malignant	Yes
	691	691	1017	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	691	691	1058	T	brain	astrocytoma, malignant	Yes
	692	692	1037	T	gland, pituitary	adenoma	No
	692	692	1037	T	liver	hepatocellular adenoma	No
	692	692	1051	T	gland, adrenal	pheochromocytoma, benign	No
	692	692	1051	T	gland, adrenal	pheochromocytoma, malignant	Yes
	692	692	1061	T	lung	bronchioloalveolar adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
2M	130	153	2020	U	subcutis	fibrosarcoma	Yes
	316	316	2012	U	gland, pituitary	adenoma	No
	319	548	2030	U	subcutis	fibrosarcoma	Yes
	339	579	2024	U	subcutis	liposarcoma	Yes
	387	387	2066	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	389	389	2016	U	body cavity, nasal	squamous cell carcinoma	Yes
	389	389	2016	U	gland, thyroid	c-cell adenoma	No
	409	495	2043	U	skin	papilloma	No
	409	409	2058	U	gland, thyroid	c-cell adenoma	No
	424	495	2043	U	subcutis	fibroma	No
	445	585	2059	U	subcutis	fibrosarcoma	Yes
	455	455	2028	U	gland, pituitary	adenoma	No
	472	643	2002	U	subcutis	fibroma	No
	479	556	2014	U	subcutis	fibroma	No
	487	692	2034	T	subcutis	fibroma	No
	487	544	2061	U	skin	basal cell tumor, malignant	Yes
	494	494	2057	U	gland, mammary	fibroadenoma	No
	495	495	2043	U	gland, adrenal	pheochromocytoma, benign	No
	521	686	2041	T	subcutis	fibroma	No
	524	524	2045	U	gland, pituitary	adenoma	No
	524	524	2050	U	skin	papilloma	No
	535	611	2032	U	skin	keratoacanthoma	No
	535	542	2038	U	skin	keratoacanthoma	No
	535	542	2038	U	subcutis	lipoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
2M	538	538	2047	U	pancreas	islet cell carcinoma	Yes
	542	542	2038	U	gland, pituitary	adenoma	No
	544	544	2061	U	brain	astrocytoma, malignant	Yes
	548	548	2044	U	gland, pituitary	adenoma	No
	551	551	2042	U	gland, adrenal	cortical carcinoma	Yes
	552	552	2009	U	kidney	liposarcoma	Yes
	553	553	2068	U	gland, pituitary	adenoma	No
	555	555	2008	U	gland, pituitary	adenoma	No
	555	555	2008	U	pancreas	islet cell adenoma	No
	556	556	2014	U	gland, adrenal	pheochromocytoma, benign	No
	560	560	2010	U	gland, pituitary	adenoma	No
	584	593	2048	U	skin	keratoacanthoma	No
	584	584	2060	U	gland, pituitary	adenoma	No
	584	584	2060	U	lymph node, mesenteric	hemangioma	No
	585	585	2059	U	stomach	papilloma	No
	593	593	2048	U	brain	astrocytoma, malignant	Yes
	593	593	2048	U	lymph node, mesenteric	hemangiosarcoma	Yes
	595	595	2040	U	gland, adrenal	pheochromocytoma, benign	No
	595	595	2040	U	gland, mammary	fibroadenoma	No
	595	595	2040	U	gland, pituitary	adenoma	No
	605	687	2003	T	subcutis	fibroma	No
	606	606	2037	U	liver	hepatocellular adenoma	No
	611	611	2032	U	gland, pituitary	adenoma	No
	612	612	2004	U	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
2M	619	619	2019	U	gland, pituitary	adenoma	No
	619	619	2019	U	skin	papilloma	No
	623	623	2064	U	gland, pituitary	adenoma	No
	627	627	2039	U	gland, pituitary	adenoma	No
	627	627	2039	U	gland, thyroid	c-cell carcinoma	Yes
	627	627	2039	U	pancreas	islet cell carcinoma	Yes
	627	627	2039	U	subcutis	fibroma	No
	629	629	2025	U	gland, parathyroid	adenoma	No
	629	629	2025	U	gland, pituitary	adenoma	No
	629	629	2025	U	gland, thyroid	c-cell adenoma	No
	638	638	2006	U	gland, adrenal	pheochromocytoma, benign	No
	639	639	2062	U	liver	cholangioma	No
	640	640	2005	U	gland, pituitary	adenoma	No
	640	640	2005	U	testis	interstitial (leydig) cell adenoma	No
	643	643	2002	U	brain	astrocytoma, malignant	Yes
	643	643	2002	U	gland, thyroid	c-cell adenoma	No
	654	680	2015	T	subcutis	fibroma	No
	654	673	2018	U	subcutis	fibroma	No
	668	691	2029	T	gland, mammary	fibroadenoma	No
	670	670	2069	U	gland, pituitary	adenoma	No
	673	673	2018	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	674	674	2065	U	gland, thyroid	follicular cell adenoma	No
	679	679	2036	T	gland, pituitary	adenoma	No
	679	679	2036	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
2M	680	680	2015	T	gland, adrenal	pheochromocytoma, malignant	Yes
	685	685	2035	T	gland, adrenal	pheochromocytoma, benign	No
	685	685	2035	T	hemolymphoreticular tissue	leukemia, large granular lymphocytic	Yes
	685	685	2035	T	pancreas	adenoma	No
	685	685	2035	T	pancreas	islet cell carcinoma	Yes
	686	686	2041	T	gland, pituitary	adenoma	No
	687	687	2003	T	gland, adrenal	cortical adenoma	No
	687	687	2003	T	gland, thyroid	c-cell adenoma	No
	687	687	2003	T	testis	interstitial (leydig) cell adenoma	No
	688	688	2070	T	lung	bronchioloalveolar carcinoma	Yes
	691	691	2017	T	body cavity, nasal	adenoma	No
	691	691	2017	T	gland, adrenal	pheochromocytoma, benign	No
	691	691	2021	T	gland, pituitary	adenoma	No
	691	691	2022	T	gland, thyroid	c-cell adenoma	No
	691	691	2022	T	pancreas	islet cell adenoma	No
	691	691	2029	T	liver	hepatocellular adenoma	No
	692	692	2033	T	gland, adrenal	pheochromocytoma, benign	No
	692	692	2034	T	gland, pituitary	adenoma	No
	692	692	2034	T	gland, thyroid	follicular cell adenoma	No
	692	692	2046	T	gland, mammary	fibroadenoma	No
	692	692	2052	T	body cavity, thoracic	paraganglioma	Yes
	692	692	2055	T	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3M	277	595	3067	U	subcutis	fibroma	No
	318	493	3069	U	skin	papilloma	No
	326	326	3033	U	hemolymphoreticular tissue	leukemia, large granular lymphocytic	Yes
	333	691	3002	T	skin	papilloma	No
	333	691	3005	T	skin	melanoma, malignant	Yes
	338	338	3063	U	body cavity, nasal	squamous cell carcinoma	Yes
	338	338	3063	U	gland, pituitary	adenoma	No
	382	660	3020	U	subcutis	fibroma	No
	403	445	3012	U	subcutis	fibroma	No
	403	692	3047	T	subcutis	fibroma	No
	424	597	3025	U	subcutis	fibroma	No
	424	493	3069	U	skin	keratoacanthoma	No
	445	681	3009	T	subcutis	lipoma	No
	445	445	3012	U	kidney	adenoma	No
	465	465	3044	U	gland, pituitary	adenoma	No
	465	465	3044	U	skin	keratoacanthoma	No
	479	673	3057	U	gland, mammary	adenoma	No
	486	486	3022	U	gland, pituitary	adenoma	No
	487	630	3036	U	subcutis	schwannoma, benign	No
	490	490	3059	U	gland, adrenal	cortical adenoma	No
	493	493	3050	U	gland, adrenal	pheochromocytoma, benign	No
	493	493	3050	U	skin	papilloma	No
	493	493	3069	U	gland, pituitary	adenoma	No
	493	493	3069	U	gland, thyroid	c-cell adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3M	508	508	3003	U	gland, pituitary	adenoma	No
	508	518	3007	U	skin	squamous cell carcinoma	Yes
	513	513	3049	U	gland, pituitary	adenoma	No
	513	513	3049	U	gland, thyroid	c-cell adenoma	No
	518	518	3064	U	gland, parathyroid	adenoma	No
	518	518	3064	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	518	518	3064	U	kidney	adenoma	No
	524	524	3039	U	gland, pituitary	adenoma	No
	529	577	3068	U	subcutis	fibrosarcoma	Yes
	543	670	3027	U	skin	squamous cell carcinoma	Yes
	543	545	3037	U	subcutis	fibrosarcoma	Yes
	545	545	3026	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	545	545	3037	U	gland, pituitary	adenoma	No
	545	545	3037	U	gland, thyroid	c-cell carcinoma	Yes
	549	557	3052	U	subcutis	fibroma	No
	557	557	3052	U	brain	astrocytoma, malignant	Yes
	563	613	3041	U	gland, mammary	adenoma	No
	567	567	3030	U	pancreas	islet cell adenoma	No
	570	673	3057	U	subcutis	schwannoma, benign	No
	576	576	3010	U	gland, pituitary	adenoma	No
	576	576	3010	U	hemolymphoreticular tissue	leukemia, large granular lymphocytic	Yes
	577	577	3068	U	gland, pituitary	adenoma	No
	584	687	3045	T	subcutis	fibroma	No
	588	588	3024	U	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3M	591	670	3027	U	skin	keratoacanthoma	No
	591	638	3053	U	skin	keratoacanthoma	No
	593	593	3031	U	muscle, skeletal	fibrosarcoma	Yes
	593	593	3031	U	testis	interstitial (leydig) cell adenoma	No
	593	593	3031	U	thymus	thymoma, benign	No
	595	595	3067	U	pancreas	islet cell adenoma	No
	599	610	3013	U	skin	keratoacanthoma	No
	600	600	3046	U	gland, pituitary	adenoma	No
	600	600	3046	U	hemolymphoreticular tissue	leukemia, large granular lymphocytic	Yes
	610	610	3013	U	gland, pituitary	adenoma	No
	610	610	3013	U	gland, thyroid	c-cell carcinoma	Yes
	610	610	3013	U	kidney	adenoma	No
	610	610	3013	U	small intestine, jejunum	leiomyosarcoma	Yes
	612	680	3008	T	subcutis	fibroma	No
	612	612	3014	U	gland, adrenal	pheochromocytoma, benign	No
	612	612	3014	U	gland, mammary	adenoma	No
	612	612	3014	U	pancreas	islet cell adenoma	No
	612	612	3017	U	gland, pituitary	adenoma	No
	612	612	3017	U	pancreas	islet cell adenoma	No
	613	613	3041	U	gland, pituitary	carcinoma	Yes
	613	613	3041	U	gland, thyroid	c-cell adenoma	No
	623	623	3062	U	gland, adrenal	pheochromocytoma, benign	No
	623	623	3062	U	gland, pituitary	adenoma	No
	626	626	3035	U	brain	meningioma, malignant	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3M	626	626	3035	U	gland, pituitary	adenoma	No
	630	630	3036	U	lymph node, mesenteric	hemangioma	No
	633	633	3015	U	gland, pituitary	adenoma	No
	633	670	3027	U	subcutis	fibroma	No
	634	634	3019	U	gland, pituitary	adenoma	No
	640	640	3023	U	brain	astrocytoma, malignant	Yes
	640	640	3023	U	gland, pituitary	adenoma	No
	640	640	3023	U	pancreas	adenoma	No
	654	680	3008	T	subcutis	schwannoma, benign	No
	670	670	3027	U	gland, pituitary	adenoma	No
	670	670	3027	U	gland, thyroid	c-cell adenoma	No
	670	670	3027	U	gland, thyroid	c-cell carcinoma	Yes
	670	670	3027	U	gland, thyroid	follicular cell adenoma	No
	672	672	3066	U	pancreas	islet cell adenoma	No
	673	673	3057	U	gland, pituitary	adenoma	No
	673	673	3057	U	gland, thyroid	c-cell adenoma	No
	673	673	3057	U	skin	squamous cell carcinoma	Yes
	679	679	3006	T	gland, pituitary	adenoma	No
	679	679	3006	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	680	680	3008	T	gland, thyroid	c-cell adenoma	No
	680	680	3008	T	pancreas	islet cell adenoma	No
	681	681	3009	T	pancreas	islet cell adenoma	No
	685	685	3056	T	gland, pituitary	adenoma	No
	686	686	3058	T	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3M	686	686	3058	T	gland, thyroid	c-cell adenoma	No
	686	686	3058	T	pancreas	islet cell carcinoma	Yes
	687	687	3045	T	gland, pituitary	adenoma	No
	688	688	3038	T	pancreas	islet cell carcinoma	Yes
	688	688	3038	T	tail	squamous cell carcinoma	Yes
	691	691	3001	T	gland, adrenal	pheochromocytoma, benign	No
	691	691	3001	T	gland, adrenal	pheochromocytoma, malignant	Yes
	691	691	3001	T	pancreas	islet cell adenoma	No
	691	691	3002	T	gland, pituitary	adenoma	No
	691	691	3005	T	body cavity, oral	squamous cell carcinoma	Yes
	692	692	3034	T	gland, adrenal	pheochromocytoma, benign	No
	692	692	3034	T	gland, pituitary	adenoma	No
	692	692	3051	T	gland, adrenal	pheochromocytoma, benign	No
	692	692	3051	T	gland, thyroid	c-cell adenoma	No
	692	692	3051	T	pancreas	islet cell adenoma	No
	692	692	3061	T	skin	keratoacanthoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
4M	267	267	4041	U	gland, pituitary	adenoma	No
	305	414	4055	U	subcutis	fibrosarcoma	Yes
	321	321	4007	U	hemolymphoreticular tissue	leukemia, large granular lymphocytic	Yes
	346	469	4046	U	subcutis	fibroma	No
	346	350	4047	U	skin	papilloma	No
	361	519	4012	U	subcutis	fibrosarcoma	Yes
	364	364	4065	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	367	367	4001	U	skin	papilloma	No
	373	373	4018	U	kidney	adenoma	No
	380	380	4004	U	gland, pituitary	adenoma	No
	424	691	4019	T	subcutis	fibroma	No
	445	652	4058	U	gland, mammary	fibroadenoma	No
	471	471	4027	U	gland, pituitary	adenoma	No
	471	471	4027	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	473	679	4050	T	subcutis	fibroma	No
	478	478	4059	U	gland, pituitary	adenoma	No
	479	688	4006	T	subcutis	fibroma	No
	479	600	4031	U	gland, mammary	adenoma	No
	501	584	4044	U	subcutis	lipoma	No
	509	509	4069	U	pancreas	islet cell adenoma	No
	518	518	4036	U	gland, pituitary	adenoma	No
	518	518	4036	U	skin	squamous cell carcinoma	Yes
	519	519	4012	U	gland, pituitary	adenoma	No
	522	692	4061	T	subcutis	fibroma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
4M	527	527	4028	U	gland, pituitary	adenoma	No
	527	527	4028	U	gland, thyroid	c-cell adenoma	No
	529	529	4038	U	gland, thyroid	c-cell adenoma	No
	529	529	4038	U	gland, thyroid	c-cell carcinoma	Yes
	531	531	4035	U	gland, pituitary	adenoma	No
	543	600	4031	U	skin	papilloma	No
	543	691	4053	T	subcutis	lipoma	No
	547	547	4032	U	pancreas	islet cell adenoma	No
	547	547	4032	U	subcutis	fibroma	No
	550	692	4070	T	subcutis	fibroma	No
	557	568	4034	U	head	sarcoma	Yes
	557	692	4070	T	gland, mammary	fibroadenoma	No
	566	566	4045	U	gland, pituitary	adenoma	No
	570	691	4039	T	subcutis	lipoma	No
	600	600	4031	U	gland, thyroid	follicular cell adenoma	No
	609	609	4025	U	gland, adrenal	cortical adenoma	No
	609	609	4025	U	gland, adrenal	pheochromocytoma, benign	No
	609	609	4025	U	meninges	meningioma, malignant	Yes
	609	609	4025	U	skin	papilloma	No
	616	616	4005	U	gland, adrenal	pheochromocytoma, benign	No
	616	616	4005	U	gland, adrenal	pheochromocytoma, malignant	Yes
	618	618	4015	U	lung	bronchioloalveolar adenoma	No
	623	623	4068	U	gland, pituitary	adenoma	No
	624	624	4048	U	pancreas	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
4M	624	624	4052	U	gland, pituitary	adenoma	No
	634	634	4037	U	gland, adrenal	pheochromocytoma, benign	No
	640	691	4040	T	skin	keratoacanthoma	No
	642	642	4067	U	gland, pituitary	adenoma	No
	642	642	4067	U	pericardium	mesothelioma, malignant	Yes
	652	652	4058	U	gland, pituitary	adenoma	No
	652	652	4058	U	gland, thyroid	c-cell adenoma	No
	652	652	4058	U	pancreas	islet cell carcinoma	Yes
	659	659	4003	U	gland, thyroid	follicular cell adenoma	No
	659	659	4003	U	pancreas	islet cell carcinoma	Yes
	659	659	4016	U	gland, pituitary	adenoma	No
	659	659	4016	U	lymph node, mesenteric	hemangiosarcoma	Yes
	659	659	4016	U	skin	papilloma	No
	661	663	4033	U	head	fibrosarcoma	Yes
	661	686	4043	T	subcutis	schwannoma, malignant	Yes
	663	663	4033	U	pancreas	islet cell adenoma	No
	666	666	4017	U	gland, pituitary	adenoma	No
	675	680	4060	T	skin	squamous cell carcinoma	Yes
	675	692	4061	T	gland, mammary	fibroadenoma	No
	679	679	4050	T	gland, pituitary	adenoma	No
	679	679	4050	T	gland, thyroid	c-cell adenoma	No
	679	679	4050	T	testis	interstitial (leydig) cell adenoma	No
	680	680	4060	T	gland, pituitary	adenoma	No
	681	681	4064	T	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
4M	681	681	4064	T	gland, thyroid	c-cell adenoma	No
	685	685	4051	T	gland, thyroid	c-cell adenoma	No
	686	686	4043	T	gland, thyroid	c-cell adenoma	No
	686	686	4043	T	muscle, skeletal	schwannoma, malignant	Yes
	686	686	4043	T	subcutis	fibroma	No
	688	688	4006	T	body cavity, thoracic	thymoma, malignant	Yes
	688	688	4006	T	subcutis	fibrosarcoma	Yes
	691	691	4013	T	gland, adrenal	pheochromocytoma, benign	No
	691	691	4013	T	gland, adrenal	pheochromocytoma, complex, benign	No
	691	691	4013	T	gland, pituitary	carcinoma	Yes
	691	691	4013	T	stomach	polyp	No
	691	691	4026	T	gland, pituitary	adenoma	No
	691	691	4039	T	gland, pituitary	adenoma	No
	691	691	4039	T	pancreas	islet cell adenoma	No
	691	691	4039	T	subcutis	fibroma	No
	691	691	4040	T	gland, thyroid	c-cell adenoma	No
	692	692	4061	T	gland, pituitary	adenoma	No
	692	692	4070	T	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
5M	129	180	5017	U	subcutis	fibrosarcoma	Yes
	228	498	5068	U	skin	papilloma	No
	249	395	5018	U	skin	keratoacanthoma	No
	284	284	5057	U	brain	meningioma, malignant	Yes
	305	316	5044	U	gland, mammary	fibroadenoma	No
	344	344	5069	U	gland, prostate	polyp	No
	352	352	5042	U	kidney	adenoma	No
	368	504	5008	U	subcutis	fibrosarcoma	Yes
	380	380	5007	U	gland, pituitary	carcinoma	Yes
	405	405	5045	U	gland, thyroid	c-cell adenoma	No
	417	641	5058	U	skin	keratoacanthoma	No
	430	430	5026	U	gland, pituitary	adenoma	No
	430	430	5026	U	gland, thyroid	c-cell adenoma	No
	439	439	5036	U	gland, pituitary	adenoma	No
	443	443	5005	U	gland, pituitary	adenoma	No
	455	455	5060	U	gland, pituitary	adenoma	No
	456	456	5034	U	small intestine, duodenum	adenocarcinoma	Yes
	473	504	5008	U	gland, mammary	fibroadenoma	No
	497	497	5066	U	gland, pituitary	adenoma	No
	497	497	5066	U	gland, thyroid	c-cell adenoma	No
	498	498	5068	U	gland, pituitary	adenoma	No
	504	504	5008	U	gland, pituitary	adenoma	No
	505	505	5051	U	gland, pituitary	adenoma	No
	508	540	5061	U	subcutis	fibrosarcoma	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
5M	512	512	5006	U	gland, pituitary	adenoma	No
	515	653	5021	T	gland, mammary	fibroadenoma	No
	515	650	5046	U	gland, mammary	fibroadenoma	No
	522	522	5053	U	gland, parathyroid	adenoma	No
	523	523	5028	U	gland, pituitary	adenoma	No
	529	558	5065	U	subcutis	fibroma	No
	553	553	5029	U	gland, mammary	adenoma	No
	553	553	5055	U	gland, pituitary	adenoma	No
	555	555	5009	U	gland, thyroid	c-cell adenoma	No
	560	561	5014	U	subcutis	fibroma	No
	570	592	5040	U	subcutis	schwannoma, benign	No
	570	653	5050	T	skin	sebaceous cell adenoma	No
	576	576	5023	U	gland, pituitary	adenoma	No
	576	576	5023	U	pancreas	islet cell adenoma	No
	584	645	5054	U	gland, mammary	fibroadenoma	No
	591	653	5002	T	gland, mammary	fibroadenoma	No
	598	598	5038	U	liver	cholangioma	No
	598	598	5038	U	skin	keratoacanthoma	No
	619	653	5002	T	skin	papilloma	No
	626	653	5002	T	subcutis	fibroma	No
	626	645	5054	U	subcutis	fibroma	No
	645	645	5054	U	gland, adrenal	pheochromocytoma, benign	No
	645	645	5054	U	pancreas	islet cell adenoma	No
	653	653	5004	T	subcutis	fibroma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
5M	653	653	5010	T	gland, pituitary	adenoma	No
	653	653	5010	T	gland, thyroid	c-cell carcinoma	Yes
	653	653	5010	T	kidney	adenoma	No
	653	653	5010	T	spleen	hemangiosarcoma	Yes
	653	653	5010	T	stomach	adenoma	No
	653	653	5019	T	gland, mammary	fibroadenoma	No
	653	653	5025	T	gland, pituitary	adenoma	No
	653	653	5030	T	pancreas	islet cell adenoma	No
	653	653	5030	T	spleen	hemangiosarcoma	Yes
	653	653	5033	T	kidney	adenoma	No
	653	653	5033	T	liver	hemangioma	No
	653	653	5033	T	stomach	adenoma	No
	653	653	5033	T	testis	hemangioma	No
	653	653	5037	T	gland, mammary	fibroadenoma	No
	653	653	5037	T	gland, pituitary	adenoma	No
	653	653	5039	T	gland, pituitary	adenoma	No
	653	653	5039	T	pancreas	islet cell adenoma	No
	653	653	5043	T	gland, pituitary	adenoma	No
	653	653	5043	T	subcutis	fibroma	No
	653	653	5050	T	gland, thyroid	c-cell adenoma	No
	653	653	5050	T	pancreas	islet cell adenoma	No
	653	653	5064	T	lymph node, mesenteric	hemangioma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Females

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1F	95	380	1518	U	gland, mammary	adenocarcinoma	Yes
	179	385	1565	U	gland, mammary	adenoma	No
	208	454	1503	U	gland, mammary	fibroadenoma	No
	208	380	1534	U	gland, mammary	fibroadenoma	No
	277	416	1505	U	gland, mammary	fibroadenoma	No
	306	454	1503	U	gland, mammary	adenoma	No
	306	326	1513	U	gland, mammary	fibroadenoma	No
	306	571	1520	U	gland, mammary	adenocarcinoma	Yes
	306	642	1546	U	gland, mammary	fibroadenoma	No
	319	355	1508	U	subcutis	fibrosarcoma	Yes
	326	326	1502	U	gland, pituitary	adenoma	No
	326	326	1513	U	gland, pituitary	adenoma	No
	354	426	1544	U	gland, mammary	adenocarcinoma	Yes
	363	363	1525	U	gland, pituitary	adenoma	No
	376	688	1543	U	gland, mammary	fibroadenoma	No
	376	452	1563	U	gland, mammary	fibroadenoma	No
	376	638	1566	U	gland, mammary	fibroadenoma	No
	380	380	1518	U	gland, pituitary	adenoma	No
	385	385	1565	U	gland, pituitary	adenoma	No
	403	457	1519	U	skin	basal cell tumor, malignant	Yes
	416	416	1505	U	gland, pituitary	adenoma	No
	426	426	1544	U	gland, mammary	adenoma	No
	426	426	1544	U	gland, pituitary	adenoma	No
	432	457	1519	U	gland, mammary	fibroadenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1F	439	662	1511	U	subcutis	lipoma	No
	439	617	1539	U	gland, mammary	fibroadenoma	No
	443	443	1551	U	gland, mammary	fibroadenoma	No
	443	443	1551	U	gland, pituitary	adenoma	No
	445	445	1509	U	gland, pituitary	adenoma	No
	446	614	1561	U	gland, mammary	adenocarcinoma	Yes
	452	452	1563	U	gland, pituitary	adenoma	No
	453	591	1527	U	gland, mammary	adenocarcinoma	Yes
	453	518	1547	U	subcutis	fibroma	No
	454	454	1503	U	gland, pituitary	adenoma	No
	459	459	1532	U	gland, pituitary	adenoma	No
	463	463	1537	U	cervix	sarcoma	Yes
	463	463	1537	U	gland, pituitary	adenoma	No
	477	477	1569	U	brain	astrocytoma, malignant	Yes
	480	698	1523	T	gland, mammary	fibroadenoma	No
	480	615	1558	U	gland, mammary	fibroadenoma	No
	480	698	1560	T	gland, mammary	fibroadenoma	No
	485	485	1550	U	gland, pituitary	adenoma	No
	487	637	1510	U	subcutis	lipoma	No
	492	513	1515	U	gland, mammary	fibroadenoma	No
	495	518	1547	U	bone	osteosarcoma	Yes
	495	698	1560	T	gland, mammary	adenoma	No
	502	698	1562	T	gland, mammary	adenoma	No
	502	554	1567	U	gland, clitoral	adenocarcinoma	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1F	509	699	1528	T	gland, mammary	fibroadenoma	No
	513	513	1515	U	gland, pituitary	adenoma	No
	513	513	1515	U	gland, thyroid	c-cell adenoma	No
	516	579	1535	U	gland, mammary	adenocarcinoma	Yes
	516	555	1552	U	gland, mammary	adenocarcinoma	Yes
	518	518	1547	U	bone, femur	hemangiosarcoma	Yes
	518	518	1547	U	gland, pituitary	adenoma	No
	523	698	1523	T	subcutis	fibrosarcoma	Yes
	530	700	1564	T	gland, mammary	fibroadenoma	No
	534	534	1530	U	gland, mammary	fibroadenoma	No
	534	534	1530	U	gland, pituitary	adenoma	No
	536	662	1511	U	gland, mammary	fibroadenoma	No
	536	574	1522	U	gland, mammary	fibroadenoma	No
	536	698	1541	T	gland, mammary	fibroadenoma	No
	536	604	1559	U	gland, mammary	fibroadenoma	No
	544	698	1507	T	gland, mammary	adenoma	No
	544	698	1523	T	gland, mammary	adenocarcinoma	Yes
	544	698	1562	T	gland, mammary	fibroadenoma	No
	554	554	1567	U	gland, pituitary	adenoma	No
	555	555	1552	U	gland, pituitary	adenoma	No
	557	695	1545	U	subcutis	osteosarcoma	Yes
	571	662	1511	U	gland, mammary	adenoma	No
	571	571	1520	U	gland, pituitary	adenoma	No
	571	688	1543	U	gland, mammary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1F	573	573	1557	U	gland, pituitary	adenoma	No
	574	574	1522	U	gland, pituitary	adenoma	No
	578	579	1535	U	gland, mammary	fibroadenoma	No
	578	695	1545	U	gland, mammary	fibroadenoma	No
	578	699	1548	T	subcutis	lipoma	No
	579	579	1535	U	gland, pituitary	adenoma	No
	591	591	1527	U	gland, pituitary	adenoma	No
	591	591	1527	U	gland, thyroid	c-cell adenoma	No
	595	595	1512	U	gland, pituitary	adenoma	No
	599	646	1526	U	gland, mammary	fibroadenoma	No
	599	601	1549	U	gland, mammary	fibroadenoma	No
	601	601	1549	U	gland, pituitary	adenoma	No
	604	604	1506	U	gland, mammary	adenocarcinoma	Yes
	604	604	1506	U	gland, pituitary	adenoma	No
	604	604	1559	U	gland, adrenal	pheochromocytoma, benign	No
	604	604	1559	U	gland, pituitary	adenoma	No
	606	699	1548	T	gland, mammary	adenoma	No
	613	655	1504	U	gland, mammary	fibroadenoma	No
	613	655	1504	U	skin	keratoacanthoma	No
	613	698	1517	T	gland, mammary	fibroadenoma	No
	614	614	1561	U	gland, pituitary	adenoma	No
	614	614	1561	U	subcutis	fibroma	No
	615	615	1558	U	gland, pituitary	adenoma	No
	617	617	1539	U	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1F	617	617	1539	U	gland, thyroid	c-cell carcinoma	Yes
	620	624	1553	U	skin	squamous cell carcinoma	Yes
	634	700	1533	T	gland, mammary	fibroadenoma	No
	637	637	1510	U	gland, pituitary	adenoma	No
	642	642	1546	U	gland, pituitary	adenoma	No
	646	646	1526	U	body cavity, oral	osteosarcoma	Yes
	646	646	1526	U	gland, pituitary	adenoma	No
	649	699	1529	T	gland, mammary	adenoma	No
	653	653	1531	U	gland, pituitary	adenoma	No
	653	653	1531	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	655	655	1504	U	gland, pituitary	adenoma	No
	655	662	1511	U	subcutis	fibroma	No
	661	661	1516	U	gland, pituitary	adenoma	No
	662	662	1511	U	gland, pituitary	adenoma	No
	662	662	1511	U	liver	hepatocellular adenoma	No
	662	699	1529	T	gland, mammary	fibroadenoma	No
	667	667	1570	U	gland, mammary	fibroadenoma	No
	667	667	1570	U	gland, pituitary	adenoma	No
	676	699	1514	T	gland, mammary	fibroadenoma	No
	676	698	1517	T	gland, mammary	adenoma	No
	683	698	1507	T	gland, mammary	fibroadenoma	No
	683	699	1548	T	gland, mammary	fibroadenoma	No
	688	688	1543	U	gland, pituitary	adenoma	No
	695	695	1545	U	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1F	697	700	1538	T	gland, mammary	fibroadenoma	No
	697	698	1568	T	gland, mammary	fibroadenoma	No
	698	698	1507	T	gland, pituitary	adenoma	No
	698	698	1507	T	gland, thyroid	c-cell adenoma	No
	698	698	1507	T	gland, thyroid	follicular cell adenoma	No
	698	698	1517	T	gland, pituitary	adenoma	No
	698	698	1523	T	gland, mammary	adenoma	No
	698	698	1523	T	gland, pituitary	adenoma	No
	698	698	1540	T	gland, mammary	fibroadenoma	No
	698	698	1541	T	gland, mammary	adenoma	No
	698	698	1541	T	gland, pituitary	adenoma	No
	698	698	1560	T	gland, pituitary	adenoma	No
	698	698	1562	T	gland, adrenal	pheochromocytoma, benign	No
	698	698	1568	T	gland, pituitary	adenoma	No
	699	699	1521	T	gland, mammary	fibroadenoma	No
	699	699	1528	T	gland, pituitary	adenoma	No
	699	699	1528	T	gland, thyroid	c-cell adenoma	No
	699	699	1529	T	uterus	polyp	No
	699	699	1548	T	gland, pituitary	adenoma	No
	699	699	1548	T	gland, thyroid	c-cell adenoma	No
	699	699	1548	T	ovary	mesothelioma, malignant	Yes
	699	699	1555	T	gland, mammary	fibroadenoma	No
	699	699	1555	T	gland, pituitary	adenoma	No
	699	699	1555	T	spleen	hemangioma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
1F	699	699	1555	T	uterus	endometrial stromal polyp	No
	700	700	1524	T	gland, mammary	fibroadenoma	No
	700	700	1538	T	gland, pituitary	adenoma	No
	700	700	1538	T	gland, thyroid	c-cell carcinoma	Yes
	700	700	1538	T	skin	keratoacanthoma	No
	700	700	1564	T	gland, mammary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
2F	60	351	2570	U	gland, mammary	adenosquamous carcinoma	Yes
	179	414	2504	U	gland, mammary	adenocarcinoma	Yes
	186	186	2541	U	brain	oligodendroglioma, malignant	Yes
	236	290	2537	U	gland, mammary	fibroadenoma	No
	270	519	2530	U	gland, mammary	fibroadenoma	No
	290	290	2537	U	gland, pituitary	adenoma	No
	290	290	2537	U	kidney	adenoma	No
	299	652	2510	U	gland, mammary	fibroadenoma	No
	341	548	2516	U	gland, mammary	fibroadenoma	No
	348	698	2505	T	gland, mammary	fibroadenoma	No
	355	464	2527	U	gland, mammary	adenoma	No
	369	649	2543	U	gland, mammary	fibroadenoma	No
	369	540	2550	U	gland, mammary	fibroadenoma	No
	383	610	2503	U	gland, mammary	fibroadenoma	No
	383	464	2527	U	gland, mammary	fibroadenoma	No
	383	693	2569	U	gland, mammary	fibroadenoma	No
	390	688	2536	U	gland, mammary	fibroadenoma	No
	390	390	2548	U	gland, pituitary	adenoma	No
	411	671	2502	U	gland, mammary	fibroadenoma	No
	411	458	2525	U	subcutis	schwannoma, benign	No
	414	414	2504	U	gland, mammary	adenoma	No
	414	414	2504	U	gland, pituitary	adenoma	No
	418	649	2557	U	gland, mammary	adenoma	No
	418	559	2558	U	gland, mammary	fibroadenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
2F	419	419	2533	U	gland, mammary	adenocarcinoma	Yes
	419	419	2533	U	gland, mammary	fibroadenoma	No
	421	421	2514	U	gland, mammary	fibroadenoma	No
	421	421	2514	U	gland, pituitary	adenoma	No
	439	698	2511	T	gland, mammary	fibroadenoma	No
	447	447	2512	U	small intestine, jejunum	leiomyosarcoma	Yes
	453	649	2557	U	gland, mammary	fibroadenoma	No
	463	463	2564	U	gland, pituitary	adenoma	No
	464	464	2527	U	gland, pituitary	adenoma	No
	466	700	2518	T	gland, mammary	fibroadenoma	No
	467	698	2542	T	gland, mammary	fibroadenoma	No
	473	569	2520	U	gland, mammary	adenocarcinoma	Yes
	487	643	2519	U	gland, mammary	fibroadenoma	No
	488	555	2524	U	gland, mammary	fibroadenoma	No
	488	566	2539	U	gland, mammary	fibroadenoma	No
	495	695	2554	U	gland, mammary	fibroadenoma	No
	495	698	2565	T	gland, mammary	fibroadenoma	No
	509	698	2505	T	skin	keratoacanthoma	No
	509	576	2528	U	gland, mammary	fibroadenoma	No
	509	698	2540	T	gland, mammary	fibroadenoma	No
	509	636	2556	U	gland, mammary	fibroadenoma	No
	516	700	2515	T	gland, mammary	fibroadenoma	No
	516	699	2551	T	gland, mammary	fibroadenoma	No
	516	700	2555	T	subcutis	fibroma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
2F	516	670	2566	U	gland, mammary	fibroadenoma	No
	523	698	2535	T	subcutis	fibrosarcoma	Yes
	524	524	2534	U	gland, pituitary	adenoma	No
	524	524	2534	U	gland, thyroid	follicular cell carcinoma	Yes
	530	564	2544	U	subcutis	lipoma	No
	536	628	2506	U	gland, mammary	fibroadenoma	No
	536	601	2507	U	gland, mammary	fibroadenoma	No
	536	699	2509	T	gland, mammary	fibroadenoma	No
	536	698	2531	T	subcutis	lipoma	No
	536	698	2535	T	gland, mammary	fibroadenoma	No
	540	540	2550	U	gland, pituitary	adenoma	No
	544	569	2520	U	gland, mammary	fibroadenoma	No
	544	700	2560	T	gland, mammary	fibroadenoma	No
	548	548	2516	U	gland, pituitary	adenoma	No
	555	555	2524	U	gland, pituitary	adenoma	No
	558	699	2546	T	gland, mammary	fibroadenoma	No
	559	559	2558	U	gland, pituitary	adenoma	No
	559	559	2558	U	uterus	endometrial stromal polyp	No
	564	610	2503	U	subcutis	schwannoma, malignant	Yes
	564	700	2517	T	gland, mammary	fibroadenoma	No
	566	566	2539	U	gland, pituitary	adenoma	No
	566	566	2539	U	pancreas	islet cell adenoma	No
	571	571	2567	U	gland, mammary	fibroadenoma	No
	571	571	2567	U	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
2F	573	573	2529	U	gland, pituitary	adenoma	No
	576	576	2528	U	gland, pituitary	adenoma	No
	576	576	2528	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	576	576	2528	U	lymph node, mesenteric	hemangiosarcoma	Yes
	585	687	2538	U	gland, mammary	fibroadenoma	No
	585	698	2540	T	subcutis	fibroma	No
	585	590	2545	U	gland, mammary	fibroadenoma	No
	585	670	2553	U	gland, mammary	fibroadenoma	No
	585	695	2554	U	gland, mammary	adenocarcinoma	Yes
	585	700	2560	T	subcutis	fibroma	No
	585	698	2565	T	subcutis	fibroma	No
	590	590	2523	U	gland, adrenal	cortical adenoma	No
	590	590	2523	U	gland, mammary	adenoma	No
	590	590	2523	U	gland, pituitary	adenoma	No
	590	590	2545	U	gland, pituitary	adenoma	No
	601	601	2507	U	gland, pituitary	adenoma	No
	602	602	2522	U	gland, pituitary	adenoma	No
	607	607	2508	U	gland, adrenal	pheochromocytoma, benign	No
	607	607	2508	U	gland, pituitary	adenoma	No
	607	607	2508	U	pancreas	islet cell carcinoma	Yes
	610	610	2503	U	gland, pituitary	adenoma	No
	613	698	2501	T	gland, mammary	fibroadenoma	No
	613	699	2521	T	gland, mammary	adenoma	No
	613	687	2532	U	gland, mammary	adenosquamous carcinoma	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
2F	613	670	2553	U	gland, mammary	adenoma	No
	613	701	2562	T	gland, mammary	fibroadenoma	No
	613	691	2568	U	gland, mammary	fibroadenoma	No
	628	698	2505	T	gland, mammary	adenoma	No
	628	628	2506	U	gland, pituitary	adenoma	No
	628	628	2506	U	ovary	granulosa cell tumor, benign	No
	628	628	2506	U	subcutis	lipoma	No
	636	636	2556	U	gland, pituitary	adenoma	No
	641	698	2540	T	gland, mammary	adenoma	No
	646	646	2563	U	gland, pituitary	adenoma	No
	648	699	2546	T	gland, mammary	adenoma	No
	649	649	2543	U	gland, pituitary	adenoma	No
	652	652	2510	U	small intestine, jejunum	adenocarcinoma	Yes
	655	701	2562	T	subcutis	lipoma	No
	655	670	2566	U	gland, clitoral	papilloma	No
	655	691	2568	U	gland, mammary	adenoma	No
	657	657	2526	U	gland, pituitary	adenoma	No
	662	695	2554	U	gland, mammary	adenoma	No
	669	687	2538	U	gland, mammary	adenoma	No
	670	670	2553	U	gland, pituitary	adenoma	No
	670	670	2566	U	gland, pituitary	adenoma	No
	670	670	2566	U	uterus	endometrial stromal polyp	No
	671	671	2502	U	gland, pituitary	adenoma	No
	687	687	2532	U	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
2F	687	687	2538	U	gland, adrenal	pheochromocytoma, benign	No
	687	687	2538	U	gland, pituitary	adenoma	No
	688	688	2536	U	gland, pituitary	adenoma	No
	691	691	2568	U	gland, pituitary	carcinoma	Yes
	693	693	2569	U	gland, pituitary	adenoma	No
	693	693	2569	U	lymph node, mesenteric	hemangioma	No
	693	693	2569	U	pancreas	adenoma	No
	695	695	2554	U	gland, pituitary	adenoma	No
	698	698	2501	T	gland, pituitary	adenoma	No
	698	698	2501	T	gland, thyroid	c-cell adenoma	No
	698	698	2501	T	gland, thyroid	c-cell carcinoma	Yes
	698	698	2511	T	gland, pituitary	adenoma	No
	698	698	2531	T	gland, mammary	fibroadenoma	No
	698	698	2531	T	gland, pituitary	adenoma	No
	698	698	2540	T	gland, pituitary	adenoma	No
	699	699	2509	T	gland, adrenal	pheochromocytoma, malignant	Yes
	699	699	2513	T	gland, pituitary	adenoma	No
	699	699	2521	T	gland, mammary	fibroadenoma	No
	699	699	2521	T	gland, pituitary	adenoma	No
	699	699	2521	T	gland, thyroid	c-cell adenoma	No
	699	699	2546	T	lymph node	hemangioma	No
	699	699	2549	T	gland, mammary	adenoma	No
	699	699	2549	T	gland, thyroid	follicular cell adenoma	No
	699	699	2549	T	pancreas	islet cell adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
2F	700	700	2515	T	gland, pituitary	adenoma	No
	700	700	2515	T	gland, thyroid	c-cell adenoma	No
	700	700	2515	T	uterus	endometrial stromal sarcoma	Yes
	700	700	2518	T	gland, adrenal	cortical adenoma	No
	700	700	2518	T	gland, pituitary	adenoma	No
	700	700	2555	T	gland, pituitary	adenoma	No
	700	700	2559	T	gland, mammary	fibroadenoma	No
	700	700	2559	T	gland, pituitary	adenoma	No
	701	701	2562	T	pancreas	islet cell adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3F	285	405	3565	U	gland, mammary	fibroadenoma	No
	307	405	3520	U	subcutis	fibroma	No
	341	440	3530	U	gland, mammary	adenocarcinoma	Yes
	341	698	3533	T	gland, mammary	fibroadenoma	No
	348	447	3568	U	gland, mammary	adenocarcinoma	Yes
	362	515	3545	U	gland, mammary	fibroadenoma	No
	376	569	3513	U	gland, mammary	fibroadenoma	No
	376	587	3537	U	subcutis	fibroma	No
	376	436	3560	U	gland, mammary	adenoma	No
	396	699	3518	T	gland, mammary	fibroadenoma	No
	396	680	3547	U	subcutis	fibroma	No
	397	397	3534	U	gland, pituitary	adenoma	No
	397	397	3534	U	gland, thyroid	c-cell adenoma	No
	405	405	3565	U	gland, adrenal	cortical adenoma	No
	419	569	3549	U	gland, mammary	fibroadenoma	No
	425	607	3506	U	gland, mammary	fibroadenoma	No
	425	481	3563	U	gland, mammary	adenosquamous carcinoma	Yes
	425	468	3566	U	gland, mammary	fibroadenoma	No
	436	436	3560	U	gland, mammary	fibroadenoma	No
	436	436	3560	U	gland, pituitary	adenoma	No
	439	517	3510	U	gland, mammary	adenoma	No
	440	440	3530	U	gland, adrenal	cortical adenoma	No
	446	660	3551	U	gland, mammary	fibroadenoma	No
	446	481	3563	U	gland, mammary	adenocarcinoma	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3F	453	607	3506	U	gland, mammary	adenosquamous carcinoma	Yes
	467	698	3559	T	gland, mammary	fibroadenoma	No
	468	468	3566	U	gland, mammary	adenoma	No
	468	468	3566	U	gland, pituitary	adenoma	No
	473	607	3521	U	gland, mammary	fibroadenoma	No
	477	477	3514	U	gland, pituitary	adenoma	No
	480	626	3535	U	gland, mammary	fibroadenoma	No
	480	698	3536	T	subcutis	fibroma	No
	481	481	3563	U	gland, mammary	adenoma	No
	481	481	3563	U	uterus	endometrial stromal polyp	No
	488	653	3523	U	gland, mammary	adenocarcinoma	Yes
	488	653	3523	U	gland, mammary	fibroadenoma	No
	488	660	3524	U	gland, mammary	fibroadenoma	No
	488	587	3525	U	gland, mammary	adenoma	No
	488	700	3544	T	gland, mammary	fibroadenoma	No
	488	600	3546	U	gland, mammary	fibroadenoma	No
	488	561	3553	U	gland, mammary	adenocarcinoma	Yes
	495	621	3501	U	gland, mammary	fibroadenoma	No
	509	569	3549	U	gland, mammary	adenocarcinoma	Yes
	509	698	3550	T	gland, mammary	fibroadenoma	No
	512	512	3519	U	gland, pituitary	adenoma	No
	516	699	3503	T	gland, mammary	fibroadenoma	No
	516	694	3564	U	gland, mammary	fibroadenoma	No
	517	517	3510	U	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3F	524	524	3528	U	brain	astrocytoma, malignant	Yes
	524	524	3528	U	gland, pituitary	adenoma	No
	528	528	3508	U	gland, pituitary	adenoma	No
	528	528	3508	U	gland, thyroid	c-cell adenoma	No
	530	590	3516	U	gland, mammary	adenoma	No
	530	693	3527	U	subcutis	fibrosarcoma	Yes
	530	674	3543	U	gland, mammary	adenoma	No
	530	674	3543	U	gland, mammary	fibroadenoma	No
	552	693	3527	U	gland, mammary	fibroadenoma	No
	552	552	3539	U	body cavity, oral	squamous cell carcinoma	Yes
	552	649	3558	U	gland, mammary	fibroadenoma	No
	557	557	3554	U	gland, pituitary	adenoma	No
	558	658	3505	U	gland, mammary	adenoma	No
	558	587	3537	U	gland, mammary	fibroadenoma	No
	561	561	3553	U	gland, pituitary	adenoma	No
	565	699	3538	T	gland, mammary	fibroadenoma	No
	569	569	3513	U	thymus	thymoma, benign	No
	569	569	3513	U	uterus	polyp	No
	577	600	3546	U	gland, mammary	adenocarcinoma	Yes
	587	587	3525	U	gland, pituitary	adenoma	No
	587	587	3525	U	uterus	adenocarcinoma	Yes
	587	587	3537	U	gland, mammary	adenocarcinoma	Yes
	587	587	3537	U	gland, pituitary	carcinoma	Yes
	588	588	3540	U	gland, mammary	fibroadenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3F	588	588	3540	U	gland, pituitary	adenoma	No
	588	588	3540	U	uterus	endometrial stromal polyp	No
	590	590	3516	U	gland, mammary	fibroadenoma	No
	590	590	3516	U	gland, pituitary	adenoma	No
	592	592	3517	U	body cavity, oral	squamous cell carcinoma	Yes
	592	592	3517	U	gland, thyroid	c-cell carcinoma	Yes
	593	593	3511	U	gland, pituitary	adenoma	No
	600	699	3504	T	gland, mammary	fibroadenoma	No
	600	660	3526	U	gland, mammary	adenoma	No
	600	699	3531	T	gland, mammary	fibroadenoma	No
	600	698	3536	T	gland, mammary	fibroadenoma	No
	600	600	3546	U	gland, pituitary	adenoma	No
	600	698	3570	T	gland, mammary	fibroadenoma	No
	602	602	3548	U	gland, pituitary	adenoma	No
	606	700	3542	T	gland, mammary	fibroadenoma	No
	606	680	3555	U	gland, mammary	fibroadenoma	No
	607	607	3506	U	gland, pituitary	adenoma	No
	613	649	3502	U	gland, clitoral	adenocarcinoma	Yes
	613	660	3551	U	gland, mammary	adenoma	No
	615	615	3552	U	gland, adrenal	cortical adenoma	No
	615	615	3552	U	gland, pituitary	adenoma	No
	621	621	3501	U	gland, mammary	adenoma	No
	621	621	3501	U	gland, pituitary	adenoma	No
	621	621	3522	U	gland, mammary	fibroadenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3F	621	621	3522	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	621	688	3562	U	subcutis	schwannoma, malignant	Yes
	621	628	3567	U	head	sarcoma	Yes
	626	626	3535	U	thymus	thymoma, benign	No
	627	627	3509	U	gland, mammary	fibroadenoma	No
	627	627	3509	U	gland, pituitary	adenoma	No
	634	653	3523	U	gland, clitoral	adenocarcinoma	Yes
	634	698	3550	T	gland, mammary	adenoma	No
	638	638	3515	U	gland, mammary	adenoma	No
	638	638	3515	U	gland, mammary	fibroadenoma	No
	638	638	3515	U	gland, pituitary	adenoma	No
	647	649	3502	U	body cavity, oral	squamous cell carcinoma	Yes
	648	698	3529	T	gland, mammary	fibroadenoma	No
	648	698	3533	T	gland, mammary	adenoma	No
	649	649	3502	U	gland, pituitary	adenoma	No
	649	649	3558	U	gland, pituitary	adenoma	No
	653	653	3523	U	gland, pituitary	adenoma	No
	658	658	3505	U	gland, mammary	fibroadenoma	No
	658	658	3505	U	gland, pituitary	adenoma	No
	658	658	3505	U	pancreas	islet cell adenoma	No
	660	660	3524	U	gland, adrenal	cortical adenoma	No
	660	660	3526	U	gland, mammary	fibroadenoma	No
	660	660	3526	U	gland, pituitary	adenoma	No
	663	700	3532	T	gland, mammary	fibroadenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3F	669	698	3529	T	gland, mammary	adenoma	No
	674	674	3543	U	gland, pituitary	adenoma	No
	680	680	3547	U	gland, adrenal	pheochromocytoma, benign	No
	680	680	3547	U	gland, adrenal	pheochromocytoma, malignant	Yes
	680	680	3547	U	uterus	endometrial stromal polyp	No
	680	680	3555	U	gland, pituitary	adenoma	No
	680	680	3555	U	kidney	adenoma	No
	680	680	3555	U	small intestine, jejunum	leiomyoma	No
	680	680	3555	U	spleen	fibrosarcoma	Yes
	683	698	3570	T	subcutis	fibroma	No
	687	687	3569	U	gland, adrenal	pheochromocytoma, malignant	Yes
	687	687	3569	U	gland, mammary	adenoma	No
	687	687	3569	U	gland, pituitary	adenoma	No
	687	687	3569	U	pancreas	islet cell adenoma	No
	687	687	3569	U	thymus	thymoma, benign	No
	688	688	3562	U	subcutis	schwannoma, benign	No
	693	693	3527	U	gland, pituitary	adenoma	No
	694	694	3564	U	gland, pituitary	adenoma	No
	694	694	3564	U	uterus	endometrial stromal polyp	No
	698	698	3512	T	gland, pituitary	adenoma	No
	698	698	3529	T	gland, pituitary	adenoma	No
	698	698	3529	T	pancreas	adenoma	No
	698	698	3529	T	subcutis	fibroma	No
	698	698	3533	T	skin	melanoma, benign	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
3F	698	698	3536	T	gland, pituitary	adenoma	No
	698	698	3550	T	uterus	endometrial stromal polyp	No
	698	698	3559	T	subcutis	fibroma	No
	698	698	3570	T	body cavity, oral	squamous cell carcinoma	Yes
	698	698	3570	T	gland, mammary	adenoma	No
	698	698	3570	T	pancreas	islet cell adenoma	No
	699	699	3503	T	gland, thyroid	c-cell adenoma	No
	699	699	3503	T	gland, thyroid	c-cell carcinoma	Yes
	699	699	3507	T	gland, adrenal	pheochromocytoma, benign	No
	699	699	3507	T	gland, pituitary	adenoma	No
	699	699	3507	T	uterus	endometrial stromal polyp	No
	699	699	3518	T	gland, pituitary	adenoma	No
	699	699	3531	T	subcutis	fibroma	No
	700	700	3532	T	gland, pituitary	adenoma	No
	700	700	3542	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	700	700	3542	T	pancreas	adenoma	No
	700	700	3542	T	subcutis	liposarcoma	Yes
	700	700	3544	T	gland, pituitary	adenoma	No
	700	700	3556	T	body cavity, oral	squamous cell carcinoma	Yes
	700	700	3557	T	uterus	endometrial stromal polyp	No
	701	701	3561	T	gland, thyroid	c-cell adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
4F	148	148	4554	U	hemolymphoreticular tissue	leukemia, large granular lymphocytic	Yes
	299	623	4514	U	gland, mammary	fibroadenoma	No
	313	313	4552	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	333	333	4544	U	gland, mammary	fibroadenoma	No
	333	333	4544	U	gland, pituitary	adenoma	No
	355	615	4565	U	gland, mammary	fibroadenoma	No
	369	573	4511	U	gland, mammary	adenocarcinoma	Yes
	376	668	4563	U	gland, mammary	fibroadenoma	No
	378	378	4535	U	bone	sarcoma	Yes
	378	378	4535	U	gland, pituitary	adenoma	No
	382	382	4517	U	gland, pituitary	adenoma	No
	383	422	4548	U	gland, mammary	fibroadenoma	No
	390	618	4562	U	gland, mammary	fibroadenoma	No
	396	454	4553	U	gland, mammary	fibroadenoma	No
	396	688	4566	U	gland, mammary	fibroadenoma	No
	401	401	4502	U	gland, pituitary	adenoma	No
	418	470	4531	U	subcutis	fibroma	No
	419	419	4545	U	gland, pituitary	adenoma	No
	422	422	4548	U	gland, pituitary	adenoma	No
	425	667	4547	U	gland, mammary	fibroadenoma	No
	439	573	4511	U	gland, mammary	adenoma	No
	439	573	4511	U	gland, mammary	fibroadenoma	No
	439	521	4564	U	gland, mammary	fibroadenoma	No
	453	701	4567	T	gland, mammary	fibroadenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
4F	454	454	4553	U	gland, pituitary	adenoma	No
	466	587	4524	A	gland, mammary	fibroadenoma	No
	469	469	4549	U	gland, mammary	fibroadenoma	No
	469	469	4549	U	gland, pituitary	adenoma	No
	469	469	4555	U	gland, pituitary	adenoma	No
	469	469	4555	U	subcutis	fibrosarcoma	Yes
	470	470	4531	U	gland, pituitary	adenoma	No
	473	550	4507	U	gland, mammary	fibroadenoma	No
	473	584	4529	U	gland, mammary	fibroadenoma	No
	478	478	4556	U	cervix	sarcoma	Yes
	481	698	4505	T	gland, mammary	fibroadenoma	No
	488	700	4518	T	gland, mammary	fibroadenoma	No
	488	700	4519	T	gland, mammary	adenosquamous carcinoma	Yes
	488	698	4543	T	subcutis	fibroma	No
	488	521	4564	U	gland, mammary	adenoma	No
	495	698	4522	T	gland, mammary	fibroadenoma	No
	495	679	4546	U	subcutis	fibrosarcoma	Yes
	516	653	4533	U	gland, mammary	fibroadenoma	No
	516	699	4534	T	subcutis	fibroma	No
	516	693	4542	U	gland, mammary	fibroadenoma	No
	516	672	4557	U	gland, mammary	fibroadenoma	No
	521	521	4564	U	gland, pituitary	adenoma	No
	523	660	4532	U	gland, mammary	fibroadenoma	No
	530	699	4501	T	gland, mammary	fibroadenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
4F	530	624	4515	U	gland, mammary	fibroadenoma	No
	533	533	4526	U	gland, pituitary	adenoma	No
	533	533	4526	U	gland, thyroid	c-cell adenoma	No
	537	667	4547	U	gland, mammary	adenoma	No
	537	667	4547	U	subcutis	fibroma	No
	537	672	4561	U	gland, mammary	fibroadenoma	No
	540	540	4508	U	body cavity, oral	squamous cell carcinoma	Yes
	540	540	4508	U	gland, mammary	fibroadenoma	No
	544	544	4539	U	gland, pituitary	adenoma	No
	544	544	4539	U	small intestine, jejunum	leiomyoma	No
	545	545	4510	U	gland, pituitary	adenoma	No
	545	545	4510	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	552	698	4509	T	gland, mammary	fibroadenoma	No
	552	699	4513	T	gland, mammary	fibroadenoma	No
	552	624	4515	U	gland, mammary	adenocarcinoma	Yes
	552	677	4538	U	gland, mammary	fibroadenoma	No
	558	698	4512	T	gland, mammary	fibroadenoma	No
	558	615	4565	U	gland, mammary	adenoma	No
	568	568	4506	U	gland, mammary	fibroadenoma	No
	568	568	4506	U	gland, pituitary	adenoma	No
	572	698	4543	T	gland, mammary	fibroadenoma	No
	572	679	4546	U	subcutis	lipoma	No
	573	573	4511	U	gland, pituitary	adenoma	No
	578	698	4512	T	gland, mammary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
4F	578	700	4521	T	gland, mammary	fibroadenoma	No
	578	660	4532	U	gland, mammary	adenoma	No
	578	701	4560	T	gland, mammary	fibroadenoma	No
	578	672	4561	U	gland, mammary	adenoma	No
	583	583	4541	U	adipose tissue	liposarcoma	Yes
	584	584	4529	U	gland, pituitary	adenoma	No
	586	638	4523	U	gland, mammary	fibroadenoma	No
	586	679	4546	U	gland, mammary	fibroadenoma	No
	587	587	4524	A	gland, mammary	adenoma	No
	587	587	4524	A	gland, pituitary	adenoma	No
	593	700	4519	T	gland, mammary	fibroadenoma	No
	600	698	4504	T	subcutis	lipoma	No
	600	699	4551	T	gland, mammary	fibroadenoma	No
	600	615	4565	U	head	sarcoma	Yes
	614	660	4532	U	subcutis	schwannoma, malignant	Yes
	614	699	4534	T	gland, mammary	fibroadenoma	No
	615	615	4565	U	lung	epithelioma	Yes
	618	618	4562	U	gland, pituitary	adenoma	No
	621	632	4525	U	gland, mammary	fibroadenoma	No
	623	623	4514	U	gland, mammary	adenoma	No
	623	623	4514	U	gland, pituitary	adenoma	No
	624	624	4550	U	brain	astrocytoma, malignant	Yes
	624	624	4550	U	gland, mammary	fibroadenoma	No
	628	638	4523	U	gland, mammary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
4F	628	632	4525	U	gland, mammary	adenoma	No
	632	632	4525	U	gland, pituitary	adenoma	No
	632	632	4525	U	gland, thyroid	follicular cell adenoma	No
	632	632	4525	U	thymus	thymoma, malignant	Yes
	638	638	4523	U	gland, pituitary	adenoma	No
	648	700	4528	T	gland, mammary	fibroadenoma	No
	653	653	4533	U	gland, mammary	adenoma	No
	653	653	4533	U	gland, pituitary	adenoma	No
	655	698	4504	T	gland, mammary	adenoma	No
	655	699	4516	T	gland, mammary	fibroadenoma	No
	656	701	4540	T	gland, mammary	fibroadenoma	No
	660	660	4532	U	gland, pituitary	adenoma	No
	662	699	4513	T	gland, mammary	adenoma	No
	662	700	4530	T	gland, mammary	fibroadenoma	No
	662	672	4557	U	gland, mammary	adenoma	No
	662	698	4569	T	gland, mammary	fibroadenoma	No
	662	698	4570	T	gland, mammary	fibroadenoma	No
	667	667	4547	U	gland, pituitary	adenoma	No
	667	667	4547	U	uterus	endometrial stromal polyp	No
	668	668	4563	U	gland, pituitary	adenoma	No
	668	668	4563	U	pancreas	adenocarcinoma	Yes
	670	698	4504	T	gland, mammary	fibroadenoma	No
	671	671	4536	U	stomach	adenoma	No
	672	672	4557	U	gland, pituitary	carcinoma	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
4F	677	677	4558	U	muscle, skeletal	fibrosarcoma	Yes
	679	679	4546	U	gland, pituitary	adenoma	No
	693	693	4542	U	body cavity, nasal	squamous cell carcinoma	Yes
	693	693	4542	U	gland, pituitary	adenoma	No
	698	698	4504	T	gland, parathyroid	adenoma	No
	698	698	4504	T	gland, pituitary	adenoma	No
	698	698	4505	T	gland, adrenal	cortical adenoma	No
	698	698	4505	T	gland, pituitary	adenoma	No
	698	698	4512	T	gland, pituitary	adenoma	No
	698	698	4512	T	pancreas	islet cell adenoma	No
	698	700	4530	T	skin	keratoacanthoma	No
	698	698	4543	T	gland, clitoral	squamous cell carcinoma	Yes
	698	698	4543	T	pancreas	islet cell adenoma	No
	698	698	4570	T	gland, pituitary	adenoma	No
	698	698	4570	T	uterus	endometrial stromal polyp	No
	699	699	4501	T	gland, thyroid	c-cell adenoma	No
	699	699	4503	T	gland, thyroid	follicular cell adenoma	No
	699	699	4513	T	gland, pituitary	adenoma	No
	699	699	4513	T	gland, thyroid	c-cell adenoma	No
	699	699	4516	T	gland, pituitary	adenoma	No
	699	699	4534	T	gland, pituitary	adenoma	No
	700	700	4518	T	eye	melanoma, benign	No
	700	700	4519	T	gland, pituitary	adenoma	No
	700	700	4519	T	gland, thyroid	c-cell adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
4F	700	700	4527	T	gland, mammary	fibroadenoma	No
	700	700	4527	T	skin	keratoacanthoma	No
	700	700	4530	T	gland, pituitary	adenoma	No
	701	701	4537	T	small intestine, jejunum	leiomyoma	No
	701	701	4559	T	body cavity, abdominal	lipoma	No
	701	701	4559	T	gland, pituitary	adenoma	No
	701	701	4559	T	pancreas	islet cell carcinoma	Yes
	701	701	4560	T	gland, pituitary	adenoma	No
	701	701	4560	T	gland, thyroid	c-cell adenoma	No
	701	701	4567	T	body cavity, nasal	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
5F	60	221	5523	U	gland, mammary	adenocarcinoma	Yes
	110	370	5520	U	gland, mammary	adenocarcinoma	Yes
	250	383	5517	U	gland, mammary	adenocarcinoma	Yes
	278	611	5550	U	gland, mammary	fibroadenoma	No
	285	422	5537	U	gland, mammary	adenoma	No
	285	526	5551	U	gland, mammary	fibroadenoma	No
	306	347	5569	U	gland, mammary	adenoma	No
	328	700	5562	T	subcutis	fibrosarcoma	Yes
	334	534	5502	U	gland, mammary	fibroadenoma	No
	345	345	5545	U	gland, mammary	fibroadenoma	No
	347	482	5555	U	gland, mammary	fibroadenoma	No
	347	347	5569	U	gland, pituitary	adenoma	No
	355	408	5508	U	gland, mammary	adenocarcinoma	Yes
	355	458	5511	U	gland, mammary	fibroadenoma	No
	355	383	5517	U	gland, mammary	fibroadenoma	No
	355	677	5563	U	gland, mammary	fibroadenoma	No
	359	359	5528	U	brain	oligodendroglioma, malignant	Yes
	369	700	5552	T	gland, mammary	fibroadenoma	No
	390	698	5516	T	gland, mammary	fibroadenoma	No
	390	629	5524	U	gland, mammary	fibroadenoma	No
	390	636	5542	U	gland, mammary	fibroadenoma	No
	390	587	5548	U	gland, mammary	fibroadenoma	No
	390	390	5553	U	brain	meningioma, malignant	Yes
	390	390	5553	U	gland, pituitary	adenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
5F	390	583	5560	U	gland, mammary	adenocarcinoma	Yes
	404	583	5560	U	gland, mammary	fibroadenoma	No
	408	408	5508	U	gland, pituitary	adenoma	No
	411	699	5547	T	gland, mammary	fibroadenoma	No
	418	621	5556	U	gland, mammary	fibroadenoma	No
	422	422	5537	U	gland, pituitary	adenoma	No
	425	511	5535	U	gland, mammary	adenoma	No
	439	552	5570	U	gland, mammary	adenocarcinoma	Yes
	439	552	5570	U	gland, mammary	fibroadenoma	No
	447	700	5567	T	gland, mammary	fibroadenoma	No
	453	698	5512	T	gland, mammary	fibroadenoma	No
	453	600	5529	U	gland, mammary	adenoma	No
	458	458	5511	U	gland, pituitary	adenoma	No
	458	458	5511	U	subcutis	fibroma	No
	460	579	5521	U	subcutis	fibroma	No
	467	690	5526	U	gland, mammary	fibroadenoma	No
	467	549	5561	U	gland, mammary	fibroadenoma	No
	467	482	5568	U	gland, mammary	fibroadenoma	No
	480	557	5505	U	gland, mammary	fibroadenoma	No
	480	610	5532	U	gland, mammary	fibroadenoma	No
	480	699	5536	T	subcutis	lipoma	No
	488	511	5535	U	gland, mammary	fibroadenoma	No
	488	699	5544	T	gland, mammary	fibroadenoma	No
	488	611	5550	U	subcutis	fibrosarcoma	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
5F	488	583	5560	U	subcutis	fibrosarcoma	Yes
	488	549	5561	U	gland, mammary	adenoma	No
	495	698	5510	T	gland, mammary	fibroadenoma	No
	495	600	5529	U	gland, mammary	fibroadenoma	No
	502	699	5543	T	gland, mammary	fibroadenoma	No
	502	549	5561	U	bone	sarcoma	Yes
	509	672	5531	U	gland, mammary	fibroadenoma	No
	509	701	5533	T	gland, mammary	adenoma	No
	509	698	5558	T	gland, mammary	fibroadenoma	No
	511	511	5535	U	gland, pituitary	adenoma	No
	516	646	5501	U	gland, mammary	fibroadenoma	No
	516	701	5541	T	gland, mammary	fibroadenoma	No
	516	700	5562	T	gland, mammary	fibroadenoma	No
	523	589	5530	U	gland, mammary	fibroadenoma	No
	525	526	5551	U	gland, mammary	adenoma	No
	526	526	5551	U	gland, pituitary	adenoma	No
	530	698	5538	T	gland, mammary	fibroadenoma	No
	533	533	5546	U	body cavity, nasal	squamous cell carcinoma	Yes
	536	698	5559	T	gland, mammary	fibroadenoma	No
	544	699	5549	T	subcutis	lipoma	No
	549	549	5561	U	cervix	endometrial stromal polyp	No
	549	549	5561	U	gland, pituitary	adenoma	No
	549	549	5561	U	larynx	fibrosarcoma	Yes
	551	600	5529	U	gland, mammary	adenocarcinoma	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
5F	552	552	5570	U	gland, thyroid	c-cell adenoma	No
	557	557	5505	U	gland, clitoral	adenocarcinoma	Yes
	557	557	5505	U	gland, pituitary	adenoma	No
	558	579	5521	U	gland, mammary	fibroadenoma	No
	559	559	5539	U	gland, pituitary	adenoma	No
	566	566	5527	U	gland, mammary	fibroadenoma	No
	566	566	5527	U	gland, pituitary	adenoma	No
	566	566	5527	U	stomach	papilloma	No
	567	567	5522	U	gland, pituitary	adenoma	No
	572	630	5554	U	gland, mammary	fibroadenoma	No
	578	698	5516	T	gland, mammary	adenoma	No
	578	700	5552	T	skin	keratoacanthoma	No
	579	579	5521	U	gland, adrenal	pheochromocytoma, benign	No
	579	579	5521	U	gland, pituitary	adenoma	No
	583	583	5560	U	gland, adrenal	cortical adenoma	No
	587	587	5518	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	587	587	5548	U	gland, pituitary	adenoma	No
	589	589	5530	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	593	698	5504	T	gland, mammary	fibroadenoma	No
	600	698	5510	T	gland, mammary	adenoma	No
	600	600	5529	U	gland, pituitary	adenoma	No
	600	610	5532	U	gland, mammary	adenocarcinoma	Yes
	600	630	5554	U	subcutis	hemangiosarcoma	Yes
	600	701	5557	T	gland, mammary	fibroadenoma	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
5F	600	701	5564	T	gland, mammary	fibroadenoma	No
	611	611	5550	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	614	698	5506	T	gland, mammary	fibroadenoma	No
	614	700	5507	T	gland, mammary	fibroadenoma	No
	614	701	5525	T	subcutis	fibroma	No
	614	677	5563	U	gland, mammary	adenoma	No
	621	621	5556	U	gland, pituitary	adenoma	No
	621	621	5556	U	uterus	endometrial stromal polyp	No
	627	699	5543	T	gland, mammary	adenoma	No
	627	701	5565	T	gland, mammary	fibroadenoma	No
	629	629	5524	U	gland, pituitary	adenoma	No
	629	629	5524	U	uterus	endometrial stromal polyp	No
	630	630	5554	U	gland, adrenal	cortical adenoma	No
	630	630	5554	U	gland, pituitary	adenoma	No
	634	673	5540	U	gland, mammary	fibroadenoma	No
	636	636	5542	U	gland, pituitary	adenoma	No
	641	690	5526	U	gland, mammary	adenoma	No
	641	701	5566	T	gland, mammary	fibroadenoma	No
	646	646	5501	U	gland, mammary	adenoma	No
	646	646	5501	U	gland, pituitary	adenoma	No
	651	651	5534	U	gland, pituitary	adenoma	No
	651	651	5534	U	muscle, skeletal	hemangiosarcoma	Yes
	651	651	5534	U	uterus	endometrial stromal polyp	No
	656	698	5558	T	subcutis	schwannoma, benign	No

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
5F	663	700	5514	T	gland, mammary	adenocarcinoma	Yes
	663	700	5514	T	gland, mammary	adenoma	No
	663	701	5525	T	gland, mammary	fibroadenoma	No
	663	700	5562	T	gland, mammary	adenoma	No
	670	700	5514	T	gland, mammary	fibroadenoma	No
	672	672	5531	U	gland, pituitary	adenoma	No
	673	673	5540	U	gland, pituitary	adenoma	No
	673	673	5540	U	uterus	endometrial stromal polyp	No
	676	701	5515	T	gland, mammary	fibroadenoma	No
	676	701	5541	T	gland, mammary	adenosquamous carcinoma	Yes
	677	699	5544	T	gland, mammary	adenoma	No
	677	677	5563	U	gland, pituitary	adenoma	No
	690	690	5526	U	gland, pituitary	adenoma	No
	690	690	5526	U	lymph node, mesenteric	neuroendocrine cell tumor, benign	No
	698	698	5504	T	gland, pituitary	adenoma	No
	698	698	5504	T	gland, thyroid	c-cell adenoma	No
	698	698	5504	T	gland, thyroid	c-cell carcinoma	Yes
	698	698	5504	T	skin	keratoacanthoma	No
	698	698	5506	T	gland, adrenal	pheochromocytoma, benign	No
	698	698	5506	T	gland, pituitary	adenoma	No
	698	698	5506	T	pancreas	islet cell adenoma	No
	698	698	5510	T	gland, pituitary	adenoma	No
	698	698	5510	T	gland, thyroid	c-cell adenoma	No
	698	698	5510	T	hemolymphoreticular tissue	leukemia, large granular lymphocytic	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
5F	698	698	5512	T	gland, pituitary	adenoma	No
	698	698	5512	T	lung	bronchioloalveolar adenoma	No
	698	698	5512	T	subcutis	fibroma	No
	698	698	5516	T	gland, pituitary	adenoma	No
	698	698	5538	T	gland, pituitary	adenoma	No
	698	698	5559	T	gland, pituitary	adenoma	No
	699	699	5536	T	gland, mammary	fibroadenoma	No
	699	699	5536	T	gland, pituitary	adenoma	No
	699	699	5543	T	gland, adrenal	pheochromocytoma, malignant	Yes
	699	699	5543	T	subcutis	fibroma	No
	699	699	5544	T	gland, pituitary	adenoma	No
	699	699	5544	T	small intestine, jejunum	leiomyoma	No
	699	699	5549	T	gland, mammary	fibroadenoma	No
	699	699	5549	T	gland, pituitary	adenoma	No
	700	700	5507	T	gland, pituitary	adenoma	No
	700	700	5507	T	gland, thyroid	c-cell carcinoma	Yes
	700	700	5509	T	gland, mammary	fibroadenoma	No
	700	700	5514	T	gland, pituitary	adenoma	No
	700	700	5552	T	gland, adrenal	pheochromocytoma, malignant	Yes
	700	700	5552	T	gland, pituitary	adenoma	No
	700	700	5552	T	gland, thyroid	c-cell adenoma	No
	700	700	5562	T	gland, mammary	adenocarcinoma	Yes
	700	700	5562	T	gland, pituitary	adenoma	No
	700	700	5562	T	kidney	liposarcoma	Yes

Table A5 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence (Continued)

Chronological Listing

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	TUMOR	Malignant
5F	700	700	5567	T	ovary	granulosa cell tumor, benign	No
	701	701	5503	T	uterus	endometrial stromal polyp	No
	701	701	5503	T	uterus	granular cell tumor, benign	No
	701	701	5515	T	uterus	endometrial stromal polyp	No
	701	701	5525	T	gland, adrenal	pheochromocytoma, benign	No
	701	701	5533	T	uterus	leiomyosarcoma	Yes
	701	701	5541	T	brain	astrocytoma, malignant	Yes
	701	701	5557	T	brain	granular cell tumor, malignant	Yes
	701	701	5564	T	gland, pituitary	adenoma	No
	701	701	5564	T	thymus	thymoma, malignant	Yes
	701	701	5566	T	gland, pituitary	adenoma	No

Table A6 Carcinogenicity Study in Mouse - Summary of Survival and Fate of Animals

Summary of Survival and Fate of Animals Explanation Page

Abbreviation	Description
E	Number of animals entering period
D	Animals found dead
A	Animals with accidental death
S	Animals sacrificed moribund
N	Animals necropsied

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Dose Level (mg/kg/day)	
	Oral	SC
1/ Reference Item (oral + SC)	0	0
2/ GSK1278863(oral) + metabolite cocktail (SC)	0.2	2.0, 2.5 and 1.3
3/ GSK1278863(oral) + Reference Item (SC)	0.8	0
4/ GSK1278863(oral) + metabolite cocktail (SC)	0.8	2.0, 2.5 and 1.3
5/GSK1278863(oral) + metabolite cocktail (SC)	3	2.0, 2.5 and 1.3

Table A6 Carcinogenicity Study in Mouse - Summary of Survival and Fate of Animals (Continued)

Male

Summary of Survival and Fate of Animals

Sex: Male

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
4	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0	60	.	.	1	1
9	60	.	.	.	0	60	.	.	.	0	60	.	.	1	1	60	.	.	.	0	59	.	.	.	0
10	60	.	.	.	0	60	.	.	.	0	59	.	.	.	0	60	.	.	1	1	59	.	.	.	0
11	60	.	.	.	0	60	.	.	.	0	59	.	.	.	0	59	.	.	.	0	59	.	.	.	0
14	60	.	.	.	0	60	.	.	.	0	59	1	.	.	1	59	.	.	.	0	59	.	.	.	0
16	60	.	.	.	0	60	.	.	.	0	58	.	.	.	0	59	.	.	.	0	59	.	.	.	0
20	60	.	.	.	0	60	.	.	1	1	58	.	.	.	0	59	.	.	.	0	59	.	.	.	0
21	60	.	.	.	0	59	.	.	.	0	58	.	.	.	0	59	.	.	.	0	59	.	.	.	0
24	60	.	.	.	0	59	.	.	1	1	58	.	.	.	0	59	.	.	.	0	59	.	.	.	0
25	60	.	.	.	0	58	.	.	.	0	58	.	.	.	0	59	.	.	.	0	59	.	.	.	0
27	60	.	.	.	0	58	.	.	.	0	58	.	.	.	0	59	.	.	.	0	59	.	.	.	0
30	60	.	.	.	0	58	.	.	.	0	58	.	.	.	0	59	.	.	.	0	59	.	.	.	0
33	60	.	.	.	0	58	.	.	.	0	58	.	.	.	0	59	.	.	.	0	59	.	.	.	0
37	60	.	.	.	0	58	.	.	.	0	58	.	.	.	0	59	.	.	.	0	59	.	.	.	0
39	60	.	.	.	0	58	.	.	.	0	58	.	.	.	0	59	1	.	.	1	59	.	.	.	0
40	60	.	.	.	0	58	1	.	.	1	58	.	.	.	0	58	.	.	.	0	59	.	.	.	0
43	60	.	.	1	1	57	.	.	.	0	58	.	.	.	0	58	.	.	.	0	59	.	.	.	0
46	59	1	.	.	1	57	.	.	.	0	58	.	.	.	0	58	.	.	.	0	59	.	.	.	0
47	58	.	.	.	0	57	1	.	1	2	58	.	.	.	0	58	.	.	.	0	59	.	.	.	0
48	58	.	.	.	0	55	.	.	.	0	58	.	.	.	0	58	.	.	.	0	59	.	.	.	0
49	58	1	.	.	1	55	.	.	.	0	58	.	.	.	0	58	1	.	.	1	59	.	.	.	0
51	57	.	.	.	0	55	.	.	.	0	58	.	.	1	1	57	.	.	.	0	59	.	.	.	0

Table A6 Carcinogenicity Study in Mouse - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Male

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
52	57	1	.	.	1	55	.	.	.	0	57	.	.	1	1	57	.	.	.	0	59	.	.	.	0
53	56	.	.	.	0	55	.	.	1	1	56	.	.	.	0	57	.	.	.	0	59	.	.	.	0
54	56	.	.	.	0	54	.	.	.	0	56	.	.	.	0	57	1	.	.	1	59	.	.	.	0
56	56	.	.	1	1	54	.	.	.	0	56	.	.	.	0	56	.	.	.	0	59	.	.	.	0
57	55	.	.	.	0	54	.	.	.	0	56	.	.	.	0	56	.	.	.	0	59	.	.	.	0
58	55	.	.	.	0	54	.	.	.	0	56	.	.	.	0	56	.	.	.	0	59	.	.	.	0
59	55	.	.	.	0	54	.	.	.	0	56	.	.	.	0	56	.	.	.	0	59	.	.	.	0
60	55	.	.	.	0	54	.	.	.	0	56	.	.	.	0	56	.	.	.	0	59	.	.	.	0
61	55	.	.	.	0	54	.	.	.	0	56	1	.	.	1	56	.	.	.	0	59	.	.	.	0
62	55	1	.	.	1	54	.	.	.	0	55	.	.	.	0	56	.	.	.	0	59	.	.	.	0
64	54	.	.	.	0	54	.	.	.	0	55	1	.	1	2	56	.	.	.	0	59	.	.	.	0
65	54	.	.	.	0	54	.	.	.	0	53	.	.	.	0	56	.	.	.	0	59	.	.	.	0
66	54	.	.	.	0	54	.	.	.	0	53	.	.	.	0	56	.	.	.	0	59	.	.	.	0
67	54	.	.	.	0	54	.	.	.	0	53	.	.	.	0	56	.	.	.	0	59	.	.	.	0
68	54	.	.	.	0	54	.	.	.	0	53	.	.	.	0	56	.	.	.	0	59	.	.	.	0
69	54	1	.	1	2	54	.	.	.	0	53	1	.	.	1	56	.	.	.	0	59	.	.	1	1
70	52	.	.	.	0	54	.	.	1	1	52	.	.	.	0	56	.	.	.	0	58	.	.	.	0
71	52	.	.	.	0	53	1	.	1	2	52	.	.	.	0	56	.	.	.	0	58	.	.	.	0
72	52	.	.	.	0	51	.	.	.	0	52	.	.	.	0	56	.	.	.	0	58	.	.	.	0
73	52	.	.	.	0	51	.	.	.	0	52	.	.	.	0	56	.	.	.	0	58	.	.	1	1
74	52	.	.	.	0	51	.	.	.	0	52	.	.	.	0	56	1	.	.	1	57	.	.	.	0
75	52	.	.	1	1	51	.	.	.	0	52	.	.	.	0	55	.	.	.	0	57	.	.	.	0

Table A6 Carcinogenicity Study in Mouse - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Male

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
76	51	.	.	.	0	51	.	.	.	0	52	.	.	.	0	55	.	.	.	0	57	.	.	.	0
77	51	1	.	.	1	51	.	.	.	0	52	.	.	.	0	55	.	.	1	1	57	.	.	.	0
78	50	.	.	2	2	51	1	.	.	1	52	.	.	.	0	54	.	.	.	0	57	.	.	.	0
79	48	.	.	1	1	50	.	.	1	1	52	.	.	.	0	54	.	.	.	0	57	1	.	2	3
80	47	.	.	.	0	49	.	.	1	1	52	.	.	.	0	54	.	.	1	1	54	.	.	.	0
81	47	.	.	1	1	48	.	.	.	0	52	.	.	.	0	53	.	.	.	0	54	.	.	2	2
82	46	.	.	.	0	48	1	.	.	1	52	.	.	1	1	53	2	.	.	2	52	.	.	.	0
83	46	.	.	1	1	47	1	.	.	1	51	1	.	.	1	51	.	.	1	1	52	.	.	.	0
84	45	.	.	.	0	46	1	.	.	1	50	.	.	.	0	50	.	.	1	1	52	.	.	2	2
85	45	.	.	.	0	45	.	.	1	1	50	.	.	.	0	49	.	.	.	0	50	.	.	.	0
86	45	1	.	.	1	44	1	.	1	2	50	.	.	.	0	49	1	.	1	2	50	.	.	.	0
87	44	1	.	1	2	42	1	.	.	1	50	.	.	.	0	47	.	.	1	1	50	1	.	1	2
88	42	.	.	1	1	41	1	.	.	1	50	.	.	1	1	46	.	.	.	0	48	.	.	2	2
89	41	.	.	.	0	40	.	.	1	1	49	.	.	1	1	46	2	.	.	2	46	.	.	1	1
90	41	.	.	.	0	39	.	.	1	1	48	.	.	.	0	44	.	.	1	1	45	2	.	.	2
91	41	.	.	1	1	38	.	.	.	0	48	1	.	.	1	43	1	.	.	1	43	1	.	2	3
92	40	1	.	1	2	38	.	.	.	0	47	2	.	2	4	42	1	.	1	2	40	.	.	.	0
93	38	.	.	.	0	38	.	.	.	0	43	.	.	.	0	40	1	.	.	1	40	1	.	1	2
94	38	.	.	.	0	38	.	.	.	0	43	.	.	1	1	39	.	.	.	0	38	.	.	.	0
95	38	.	.	.	0	38	.	.	.	0	42	.	.	.	0	39	.	.	.	0	38	.	.	.	0
96	38	.	.	.	0	38	1	.	1	2	42	.	.	.	0	39	1	.	1	2	38	1	.	.	1
97	38	.	.	.	0	36	.	.	.	0	42	.	.	2	2	37	1	.	2	3	37	.	.	1	1

Table A6 Carcinogenicity Study in Mouse - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Male

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
98	38	.	.	.	0	36	.	.	.	0	40	.	.	.	0	34	.	.	.	0	36	.	.	.	0
99	38	.	.	1	1	36	.	.	.	0	40	.	.	.	0	34	.	.	.	0	36	.	.	.	0
100	37	.	.	1	1	36	.	.	1	1	40	1	.	1	2	34	.	.	.	0	36	1	.	2	3
101	36	.	.	.	0	35	.	.	1	1	38	.	.	.	0	34	1	.	2	3	33	.	.	.	0
102	36	.	.	2	2	34	.	.	.	0	38	1	.	1	2	31	.	.	.	0	33	.	.	.	0
103	34	.	.	.	0	34	.	.	1	1	36	1	.	.	1	31	.	.	1	1	33	.	.	.	0
104	34	.	.	.	0	33	.	.	.	0	35	3	.	.	3	30	1	.	1	2	33	.	.	.	0
105	34	.	.	.	17	33	.	.	.	19	32	.	.	.	19	28	.	.	.	17	33	.	.	.	20
106	17	.	.	.	17	14	.	.	.	14	13	.	.	.	13	11	.	.	.	11	13	.	.	.	13

Table A6 Carcinogenicity Study in Mouse - Summary of Survival and Fate of Animals (Continued)

Female

Summary of Survival and Fate of Animals

Sex: Female

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
4	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0
9	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0
10	60	.	.	.	0	60	.	.	1	1	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0
11	60	.	.	.	0	59	.	1	.	1	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0
14	60	.	.	.	0	58	.	.	.	0	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0
16	60	.	.	.	0	58	1	.	.	1	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0
20	60	.	.	.	0	57	.	.	.	0	60	.	.	.	0	60	.	.	.	0	60	.	.	.	0
21	60	.	.	.	0	57	.	.	.	0	60	.	.	.	0	60	.	.	1	1	60	.	.	.	0
24	60	.	.	.	0	57	.	.	.	0	60	.	.	.	0	59	.	.	.	0	60	.	.	.	0
25	60	.	.	.	0	57	.	.	.	0	60	1	.	.	1	59	.	.	.	0	60	.	.	.	0
27	60	.	.	.	0	57	.	.	1	1	59	.	.	.	0	59	.	.	.	0	60	.	.	.	0
30	60	.	.	.	0	56	.	.	.	0	59	.	.	.	0	59	.	.	.	0	60	1	.	.	1
33	60	.	.	.	0	56	.	.	.	0	59	1	.	.	1	59	.	.	.	0	59	.	.	.	0
37	60	.	.	.	0	56	.	.	.	0	58	.	.	.	0	59	.	.	.	0	59	.	.	1	1
39	60	.	.	.	0	56	.	.	.	0	58	.	.	.	0	59	.	.	.	0	58	.	.	.	0
40	60	.	.	1	1	56	.	.	.	0	58	.	.	.	0	59	.	.	.	0	58	.	.	.	0
43	59	.	.	.	0	56	.	.	.	0	58	.	.	.	0	59	.	.	.	0	58	.	.	.	0
46	59	.	.	.	0	56	.	.	.	0	58	.	.	.	0	59	.	.	.	0	58	.	.	.	0
47	59	.	.	.	0	56	.	.	.	0	58	.	.	.	0	59	.	.	.	0	58	.	.	.	0
48	59	.	.	1	1	56	.	.	.	0	58	.	.	.	0	59	.	.	.	0	58	.	.	.	0
49	58	.	.	.	0	56	.	.	.	0	58	.	.	.	0	59	.	.	.	0	58	.	.	.	0
51	58	.	.	.	0	56	1	.	.	1	58	.	.	.	0	59	.	.	.	0	58	.	.	.	0

Table A6 Carcinogenicity Study in Mouse - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Female

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
52	58	1	.	1	2	55	.	.	.	0	58	.	.	.	0	59	.	.	.	0	58	1	.	.	1
53	56	.	.	.	0	55	.	.	.	0	58	.	.	.	0	59	.	.	.	0	57	.	.	.	0
54	56	.	.	.	0	55	.	.	.	0	58	.	.	.	0	59	.	.	.	0	57	1	.	.	1
56	56	.	.	.	0	55	.	.	.	0	58	.	.	.	0	59	.	.	.	0	56	.	.	.	0
57	56	.	.	.	0	55	.	.	.	0	58	.	.	.	0	59	.	.	.	0	56	.	.	1	1
58	56	.	.	.	0	55	.	.	1	1	58	.	.	.	0	59	.	.	.	0	55	2	.	.	2
59	56	.	.	1	1	54	.	.	.	0	58	.	.	.	0	59	.	.	.	0	53	.	.	.	0
60	55	.	.	.	0	54	.	.	.	0	58	.	.	1	1	59	.	.	.	0	53	.	.	.	0
61	55	.	.	.	0	54	.	.	.	0	57	1	.	.	1	59	.	.	.	0	53	.	.	.	0
62	55	.	.	.	0	54	.	.	.	0	56	.	.	.	0	59	.	.	.	0	53	.	.	.	0
64	55	.	.	1	1	54	.	.	.	0	56	.	.	.	0	59	.	.	.	0	53	.	.	.	0
65	54	.	.	.	0	54	.	.	.	0	56	.	.	.	0	59	.	.	.	0	53	.	.	1	1
66	54	.	.	.	0	54	.	.	.	0	56	.	.	1	1	59	.	.	.	0	52	.	.	1	1
67	54	1	.	.	1	54	.	.	.	0	55	.	.	.	0	59	.	.	.	0	51	.	.	.	0
68	53	.	.	.	0	54	.	.	.	0	55	.	.	1	1	59	.	.	1	1	51	.	.	.	0
69	53	.	.	.	0	54	.	.	3	3	54	.	.	.	0	58	.	.	.	0	51	1	.	.	1
70	53	.	.	.	0	51	.	.	1	1	54	.	.	.	0	58	.	.	.	0	50	.	.	1	1
71	53	.	.	.	0	50	.	.	1	1	54	.	.	.	0	58	1	.	.	1	49	1	.	1	2
72	53	.	.	.	0	49	.	.	.	0	54	.	.	.	0	57	.	.	1	1	47	1	.	.	1
73	53	.	.	2	2	49	.	.	.	0	54	.	.	.	0	56	.	.	.	0	46	.	.	.	0
74	51	.	.	1	1	49	.	.	.	0	54	.	.	.	0	56	.	.	.	0	46	.	.	.	0
75	50	.	.	.	0	49	.	.	.	0	54	.	.	.	0	56	.	.	1	1	46	.	.	.	0

Table A6 Carcinogenicity Study in Mouse - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Female

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
76	50	.	.	1	1	49	.	.	.	0	54	.	.	.	0	55	.	.	.	0	46	.	.	.	0
77	49	.	.	.	0	49	.	.	.	0	54	.	.	1	1	55	1	.	.	1	46	.	.	.	0
78	49	.	.	.	0	49	.	.	.	0	53	.	.	.	0	54	.	.	.	0	46	.	.	.	0
79	49	.	.	.	0	49	.	.	.	0	53	.	.	1	1	54	.	.	.	0	46	.	.	1	1
80	49	.	.	.	0	49	1	.	.	1	52	.	.	3	3	54	.	.	.	0	45	.	.	.	0
81	49	1	.	.	1	48	1	.	.	1	49	.	.	.	0	54	1	.	2	3	45	.	.	1	1
82	48	.	.	.	0	47	.	.	.	0	49	.	.	.	0	51	.	.	1	1	44	.	.	.	0
83	48	.	.	1	1	47	.	.	.	0	49	.	.	1	1	50	.	.	.	0	44	1	.	.	1
84	47	.	.	.	0	47	1	.	.	1	48	.	.	.	0	50	.	.	.	0	43	1	.	.	1
85	47	.	.	.	0	46	.	.	1	1	48	1	.	.	1	50	.	.	.	0	42	.	.	1	1
86	47	.	.	1	1	45	.	.	.	0	47	1	.	.	1	50	.	.	2	2	41	.	.	1	1
87	46	.	.	.	0	45	.	.	1	1	46	.	.	.	0	48	.	.	.	0	40	.	.	1	1
88	46	1	.	1	2	44	.	.	.	0	46	.	.	.	0	48	.	.	.	0	39	2	.	.	2
89	44	.	.	2	2	44	.	.	1	1	46	.	.	1	1	48	.	.	.	0	37	.	.	.	0
90	42	.	.	.	0	43	1	.	.	1	45	.	.	1	1	48	.	.	1	1	37	1	.	.	1
91	42	.	.	1	1	42	.	.	1	1	44	.	.	1	1	47	.	.	.	0	36	.	.	1	1
92	41	.	.	1	1	41	.	.	.	0	43	.	.	.	0	47	.	.	2	2	35	1	.	1	2
93	40	.	.	.	0	41	.	.	.	0	43	.	.	2	2	45	.	.	.	0	33	.	.	.	0
94	40	.	.	1	1	41	.	.	1	1	41	.	.	1	1	45	.	.	.	0	33	.	.	.	0
95	39	.	.	.	0	40	.	.	1	1	40	.	.	1	1	45	.	.	.	0	33	.	.	1	1
96	39	.	.	1	1	39	1	.	.	1	39	1	.	.	1	45	1	.	1	2	32	.	.	1	1
97	38	.	.	1	1	38	1	.	.	1	38	.	.	.	0	43	1	.	2	3	31	.	.	.	0

Table A6 Carcinogenicity Study in Mouse - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Female

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
98	37	.	.	2	2	37	.	.	3	3	38	.	.	1	1	40	.	.	.	0	31	.	.	1	1
99	35	.	.	.	0	34	.	.	1	1	37	1	.	.	1	40	.	.	.	0	30	1	.	.	1
100	35	1	.	.	1	33	.	.	5	5	36	1	.	.	1	40	.	.	1	1	29	.	.	1	1
101	34	.	.	1	1	28	.	.	.	0	35	.	.	.	0	39	.	.	.	0	28	.	.	1	1
102	33	.	.	2	2	28	.	.	.	0	35	.	.	.	0	39	.	.	.	0	27	.	.	1	1
103	31	.	.	.	0	28	.	.	.	0	35	.	.	2	2	39	1	.	1	2	26	.	.	.	0
104	31	1	.	1	2	28	.	.	1	1	33	.	.	1	1	37	.	.	1	1	26	.	.	.	0
105	29	.	.	.	17	27	.	.	.	18	32	.	.	.	17	36	.	.	.	18	26	.	.	.	17
106	12	.	.	.	12	9	.	.	.	9	15	.	.	.	15	18	.	.	.	18	9	.	.	.	9

Table A7 Carcinogenicity Study in Rat - Summary of Survival and Fate of Animals

Summary of Survival and Fate of Animals Explanation Page

Abbreviation	Description
E	Number of animals entering period
D	Animals found dead
A	Animals with accidental death
S	Animals sacrificed moribund
N	Animals necropsied

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Dose Level [a] (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration [a] (mg/mL)	Animal No.[b]			
				Main Study		Toxicokinetic Study [e]	
				Males	Females	Males	Females
1/ Reference Item	0	10	0	1001 to 1070	1501 to 1570	1071 to 1076	1571 to 1576
2/ GSK1278863	0.02	2 [d]	0.01	2001 to 2070	2501 to 2570	2071 to 2073	2571 to 2573
3/ GSK1278863	0.1	10	0.01	3001 to 3070	3501 to 3570	3071 to 3076	3571 to 3576
4/ GSK1278863	0.8	10	0.08	4001 to 4070	4501 to 4570	4071 to 4073	4571 to 4573
5/ GSK1278863	4 (Males) 7 (Females)	10 10	0.4 (Males) 0.7 (Females)	5001 to 5070	5501 to 5570	5071 to 5079	5571 to 5579
6/ Health Screen [c]	-	-	-	6001 to 6010	6501 to 6510	-	-

- = Not applicable.

[a] Doses and concentrations were expressed in terms of the parent compound.

[b] Any animal number replaced or reassigned during the study was documented in the study record and was included in the Final Report.

[c] Data used for health assessment only and retained on file.

[d] Dose volume was generally administered at a precision of 2 decimals: from dosing initiation until the mean body weight per sex reaches ≥ 500g (except for individual with a body weight ≥ 500g, dose volume was individually rounded up at 1 decimal). Then, the dose volume was measured at 1 decimal.

[e] Additional TK rats were added to Groups 1, 3 and 5 to allow collection of tissues for transcriptomic analysis. Additional TK rats were added to Group 5 to ensure toxicokinetics could be assessed appropriately as elevated hematocrits in previous studies have led to difficulty obtaining adequate plasma volume.

Table A7 Carcinogenicity Study in Rat - Summary of Survival and Fate of Animals (Continued)

Male

Summary of Survival and Fate of Animals

Sex: Male

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
8	70		.	.	0	70	.	.	.	0	70	.	.	.	0	70	1	.	.	1	70	.	.	.	0
11	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	69	.	.	.	0	70	1	.	.	1
12	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	69	.	.	.	0	69	1	.	.	1
13	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	69	1	.	.	1	68	.	.	.	0
16	70	1	.	.	1	70	.	.	.	0	70	.	.	.	0	68	.	.	.	0	68	.	.	.	0
18	69	.	.	.	0	70	.	.	.	0	70	.	.	.	0	68	.	.	.	0	68	.	.	.	0
20	69	1	.	.	1	70	.	.	.	0	70	.	.	.	0	68	.	.	.	0	68	.	.	.	0
21	68	.	.	.	0	70	.	.	.	0	70	.	.	.	0	68	1	.	.	1	68	.	.	.	0
22	68	1	.	.	1	70	.	.	1	1	70	1	.	.	1	67	.	.	.	0	68	.	.	.	0
23	67	.	.	.	0	69	.	.	.	0	69	.	.	.	0	67	2	.	.	2	68	.	.	.	0
24	67	1	.	.	1	69	.	.	.	0	69	.	.	.	0	65	.	.	.	0	68	.	.	.	0
25	66	.	.	2	2	69	.	.	.	0	69	.	.	.	0	65	.	.	.	0	68	1	.	.	1
26	64	.	.	.	0	69	.	.	.	0	69	.	.	.	0	65	.	.	.	0	67	.	.	1	1
27	64	.	.	.	0	69	.	.	.	0	69	.	.	.	0	65	.	.	.	0	66	1	.	.	1
30	64	.	.	.	0	69	.	.	.	0	69	.	.	.	0	65	1	.	.	1	65	.	.	.	0
31	64	.	.	.	0	69	.	.	.	0	69	.	.	.	0	64	1	.	.	1	65	1	.	.	1
32	64	.	.	.	0	69	.	.	.	0	69	.	.	.	0	63	.	.	.	0	64	1	.	.	1
33	64	.	.	.	0	69	.	.	.	0	69	.	.	.	0	63	1	.	.	1	63	.	.	.	0
34	64	1	.	.	1	69	.	.	.	0	69	.	.	.	0	62	.	.	.	0	63	.	.	.	0
35	63	1	.	.	1	69	1	.	.	1	69	.	.	.	0	62	.	.	.	0	63	.	.	.	0
39	62	.	.	.	0	68	2	.	.	2	69	.	.	.	0	62	.	.	1	1	63	1	.	.	1
40	62	.	.	.	0	66	.	.	.	0	69	1	.	.	1	61	.	.	.	0	62	2	.	.	2

Table A7 Carcinogenicity Study in Rat - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Male

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
41	62	.	.	.	0	66	.	.	.	0	68	.	.	.	0	61	1	.	.	1	60	2	.	.	2
42	62	.	.	.	0	66	.	.	.	0	68	1	.	.	1	60	.	.	.	0	58	1	.	.	1
43	62	.	.	.	0	66	.	.	.	0	67	1	.	.	1	60	.	.	.	0	57	1	.	.	1
44	62	.	.	.	0	66	1	.	.	1	66	.	.	.	0	60	.	.	.	0	56	.	.	.	0
45	62	.	.	.	0	65	.	.	.	0	66	.	.	.	0	60	.	.	.	0	56	.	.	.	0
46	62	.	.	.	0	65	.	.	1	1	66	.	.	1	1	60	.	.	1	1	56	1	.	.	1
47	62	.	.	1	1	64	1	.	.	1	65	.	.	1	1	59	.	.	.	0	55	1	.	.	1
48	61	.	.	.	0	63	1	.	.	1	64	.	.	.	0	59	.	.	.	0	54	1	.	.	1
49	61	1	.	.	1	62	.	.	.	0	64	.	.	1	1	59	.	.	.	0	53	.	.	.	0
50	60	.	.	.	0	62	1	.	.	1	63	.	.	.	0	59	2	.	.	2	53	1	.	.	1
51	60	.	.	.	0	61	.	.	.	0	63	.	.	.	0	57	.	.	.	0	52	2	.	.	2
52	60	.	.	.	0	61	.	.	.	0	63	1	.	.	1	57	1	.	.	1	50	.	.	.	0
53	60	1	.	.	1	61	.	.	.	0	62	.	.	.	0	56	2	.	.	2	50	.	.	.	0
54	59	.	.	1	1	61	.	.	.	0	62	.	.	.	0	54	1	.	.	1	50	.	.	.	0
55	58	.	.	.	0	61	.	.	.	0	62	.	.	.	0	53	1	.	.	1	50	.	.	1	1
56	58	.	.	.	0	61	.	.	2	2	62	.	.	.	0	52	.	.	.	0	49	.	.	.	0
57	58	.	.	.	0	59	.	.	.	0	62	.	.	.	0	52	.	.	.	0	49	2	.	.	2
58	58	.	.	1	1	59	.	.	.	0	62	.	.	.	0	52	.	.	.	0	47	.	.	1	1
59	57	1	.	.	1	59	1	.	.	1	62	.	.	.	0	52	.	.	.	0	46	.	.	.	0
60	56	.	.	.	0	58	.	.	.	0	62	.	.	.	0	52	.	.	1	1	46	1	.	.	1
61	56	.	.	.	0	58	1	.	.	1	62	.	.	.	0	51	1	.	.	1	45	1	.	.	1
62	56	1	.	.	1	57	.	.	.	0	62	.	.	.	0	50	1	.	.	1	44	.	.	1	1

Table A7 Carcinogenicity Study in Rat - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Male

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
63	55	.	.	.	0	57	.	.	.	0	62	.	.	.	0	49	.	.	.	0	43	.	.	1	1
64	55	1	.	1	2	57	.	.	.	0	62	1	1	.	2	49	1	.	.	1	42	2	.	.	2
65	53	1	.	.	1	57	.	.	1	1	60	.	.	.	0	48	.	.	.	0	40	1	.	.	1
66	52	2	.	.	2	56	.	.	.	0	60	.	.	.	0	48	.	.	.	0	39	1	.	.	1
67	50	.	.	.	0	56	.	.	.	0	60	1	.	.	1	48	2	.	.	2	38	.	.	.	0
68	50	.	.	1	1	56	.	.	.	0	59	.	.	.	0	46	.	.	1	1	38	.	.	.	0
69	49	.	.	.	0	56	.	.	.	0	59	.	.	.	0	45	.	.	1	1	38	1	.	.	1
70	49	.	.	.	0	56	.	.	.	0	59	4	.	.	4	44	.	.	.	0	37	.	.	.	0
71	49	3	.	.	3	56	2	.	.	2	55	1	.	1	2	44	1	.	.	1	37	1	.	.	1
72	46	.	.	.	0	54	1	.	.	1	53	.	.	.	0	43	.	.	.	0	36	1	.	2	3
73	46	.	.	.	0	53	1	.	.	1	53	.	.	1	1	43	1	.	.	1	33	.	.	1	1
74	46	1	.	.	1	52	.	.	.	0	52	.	.	3	3	42	.	.	1	1	32	1	.	.	1
75	45	.	.	.	0	52	2	.	.	2	49	.	.	1	1	41	.	.	1	1	31	2	.	.	2
76	45	.	.	.	0	50	.	.	.	0	48	1	.	.	1	40	3	.	.	3	29	.	.	.	0
77	45	.	.	.	0	50	1	.	.	1	47	.	.	.	0	37	.	.	.	0	29	.	.	.	0
78	45	.	.	.	0	49	1	.	2	3	47	3	.	.	3	37	1	.	.	1	29	.	.	1	1
79	45	1	.	.	1	46	4	.	1	5	44	.	.	.	0	36	1	.	.	1	28	1	.	1	2
80	44	.	.	.	0	41	3	.	1	4	44	.	.	1	1	35	.	.	.	0	26	1	.	1	2
81	44	1	.	1	2	37	.	.	.	0	43	1	.	.	1	35	1	.	.	1	24	.	.	1	1
82	42	.	.	.	0	37	1	.	.	1	42	.	.	.	0	34	.	.	1	1	23	.	.	.	0
83	42	2	.	1	3	36	1	.	.	1	42	1	.	1	2	33	1	.	.	1	23	.	.	1	1
84	39	.	.	2	2	35	.	.	2	2	40	2	.	.	2	32	1	.	.	1	22	1	.	.	1

Table A7 Carcinogenicity Study in Rat - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Male

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
85	37	1	.	.	1	33	1	.	1	2	38	2	.	1	3	31	.	.	.	0	21	1	.	.	1
86	36	.	.	.	0	31	.	.	.	0	35	.	.	2	2	31	1	.	.	1	20	1	.	.	1
87	36	.	.	.	0	31	1	.	.	1	33	.	.	.	0	30	.	.	1	1	19	.	.	.	0
88	36	.	.	1	1	30	.	.	2	2	33	.	.	4	4	29	2	.	.	2	19	.	.	.	0
89	35	2	.	1	3	28	.	.	2	2	29	1	.	1	2	27	1	.	1	2	19	1	.	.	1
90	32	2	.	1	3	26	2	.	.	2	27	.	.	2	2	25	.	.	2	2	18	.	.	.	0
91	29	1	.	.	1	24	.	.	.	0	25	2	.	.	2	23	1	.	.	1	18	.	.	.	0
92	28	1	.	.	1	24	3	.	1	4	23	1	.	1	2	22	.	.	1	1	18	1	.	.	1
93	27	1	.	.	1	20	.	.	.	0	21	.	.	.	0	21	.	.	.	0	17	1	.	1	2
94	26	.	.	1	1	20	.	.	.	0	21	.	.	.	0	21	.	.	1	1	15	.	.	.	15
95	25	.	.	.	0	20	.	.	.	0	21	.	.	1	1	20	.	.	3	3	0	.	.	.	0
96	25	1	.	2	3	20	1	.	.	1	20	.	.	2	2	17	.	.	1	1	0	.	.	.	0
97	22	2	.	.	3	19	1	.	1	3	18	.	.	1	2	16	.	.	.	1	0	.	.	.	0
98	19	.	.	.	4	16	.	.	.	4	16	.	.	.	4	15	.	.	.	4	0	.	.	.	0
99	15	.	.	.	15	12	.	.	.	12	12	.	.	.	12	11	.	.	.	11	0	.	.	.	0

Table A7 Carcinogenicity Study in Rat - Summary of Survival and Fate of Animals (Continued)

Female

Summary of Survival and Fate of Animals

Sex: Female

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
8	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0
11	70	1	.	.	1	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0
12	69	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0
13	69	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0
16	69	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0
18	69	1	.	.	1	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0
20	68	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0
21	68	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	.	.	.	0
22	68	.	.	.	0	70	.	.	.	0	70	.	.	.	0	70	1	.	.	1	70	.	.	.	0
23	68	1	.	.	1	70	.	.	.	0	70	.	.	.	0	69	.	.	.	0	70	.	.	.	0
24	67	.	.	.	0	70	.	.	.	0	70	.	.	.	0	69	.	.	.	0	70	.	.	.	0
25	67	.	.	.	0	70	.	.	.	0	70	.	.	.	0	69	.	.	.	0	70	.	.	.	0
26	67	.	.	.	0	70	.	.	.	0	70	.	.	.	0	69	.	.	.	0	70	.	.	.	0
27	67	.	.	.	0	70	1	.	.	1	70	.	.	.	0	69	.	.	.	0	70	.	.	.	0
30	67	.	.	.	0	69	.	.	.	0	70	.	.	.	0	69	.	.	.	0	70	.	.	.	0
31	67	.	.	.	0	69	.	.	.	0	70	.	.	.	0	69	.	.	.	0	70	.	.	.	0
32	67	.	.	.	0	69	.	.	.	0	70	.	.	.	0	69	.	.	.	0	70	.	.	1	1
33	67	.	.	.	0	69	.	.	.	0	70	.	.	.	0	69	.	.	.	0	69	.	.	.	0
34	67	.	.	.	0	69	.	.	.	0	70	.	.	.	0	69	.	.	.	0	69	.	.	.	0
35	67	.	.	.	0	69	.	.	.	0	70	.	.	.	0	69	.	.	.	0	69	.	.	.	0
39	67	.	.	.	0	69	.	.	.	0	70	.	.	.	0	69	.	.	.	0	69	.	.	.	0
40	67	.	.	.	0	69	.	.	.	0	70	.	.	.	0	69	.	.	.	0	69	.	.	.	0

Table A7 Carcinogenicity Study in Rat - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Female

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
41	67	.	.	.	0	69	.	.	.	0	70	.	.	.	0	69	.	.	.	0	69	.	.	.	0
42	67	.	.	.	0	69	.	.	1	1	70	.	.	.	0	69	.	.	.	0	69	.	.	.	0
43	67	.	.	.	0	68	.	.	.	0	70	.	.	.	0	69	.	.	.	0	69	.	.	.	0
44	67	.	.	.	0	68	.	.	.	0	70	.	.	.	0	69	.	.	.	0	69	.	.	.	0
45	67	.	.	.	0	68	.	.	.	0	70	.	.	.	0	69	1	.	.	1	69	.	.	.	0
46	67	.	.	.	0	68	.	.	.	0	70	.	.	.	0	68	.	.	.	0	69	.	.	.	0
47	67	.	.	2	2	68	.	.	.	0	70	.	.	.	0	68	.	.	.	0	69	.	.	.	0
48	65	.	.	.	0	68	.	.	.	0	70	.	.	.	0	68	1	.	.	1	69	.	.	.	0
49	65	.	.	.	0	68	.	.	.	0	70	.	.	.	0	67	.	.	.	0	69	.	.	.	0
50	65	.	.	.	0	68	.	.	1	1	70	.	.	.	0	67	.	.	.	0	69	.	.	2	2
51	65	.	.	1	1	67	.	.	1	1	70	.	.	.	0	67	.	.	.	0	67	.	.	.	0
52	64	.	.	1	1	66	.	.	.	0	70	.	.	.	0	67	.	.	.	0	67	.	.	1	1
53	63	.	.	.	0	66	.	.	.	0	70	.	.	.	0	67	.	.	.	0	66	.	.	1	1
54	63	.	.	.	0	66	.	.	.	0	70	.	.	.	0	67	.	.	1	1	65	.	.	.	0
55	63	.	.	3	3	66	.	.	.	0	70	.	.	.	0	66	.	.	1	1	65	.	.	1	1
56	60	.	.	.	0	66	.	.	1	1	70	.	.	.	0	65	.	.	.	0	64	.	.	1	1
57	60	.	.	.	0	65	.	.	.	0	70	.	.	1	1	65	.	.	.	0	63	.	.	.	0
58	60	.	.	.	0	65	.	.	.	0	69	.	.	2	2	65	.	.	1	1	63	.	.	.	0
59	60	.	.	.	0	65	.	.	.	0	67	.	.	.	0	64	.	.	.	0	63	.	.	1	1
60	60	1	.	.	1	65	.	.	2	2	67	.	.	.	0	64	.	.	1	1	62	.	.	.	0
61	59	.	.	1	1	63	.	.	1	1	67	.	.	.	0	63	.	.	1	1	62	.	.	1	1
62	58	.	.	.	0	62	.	.	.	0	67	.	.	.	0	62	.	.	.	0	61	.	.	.	0

Table A7 Carcinogenicity Study in Rat - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Female

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
63	58	.	.	.	0	62	.	.	.	0	67	.	.	2	2	62	.	.	.	0	61	.	.	.	0
64	58	.	.	2	2	62	1	.	.	1	65	.	.	1	1	62	.	.	.	0	61	.	.	.	0
65	56	.	.	2	2	61	.	.	.	0	64	.	.	.	0	62	.	.	1	1	61	.	.	.	0
66	54	.	.	2	2	61	1	.	1	2	64	.	.	.	0	61	.	.	.	0	61	1	.	.	1
67	52	.	.	1	1	59	.	.	2	2	64	.	.	1	1	61	.	.	2	2	60	.	.	.	0
68	51	.	.	.	0	57	.	.	.	0	63	.	.	.	0	59	.	.	1	1	60	.	.	.	0
69	51	.	.	1	1	57	.	.	.	0	63	.	.	2	2	58	.	.	1	1	60	.	.	2	2
70	50	.	.	1	1	57	.	.	.	0	61	.	.	.	0	57	.	.	.	0	58	.	.	.	0
71	49	.	.	.	0	57	.	.	.	0	61	.	.	.	0	57	.	.	.	0	58	.	.	.	0
72	49	.	.	.	0	57	.	.	.	0	61	.	.	.	0	57	.	.	.	0	58	.	.	.	0
73	49	.	.	.	0	57	.	.	.	0	61	.	.	.	0	57	.	.	.	0	58	1	.	.	1
74	49	1	.	1	2	57	.	.	.	0	61	.	.	3	3	57	.	.	.	0	57	.	.	.	0
75	47	.	.	.	0	57	.	.	2	2	58	.	.	1	1	57	.	.	1	1	57	.	.	.	0
76	47	.	.	.	0	55	.	.	.	0	57	.	.	1	1	56	.	.	.	0	57	.	.	1	1
77	47	.	.	1	1	55	.	.	.	0	56	.	.	.	0	56	.	.	1	1	56	.	.	2	2
78	46	.	.	.	0	55	.	.	1	1	56	.	.	.	0	55	1	.	2	3	54	.	.	.	0
79	46	.	.	.	0	54	.	.	1	1	56	.	.	1	1	52	1	.	.	1	54	.	.	2	2
80	46	.	.	2	2	53	.	.	2	2	55	1	.	.	1	51	.	.	.	0	52	.	.	2	2
81	44	.	.	.	0	51	2	.	.	2	54	.	.	1	1	51	.	.	.	0	50	.	.	2	2
82	44	.	.	3	3	49	.	.	3	3	53	.	.	2	2	51	1	.	1	2	48	.	.	.	0
83	41	.	.	1	1	46	1	.	.	1	51	.	.	.	0	49	.	.	.	0	48	.	.	1	1
84	40	.	.	.	0	45	.	.	.	0	51	1	.	2	3	49	2	1	.	3	47	1	.	2	3

Table A7 Carcinogenicity Study in Rat - Summary of Survival and Fate of Animals (Continued)

Summary of Survival and Fate of Animals

Sex: Female

Group:	1					2					3					4					5				
Week	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N	E	D	A	S	N
85	40	.	.	2	2	45	1	.	1	2	48	.	.	3	3	46	.	.	.	0	44	1	.	.	1
86	38	.	.	1	1	43	.	.	2	2	45	.	.	2	2	46	.	.	.	0	43	.	.	1	1
87	37	1	.	1	2	41	.	.	1	1	43	1	.	1	2	46	.	.	.	0	42	.	.	.	0
88	35	1	.	1	2	40	.	.	1	1	41	.	.	1	1	46	.	.	1	1	42	.	.	2	2
89	33	.	.	1	1	39	.	.	.	0	40	.	.	2	2	45	.	.	2	2	40	.	.	1	1
90	32	.	.	1	1	39	.	.	1	1	38	1	.	2	3	43	.	.	2	2	39	1	.	1	2
91	31	.	.	1	1	38	.	.	1	1	35	.	.	.	0	41	1	.	.	1	37	.	.	1	1
92	30	.	.	2	2	37	.	.	1	1	35	.	.	1	1	40	.	.	1	1	36	.	.	.	0
93	28	.	.	1	1	36	.	.	3	3	34	.	.	2	2	39	.	.	.	0	36	.	.	2	2
94	27	1	.	1	2	33	1	.	1	2	32	.	.	2	2	39	.	.	1	1	34	.	.	.	0
95	25	2	.	.	2	31	.	.	.	0	30	.	.	3	3	38	.	.	1	1	34	.	.	.	0
96	23	.	.	1	1	31	1	.	3	4	27	.	.	.	0	37	1	.	4	5	34	.	.	1	1
97	22	.	.	.	0	27	.	.	.	0	27	.	.	1	1	32	.	.	3	3	33	.	.	2	2
98	22	.	.	.	0	27	.	.	.	0	26	.	.	2	2	29	.	.	.	0	31	.	.	.	0
99	22	.	.	1	1	27	.	.	5	5	24	.	.	3	3	29	.	.	2	2	31	1	.	.	1
100	21	.	.	1	21	22	.	.	1	21	21	.	.	1	20	27	.	.	.	21	30	.	.	.	21
101	0	.	.	.	0	1	.	.	.	1	1	.	.	.	1	6	.	.	.	6	9	.	.	.	9

1. TOXICOLOGY: OVERVIEW FOR DAPRODUSTAT

Table 1.1 List of Single Dose Toxicity Studies Performed with Daprodustat

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Minimal lethal dose	Mouse (CD-1)	6F	Oral (gavage)	A	300, 1000, 1500, 2000	Single	Yes	GSK	CD2009/00778 (G09147)	m4.2.3.1
Minimal lethal dose	Rat (Sprague Dawley)	6F	Oral (gavage)	A	1000, 1500, 2000	Single	Yes	GSK	CD2009/00777 (G09148)	m4.2.3.1
Dermal irritation	Rabbit (New Zealand White)	3M	Dermal	A	0.5%, 1%, 2%	Single	Yes	GSK	2011N123167 (L42844)	m4.2.3.1
Maximum tolerated dose	Dog (beagle)	1M/1F	Oral (gavage)	A	6, 20, 60, 120, 180	Single	No	GSK	CD2006/01837 (D06386)	m4.2.3.1
Dermal Irritation	Minipig (Gottingen)	4M	Dermal	A	5%, 10%, 20%, 35%	Single	No	GSK	2013N180775 (F43142N)	m4.2.3.1
Maximum tolerated dose	Monkey (cynomolgus)	2M/2F	Oral (gavage)	A	10, 30, 100, 300, 600	Single	No	GSK	CD2009/00639 (D09120)	m4.2.3.1

Key:
A = All studies were conducted with daprodustat (GSK1278863), the parent form.

Testing Facility:
GSK = GlaxoSmithKline.

Table 1.2 List of Repeat Dose Toxicity Studies Performed with Daprodustat and Metabolites of Daprodustat

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Studies with Daprodustat										
Repeat dose toxicity	Mouse (CD-1)	6M/6F[a]	Oral (gavage)	A	30, 100, 300	14 days	No	GSK	CD2009/00900 (D09169)	m4.2.3.2
Repeat dose toxicity	Mouse (CD-1)	12M/12F[b]	Oral (gavage)	A	**3**, 30, 60	13 weeks	Yes	[redacted]	2011N112096 (G10121)	m4.2.3.2
Repeat dose toxicity (Daprodustat + M2, M3 & M13)	Mouse (CD-1)	12M/ 12F[l]	Oral (gavage) Subcutaneous (injection)	A D, E, N	6[k], 20[k] (daprodustat) 2.0 (M2), 2.5 (M3), 1.3 (M13)	13 weeks	Yes	[redacted]	2014N199031 (M70456G)	m4.2.3.2
Repeat dose toxicity	Rat (Sprague Dawley)	4M[c]	Oral (gavage)	A	10, 30, 60	14 days	No	GSK	RD2006/01192 (R41921)	m4.2.3.2
Repeat dose toxicity	Rat (Sprague Dawley)	4F[c]	Oral (gavage)	A	100, 250, 500	14 days	No	[redacted]	CD2008/01306 (D08114)	m4.2.3.2
Repeat dose toxicity	Rat (Sprague Dawley)	10M/10F[d]	Oral (gavage)	A	**2**, 7, 20	4 weeks	Yes	GSK	RD2007/01333 (R42197)	m4.2.3.2
Repeat dose toxicity	Rat (Sprague Dawley)	15M/ 15F[d,e]	Oral (gavage)	A	0.8, **4**, 20, 100	13 weeks	Yes	GSK	CD2009/00951 (G09057)	m4.2.3.2

List of Repeat Dose Toxicity Studies Performed with Daprodustat and Metabolites of Daprodustat (Continued)

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Repeat dose toxicity	Rat (Sprague Dawley)	12M/12F[f]	Oral (gavage)	A	0.8, **4**, 10	26 weeks	Yes	[redacted]	2011N126130 (G10276)	m4.2.3.2
Repeat dose dermal irritation	Rabbit (New Zealand White)	3M or 6M	Dermal	A	0.5%, 1%, 2%	14 days	Yes	GSK	2011N125481 (L42845)	m4.2.3.2
Repeat dose toxicity	Dog (beagle)	2M/2F	Oral (gavage or capsule)	A	90	3 days	No	GSK	RD2007/01367 (D42209)	m4.2.3.2
Repeat dose toxicity	Dog (beagle)	1M/1F	Oral (gavage)	A	20, 60, 120	7 days	No	GSK	CD2007/00353 (D07078)	m4.2.3.2
Repeat dose toxicity	Dog (beagle)	3M/3F	Oral (capsule)	A	**3**, 30, 90	4 weeks	Yes	GSK	RD2007/01336 (D42196)	m4.2.3.2
Repeat dose toxicity	Dog (beagle)	4M/4F[g]	Oral (capsule)	A	1, **3**, 30/15[h]	13 weeks	Yes	[redacted]	CD2009/00952 (G09058)	m4.2.3.2
Repeat dose dermal irritation	Minipig (Gottingen)	1M/1F	Dermal	A	0.5%, 1.0%, 2.0%	14 days	No	[redacted]	2012N148386 (D12086)	m4.2.3.2
Repeat dose dermal irritation	Minipig (Göttingen)	1M/1F	Dermal	A	10, 20 or 35%	14 Days	No	[redacted]	2013N185591 (F70438N)	m4.2.3.2
Repeat dose dermal irritation	Minipig (Gottingen)	3M	Dermal	A	2, 10, 35%	4 weeks	No	[redacted]	2015N231048 (F70727N)	m4.2.3.2

List of Repeat Dose Toxicity Studies Performed with Daprodustat and Metabolites of Daprodustat (Continued)

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Repeat dose dermal irritation	Minipig (Gottingen)	4M/4F	Dermal	A	5, 10, 20%	13 weeks	Yes	[redacted]	2016N273683 (F70916G)	m4.2.3.2
Repeat dose toxicity	Monkey (cynomolgus)	1M/1F	Oral (gavage)	A	10, 30, 100	14 days	No	GSK	CD2009/00780 (D09121)	m4.2.3.2
Repeat dose toxicity	Monkey (cynomolgus)	4M/4F[i]	Oral (gavage)	A	5, **20**, 100	13 weeks	Yes	[redacted]	2010N108482 (G10005)	m4.2.3.2
Repeat dose toxicity	Monkey (cynomolgus)	4M/4F[j]	Oral (gavage)	A	**3**, 10, 50	39 weeks	Yes	[redacted]	2011N126131 (G10277)	m4.2.3.2

List of Repeat Dose Toxicity Studies Performed with Daprodustat and Metabolites of Daprodustat (Continued)

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Study with Metabolite										
M13 dose range	Mouse (CD-1)	3M/3F	Intravenous (bolus)	N	40, 80, 120, 200, 350, 400	2 days	No	GSK	2011N123943 (M29825)	m4.2.3.7.5
M2, M3 and M13: Irritation	Mouse (CD-1)	3M	Subcutaneous	D, E, N	2.0, 6.0 (M2), 2.5, 7.5 (M3), 1.3, 3.9 (M13)	7 days	No	GSK	2013N169136 (M43081N)	m4.2.3.7.5

Key:

For pivotal toxicity studies, the no observed adverse effect level (NOAEL) is bolded.

A = Daprodustat (GSK1278863, Parent form). D = M2 metabolite of daprodustat, GSK2391220 (Parent form). E = M3 metabolite of daprodustat, GSK2506104 (Parent form). N = M13 metabolite of daprodustat, GSK2531401 (Parent form).

a = An additional 18M/18F were added at 30 mg/kg/day for toxicokinetic investigations only.

b = An additional 42M/42F were added at 3, 30 and 60 mg/kg/day and 6M/6F were added to the vehicle control for toxicokinetic investigations, and an additional 21M/21F were added at 30 mg/kg/day for metabolite investigations.

c = An additional 3M or 3F group were included for toxicokinetic investigations.

d = An additional 3M/3F group were included for toxicokinetic investigations.

e = An additional 5M/5F were added at the control and 20 and 100 mg/kg/day groups for a 4 week recovery.

f = An additional 9M/9F were added at 10 mg/kg and 3M/3F were added to the vehicle control and 0.8 and 4 mg/kg groups for toxicokinetic evaluation.

g = An additional 2M/2F were included at the control and 30/15 mg/kg/day groups for a 4 week recovery.

h = On Day 17, the dose was reduced from 30 mg/kg/day to 15 mg/kg/day for females only.

i = An additional 2M/2F were added at the control and 20 and 100 mg/kg/day groups for a 4 week recovery.

j = An additional 2M/2F were included at the control and 50 mg/kg/day groups for a 6 week recovery.

k = This daprodustat dose group was also administered a cocktail of metabolites [2.0 (M2), 2.5 (M3) and 1.3 (M13) mg/kg/day] by once daily subcutaneous injection.

l = An additional 48M/48F were added at 6, 20 mg/kg/day and 6M/6F were added to the vehicle control for toxicokinetic investigations.

Testing Facility:

[redacted] = [redacted]

[redacted] = [redacted]

GSK = GlaxoSmithKline

[redacted] = [redacted]

Table 1.3 List of Genotoxicity Studies Performed with Daprodustat and Metabolites of Daprodustat

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Studies with Daprodustat										
Ames test	S. typhimurium and E. coli	NA	In vitro	A	5 to 500 μg/plate[a]	NA	Yes	[redacted]	WD2007/01575 (V27887)	m4.2.3.3.1
Mouse lymphoma	L5178Y ($TK^{+/-}$) cells	NA	In vitro	A	5 to 70 μg/mL[b]	NA	Yes	[redacted]	WD2007/01578 (V27888)	m4.2.3.3.1
Micronucleus	Rat (Sprague Dawley)	6M[c]	Oral (gavage)	A	1000, 2000	2 days	Yes	[redacted]	WD2007/01574 (R27886)	m4.2.3.3.2
Chromosome aberration	Rat (Han Wistar)	6M	Oral (gavage)	A	500, 1000, 2000	Single	Yes	[redacted]	2012N133264 (R29957)	m4.2.3.3.2
Comet	Rat (Sprague Dawley)	5M	Oral (gavage)	A	250, 500, 1000	2 days	Yes	GSK	2012N139517 (R30069)	m4.2.3.3.2
Studies with Metabolites										
GSK2391220 (M2) Ames test	S. typhimurium and E. coli	NA	In vitro	D	50 to 5000 μg/plate	NA	Yes	GSK	2011N120130 (V29664)	m4.2.3.7.5
GSK2506104 (M3) Ames test	S. typhimurium and E. coli	NA	In vitro	E	50 to 5000 μg/plate	NA	Yes	GSK	2011N119269 (V29751)	m4.2.3.7.5
GSK2531403 (M3) Ames test	S. typhimurium and E. coli	NA	In vitro	F	50 to 5000 μg/plate	NA	Yes	GSK	2011N119441 (V29666)	m4.2.3.7.5

List of Genotoxicity Studies Performed with Daprodustat and Metabolites of Daprodustat (Continued)

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
GSK2487818 (M4) Ames test	S. typhimurium and E. coli	NA	In vitro	G	50 to 5000 μg/plate	NA	Yes	GSK	2012N143001 (V30227)	m4.2.3.7.5
GSK2506102 (M5) Ames test	S. typhimurium and E. coli	NA	In vitro	J	50 to 5000 μg/plate	NA	Yes	GSK	2012N150862 (V30314G)	m4.2.3.7.5
GSK2531398 (M6) Ames test	S. typhimurium and E. coli	NA	In vitro	K	50 to 5000 μg/plate	NA	Yes	GSK	2012N150330 (V30313G)	m4.2.3.7.5
GSK2531401 (M13) Ames test	S. typhimurium and E. coli	NA	In vitro	N	50 to 5000 μg/plate	NA	Yes	GSK	2011N120131 (V29665)	m4.2.3.7.5
GSK2391220 (M2) Mouse lymphoma	L5178Y ($TK^{+/-}$) cells	NA	In vitro	D	200 to 1278.4 μg/mL	NA	Yes	GSK	2011N124122 (V29807)	m4.2.3.7.5
GSK2506104 (M3) Mouse lymphoma	L5178Y ($TK^{+/-}$) cells	NA	In vitro	E	500 to 1466 μg/mL	NA	Yes	GSK	2011N118972 (V29760)	m4.2.3.7.5
GSK2531403 (M3) Mouse lymphoma	L5178Y ($TK^{+/-}$) cells	NA	In vitro	F	500 to 1711 μg/mL	NA	Yes	GSK	2011N120944 (V29743)	m4.2.3.7.5

List of Genotoxicity Studies Performed with Daprodustat and Metabolites of Daprodustat (Continued)

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
GSK2531401 (M13) Mouse lymphoma	L5178Y ($TK^{+/-}$) cells	NA	In vitro	N	40 to 425 μg/mL	NA	Yes	GSK	2011N120224 (V29742)	m4.2.3.7.5
GSK2531401 (M13) Comet assay	Mouse (CD-1)	4 or 5 or 6M[d]	Intravenous (bolus)	N	25, 100, 200[e]	2 days	Yes	GSK	2011N124885 (M29835)	m4.2.3.7.5
GSK2531401 (M13) Chromosome aberration	Mouse (CD-1)	5 or 6M[d]	Intravenous (infusion)	N	25, 100, 200	Single	Yes	[redacted]	2012N132787 (M29910)	m4.2.3.7.5

Key:
A = Daprodustat (Parent form). D = M2 metabolite of daprodustat, GSK2391220 (Parent form). E = M3 metabolite of daprodustat, GSK2506104 (Parent form). F = M3 metabolite of daprodustat, GSK2531403 (Parent form). G = M4 metabolite of daprodustat, GSK2487818 (Parent form). J = M5 metabolite of daprodustat, GSK2506102 (Parent form). K = M6 metabolite of daprodustat, GSK2531398 (Parent form). N = M13 metabolite of daprodustat, GSK2531401 (Parent form). NA = Not applicable.
a = Dose limited by precipitation.
b = Dose limited by cytotoxicity.
c = An additional 3M at 2000 mg/kg were included for toxicokinetic investigations only on Day 1.
d = Plasma samples were taken from satellite groups (3M/group) after the first dose to confirm exposure to GSK2531401.
e = 300 mg/kg/day was included, but due to morbidity, it was considered in excess of the maximum tolerated dose and thus not evaluated for genotoxicity.

Testing Facility:
[redacted] = [redacted]
[redacted] = [redacted]
GSK = GlaxoSmithKline.

Table 1.4 List of Carcinogenicity Studies Performed with Daprodustat and Metabolites of Daprodustat

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Carcinogenicity	Mouse (CD-1)	60M/60F	Oral (gavage)	A D, E, N	0.2[a], 0.8[b], 0.8[a], 3[a], (daprodustat) 2.0 (M2), 2.5 (M3), 1.3 (M13)	Up to 105 weeks	Yes	[redacted]	2014N221714 (M70585G)	m4.2.3.4.1
Carcinogenicity	Rat (Sprague Dawley)	70M/70F	Oral (gavage)	A	0.02, 0.1, 0.8, or 4 0.02, 0.1, 0.8, or 7	Up to 95 weeks 99 weeks	Yes	[redacted]	2014N196080 (R70375G)	m4.2.3.4.1

Key:
A = Daprodustat (Parent form). D = M2 metabolite of daprodustat, GSK2391220 (Parent form). E = M3 metabolite of daprodustat, GSK2506104 (Parent form). N = M13 metabolite of daprodustat, GSK2531401 (Parent form).
a = 0.2, 0.8 and 3 mg/kg/day daprodustat groups were also administered a cocktail of metabolites [GSK2391220 (M2), GSK2506104 (M3) and GSK2531401 (M13)] by SC injection at 2, 2.5, and 1.3 mg/kg/day, respectively.
b = An additional 0.8 mg/kg/day group was administered daprodustat and once daily subcutaneous injection of the subcutaneous vehicle (no metabolites).

Testing Facility:
[redacted] = [redacted]

Table 1.5 List of Reproductive and Developmental Toxicity Studies Performed with Daprodustat and Metabolites of Daprodustat

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Male fertility	Rat (Sprague Dawley)	25M	Oral (gavage)	A	0.8, 4, 20	Up to 59 days	Yes	[redacted]	CD2009/00389 (G09059)	m4.2.3.5.1
Female fertility and early embryonic development	Rat (Sprague Dawley)	25F	Oral (gavage)	A	2, 7, 100	Up to 35 days	Yes	[redacted]	CD2009/00236 (G08250)	m4.2.3.5.1
Embryofetal development	Rat (Sprague Dawley)	17-20F (pregnant)	Oral (gavage)	A	0.5, 7, 60	12 days (Days 6 to 17 pc)	Yes	[redacted]	CD2009/00388 (G09060)	m4.2.3.5.2
PPND dose range	Rat (Sprague Dawley)	5F (pregnant)	Oral[b] (gavage)	A D, E, N	10[c], 40[d], 40[e], 60[f], 60[g] (daprodustat) 2.5, 7.5 (M2), 3.2, 9.6 (M3), 1.8, 5.4 (M13)	25 days (GD 6 to LD 6)	No	[redacted]	2016N305715 (R71028N)	m4.2.3.5.3
PPND[i]	Rat (Sprague Dawley)	22-23F (pregnant/ lactating)	Oral (gavage) SC	A D, E, N	0.8[h,j], 7[h,j], 40[h,j] (daprodustat) 2.5 (M2), 3.2 (M3), 1.8 (M13)	37 days (GD6 to LD21)	Yes	[redacted]	2018N365151 (R71242G)	m4.2.3.5.3
Embryofetal development dose range	Rabbits (Dutch Belted)	3 or 4F (pregnant)	Oral (gavage)	A	4, 30, 60, 125, 250	13 days (Days 7 to 19 pc)	No	GSK	CD2008/01041 (D08169)	m4.2.3.5.2
Embryofetal development	Rabbits (Dutch Belted)	21-22F (pregnant)	Oral (gavage)	A	4, 30, 60	13 days (Days 7 to 19 pc)	Yes	[redacted]	CD2009/00390 (G09061)	m4.2.3.5.2

List of Reproductive and Developmental Toxicity Studies Performed with Daprodustat and Metabolites of Daprodustat (Continued)

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Toxicokinetic study[a]	Rabbits (Dutch Belted)	2 or 4F (pregnant)	Oral (gavage)	A	60	5 Days (Days 7 to 11 pc)	Yes	GSK	2012N140611 (G12109)	m4.2.3.5.2

Key:
A = Daprodustat (Parent form). D = M2 metabolite of daprodustat, GSK2391220 (Parent form). E = M3 metabolite of daprodustat, GSK2506104 (Parent form). N = M13 metabolite of daprodustat, GSK2531401 (Parent form).
GD = Gestation day. LD = Lactation day. pc = Post coitum. PPND = Pre- and post-natal development.
a = Study included an evaluation of systemic exposure to daprodustat and metabolites.
b = Daprodustat was administered orally, but some groups were also administered a cocktail of metabolites (M2, 3 and 13) of daprodustat or vehicle subcutaneously.
c = Given daprodustat at 10 mg/kg/day and metabolite cocktail - 2.5, 3.2, and 1.8 mg/kg/day (for M2, 3 or 13, respectively).
d = Given daprodustat at 40 mg/kg/day and vehicle (25 mM Phosphate Buffer, pH 7.4).
e = Given daprodustat at 40 mg/kg/day and metabolite cocktail - 2.5, 3.2, and 1.8 mg/kg/day (for M2, 3 or 13, respectively).
f = Given daprodustat at 60 mg/kg/day and metabolite cocktail - 2.5, 3.2, and 1.8 mg/kg/day (for M2, 3 or 13, respectively).
g = Given daprodustat at 60 mg/kg/day and metabolite cocktail - 7.5, 9.6, and 5.4 mg/kg/day (for M2, 3 or 13, respectively).
h = This daprodustat dose group was also administered a cocktail of metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)] by SC injection at 2.5, 3.2 and 1.8 mg/kg/day, respectively.
i = Study also evaluated F_1 pups on PND10.

Testing Facility:
[redacted] = [redacted]
GSK = GlaxoSmithKline.
[redacted] = [redacted]

Table 1.6 List of Local Tolerance Studies Performed with Daprodustat

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg) or Concentration (w/w)	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Eye irritation	SkinEthic reconstructed human corneal model	NA	In vitro	A	30 mg	NA	Yes	[redacted]	2012N133177 (41101688)	m4.2.3.6
Ocular irritation	Bovine Corneal Opacity and Permeability Assay	NA	In vitro	A	100% (750 mg)[e] 5%, 10%, 20%	NA	Yes	[redacted]	2016N293568 (V31530G)	m4.2.3.6
Dermal irritation	SkinEthic reconstructed human epidermal model	NA	In vitro	A	25 mg	NA	Yes	[redacted]	2012N133176 (41101687)	m4.2.3.6
Dermal irritation	Human EpiDerm™ skin tissue	NA	In vitro	A	0.2%	NA	Yes	[redacted]	2012N152037 (11AA57-AA60)	m4.2.3.6
Local lymph node	Mouse (CBA/CaCrl)	5F	Topical[a]	A	0.5%, 1%, 2%	3 days	Yes	[redacted]	2012N132983 (G11248)	m4.2.3.6

List of Local Tolerance Studies Performed with Daprodustat (Continued)

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg) or Concentration (w/w)	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Local lymph node	Mouse (CBA/CaCrl)	1F[c]	Topical[b]	A	10%, 25%, 50%	3 days	Yes	[redacted]	2013N163877 (41204918)	m4.2.3.6
		5F[d]			10%					

Key:
A = Daprodustat (Parent form). NA = Not applicable.
a = Dosed as a percent formulation in petrolatum.
b = Dosed as an emulsion in acetone/olive oil 4:1 and 50 µl (25 µl/ear).
c = Preliminary screening groups.
d = Test Group.
e = Unformulated parent was administered.

Testing Facility:
[redacted] = [redacted]
[redacted] = [redacted]
[redacted] = [redacted]
[redacted] = [redacted]

Table 1.7 List of Other Toxicity Studies Performed with Daprosustat and Metabolites of Daprodustat

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Studies with Daprodustat										
Hemolysis study	Rat (Sprague Dawley)	NA	In vitro	A	0.5, 1, 2 mg/mL	NA	No	GSK	CD2008/01038 (I08189)	m4.2.3.7.7
Hemolysis study	Human	NA	In vitro	A	0.0488, 0.0952, 0.1818 mg/mL	NA	Yes	GSK	2012N131637 (G11256)	m4.2.3.7.7
Investigative study (gastric toxicity)	Rat (Sprague Dawley)	6M[a]	IV (infusion)	A	20, 40	14 days	No	[redacted]	CD2008/01740 (I08185)	m4.2.3.7.7
Investigative study (plasma glucose)	Rat (Sprague Dawley)	6M	Oral (gavage)	A	60	14 days	No	GSK	2012N135152 (I12031)	m4.2.3.7.7
Studies with Metabolite										
GSK2531401 (M13) Inhibition of topoisomerase II relaxation	Human	NA	In vitro	N	0.01 to 1000 μM	NA	No	[redacted]	2011N130337	m4.2.3.7.5
GSK2531401 (M13) Topoisomerase II alpha inhibition	Human	NA	In vitro	N	2 to 2000 μM	NA	No	GSK	2012N139337	m4.2.3.7.5

Key:
A = Daprodustat (parent form). IV = Intravenous. N = M13 metabolite (GSK2531401) of daprodustat .
NA = Not applicable.
a = An additional 3M/group were included for toxicokinetic investigations only.

Testing Facility:
[redacted] = [redacted]
GSK = GlaxoSmithKline.
[redacted] = [redacted]

2. TOXICOKINETICS: OVERVIEW OF TOXICOKINETICS STUDIES

Table 2.1 Toxicokinetics: Overview of Toxicokinetics Studies

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Report No. (Study No.)	Location in CTD
Toxicokinetics	Rat (Sprague Dawley)	Oral (gavage)	0.02, 0.1, 0.8, 7	NO	2013N184197 (R70458N)	m4.2.2.2
Toxicokinetics	Dog (beagle)	Oral (gavage)	120	NO	CD2006/01837 (D06386)	m4.2.3.1
Toxicokinetics	Minipig (Göttingen)	Dermal	10%, 35%	NO	2013N180775 (F43142N)	m4.2.3.1
Toxicokinetics	Monkey (cynomolgus)	Oral (gavage)	10, 30, 100, 300, 600	NO	CD2009/00639 (D09120)	m4.2.3.1
Toxicokinetics	Mouse (CD-1)	Oral (gavage)	30	NO	CD2009/00900 (D09169)	m4.2.3.2
Toxicokinetics	Mouse (CD-1)	Oral (gavage)	3, 30, 60	YES	2011N112096 (G10121)	m4.2.3.2
Toxicokinetics of circulating metabolites	Mouse[d] (CD-1)	Oral (gavage)	30	YES	2011N117145 (10DMM034)	m4.2.2.2
Toxicokinetics of daprodustat and metabolites (co-administered)	Mouse (CD-1)	Oral (gavage) SC (Injection)	6[a], 20[a] (daprodustat) 2.0 (M2), 2.5 (M3), 1.3 (M13)	YES	2014N199031 (M70456G)	m4.2.3.2

Toxicokinetics: Overview of Toxicokinetics Studies (Continued)

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Report No. (Study No.)	Location in CTD
Toxicokinetics	Mouse (CD-1)	Oral (gavage)	0.2[a], 0.8[a], 3[a] (daprodustat) 2.0 (M2), 2.5 (M3), 1.3 (M13)	YES	2014N221714 (M70585G)	m4.2.3.4.1
Toxicokinetics	Mouse (CD-1)	SC (Injection)	2.0 (M2), 2.5 (M3), 1.3 (M13)	NO	2014N208198 (M70590N)	m4.2.1.1
Toxicokinetics	Rat (Sprague Dawley)	IV (4 hour infusion)	20, 40	NO	CD2008/01740 (I08185)	m4.2.3.7.7
Toxicokinetics	Rat (Sprague Dawley)	Oral (gavage)	10[a], 40[a], 40, 60[a], 60[a] (daprodustat) 2.5 (M2), 3.2 (M3), 1.8 (M13)	NO	2016N305715 (R71028N)	m4.2.3.5.3
Toxicokinetics	Rat (Sprague Dawley)	Oral (gavage)	10, 30, 60	NO	RD2006/01192 (R41921)	m4.2.3.2
Toxicokinetics	Rat (Sprague Dawley)	Oral (gavage)	100, 250, 500	NO	CD2008/01306 (D08114)	m4.2.3.2
Toxicokinetics	Rat (Sprague Dawley)	Oral (gavage)	2, 7, 20	YES	RD2007/01333 (R42197)	m4.2.3.2
Toxicokinetics	Rat (Sprague Dawley)	Oral (gavage)	0.8, 4, 20, 100	YES	CD2009/00951 (G09057)	m4.2.3.2
Toxicokinetics	Rat (Sprague Dawley)	Oral (gavage)	0.8, 4, 10	YES	2011N126130 (G10276)	m4.2.3.2

Toxicokinetics: Overview of Toxicokinetics Studies (Continued)

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Report No. (Study No.)	Location in CTD
Toxicokinetics	Rat (Sprague Dawley)	Oral (gavage)	0.02, 0.1, 0.8, or 4 0.02, 0.1, 0.8, or 7	YES	2014N196080 (R70375G)	m4.2.3.4.1
Toxicokinetics	Rat (Sprague Dawley) (pregnant)	Oral (gavage) SC	0.8[a], 7[a], 40[a] (daprodustat) 2.5 (M2), 3.2 (M3), 1.8 (M13)	YES	2018N365151 (R71242G)	m4.2.3.5.3
Toxicokinetics	Rabbits (Dutch Belted) (pregnant)	Oral (gavage)	60	YES	2012N140611 (G12109)	m4.2.3.5.2
Toxicokinetics	Rabbits (Dutch Belted) (pregnant)	Oral (gavage)	4, 30, 60, 125, 250	NO	CD2008/01041 (D08169)	m4.2.3.5.2
Toxicokinetics	Rabbits (Dutch Belted) (pregnant)	Oral (gavage)	4, 30, 60	YES	CD2009/00390 (G09061)	m4.2.3.5.2
Toxicokinetics	Rabbit (New Zealand White)	Dermal	2%	YES	2011N125481 (L42845)	m4.2.3.2
Toxicokinetics	Dog (beagle)	Oral (gavage & capsule)	90	NO	RD2007/01367 (D42209)	m4.2.3.2
Toxicokinetics	Dog (beagle)	Oral (gavage)	20, 60, 120	NO	CD2007/00353 (D07078)	m4.2.3.2
Toxicokinetics	Dog (beagle)	Oral (capsule)	3, 30, 90	YES	RD2007/01336 (D42196)	m4.2.3.2

Toxicokinetics: Overview of Toxicokinetics Studies (Continued)

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Report No. (Study No.)	Location in CTD
Toxicokinetics	Dog (beagle)	Oral (capsule)	1, 3, 30/15[b]	YES	CD2009/00952 (G09058)	m4.2.3.2
Toxicokinetics	Minipig (Göttingen)	Dermal	0.5%, 1%, 2% w/w applied daily to 10% BSA	NO	2012N148386 (D12086)	m4.2.3.2
Toxicokinetics	Minipig (Göttingen)	Dermal	10, 20, 35% w/w applied daily to 10% BSA	NO	2013N185591 (F70438N)	m4.2.3.2
Toxicokinetics	Minipig (Göttingen)	Dermal	2, 10, 35% w/w applied daily to 10% BSA	NO	2015N231048 (F70727N)	m4.2.3.2
Toxicokinetics	Minipig (Göttingen)	Dermal	5, 10, 20% w/w applied daily to 10% BSA	YES	2016N273683 (F70916G)	m4.2.3.2
Toxicokinetics	Monkey (cynomolgus)	Oral (gavage)	10, 30, 100	NO	CD2009/00780 (D09121)	m4.2.3.2

Toxicokinetics: Overview of Toxicokinetics Studies (Continued)

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Report No. (Study No.)	Location in CTD
Toxicokinetics	Monkey (cynomolgus)	Oral (gavage)	5, 20, 100	YES	2010N108482 (G10005)	m4.2.3.2
Toxicokinetics of circulating metabolites	Monkey[c] (cynomolgus)	Oral (gavage)	5, 20, 100	YES	2011N117143 (10DMM033)	m4.2.2.2
Toxicokinetics	Monkey (cynomolgus)	Oral (gavage)	3, 10, 50	YES	2011N126131 (G10277)	m4.2.3.2

Key:

a = Groups were also administered a cocktail of metabolites [GSK2391220 (M2), GSK2506104 (M3) and GSK2531401 (M13)] by SC injection.

b = On Day 17, the dose was reduced from 30 mg/kg/day to 15 mg/kg/day for females only

c = Samples obtained from the 13 week toxicity study in the monkey [Report 2010N108482, m4.2.3.2].

d = Samples obtained from the 13 week toxicity study in the mouse [Report 2011N112096, m4.2.3.2].

3. TOXICOKINETICS: OVERVIEW OF TOXICOKINETICS DATA

Table 3.1 Toxicokinetics: Overview of Oral Toxicokinetics Data at Steady State¥ - AUC_{0-T} (μg.h/mL)

Dose	Mouse		Rat		Rabbit		Dog		Monkey		Human
(mg/kg/day)	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	
0.02			6.53[n]	10.4[n]							
0.1			42.8[n]	38.9[n]							
0.2	13.1[e, *]	28.1[e, *]									
0.44¥											1.184[z]
0.8	43.2[e, *]	92.8[e, *]	242[n]	306[n]							
0.8			NA[#]	98.4[k, *]							
0.8			152[l]	167[l]							
0.8			208[m]	259[m]							
1							7.39[u]	8.06[u]			
2			403[j]	495[j]							
3	151[c]	211[c]					18.2[t]	23.4[t]	4.55[y]	2.69[y]	
3	141[e, *]	335[e, *]					17.8[u]	20.3[u]			
4			889[n]	NA	NA[#]	22.8[p]					
4			606[l]	701[l]	NA[#]	17.9[q]					
4			607[m]	964[m]							
5									5.44[x]	3.67[x]	
6	274[b, *]	464[b, *]									
7			1197[j]	1086[j]							
7			NA	1430[n]							
7			NA[#]	613[k]							
10			NA[#]	1030[g, *]					10.0[v]	8.97[v]	
10			946[h]	NA[Ω]					7.76[y]	11.2[y]	
10			807[m]	1377[m]							
15							NA	67.1[u]			
20	525[b, *]	897[b, *]	1726[j]	1900[j]			49.5[s]	67.0[s]	16.2[x]	13.3[x]	
20			1040[l]	2140[l]							
30	818[a]	992[a]	1980[f]	NA[Ω]	NA[#]	133[p]	88.3[t]	90.8[t]	29.5[v]	16.1[v]	
30	520[c]	817[c]	1241[h]	NA[Ω]	NA[#]	83.3[q]	94.9[u]	NA			
30	819[d]	1118[d]									

Toxicokinetics: Overview of Oral Toxicokinetics Data at Steady State¥ - AUC_{0-T} (μg.h/mL) (Continued)

Dose	Mouse		Rat		Rabbit		Dog		Monkey		Human
(mg/kg/day)	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	
40			NA#	2100g, *							
40			NA#	2100g							
40			NA#	1620k, *							
50									30.2y	29.4y	
60	722c	943c	1745h	NAΩ	NA#	188o	57.5s	114s			
60					NA#	197p	NAt, ‡	NAt, ‡			
60					NA#	148q					
90							249r	250r			
90							188r	185r			
90							NAt, ‡	NAt, ‡			
100			NA#	2994i					60.3v	91.6v	
100			2200l	2780l					52.2x	34.3x	
120							93.7s	135s			
125					NA#	323q					
250			NA#	3184i	NA#	849q					
500			NA#	NA‡							

Note: Mean toxicokinetic data for daprodustat at end of study steady state [AUC_{0-T} (μg.h/mL)], unless otherwise stated.

Key:

a = Study CD2009/00900. b = Study 2014N199031. c = Study 2011N112096. d = Study 2011N117145. e = Study 2014N221714. f = Study 2012N153858. g = Study 2016N305715.
h = Study RD2006/01192. i = Study CD2008/01306. j = Study RD2007/01333. k = Study 2018N365151; values from LD21. l = Study CD2009/00951. m = Study 2011N126130. n = Study 2014N196080.
o = Study 2012N140611. p = Study CD2009/00390. q = Study CD2008/01041. r = Study RD2007/01367. s = Study CD2007/00353. t = Study RD2007/01336. u = Study CD2009/00952.
v = Study CD2009/00780. x = Study 2010N108482. y = Study 2011N126131.
z = Predicted human AUC at steady-state from a 24 mg daprodustat simulation for a typical (54kg) Japanese dialysis subject on a non-dialysis day [Reference Report 2019N405983].
* = This daprodustat dose group also included co-administration of metabolites M2, M3 and M13.
‡ = Animals for study at this dose either died or were killed due to poor condition.
Ω = Study only dosed males.
= Study only dosed females.
¥ = Represents last sampling interval assessed for toxicokinetics at respective doses indicated.
NA = Not applicable, animals of this sex were either not dosed or died/were terminated prior to the end of the study.

4. TOXICOLOGY: DRUG SUBSTANCE

Table 4.1 Toxicology: Drug Substance

Batch Number	Purity (% w/w)	Specified Impurities (% w/w)		Report No. (Study No.)	Type of Study
		GW342946X	GSK1714346A		
PROPOSED SPECIFICATION		**≤0.15%**	**≤0.15%**		
101257943[a]	99.3	≤0.15%	≤0.15%	2012N148386 (D12086)	Repeat dose dermal irritation in minipigs
111280742[a]	99.3	NA	NA	2011N123167 (L42844)	Single dose irritation in rabbits
111280742[a]	99.3	NA	NA	2013N180775 (F43142N)	Single dose irritation in minipigs
111280742[a]	99.3	NA	NA	2015N231048 (F70727N)	Repeat dose dermal irritation in minipigs
111280742[a]	99.3	NA	NA	2011N125481 (L42845)	Repeat dose dermal irritation in rabbits
132377076[b]	99.9	≤0.15%	≤0.15%	2016N305715 (R71028N)	Pre- and post-natal development Dose Range in rats
132377077[b]	100	≤0.15%	≤0.15%	2016N305715 (R71028N)	Pre- and post-natal development Dose Range in rats
132377077[b]	100	≤0.15%	≤0.15%	2014N199031 (M70456G)	Repeat dose toxicity in mice
152389102[c]	99.9	≤0.15%	≤0.15%	2016N273683 (F70916G)	Repeat dose dermal toxicity in minipigs
152389102[c]	99.9	≤0.15%	≤0.15%	2016N293568 (V31530G)	In vitro ocular irritation

Toxicology: Drug Substance (Continued)

Batch Number	Purity (% w/w)	Specified Impurities (% w/w)		Report No. (Study No.)	Type of Study
		GW342946X	GSK1714346A		
PROPOSED SPECIFICATION		**≤0.15%**	**≤0.15%**		
091214093[a]	99.6	NA	NA	2012N133177 (41101688)	In vitro eye irritation
091214093[a]	99.6	NA	NA	2012N152037 (11AA57-AA60)	In vitro dermal irritation (gel, ointment and cream)
101257943[a]	99.3	≤0.15%	≤0.15%	2012N152037 (11AA57-AA60)	In vitro dermal irritation (gel, ointment and cream)
091214093[a]	99.6	NA	NA	2012N132983 (G11248)	Local lymph node in mice
091214093[a]	99.6	NA	NA	2012N131637 (G11256)	In vitro hemolysis study
091214093[a]	99.6	NA	NA	2012N133176 (41101687)	In vitro dermal irritation
091214093[a]	99.6	NA	NA	2013N163877 (41204918)	Local lymph node in mice
8863B3B001[b]	100	≤0.15%	≤0.15%	2014N221714 (M70585G)	Carcinogenicity in mice
8863B3B001[b]	100	≤0.15%	≤0.15%	2014N196080 (R70375G)	Carcinogenicity in rats
8863B3B007[b]	99.9	≤0.15%	≤0.15%	2018N365151 (R71242G)	Pre- and post-natal development in rats
KD207077-049A1[a]	100	NA	NA	CD2006/01837 (D06386)	Single dose toxicity in dogs

Toxicology: Drug Substance (Continued)

Batch Number	Purity (% w/w)	Specified Impurities (% w/w)		Report No. (Study No.)	Type of Study
		GW342946X	GSK1714346A		
PROPOSED SPECIFICATION		≤0.15%	≤0.15%		
KD207077-049A1[a]	100	NA	NA	CD2007/00353 (D07078)	Repeat dose toxicity in dogs
KD207077-046A2[a]	99.7	NA	NA	RD2006/01192 (R41921)	Repeat dose toxicity in rats
NE-021129-Batch-01-2007[a]	99.8	NA	NA	CD2008/01306 (D08114)	Repeat dose toxicity in rats
NE-021129-Batch-01-2009[a]	99.3	NA	NA	CD2009/00778 (G09147)	Single dose toxicity in mice
NE-021129-Batch-01-2009[a]	99.3	NA	NA	CD2009/00777 (G09148)	Single dose toxicity in rats
NE-021129-Batch-01-2009[a]	99.3	NA	NA	CD2009/00639 (D09120)	Single dose toxicity in monkeys
NE-021129-Batch-01-2007[a]	99.8	NA	NA	RD2007/01333 (R42197)	Repeat dose toxicity in rats
NE-021129-Batch-01-2007[a]	99.8	NA	NA	RD2007/01367 (D42209)	Repeat dose toxicity in dogs
NE-021129-Batch-01-2007[a]	99.8	NA	NA	RD2007/01336 (D42196)	Repeat dose toxicity in dogs
NE-021129-Batch-01-2007[a]	99.8	NA	NA	WD2007/01575 (V27887)	In vitro Ames test
NE-021129-Batch-01-2007[a]	99.8	NA	NA	WD2007/01578 (V27888)	In vitro Mouse lymphoma

Toxicology: Drug Substance (Continued)

Batch Number	Purity (% w/w)	Specified Impurities (% w/w)		Report No. (Study No.)	Type of Study
		GW342946X	GSK1714346A		
PROPOSED SPECIFICATION		≤0.15%	≤0.15%		
NE-021129-Batch-01-2007[a]	99.8	NA	NA	WD2007/01574 (R27886)	Rat micronucleus
NE-021129-Batch-01-2007[a]	99.8	NA	NA	CD2008/01038 (I08189)	In vitro hemolysis study
NE-021129-Batch-01-2007[a]	99.8	NA	NA	CD2008/01740 (I08185)	Investigative study (gastric toxicity) in rats
NE-021129-Batch-01-2009[a]	99.3	NA	NA	CD2009/00900 (D09169)	Repeat dose toxicity in mice
NE-021129-Batch-01-2009[a]	99.3	NA	NA	2011N112096 (G10121)	Repeat dose toxicity in mice
NE-021129-Batch-01-2009[a]	99.3	NA	NA	CD2009/00951 (G09057)	Repeat dose toxicity in rats
NE-021129-Batch-01-2009[a]	99.3	NA	NA	2011N126130 (G10276)	Repeat dose toxicity in rats
NE-021129-Batch-01-2009[a]	99.3	NA	NA	CD2009/00952 (G09058)	Repeat dose toxicity in dogs
NE-021129-Batch-01-2009[a]	99.3	NA	NA	CD2009/00780 (D09121)	Repeat dose toxicity in monkeys
NE-021129-Batch-01-2009[a]	99.3	NA	NA	2010N108482 (G10005)	Repeat dose toxicity in monkeys
NE-021129-Batch-01-2009[a]	99.3	NA	NA	2011N126131 (G10277)	Repeat dose toxicity in monkeys
NE-021129-Batch-01-2009[a]	99.3	NA	NA	2013N185591 (F70438N)	Repeat dose dermal irritation in minipigs

Toxicology: Drug Substance (Continued)

Batch Number	Purity (% w/w)	Specified Impurities (% w/w)		Report No. (Study No.)	Type of Study
		GW342946X	GSK1714346A		
PROPOSED SPECIFICATION		≤0.15%	≤0.15%		
NE-021129-Batch-01-2009[a]	99.3	NA	NA	2012N133264 (R29957)	Rat chromosome aberration
NE-021129-Batch-01-2009[a]	99.3	NA	NA	2012N139517 (R30069)	Rat comet
NE-021129-Batch-01-2007[a]	99.8	NA	NA	CD2009/00236 (G08250)	Female fertility and early embryonic development in rats
NE-021129-Batch-01-2007[a]	99.8	NA	NA	CD2008/01041 (D08169)	Embryofetal development in rabbits
NE-021129-Batch-01-2009[a]	99.3	NA	NA	CD2009/00389 (G09059)	Male fertility in rats
NE-021129-Batch-01-2009[a]	99.3	NA	NA	CD2009/00388 (G09060)	Embryofetal development in rats
NE-021129-Batch-01-2009[a]	99.3	NA	NA	CD2009/00390 (G09061)	Embryofetal development in rabbits
NE-021129-Batch-01-2009[a]	99.3	NA	NA	2012N140611 (G12109)	Toxicokinetic study in rabbits
NE-021129-Batch-01-2009[a]	99.3	NA	NA	2012N135152 (I12031)	Investigative study (plasma glucose) in rats

Key:

NA = For the commercial batches, impurities are controlled according to ICH Q3A(R2) (see m.2.3.S.2.6 and m2.3.S.4.5). Impurities for this batch are not specified, and are below the reporting threshold, in the batches manufactured using the proposed commercial route of synthesis.

a = Batch manufactured using Route A.

b = Batch manufactured using Route B1.

c = Batch manufactured using Route B2.

5. SINGLE-DOSE TOXICITY: NONPIVOTAL STUDIES

Table 5.1 Single-Dose Toxicity

Species/ Strain	Route (Vehicle/ Formulation)	Doses (mg/kg)	Number of Animals/ Sex	Maximum Non-Lethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Noteworthy Findings	Report No. (Study No.)
Dog (beagle)	Oral (gavage)	6, 20, 60, 120, 180	1M/1F	ND	ND	A dose of 180 mg/kg was not tolerated. Emesis was noted for the male (multiple episodes) and female (single episodes) given ≥120 mg/kg and abnormal feces were noted for the male given ≥20 mg/kg and female given ≥120 mg/kg. The incidence and severity of emesis and fecal changes were dose related and most extensive for the male given 180 mg/kg. In addition, decreased appetite and slight reductions in body weight were noted for the female given ≥120 mg/kg.	CD2006/01837 (D06386)
Minipig (Gottingen)	Dermal	0, 5%, 10%, 20%, 35%[a]	4M[b]	ND	ND	No dermal irritation was observed during the study.	2013N180775 (F43142N)
Monkey (cynomolgus)	Oral (gavage)	10, 30, 100, 300, 600	2M/2F	ND	ND	Emesis occurred at doses ≥300 mg/kg and was not tolerated at 600 mg/kg. Additional clinical observations included fecal consistency changes at ≥100 mg/kg and instances of reduced eating at all doses administered.	CD2009/00639 (D09120)

Key:

a = The irritation potential of single dermal applications (0.5 g/site) at concentrations of 0% (vehicle), 5%, 10%, 20%, and 35% were assessed, as well as the toxicokinetics of GSK1278863 following a single dermal application (1 g/kg) to 10% of the total body surface area at concentrations of 10% or 35%. Test sites were non-abraded and semi-occluded.

b = The first 2 males were used for the dose-range irritation phase (all dose concentrations) and the toxicokinetic phase (10% concentration). The last 2 males were used for the toxicokinetic phase (35% concentration).

ND = Not Determined.

6. SINGLE-DOSE TOXICITY: PIVOTAL STUDIES

Table 6.1 GSK1278863A: Single Dose Oral Toxicity Study in Female Mice with a 14 Day Observation Period

Study Type: Single Dose Toxicity	**Report Title:** GSK1278863A: Single Dose Oral Toxicity Study in Female Mice with a 14 Day Observation Period	**Test Article:** GSK1278863A (parent compound) **Batch No.:** NE-021129-Batch-01-2009
Species/Strain: Mouse/CD-1	**Duration of Dosing:** 1 day **Duration of Observation Period:** 14 days	**Study No.:** G09147 **Location in CTD:** m4.2.3.1
Initial Age: 9.7 to 11.1 weeks	**Route/Frequency:** Oral by gavage/single dose	**GSK Document Number:** CD2009/00778
Date of First Dose: 21 September 2009	**Vehicle/Formulation:** 1% methylcellulose (400 cps @2%)	**Study in Compliance with GLP:** Yes

Data Collected: Clinical observations, body weight and macroscopic pathology.

Conclusion: GSK1278863 was given as single, oral doses of 300, 1000, 1500 or 2000 mg/kg to female CD-1 mice (6/group) followed by a 14 day observation period. Four mice given 2000 mg/kg and 3 mice given 1500 mg/kg were either found dead or euthanized in poor clinical condition. Partially closed eyes were noted in mice given ≥300 mg/kg, and transient body weight loss and fecal abnormalities were noted in mice given ≥1000 mg/kg. Transient lack of body weight gain was noted in mice given 300 mg/kg. Based on these data, doses ≥1500 mg/kg were not tolerated, and the minimal lethal single dose in this study was between 1000 and 1500 mg/kg.

GSK1278863A: Single Dose Oral Toxicity Study in Female Mice with a 14 Day Observation Period (Continued)

Study Type: Single Dose Toxicity | **Study No.:** G09147

	Females			
Dose (mg/kg)[1]	**300**	**1000**	**1500**	**2000**
Numbers of Females:	6	6	6	6
Noteworthy Findings:				
Unscheduled Deaths:	1	0	3	4
	Four of 6 mice given 2000 mg/kg and 3 of 6 mice given 1500 mg/kg were found dead or euthanized in poor clinical condition on either Days 1, 3 or 8 (2000 mg/kg) or Day 2 (1500 mg/kg). Observations in these mice included decreased activity, cold to touch, loss of skin elasticity, unkempt coat and/or reduced feces. Prior to euthanasia, body weight values available from one mouse each given 2000 mg/kg or 1500 mg/kg were decreased to 0.68X Day 1 value on Day 8 and 0.94X Day 1 value on Day 2, respectively. At necropsy, multifocal red discoloration of the glandular mucosa of the stomach was noted in one mouse given 2000 mg/kg. One mouse given 300 mg/kg was euthanized in poor clinical condition on Day 2, likely attributable to dosing error based on macroscopic findings. Additional clinical observations noted in early decedents were similar to those that survived until scheduled necropsy and are described below.			
Clinical Observations in Surviving Mice:	Partially closed eyes were noted in mice given ≥300 mg/kg for up to 2 days after dosing. Changes in fecal consistency (soft and/or loose/watery feces) were noted in mice given ≥1000 mg/kg and changes in fecal color (tan) were noted in mice given 1000 mg/kg.			
Body Weight[2]:				
Day 1	27.93 g	27.55 g	28.78 g	28.75 g
Day 4	1.01X	0.94X	0.90X	0.87X
Day 8	1.07X	0.95X	0.85X	0.79X
Day 12	1.09X	1.03X	0.91X	0.78X
Day 14	1.11X	1.04X	1.01X	0.85X

Key:
1 = Doses are expressed in terms of the parent compound.
2 = Group means are shown in grams for Day 1 values, and change from Day 1 mean is shown for remaining intervals.

Table 6.2 GSK1278863A: Single Dose Oral Toxicity Study in Female Rats with a 14 Day Observation Period

Study Type: Single Dose Toxicity	**Report Title:** GSK1278863A: Single Dose Oral Toxicity Study in Female Rats with a 14 Day Observation Period	**Test Article:** GSK1278863A (parent compound) **Batch No.:** NE-021129-Batch-01-2009
Species/Strain: Rat/CRL:CD (SD)	**Duration of Dosing:** 1 day **Duration of Observation Period:** 14 days	**Study No.:** G09148 **Location in CTD:** m4.2.3.1
Initial Age: 10 to 12 weeks	**Route/Frequency:** Oral gavage/single dose	**GSK Document Number:** CD2009/00777
Date of First Dose: 21 September 2009	**Vehicle/Formulation:** 1% methylcellulose (400 cps @2%)	**Study in Compliance with GLP:** Yes

Data Collected: Clinical observations, body weight and macroscopic pathology.

Conclusion: GSK1278863 was given as single, oral doses of 1000, 1500 or 2000 mg/kg to female Crl:CD (SD) rats (6/group) followed by a 14 day observation period. Three rats given 1500 mg/kg/day and 3 rats given 2000 mg/kg were either found dead or euthanized in poor clinical condition. Fecal abnormalities (consistency and color) were noted in rats given ≥1000 mg/kg. Based on these data, doses ≥1500 mg/kg were not tolerated, and the minimal lethal single dose in this study was between 1000 and 1500 mg/kg.

GSK1278863A: Single Dose Oral Toxicity Study in Female Rats with a 14 Day Observation Period (Continued)

Study Type: Single Dose Toxicity | **Study No.:** G09148

Dose (mg/kg)[1]	**1000**	**1500**	**2000**
Number of Females:	6	6	6
Noteworthy Findings			
Unscheduled Deaths:	0	3	3
	Three rats/group given doses ≥1500 mg/kg were found dead or euthanized in poor clinical condition on Days 1 or 2 (1500 mg/kg) or Days 2, 3 or 5 (2000 mg/kg). Prior to death, findings in these rats included body weight loss, thin appearance, unkempt coat, red and/or brown discharge from nose and/or anus and coat staining in anal region (orange/brown) in rats given 2000 mg/kg, tiptoe gait in rats given ≥1500 mg/kg, and unsteady gait, decreased activity and blue extremities in rats given 1500 mg/kg. Additional clinical observations noted in early decedents were similar to those that survived until scheduled necropsy.		
Clinical Observations in Surviving Rats:	Hunched posture, discolored bedding (red) and reduced feces were noted in rats given 2000 mg/kg. Signs of dehydration and partially closed eyes were noted in rats given ≥1500 mg/kg. Soft, mucoid, loose/watery and/or tan feces were noted in rats given ≥1000 mg/kg. Clinical observations had resolved by Day 7.		
Body Weight[2]:			
Day 1	238.05 g	246.93 g	237.77 g
Day 4	1.06X	0.98X	0.92X
Day 8	1.12X	1.04X	0.94X
Day 12	1.16X	1.07X	1.09X
Day 14	1.16X	1.09X	1.13X

GSK1278863A: Single Dose Oral Toxicity Study in Female Rats with a 14 Day Observation Period (Continued)

Study Type: Single Dose Toxicity | **Study No.:** G09148

Dose (mg/kg)[1]	**1000**	**1500**	**2000**
Macroscopic Observations in Early Decedents - Number of Females:	**0**	**3**	**3**
Adrenals			
Increased size	0	0	1
Mesenteric Lymph Node			
Discoloration; red	0	0	1
Stomach			
Glandular region; discoloration; red; multifocal	0	0	1
Macroscopic Observations in Surviving Animals - Number of Females:	**6**	**3**	**3**
Stomach			
Discoloration; pale	0	1	0
Thymus			
Adhesion; focal	0	0	1
Discoloration; red; multifocal	0	1	0

Key:
1 = Doses are expressed in terms of the parent compound.
2 = Group means are shown in grams for Day 1 values, and change from Day 1 mean is shown for remaining intervals.

Table 6.3 GSK1278863A: Single Dose Dermal Irritation Study in Rabbits

Study Type: Single-Dose Dermal Irritation

Report Title: GSK1278863A: Single-Dose Dermal Irritation Study in Rabbits (GlaxoSmithKline Study No. L42844)

Test Article: GSK1278863A (parent compound)
Batch No.: 111280742

Species/Strain: New Zealand White rabbit

Duration of Exposure: 24 hours

Study No.: L42844

Initial Age: 8 months

Route: Dermal (occluded, intact and abraded sites)

Location in CTD: m4.2.3.1

Date of Dosing: 27 September 2011

Vehicle/Formulation: petrolatum/suspension

Study in Compliance with GLP: Yes

GSK Document Number: 2011N123167

Data Collected: clinical observations, body weight, and dermal irritation scores

Conclusion: GSK1278863A was applied to the intact and abraded skin of male New Zealand White rabbits for 24 hours at concentrations of 0% (vehicle), 0.5%, 1%, or 2%. GSK1278863 formulations caused no dermal irritation, and GSK1278863 is considered a non-irritant under the conditions of this study.

	Male			
Dose (%)[1]	**0**	**0.5**	**1**	**2**
Numbers of Animals:	3	3	3	3
Noteworthy Findings:				
Calculated Primary Irritation Index	0 (non-irritant)			

Key:
1 = Doses are expressed in terms of the parent compound.

7. REPEAT-DOSE TOXICITY: NONPIVOTAL STUDIES

Table 7.1 Repeat-Dose Toxicity: Nonpivotal Studies

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Studies with Daprodustat						
Mouse (CD-1)	Oral (gavage)	14 days	30, 100, 300	6M/6F[a]	Nine mice were either found dead or euthanized in poor clinical condition prior to the end of the study. Macroscopic and/or microscopic findings in 4 decedents, including 2 controls, were consistent with gavage error and the cause of death of 2 toxicokinetic mice could not be determined as a necropsy was not performed. One female given 100 mg/kg/day and 1 male and 1 female given 300 mg/kg/day were euthanized on Day 6 following body weight loss and observations of loss of skin elasticity and piloerection. Since the cause of moribund condition in these 3 mice could not be determined, the deaths were therefore considered test article-related. In-life findings in surviving mice included decreased body weight (transient in most mice) at ≥100 mg/kg/day and decreased activity, cold-to-touch, hunched posture and/or loss of skin elasticity at 300 mg/kg/day. Test article-related microscopic findings in surviving mice and/or in decedent mice related to daprodustat administration were observed in the spleen (minimal to moderate extramedullary hematopoiesis) and bone marrow (minimal to moderate erythroid hyperplasia) of mice given ≥30 mg/kg/day and were considered related to pharmacology. Lymphocytolysis/lymphoid depletion of the spleen and/or thymus was observed in surviving mice given ≥100 mg/kg/day and in several early decedents and was considered secondary to poor clinical condition.	CD2009/00900 (D09169)

Repeat-Dose Toxicity: Nonpivotal Studies (Continued)

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Rat (Sprague Dawley)	Oral (gavage)	14 days	10, 30, 60	4M[b]	Treatment with daprodustat produced adverse stomach erosions in rats given ≥30 mg/kg/day with secondary decreases in serum protein (60 mg/kg/day) and a systemic inflammatory response (≥30 mg/kg/day). Dose dependent, minimal to mild periportal hepatocellular vacuolation was observed in livers of rats administered doses ≥10 mg/kg/day. Alkaline phosphatase activity was increased in rats given ≥10 mg/kg/day, and triglycerides were increased in rats given ≥30 mg/kg/day. Platelets were mildly decreased at 60 mg/kg/day. Pharmacologically mediated increases in erythropoeisis were present in rats given ≥10 mg/kg/day.	RD2006/01192 (R41921)

Repeat-Dose Toxicity: Nonpivotal Studies (Continued)

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Rat (Sprague Dawley)	Oral (gavage)	14 days	100, 250, 500	4F[c]	Doses ≥250 mg/kg/day were not tolerated. Test article-related morbidity/mortality occurred in 4 of 7 rats given 500 mg/kg/day on Days 5 or 7 and in 1 of 7 rats given 250 mg/kg/day on Day 12. Deaths were associated with documented or presumed gastric and/or duodenal erosion/ulceration. The remaining rats given 500 mg/kg/day were euthanized on Day 8 due to declining clinical condition. Dehydration, fecal abnormalities and red fur staining were noted in rats given ≥250 mg/kg/day. Dose-responsive microscopic changes were seen in the stomach (mucosal erosion/ulceration, mural inflammation) of rats given ≥100 mg/kg/day and in the small and large intestine (villous/mucosal hyperplasia) and kidney (cortical tubular vacuolation) of rats given ≥250 mg/kg/day. Changes noted in the spleen (increased extramedullary hematopoiesis) at doses ≥250 mg/kg/day and bone marrow (hypercellularity) at 500 mg/kg/day as well as increases in reticulocytes and red blood cell parameters at doses ≥100 mg/kg/day were consistent with the pharmacologic activity of daprodustat. Increased mean alanine aminotransferase concentration was noted at 250 mg/kg/day and lacked a histologic correlate. Decreased mean lymphocyte counts and increased triglyceride and decreased glucose concentrations were noted at doses ≥100 mg/kg/day.	CD2008/01306 (D08114)

Repeat-Dose Toxicity: Nonpivotal Studies (Continued)

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Dog (beagle)	Oral (gavage or capsule)	3 days	90	2M/2F	Dogs dosed by oral gavage in a fed state vomited more than dogs dosed by capsule in a fasted state. Dogs dosed by capsule in a fasted state had more fecal changes (green and/or loose/watery) than dogs dosed by oral gavage in a fed state. There were no marked differences in mean AUC_{0-t} and C_{max} values between male and female dogs within each dosing regimen or in gender-averaged values between the capsule and oral gavage administration.	RD2007/01367 (D42209)
Dog (beagle)	Oral (gavage)	7 days	20, 60, 120	1M/1F	Daprodustat-related clinical observations included emesis (≥20 mg/kg/day), fecal alterations (≥60 mg/kg/day) and decreased food consumption and body weights (120 mg/kg/day). Pharmacologically-mediated increases in RBC count, hemoglobin, hematocrit and reticulocytes at ≥20 mg/kg/day were associated with secondary increases in platelet and/or leukocyte parameters in dogs given ≥60 mg/kg/day. Serum alkaline phosphatase was increased for the female given 120 mg/kg/day.	CD2007/00353 (D07078)
Minipig (Gottingen)	Dermal	14 days	0.5%, 1.0%, 2.0%	1M/1F	No noteworthy findings	2012N148386 (D12086)
Minipig (Göttingen)	Dermal	14 Days	10, 20 or 35% (w/w)	1M/1F	No noteworthy findings	2013N185591 (F70438N)

Repeat-Dose Toxicity: Nonpivotal Studies (Continued)

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Minipig (Gottingen)	Dermal	28 days	2, 10, 35% (w/w)	3M	All animals survived to their scheduled necropsy. There was no systemic toxicity based on clinical observations, body weight, food consumption and clinical pathology. Test article-related clinical or macroscopic findings of erythema and scabbing and microscopic findings of slight to mild epidermal exudates and superficial dermal edema were seen in the treated skin of minipigs given 35% (w/w) daprodustat.	2015N231048 (F70727N)
Monkey (cynomolgus)	Oral (gavage)	14 days	10, 30, 100	1M/1F	Decreased food consumption (up to Day 7), occasional vomiting, moderate post dose salivation and transient changes in fecal consistency were noted in monkeys given 100 mg/kg/day. Increased ALT concentration and decreased cholesterol concentration were also noted at 100 mg/kg/day. Pharmacologically-mediated increases in total red blood cell count, hemoglobin, hematocrit and red cell distribution width values were seen at ≥30 mg/kg/day with associated increases in reticulocytes noted in males given ≥30 mg/kg/day and females given ≥10 mg/kg/day.	CD2009/00780 (D09121)

Repeat-Dose Toxicity: Nonpivotal Studies (Continued)

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Studies with Metabolite						
Mouse (CD-1)	IV (bolus)	2 days	40, 80, 120, 200, 350, 400 (M13)	3M/3F	A maximum tolerated dose of between 200 and 350 mg/kg/day GSK2531401 (M13 metabolite of daprodustat) was determined in this study, following two intravenous doses given 24 hours apart to groups of 3 male and 3 female mice. Although there was no effect on %PCE at this dose level, increases in mean reticulocyte counts were observed at all dose levels assessed (40, 80, 120 and 200 mg/kg/day, reflected as an increase in the high fluorescence reticulocyte subpopulation absolute counts) indicating an increase in the rate of erythropoiesis.	2011N123943 (M29825)
Mouse (CD1)	SC	7 days	2.0 , 6.0 (M2); 2.5 , 7.5 (M3); 1.3 , 3.9 (M13)	3M	No test article-related effects were observed; therefore, under the conditions of this study, the test article formulations are considered nonirritating.	2013N169136 (M43081N)

Key:
a = Eighteen mice/sex were added at 30 mg/kg/day for toxicokinetic evaluation and an extra 10 mice/sex were added at 30 mg/kg for metabolite analysis (reported separately).
b = An additional 3 males/group were given 10, 30, or 60 mg/kg/day to provide samples for toxicokinetic evaluation.
c = 4 females/group for toxicology evaluations and 3 females/group for toxicokinetic evaluation (Days 1 and 14).
ALT = Alanine aminotransferase
IV = Intravenous.
RBC = Red blood cell.
SC = Subcutaneous.

8. REPEAT-DOSE TOXICITY: PIVOTAL STUDIES

Table 8.1 GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Mouse

Study Type: Repeat Dose Toxicity	**Report Title:** GSK1278863A: A 13-week Oral Gavage Toxicity Study in the Mouse	**Test Article:** GSK1278863A (parent compound) **Batch No.:** NE-021129-Batch 01-2009
Species/Strain: Crl:CD1 (ICR) mouse	**Duration of Dosing:** 13 weeks	**GSK Reference No.:** G10121
		Location in CTD: m4.2.3.2
Initial Age: Approximately 7 weeks	**Route/Frequency:** Oral by gavage, once daily	**GSK Document Number:** 2011N112096
Date of First Dose: 07 July 2010	**Vehicle/Formulation:** 1% Methylcellulose (400 cps) in ultra pure water	**Study in Compliance with GLP:** Yes

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

Conclusion: GSK1278863A (vehicle, 3, 30 and 60 mg/kg/day) was administered by daily oral gavage to male and female mice for 13 weeks. GSK1278863 at doses ≥30 mg/kg/day evoked pharmacologically-mediated increased hematopoiesis with associated increased red cell mass, reticulocytes, and red cell indices. Increased hematocrit resulted in poor peripheral perfusion and/or thrombosis in mice given ≥30 mg/kg/day which led to ischemic changes in heart (myocardial degeneration/necrosis, myocardial/perivascular fibrosis, vascular inflammation, valvular degeneration/inflammation and aortic arch degeneration) and kidney (unilateral renal necrosis and proliferative glomerulopathy); and generalized congestion. Deaths occurred at 60 mg/kg/day, attributable to the aforementioned changes. GSK1278863 at ≥30 mg/kg/day was also associated with nerve fiber degeneration in sciatic nerve, axonal degeneration in lumbar spinal cord and myofiber atrophy in hindlimb skeletal muscle.

Based on adverse effects confined to doses ≥30 mg/kg/day, the no observed adverse effect level (NOAEL) was 3 mg/kg/day (mean $AUC_{0\text{-}t}$ 181 μg.h/mL, range 151 to 211 μg.h/mL and mean C_{max} 14.5 μg/mL, range 12.3 to 16.7 μg/mL [gender-averaged based on Week 4 values]).

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10121

		Male				Female			
Daily Dose (mg/kg/day)		**0**	**3**	**30**	**60**	**0**	**3**	**30**	**60**
Numbers of Animals:	Main	12	12	12	12	12	12	12	12
	Toxicokinetic	6	42	42	42	6	42	42	42
	Metabolite Investigation[a]	0	0	21	0	0	0	21	0
AUC_{0-t} (μg.h/mL)	Day 1	NC	140	629	1002	NC	176	829	1229
	Week 4	NC	151	520	722	NC	211	817	943
C_{max} (μg/mL)	Day 1	NQ	11.5	62.9	78.2	NQ	11.1	63.9	94.8
	Week 4	NQ	12.3	46.0	52.0	NQ	16.7	55.3	68.9
Noteworthy Findings									
Unscheduled Deaths		-	-	-	2[b]	-	-	-	4[b]
Clinical Observations		Test article-related clinical signs included skin redness (at muzzle, forepaws, hindpaws, pinna and/or tail) in animals given ≥30 mg/kg/day, starting at Week 4 of treatment. Sporadic observations of red skin or blue skin were noted on the scrotum of few males given 60 mg/kg/day. Sporadic observations of blue skin (at mouth and/or muzzle) were noted for female given ≥30 mg/kg/day and males at 60 mg/kg/day. Slight to severe limited usage of the hindlimbs was noted for one female given 30 mg/kg/day and six females at 60 mg/kg/day. A single female given 60 mg/kg/day was noted with tremor on Day 56 and with non-sustained convulsion (muscular contraction followed by relaxation in rapid succession) on Days 64 and 70.							
Body Weight (X control)[c] – Week 13		44.88g	0.94X	0.96X	0.91X	31.36g	1.00X	1.06X	1.06X
Absolute Body Weight Gain from Week -1 to Week 13 (X control)[c]		12.57g	0.86X	0.84X	0.75X	7.19g	1.00X	1.21X	1.19X
Food Consumption (X control)[c]		Over the course of the study, statistically significant test article-related decreases in group mean food consumption were consistently noted in males given 60 mg/kg/day (weekly values decreased as much as 0.76X control).							

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10121

	Male				Female			
Daily Dose (mg/kg/day)	0	3	30	60	0	3	30	60
Ophthalmoscopy (Week 13) (Number of animals)	12	12	12	10	12	12	12	8
Choroid hyperemia, fundus increased redness (bilateral)	0	0	12	10	0	3	12	8
Retina vessels congestion (bilateral)	0	0	10	10	0	0	12	8
Hematology (Week 13)								
Total red blood cell count (10^{12}/L)	9.563	9.067	12.272***	13.282***	9.382	9.692	13.570***	14.600***
Hemoglobin (g/L)	140.0	138.0	208.7***	236.8***	137.7	152.5	242.8***	265.0***
Hematocrit (%)	45.38	44.33	66.60***	77.30***	44.83	48.13	78.00***	88.25***
Reticulocyte count (10^9/L)	220.15	286.80	360.72	849.08***	213.08	407.08	531.46*	603.40
Mean corpuscular hemoglobin (pg)	14.67	15.23	16.97***	17.86***	14.68	15.72**	17.92***	18.25***
Mean corpuscular volume (fL)	47.53	48.93	54.25***	58.22***	47.83	49.67	57.64***	60.30***
Red cell distribution width (%)	12.93	12.02	13.15	14.78**	12.17	12.10	14.30***	16.55***
Platelet count (10^9/L)	1445.2	1228.0	889.8***	649.4***	1301.2	1091.3	614.6***	622.5***
Lymphocyte counts (10^9/L)	2.482	3.230	5.152	5.124	4.823	5.493	6.578	7.575
Clinical Chemistry (Week 13)								
Total bilirubin (μmol/L)	1.8	2.5	5.3***	5.0	2.0	2.0	-	-
Urea (mmol/L)	7.05	7.83	7.98	8.44	6.33	6.62	6.30	7.78*
Creatinine (μmol/L)	18.0	18.0	21.0	27.0*	18.0	18.0	24.0*	-
Glucose (mmol/L)	11.05	10.45	8.57	8.05	11.37	9.42	8.15*	5.67***
Triglycerides (mmol/L)	1.687	1.828	2.473*	4.105***	0.918	1.277	2.045**	-

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10121

	Male				Female			
Daily Dose (mg/kg/day)	0	3	30	60	0	3	30	60
Organ Weights (X control)[c]								
Heart								
Absolute (g)	0.21589	1.00X	1.13X	1.15X	0.15802	1.03X	1.38X***	1.57X***
Relative (%; to body weight)	0.48767	1.07X	1.17X*	1.25X***	0.51889	1.03X	1.28X**	1.47X***
Kidney								
Absolute (g)	0.64644	0.94X	0.99X	0.90X	0.37344	1.01X	1.08X	1.27X***
Relative (%; to body weight)	1.46349	1.00X	1.02X	0.98X	1.22704	1.00X	1.00X	1.19X***
Liver								
Absolute (g)	2.0763	0.94X	1.02X	1.04X	1.3606	0.98X	1.19X**	1.33X***
Relative (%; to body weight)	4.67604	1.01X	1.07X	1.14X***	4.45249	0.98X	1.10X	1.25X***
Spleen								
Absolute (g)	0.10448	1.02X	1.74X**	3.11X***	0.11306	1.01X	2.69X***	3.15X***
Relative (%; to body weight)	0.23551	1.09X	1.82X**	3.41X***	0.36946	1.01X	2.51X***	2.95X***
Microscopic Examination (number of animals)	12	12	12	12	12	12	12	12
Abdomen								
Hemorrhage								
Moderate	0	0	0	1	0	0	0	0
Adrenal								
Hemorrhage								
Minimal	0	0	0	0	0	0	0	1
Aorta								
Hemorrhage								
Moderate	0	0	0	1	0	0	0	0
Thrombosis								
Marked	0	0	0	1	0	0	0	0

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10121

	Male				Female			
Daily Dose (mg/kg/day)	0	3	30	60	0	3	30	60
Blood Vessel								
Hemorrhage								
Minimal	0	0	0	1	0	0	0	0
Bone Marrow								
Hyperplasia: erythroid								
Minimal	0	0	1	2	0	2	9	0
Slight	0	0	0	6	0	0	3	5
Moderate	0	0	0	4	0	0	0	7
Brain								
Thrombosis								
Minimal	0	0	0	0	0	0	0	2
Whole body[d]								
Congestion								
Minimal	0	2	9	7	0	1	7	1
Slight	0	0	3	4	0	0	2	4
Moderate	0	0	0	1	0	0	0	4
Marked	0	0	0	0	0	0	0	3
Duodenum								
Thrombosis								
Minimal	0	0	0	0	0	0	0	1
Esophagus								
Hemorrhage								
Minimal	0	0	0	0	0	0	0	1
Ileum								
Hemorrhage								
Slight	0	0	0	0	0	0	0	1

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10121

	Male				Female			
Daily Dose (mg/kg/day)	0	3	30	60	0	3	30	60
Nasal Cavity/sinuses								
Degeneration: respiratory epithelium								
Minimal	0	0	0	2	0	0	0	0
Slight	0	0	0	1	0	0	1	0
Degeneration/regeneration: olfactory epithelium								
Minimal	0	0	1	2	0	0	1	2
Slight	0	1	2	2	0	0	0	4
Moderate	0	0	0	2	0	0	1	0
Exudate								
Minimal	0	0	1	1	0	0	1	0
Slight	0	0	0	1	0	0	0	0
Heart								
Fibrosis								
Minimal	0	0	1	0	0	0	0	2
Inflammation: vascular								
Minimal	0	0	0	1	0	0	1	0
Slight	0	0	0	1	0	0	0	0
Degeneration and/or necrosis: myocardial								
Slight	0	0	0	1	0	0	0	0
Degeneration/inflammation: valvular								
Minimal	0	0	1	0	0	0	0	0
Slight	0	0	0	1	0	0	0	0
Degeneration: aortic arch								
Minimal	0	0	0	0	0	0	1	0

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10121

	Male				Female			
Daily Dose (mg/kg/day)	0	3	30	60	0	3	30	60
Kidney								
Basophilia: tubular								
Minimal	3	2	2	8	3	1	9	5
Slight	0	0	0	0	1	0	0	1
Moderate	0	0	0	0	0	0	0	3
Glomerulopathy: proliferative[e]								
Minimal	0	0	1	9	0	0	8	5
Slight	0	0	0	1	0	0	1	1
Moderate	0	0	0	0	0	0	0	2
Marked	0	0	0	0	0	0	0	1
Cast: hyaline								
Minimal	0	0	0	6	2	0	8	5
Slight	0	0	0	0	0	0	1	4
Deposits pigment								
Minimal	0	0	0	2	0	1	8	6
Slight	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	0	0	1	0
Necrosis								
Marked	0	0	0	1	0	0	0	0
Severe	0	0	0	1	0	0	1	0
Hemorrhage								
Minimal	0	1	0	0	0	0	0	0
Moderate	0	0	0	1	0	0	0	0

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10121

	Male				Female			
Daily Dose (mg/kg/day)	0	3	30	60	0	3	30	60
Liver								
Deposits: pigments								
Minimal	0	0	4	7	0	0	8	3
Slight	0	0	1	4	0	0	4	6
Hematopoiesis: extramedullary								
Minimal	0	0	1	7	0	1	10	7
Slight	0	0	0	2	0	0	0	2
Thrombosis								
Slight	0	0	0	0	0	0	0	1
Lung								
Hemorrhage								
Minimal	0	0	0	0	0	2	0	0
Moderate	0	0	0	0	0	0	0	2
Lymph Node								
Hemorrhage								
Minimal	0	0	0	1	0	0	0	0
Muscle skeletal								
Atrophy: myofiber								
Minimal	0	0	0	0	0	0	0	8
Slight	0	0	0	0	0	0	1	0
Nerve sciatic								
Degeneration: nerve fiber								
Minimal	0	0	0	2	0	0	4	5
Slight	0	0	0	0	0	0	1	6

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10121

	Male				Female			
Daily Dose (mg/kg/day)	0	3	30	60	0	3	30	60
Pancreas								
Hemorrhage								
Minimal	0	0	0	1	0	0	0	0
Prostate								
Hemorrhage								
Minimal	0	1	4	1	-	-	-	-
Spinal cord lumbar								
Axonal Degeneration: root								
Minimal	0	0	0	2	0	0	4	1
Slight	0	0	0	1	0	0	2	6
Moderate	0	0	0	0	0	0	0	4
Spleen								
Hematopoiesis/extramedullary: increased								
Minimal	0	0	9	0	0	1	2	0
Slight	0	0	2	2	0	0	3	1
Moderate	0	0	1	9	0	0	6	6
Marked	0	0	0	1	0	0	1	5
Deposits: pigment								
Minimal	0	0	4	4	0	2	7	7
Slight	0	0	0	0	0	0	1	0
Thrombosis								
Minimal	0	0	0	0	0	0	0	1

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10121

	Male				Female			
Daily Dose (mg/kg/day)	0	3	30	60	0	3	30	60
Stomach								
Erosion/ulceration: glandular mucosa								
Minimal	0	0	0	0	0	0	0	3
Hemorrhage								
Minimal	0	0	0	0	0	0	1	1
Slight	0	0	0	0	0	0	0	1
Thymus								
Atrophy/necrosis: lymphoid								
Minimal	0	0	0	0	0	0	0	2
Slight	0	0	0	1	0	0	0	1
Marked	0	0	0	0	0	0	0	2
Hemorrhage								
Minimal	0	1	0	0	0	0	0	1

Key:

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

- No noteworthy findings / Not examined; NC = Not calculable; NQ = Not quantifiable (below limit of quantification).

a = Twenty one mice/sex were added to the 30 mg/kg/day group for metabolite investigations which were conducted by the Sponsor and reported separately.

b = There was a total of 6 deaths/moribundities (2 males and 4 females) during the course of the study, all in the 60 mg/kg/day group of which five (1 male and 4 females) were considered test article-related and were considered secondary to congestion, hemorrhage and/or thrombosis seen in miscellaneous organs as a result of pharmacology-mediated increased hematopoiesis and increased hematocrit. The other male given 60 mg/kg/day was euthanized due to poor clinical condition (labored breathing) related to nasal cavity epithelium effects secondary to reflux of the test material and/or stomach contents during withdrawal of the catheter tube. Therefore, it was not considered a direct effect of the test article. Preterminal animals presented similar microscopic changes to terminally euthanized animals; therefore, microscopic findings for these animals are presented along with the Week 13 findings.

c = For controls, group means are shown; for treated groups, X change as compared to controls. Statistical significance is based on actual data not change.

d = The term “whole body” is used as a synonym for the term “carcass” used in the tables and appendices of the study report.

e = Glomerulopathy occurred in the presence of thrombosis in 3 females given 60 mg/kg/day.

Table 8.2 GSK1278863A + Metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: A 13-Week Oral Gavage and Subcutaneous Injection Toxicity Study in the Mouse

Study Type: Repeat Dose Toxicity	**Report Title:** GSK1278863A + metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: A 13-Week Oral Gavage and Subcutaneous Injection Toxicity Study in the Mouse	**Test Item:** GSK1278863A + metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13) **Batch (Lot) No.:** GSK1278863A: 132377077 GSK2391220A (M2): H11454-120-1A GSK2506104A (M3): H12118-099-1C GSK2531401A (M13): H11451-114-A1
Species/Strain: Mouse Crl:CD1 (ICR)	**Duration of Dosing:** 13 Weeks	**GSK Reference No.:** M70456G
Initial Age: 7-8 weeks at dosing onset	**Route/Frequency:** GSK1278863: Oral by gavage, once daily Metabolite cocktail (M2+M3+M13): subcutaneous, once daily given immediately following oral dose of GSK1278863	**GSK Document Number:** 2014N199031 **Location in CTD:** m4.2.3.2
Date of First Dose: 06 February 2014	**Vehicle/Formulation:** Oral Formulation: 1% (w/v) Methylcellulose (400 cP at 2%) in Ultra Pure Water; Metabolite cocktail: aqueous 25 mM phosphate buffer, pH 7.4 (±0.2)	**Study in Compliance with GLP:** Yes

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

Conclusion: GSK1278863A (parent compound) was given to mice (12/sex/group) at 0 (vehicle), 6, or 20 mg/kg/day once daily by oral gavage followed immediately by daily subcutaneous injection of a metabolite cocktail containing three major circulating human metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13) at 2, 2.5 and 1.3 mg/kg/day, respectively] for 13 weeks. There were two mortalities during the course of this study which were considered related to complications from the oral gavage procedure and unrelated to the test items. GSK1278863 at doses ≥6 mg/kg/day [given with the metabolites] was associated with pharmacologically-mediated increased hematopoiesis with associated increased red cell mass, reticulocytes, and red cell indices. Increased hematocrit resulted in poor peripheral perfusion in mice given ≥6 mg/kg/day which led to generalized congestion and pigment accumulation in kidney and liver, consistent with increased red blood cell turnover. Axonal degeneration in sciatic nerve and nerve roots of the lumbar spinal cord (cauda equina) were also seen at ≥6 mg/kg/day.

GSK1278863A + Metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: A 13-Week Oral Gavage and Subcutaneous Injection Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity				**GSK Reference No.:** M70456G		
Daily Doses (mg/kg/day)		**Male**			**Female**	
Oral Dose of GSK1278863	0	6	20	0	6	20
Subcutaneous Doses of Metabolite Cocktail[a]						
GSK2391220A (M2)	0	2.0	2.0	0	2.0	2.0
GSK2506104A (M3)	0	2.5	2.5	0	2.5	2.5
GSK2531401A (M13)	0	1.3	1.3	0	1.3	1.3
Numbers of Animals:						
Main	12	12	12	12	12	12
Toxicokinetic	6	48	48	6	48	48
GSK1278863						
$AUC_{(0-t)}$ (μg.h/mL)						
Day 1	NC	260	422	NC	291	628
Week 4	NC	274	525	NC	464	897
C_{max} (μg/mL)						
Day 1	NQ[b]	15.8	31.8	NQ[b]	17.2	37.4
Week 4	NQ	19.3	38.4	NQ[b]	30.4	59.5
GSK2391220						
AUC(0-t) (μg.h/mL)						
Day 1	NC	1.21	1.15	NC	1.11	1.37
Week 4	NC	1.27	1.23	NC	1.50	1.65
Cmax (μg/mL)						
Day 1	NQ[c]	2.71	2.48	NQ[c]	2.58	3.82
Week 4	NQ	2.22	1.79	NQ	3.02	2.95
GSK2506104						
AUC(0-t) (μg.h/mL)						
Day 1	NC	1.49	1.42	NC	1.22	1.50
Week 4	NC	1.60	1.58	NC	1.69	1.90
Cmax (μg/mL)						
Day 1	NQ[c]	3.30	3.01	NQ[c]	2.96	4.50
Week 4	NQ	2.76	2.34	NQ	3.48	3.51

GSK1278863A + Metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: A 13-Week Oral Gavage and Subcutaneous Injection Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity				**GSK Reference No.:** M70456G		
Daily Doses (mg/kg/day)		**Male**			**Female**	
Oral Dose of GSK1278863	0	6	20	0	6	20
Subcutaneous Doses of Metabolite Cocktail[a]						
GSK2391220A (M2)	0	2.0	2.0	0	2.0	2.0
GSK2506104A (M3)	0	2.5	2.5	0	2.5	2.5
GSK2531401A (M13)	0	1.3	1.3	0	1.3	1.3
GSK2531401						
$AUC_{(0\text{-}t)}$ (μg.h/mL)						
Day 1	NC	1.07	1.05	NC	0.371	0.539
Week 4	NC	1.16	1.18	NC	1.19	1.33
C_{max} (μg/mL)						
Day 1	NQ[c]	2.08	1.99	NQ	0.672	0.762
Week 4	NQ	1.72	1.48	NQ	2.32	2.23
Noteworthy Findings						
Unscheduled Deaths						
Main	0	0	0	0	0	1[d]
Toxicokinetic	0	0	0	0	1[d]	0
Clinical Observations	Dose–dependent skin reddening at the extremities (forelimb, hindlimb, pinna, tail, muzzle and/or at the dorsal thoracic region) were observed. In mice given 6 mg/kg/day, the observations began as early as Week 4 and at an earlier onset at 20 mg/kg/day, i.e. Week 1, and progressed in both dose groups until the last dosing occasion for some individuals. Increased respiratory rate was noted on numerous occasions for some animals given 20 mg/kg/day, often accompanied with shallow breathing. Discolored (purple) skin was noted on the muzzle of one male and in six females given 20 mg/kg/day from Week 9 to the end of the dosing period.					
Ophthalmoscopy (Week 13)	At the end of the dosing period, dose-related ocular findings (retinal vessel congestion and choroidal hyperemia) were noted. As such ocular observations are often noted in the presence of polycythemia and were noted in previous rodent studies with GSK1278863, these ocular changes were considered to be secondary to the high red blood cell count.					
(number of animals)	12	12	12	12	12	11[f]
Retina Vessels Congestion, bilateral	0	4	12	0	10	11
Chorodal Hyperemia (Red Fundus Appearance), bilateral	0	2	12	0	9	11

GSK1278863A + Metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: A 13-Week Oral Gavage and Subcutaneous Injection Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity				**GSK Reference No.:** M70456G		
Daily Doses (mg/kg/day)	**Male**			**Female**		
Oral Dose of GSK1278863	0	6	20	0	6	20
Subcutaneous Doses of Metabolite Cocktail[a]						
GSK2391220A (M2)	0	2.0	2.0	0	2.0	2.0
GSK2506104A (M3)	0	2.5	2.5	0	2.5	2.5
GSK2531401A (M13)	0	1.3	1.3	0	1.3	1.3
Hematology (Groups Means; Week 13)						
Total red blood cell count (10^{12}/L)	8.613	11.107††	13.279†††	8.737	13.388††	14.554†††
Hemoglobin (g/L)	131.8	179.6††	227.6†††	136.4	223.6†††	257.8†††
Hematocrit (%)	42.34	58.31††	75.95†††	42.06	72.71††	83.30†††
Reticulocyte count (10^9/L)	295.56	412.25†	569.70††	226.68	549.06***	577.62***
Mean corpuscular hemoglobin (pg)	15.33	16.17*	17.13***	15.65	16.71*	17.72***
Mean corpuscular volume (fL)	49.15	52.45*	57.01***	48.11	54.28***	57.23***
Red cell distribution width (%)	12.49	13.19	14.59†††	12.14	13.34**	14.41***
Platelet count (10^9/L)	1157.3	944.3*	557.4***	1059.1	582.3††	328.1†††
Clinical Chemistry (Groups Means; Week 13)						
Glucose (mmol/L)	13.102	10.908	9.868*	11.547	8.781**	7.733**
Creatinine (μmol/L)	9.8	12.6	16.2†	11.7	14.4	18.0

GSK1278863A + Metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: A 13-Week Oral Gavage and Subcutaneous Injection Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity				**GSK Reference No.:** M70456G		
Daily Doses (mg/kg/day)	**Male**			**Female**		
Oral Dose of GSK1278863	0	6	20	0	6	20
Subcutaneous Doses of Metabolite Cocktail[a]						
GSK2391220A (M2)	0	2.0	2.0	0	2.0	2.0
GSK2506104A (M3)	0	2.5	2.5	0	2.5	2.5
GSK2531401A (M13)	0	1.3	1.3	0	1.3	1.3
Organ Weights (Xcontrol)[e]						
Spleen						
Absolute (g)	0.1028	1.27X †	2.32X †††	0.1195	1.74X ††	2.66X ††
Relative to body weight (%)	0.2288	1.36X †	2.42X †††	0.3573	1.81X ††	2.67X †††
Heart						
Absolute (g)	0.2298	1.00X	1.13X **	0.1673	1.04X	1.25X †††
Relative to body weight (%)	0.5148	1.06X	1.16X **	0.5002	1.08X	1.27X ***
Thymus						
Absolute (g)	0.0271	0.90X	0.81X	0.0392	0.85X	0.89X
Relative to body weight (%)	0.0605	0.97X	0.82X	0.1155	0.90X	0.92X

GSK1278863A + Metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: A 13-Week Oral Gavage and Subcutaneous Injection Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** M70456G

Daily Doses (mg/kg/day)	**Male**			**Female**		
Oral Dose of GSK1278863	0	6	20	0	6	20
Subcutaneous Doses of Metabolite Cocktail[a]						
GSK2391220A (M2)	0	2.0	2.0	0	2.0	2.0
GSK2506104A (M3)	0	2.5	2.5	0	2.5	2.5
GSK2531401A (M13)	0	1.3	1.3	0	1.3	1.3
Macroscopic Examination						
(number of animals)	12	12	12	12	12	12[g]
Dark Discoloration of the Entire Carcass[h]	0	0	2	0	4	9
Microscopic Examination						
(number of animals)	12	12	12	12	12	12[g]
Spinal cord, lumbar						
Degeneration; axonal; cauda equina						
Minimal	0	0	2	0	2	6[g]
Nerve, Sciatic						
Degeneration; axonal						
Minimal	0	0	1	0	0	4
Thymus						
Atrophy; lymphoid						
Minimal	2	3	2	3	1	4
Mild	0	1	5	0	0	1
Moderate	0	0	0	0	1	1[g]
Bone marrow, sternum						
Increased erythropoiesis						
Minimal	0	10	5	0	11	4[g]
Mild	0	0	7	0	0	7
Increased erythropoiesis; red pulp						
Minimal	0	9	4	0	3	1
Mild	0	2	7	0	7	5[g]
Moderate	0	0	1	0	0	6

GSK1278863A + Metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: A 13-Week Oral Gavage and Subcutaneous Injection Toxicity Study in the Mouse (Continued)

Study Type: Repeat Dose Toxicity				**GSK Reference No.:** M70456G		
Daily Doses (mg/kg/day)		**Male**			**Female**	
Oral Dose of GSK1278863	0	6	20	0	6	20
Subcutaneous Doses of Metabolite Cocktaia						
GSK2391220A (M2)	0	2.0	2.0	0	2.0	2.0
GSK2506104A (M3)	0	2.5	2.5	0	2.5	2.5
GSK2531401A (M13)	0	1.3	1.3	0	1.3	1.3
Liver						
Accumulation; pigment, kupffer cell						
Minimal	0	0	4	0	6	8
Mild	0	0	1	0	0	2
Increased hematopoieisis						
Minimal	0	0	0	0	0	2
Kidney						
Pigmentation; epithelial, tubular						
Minimal	0	0	0	0	0	2

GSK1278863A + Metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: A 13-Week Oral Gavage and Subcutaneous Injection Toxicity Study in the Mouse (Continued)

Key:

* p < 0.05, ** p < 0.01, *** p < 0.001 (Dunnet); † p < 0.05, †† p < 0.01, ††† p < 0.001 (Dunn)

NC = Not Calculable; NQ = Not Quantifiable (below limit of quantification)

a = The metabolite cocktail contained 3 major circulating human metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)] formulated together in 0.5% sodium chloride with aqueous 25 mM phosphate buffer, pH 7.4 (+/- 0.2) and administered subcutaneously as soon as feasible after the oral dose of the parent compound

b = GSK1278863 was quantifiable in 3 out of 12 plasma samples collected from control animals. The quantifiable concentrations (confirmed by repeat analysis) were 10.8, 103 and 11.2 ng/mL, respectively, for male mouse 1018 on Day 1, female mouse 1517 on Day 1 and female mouse 1513 on Week 4. The lower limit of quantification (LLQ) of the analytical method was 10 ng/mL for GSK1278863.

c = In all 12 samples collected from vehicle control (0 mg/kg/day) mice, the plasma concentrations of GSK2391220 (M2), GSK2506104 (M3) and GSK2531401 (M13) were below the LLQ (0.200 ng/mL) of the analytical method with the exception of two mice 1018 and 1517 with the result of NR (not reportable) due to insufficient volume of sample for repeat analysis.

d = One 6 mg/kg/day toxicokinetic female (No. 2528) was euthanized on Day 23 in moribund condition and one 20 mg/kg/day main study female (No. 3506) was found dead on Day 74. Based upon the macroscopic findings, complications stemming from the oral gavage procedure were considered the likely cause of morbidity/death in both cases; therefore, neither was considered test item-related.

e = For controls group means are shown, for treated groups X change as compared to controls. Statistical significance is based on actual data not change from control values.

f = Excludes female (No. 3506) which died prior to Week 13 ophthalmology exams.

g = Includes decedent female (No. 3506).

h = In addition, dark discoloration and/or dark foci were noted in various organs (pituitary, kidney, liver, lung, skeletal muscle, pancreas, stomach, urinary bladder, uterus, and vagina) of individual males and/or females given ≥6 mg/kg/day. These tinctorial changes were considered related to pharmacology-related physiologic congestion in many of these tissues/organs, as there were no microscopic correlates.

Table 8.3 GSK1278863A: 4 Week Oral Toxicity Study in Male and Female Rats

Study Type: Repeat Dose Toxicity

Report Title: GSK1278863A: 4 Week Oral Toxicity Study in Male and Female Rats

Test Article: GSK1278863A (parent compound)
Batch No.: NE-021129-Batch-01-2007

Species/Strain: Rat/Crl:CD(SD)

Duration of Dosing: Up to 28/29 days

Study No.: R42197

Initial Age: 11 weeks

Route/Frequency: Oral by gavage, once daily

GSK Document Number: RD2007/01333

Location in CTD: m4.2.3.2

Date of First Dose: 1 November 2007

Vehicle/Formulation: 1% methylcellulose in reverse osmosis-treated water

Study in Compliance with GLP: Yes

Data Collected: Toxicokinetics, clinical observations, body weight, food consumption, ophthalmoscopy, hematology, coagulation, clinical chemistry, urinalysis, organ weights, macroscopic and microscopic pathology (including stage-dependent evaluation of spermatogenesis).

Conclusion: The oral administration of GSK1278863A to male and female rats for 28/29 days produced stomach erosions and ulcers at doses of 7 and 20 mg/kg/day. Pharmacologically-mediated enhanced erythropoiesis was reflected by increased erythroid parameters in the peripheral blood of rats given 7 and 20 mg/kg/day and by erythroid hyperplasia in the bone marrow and increased extramedullary hematopoiesis in the spleen in rats at all dose levels. Based upon the presence of the stomach erosions/ulcers, the no observed adverse effect level is 2 mg/kg/day (mean $AUC_{0\text{-}t}$ 449 μg h/mL, range 350 to 648 μg h/mL; mean C_{max} 28.9 μg/mL, range 23.1 to 37.1 μg/mL [gender-averaged based on Day 28 values]).

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**2**	**7**	**20**	**0**	**2**	**7**	**20**
Numbers of Animals:	Main	10	10	10	10	10	10	10	10
	Toxicokinetic	3	3	3	3	3	3	3	3
$AUC_{0\text{-}24}$ (μg.h/mL):	Day 1	NQ	191	572	1450	NQ	231	525	1300
	Day 28	NQ	403	1197	1726	NQ	495	1086	1900
C_{max} (μg/mL):	Day 1	NA	12.7	34.8	94.7	NA	16.8	38.1	90.4
	Day 28	NA	26.5	75.1	96.0	NA	31.3	69.7	110

GSK1278863A: 4 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** R42197

	Male				Female			
Daily Dose (mg/kg/day)[1]	**0**	**2**	**7**	**20**	**0**	**2**	**7**	**20**
Noteworthy Findings:								
Unscheduled Deaths:	0	0	0	0	0	1[2]	0	0
Hematology:								
Hematocrit (L/L)	0.473	0.484	0.497	0.654**	0.443	0.450	0.491**	0.637**
Hemoglobin (g/L)	168.4	172.3	173.8	230.0**	160.0	159.9	173.7**	226.1**
Red blood cell count (x10E12/L)	8.516	8.698	8.849	10.734**	7.931	8.011	8.579**	10.536**
Mean cell volume (fL)	55.56	55.48	56.22	60.81**	55.64	56.11	57.17*	60.44**
Mean cell hemoglobin (pg)	19.81	19.86	19.62	21.41**	20.23	19.94	20.24	21.46**
Red cell distribution width (%)	11.45	11.65	11.73	13.71**	11.25	11.20	11.40	12.72**
Reticulocytes (x10E9/L)	201.91	200.75	219.47	422.72**	209.12	216.16	208.53	344.25**
Platelets (x10E9/L)	1218.9	1256.2	1250.6	909.0**	1273.3	1206.6	1233.9	785.9**
Neutrophils (x10E9/L)	1.198	1.347	1.419	1.837**	0.740	0.931	1.069	0.977
Monocytes (x10E9/L)	0.212	0.215	0.201	0.293*	0.172	0.141	0.238	0.216
Basophils (x10E9/L)	0.028	0.036	0.030	0.076**	0.018	0.019	0.021	0.048**
Clinical Chemistry:								
Total iron binding capacity (μmol/L)	99.4	109.9*	128.7**	132.3**	110.9	109.4	124.6*	120.7*
Unsaturated iron binding capacity (μmol/L)	61.4	70.1	73.9	81.3*	51.5	56.4	58.1	65.7*
Total bilirubin (μmol/L)	2.81	2.71	2.54	3.25*	3.24	2.88	2.90	3.02
Globulin (g/L)	29.1	28.9	28.2	27.0*	31.1	29.4*	28.4**	26.4**
Total protein (g/L)	60.9	60.9	60.1	58.9	66.7	64.7	63.1**	60.5**
Cholesterol (mmol/L)	1.531	1.352	1.113**	1.061**	2.080	1.872	1.407**	1.034**
Triglycerides (mmol/L)	0.543	0.553	0.875*	2.305**	0.637	0.439	0.537	0.797
Alanine aminotransferase (U/L)	25.9	28.2	34.9**	34.3**	32.5	23.1	26.5	25.0
Alkaline phosphatase (U/L)	123.1	115.1	127.8	158.6*	74.4	81.4	78.1	88.9
Glutamate dehydrogenase (U/L)	7.62	8.50	16.11**	14.24**	21.24	7.74	10.66	10.62
Globulin (g/L)	29.1	28.9	28.2	27.0*	31.1	29.4*	28.4**	26.4**

GSK1278863A: 4 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** R42197

	Male				Female			
Daily Dose (mg/kg/day)[1]	**0**	**2**	**7**	**20**	**0**	**2**	**7**	**20**
Organ Weights[3]:								
Spleen Absolute (g)	0.7633 g	1.06X	0.96X	1.10X	0.5138 g	1.11X	1.10X	1.16X*
Relative (% body weight)	0.179	0.186	0.171	0.190	0.199	0.218	0.218	0.233*
Macroscopic Examination (Number of Animals):	**10**	**10**	**10**	**10**	**10**	**9**	**10**	**10**
Stomach - Glandular Region								
Red area	1	0	2	9	0	1	2	7
White area	0	0	0	4	0	0	0	1
Depressed area	0	0	0	0	0	0	0	1
Microscopic Examination (Number of Animals):	**10**	**10**	**10**	**10**	**10**	**9**	**10**	**10**
Stomach								
Erosion/ulcer; glandular region; focal								
Minimal	0	0	0	0	1	0	0	1
Mild	1	0	0	2	0	0	2	0
Moderate	0	0	0	1	0	1	0	2
Erosion/ulcer; glandular region; multifocal								
Mild	0	0	0	0	0	0	0	1
Moderate	0	0	0	4	0	0	0	3
Marked	0	0	0	2	0	0	0	0
Hemorrhage; glandular region; focal								
Minimal	0	0	1	0	0	0	0	0
Hemorrhage; glandular region; multifocal								
Minimal	0	0	1	1	0	0	0	0
Mild	0	0	0	5	0	0	0	3
Edema; submucosal; diffuse								
Minimal	0	0	1	0	0	0	0	1
Mild	0	0	0	4	0	0	1	3

GSK1278863A: 4 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** R42197

	Male				Female			
Daily Dose (mg/kg/day)[1]	**0**	**2**	**7**	**20**	**0**	**2**	**7**	**20**
Microscopic Examination (Continued) (Number of Animals):	**10**	**10**	**10**	**10**	**10**	**9**	**10**	**10**
Stomach (Continued)								
Inflammation; suppurative; glandular region Minimal	0	0	0	0	0	0	0	1
Mild	0	0	0	2	0	0	1	3
Inflammatory cell infiltrate; eosinophilic; submucosa Moderate	0	0	0	0	0	0	0	1
Liver								
Hepatocellular vacuolation, periportal Minimal	5	2	4	6	3	2	6	6
Mild	0	0	0	3	0	0	0	2
Spleen								
Extramedullary hematopoiesis; increased Minimal	1	3	7	2	0	4	6	4
Mild	0	0	1	7	0	0	1	3
Moderate	0	0	0	1	0	0	0	0
Bone Marrow, Femur								
Hyperplasia, erythroid Minimal	0	10	10	6	0	8	7	7
Mild	0	0	0	3	0	0	3	2
Bone Marrow, Sternum								
Hyperplasia, erythroid Minimal	0	10	10	2	0	8	6	4
Mild	0	0	0	8	0	0	4	6

GSK1278863A: 4 Week Oral Toxicity Study in Male and Female Rats (Continued)

Key: * = p<0.05. ** = p<0.01. NA = Not applicable. NQ = Not quantifiable.

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

2 = One 2 mg/kg/day female, Animal #39, was euthanized on Day 20 for humane reasons due to a physical, non-treatment-related injury sustained on Day 17.

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

Table 8.4 GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats

Study Type: Repeat Dose Toxicity	**Report Title:** GSK1278863: 13 Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by a 4 Week Recovery Period	**Test Article:** GSK1278863A (parent compound) **Batch No.:** NE-021129-BATCH-01-2009
Species/Strain: Rat Crl:CD®(SD)	**Duration of Dosing:** 13 weeks **Duration of Recovery:** 4 weeks	**GSK Reference No.:** G09057
Initial Age: 7 weeks	**Route/Frequency:** Oral by gavage, once daily	**GSK Document Number:** CD2009/00951 **Location in CTD:** m4.2.3.2
Date of First Dose: 14 April 2009	**Vehicle/Formulation:** 1% aqueous methylcellulose	**Study in Compliance with GLP:** Yes

Data Collected: Clinical observations; body weights; food consumption measurements; water consumption (visual assessment); haematology, coagulation, clinical chemistry and urinalysis; ophthalmoscopic observations; organ weights; and macroscopic and microscopic observations. Toxicokinetic evaluation was performed on samples collected on Day 1 and in Weeks 4 and 13, samples were also taken pre-treatment and at T_{max} from all surviving Group 5 (100 mg/kg/day) animals prior to their termination in Week 9.

Conclusion: GSK1278863 (vehicle, 0.8, 4, 20, 100 mg/kg/day) was given orally to male and female rats once daily for up to 13 weeks. Morbidity and mortality resulted in the early termination of the 100 mg/kg/day group during Week 9. Polycythemia attributed to pharmacologically-mediated increased haemopoiesis in bone marrow, spleen and/or liver resulted in adverse effects in the heart (valvulopathy, atrial thrombus, valvular thrombus, endocardial hyperplasia and cardiomyopathy), lung (chronic passive congestion), kidney (infarct, thrombus, cortical tubular pigment and tubular basophilia), brain (focal degeneration of neuropil, consistent with ischaemia) and stomach (glandular erosion/ulceration, submucosal inflammatory cell infiltrate, haemorrhage and vascular medial hypertrophy) in rats given ≥20 mg/kg/day. Following a 4 week recovery period, test article-related changes in body weight, food consumption, and hematology and clinical chemistry parameters were generally reversible. Microscopically, haemopoiesis was evident in spleen and bone marrow, and test article-related findings were still present in the heart, kidney and stomach of rats previously given 20 or 100 mg/kg/day. Based on the absence of adverse test article-related findings, the no observed adverse effect level (NOAEL) was 4 mg/kg/day (mean AUC_{0-t} 654 μg.h/mL, mean C_{max} 52.1 μg/mL [gender-averaged based on Week 13 values]).

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

		Male					Female				
Daily Dose (mg/kg/day)[a]		**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Numbers of Animals:	Main	15	15	15	15	15	15	15	15	15	15
	Recovery	5	-	-	5	5	5	-	-	5	5
	Toxicokinetic	3	3	3	3	3	3	3	3	3	3
AUC_{0-24} (μg.h/mL):	Day 1	-	101	495	1480	2450	-	103	379	1620	2900
	Week 4	-	170	567	1370	2200	-	159	734	1780	2780
	Week 13	-	152	606	1040	-	-	167	701	2140	-
C_{max} (μg/mL):	Day 1	-	5.95	29.3	83	128	-	6.37	27.8	92.2	134
	Week 4	-	11.8	42.4	98	122	-	10.9	59.1	105	150
	Week 13	-	12.0	48.9	102	-	-	11.4	55.2	138	-
Noteworthy Findings:											
Unscheduled Deaths:											
Main study animals		1	0	0	2	11	0	0	0	0	5
Toxicokinetic animals		0	0	0	0	1	0	0	0	0	0
Decedent Findings:		Clinical signs of reaction to treatment were largely confined to moribund animals given 100 mg/kg/day that were subsequently killed on Day 60 (Week 9). These signs generally included hunched posture, thin appearance, sluggish appearance, abnormal respiration and piloerection. Reddening of the extremities was seen during Week 9 in a few animals given 100 mg/kg/day prior to their termination on Day 60. Other signs seen in one or two animals given 100 mg/kg/day included pale body, semi-closed eyelids, red discharge from nose/mouth, prostration and convulsive episode.									
Decedent Histopathology:											
Heart (No. Examined):		**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Cardiomyopathy	Minimal	1	0	0	1	4	0	0	0	0	3
	Slight	0	0	0	1	2	0	0	0	0	0
	Moderate	0	0	0	0	1	0	0	0	0	0
Valvulopathy	Minimal	0	0	0	0	2	0	0	0	0	0
	Slight	0	0	0	0	5	0	0	0	0	4
	Moderate	0	0	0	2	2	0	0	0	0	1

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

		Male					Female				
Daily Dose (mg/kg/day)[a]		**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Heart - continued (No. Examined):		**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Endocardial hyperplasia	Minimal	0	0	0	0	4	0	0	0	0	0
	Slight	0	0	0	0	2	0	0	0	0	1
Valvular thrombus	Present	0	0	0	2	8	0	0	0	0	5
Atrial thrombus	Present	0	0	0	1	2	0	0	0	0	0
Kidney (No. Examined):		**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Infarction	Slight	0	0	0	0	1	0	0	0	0	0
	Moderately severe	0	0	0	1	0	0	0	0	0	0
	Severe	0	0	0	1	0	0	0	0	0	0
Thrombus	Present	0	0	0	1	0	0	0	0	0	0
Pigment	Minimal	0	0	0	1	3	0	0	0	0	2
	Slight	0	0	0	0	2	0	0	0	0	0
	Moderate	0	0	0	0	1	0	0	0	0	0
Congestion	Present	0	0	0	1	6	0	0	0	0	2
Basophilic tubules	Moderate	0	0	0	0	1	0	0	0	0	0
Lung (No. Examined):		**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Congestion	Present	1	0	0	2	1	0	0	0	0	5
Chronic passive congestion	Slight	0	0	0	0	4	0	0	0	0	0
	Moderate	0	0	0	0	1	0	0	0	0	0
	Moderately severe	0	0	0	0	1	0	0	0	0	0
Brain (No. Examined):		**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Focal degeneration of neuropil	Minimal	0	0	0	0	1	0	0	0	0	0
	Slight	0	0	0	0	1	0	0	0	0	0
Congestion	Present	0	0	0	0	0	0	0	0	0	1
Mandibular Lymph Node (No. Examined):		**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Atrophy	Minimal	0	0	0	0	1	0	0	0	0	0
Congestion	Present	0	0	0	1	5	0	0	0	0	2

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

	Male					Female				
Daily Dose (mg/kg/day)[a]	**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Stomach (No. Examined):	**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Glandular stomach erosion/ulcer										
Minimal	0	0	0	0	3	0	0	0	0	1
Slight	0	0	0	1	2	0	0	0	0	0
Submucosal inflammatory cell infiltrate										
Minimal	0	0	0	0	7	0	0	0	0	3
Slight	0	0	0	1	1	0	0	0	0	0
Congestion/haemorrhage Minimal	0	0	0	1	2	0	0	0	0	4
Slight	0	0	0	0	1	0	0	0	0	0
Vascular medial hypertrophy Minimal	0	0	0	0	0	0	0	0	0	1
Femur and Marrow (No. Examined):	**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Increased haemopoiesis Minimal	0	0	0	2	7	0	0	0	0	3
Slight	0	0	0	0	1	0	0	0	0	1
Moderate	0	0	0	0	1	0	0	0	0	0
Sternum and Marrow (No. Examined):	**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Increased haemopoiesis Minimal	0	0	0	2	8	0	0	0	0	4
Moderate	0	0	0	0	1	0	0	0	0	0
Liver (No. Examined):	**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Haemopoiesis Slight	0	0	0	0	3	0	0	0	0	2
Congestion Present	1	0	0	2	3	0	0	0	0	3
Spleen (No. Examined):	**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Haemopoiesis Minimal	1	0	0	0	2	0	0	0	0	1
Slight	0	0	0	0	3	0	0	0	0	1
Moderate	0	0	0	1	5	0	0	0	0	2
Moderately severe	0	0	0	1	0	0	0	0	0	1
Severe	0	0	0	0	1	0	0	0	0	0

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

		Male					Female				
Daily Dose (mg/kg/day)[a]		**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Spleen – continued (No. Examined):		**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Congestion	Slight	0	0	0	0	1	0	0	0	0	0
	Moderate	0	0	0	0	0	0	0	0	0	1
	Moderately severe	0	0	0	0	1	0	0	0	0	0
Ileum (No. Examined):		**1**	**0**	**0**	**1**	**11**	**0**	**0**	**0**	**0**	**5**
Inflammation	Moderate	0	0	0	0	0	0	0	0	0	1
Erosion/ulcer	Slight	0	0	0	0	1	0	0	0	0	0
	Moderate	0	0	0	0	1	0	0	0	0	0
Congestion	Present	0	0	0	0	1	0	0	0	0	4
Caecum (No. Examined):		**0**	**0**	**0**	**0**	**10**	**0**	**0**	**0**	**0**	**5**
Inflammation	Minimal	0	0	0	0	1	0	0	0	0	0
	Moderately severe	0	0	0	0	0	0	0	0	0	1
Erosion/ulcer	Moderate	0	0	0	0	2	0	0	0	0	0
	Moderately severe	0	0	0	0	1	0	0	0	0	0
Congestion	Present	0	0	0	0	3	0	0	0	0	4
Mesenteric Lymph Node (No. Examined):		**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Congestion	Present	0	0	0	1	5	0	0	0	0	1
Duodenum (No. Examined):		**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Congestion	Present	0	0	0	0	1	0	0	0	0	1
Jejunum (No. Examined):		**1**	**0**	**0**	**1**	**10**	**0**	**0**	**0**	**0**	**4**
Congestion	Present	0	0	0	0	0	0	0	0	0	2
Adrenal (No. Examined):		**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Congestion	Present	0	0	0	1	3	0	0	0	0	3
Thymus (No. Examined):		**1**	**0**	**0**	**2**	**11**	**0**	**0**	**0**	**0**	**5**
Congestion	Present	1	0	0	2	2	0	0	0	0	3

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G09057

	Male					Female				
Daily Dose (mg/kg/day)[a]	**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Clinical Observations:	Post dose observations of reddening of the extremities were observed during Week 7 in a few animals given 20 mg/kg/day and in the majority of these animals from Week 9 of treatment. Reddening of the extremities was observed shortly after dosing and generally persisted for up to 4 hours post dose. Hyperactivity was observed shortly after dosing from Week 4 in several GSK1278863-treated animals. Salivation, mouth rubbing and associated limb paddling were seen shortly after dosing from Week 1 or 2 in several animals given 20 mg/kg/day or above and may be associated with the taste of the formulations.									
Body Weight (X Control[b]):										
Start to Week 4	113.7 g	1X	1.1X	1.1X	0.53X***	57.0 g	1.1X	1.1X	1.2X	1X
Start to Week 8	183.8 g	1X	1.1X	1.1X	0.65X***	92.7 g	0.98X	1.1X	1.1X	1X
Weeks 8 to 13[c]	44.0 g	0.8X	0.8X	0.9X	1.8X***	11.2 g	1.1X	1.3X	1.6X*	1.3X
Weeks 13 to 17 (recovery)	9.9 g	-	-	2X	-	9.3 g	-	-	0.2X	-
Food Consumption (X Control[b]):										
Weeks 1 to 4	187.8 g	1X	1X	1X	0.79X***	127.7 g	1X	1X	1.1X	0.9X
Weeks 1 to 8	189.9 g	1X	1X	1X	0.79X***	133.8 g	1X	1X	1X	0.9X
Weeks 9 to 13[c]	192.3 g	1X	1X	0.9X	1.1X	132.3 g	1X	1X	1X	1.1X
Haematology:										
Haemoglobin Concentration (g/dL)										
Week 4	16.3	16.3	16.5	21.9***	20.2**	15.9	15.8	16.4*	21.8***	22.0***
Week 9	-	-	-	-	20.4	-	-	-	-	22.3
Week 13 (recovery Group 5)	16.1	16.2	16.5	24.0***	15.5	14.8	14.7	15.3	22.7***	14.8
Week 17 (recovery)	15.6	-	-	17.9**	-	14.9	-	-	15.3	-
Red Blood Cell Count (10^{12}/L)										
Week 4	8.53	8.54	8.34	10.31***	10.66***	8.35	8.33	8.61	10.78***	11.02***
Week 9	-	-	-	-	13.20	-	-	-	-	12.31
Week 13 (recovery Group 5)	9.52	9.57	9.42	12.42***	9.96	8.01	7.96	8.32	11.29***	8.20
Week 17 (recovery)	9.54	-	-	9.53	-	8.17	-	-	8.13	-

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

	Male					Female				
Daily Dose (mg/kg/day)[a]	**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Packed Cell Volume (%)										
Week 4	47.0	46.7	47.5	64.2***	61.4***	45.6	45.8	47.5	64.0***	65.5***
Week 9	-	-	-	-	64.3	-	-	-	-	65.6
Week 13 (recovery Group 5)	48.0	48.1	49.2	72.3***	48.0	44.0	43.6	45.1	65.1***	42.8
Week 17 (recovery)	48.0	-	-	51.6	-	44.6	-	-	44.2	-
Reticulocyte Count (10^9/L)										
Week 4	218.2	207.4	235.3	505.4***	564.9***	213.1	186.1	183.3	348.6***	543.8***
Week 9	-	-	-	-	780.8	-	-	-	-	588.6
Week 13 (recovery Group 5)	219.5	198.2	212.7	447.5***	145.9	213.2	211.5	209.5	294.2***	134.7*
Week 17 (recovery)	211.1	-	-	63.6***	-	140.4	-	-	99.7	-
Mean Cell Volume (fL)										
Week 4	55.1	54.8	56.9*	62.4***	58.1	54.6	55.0	55.2	59.4***	59.9*
Week 9	-	-	-	-	49.0	-	-	-	-	53.8
Week 13 (recovery Group 5)	50.5	50.4	52.2	58.3***	48.5	55.0	54.9	54.2	57.8*	52.5
Week 17 (recovery)	50.4	-	-	54.2**	-	54.6	-	-	54.4	-
Mean Cell Haemoglobin (pg)										
Week 4	19.1	19.1	19.8*	21.3***	19.0	19.1	19.0	19.1	20.3***	20.1
Week 9	-	-	-	-	15.6	-	-	-	-	18.3
Week 13 (recovery Group 5)	16.9	17.0	17.5	19.4***	15.6**	18.5	18.5	18.4	20.1***	18.1
Week 17 (recovery)	16.3	-	-	18.8***	-	18.2	-	-	18.8	-
Red Cell Distribution Width (%)										
Week 4	12.4	12.1	12.4	15.1***	20.8***	11.3	11.2	11.0	13.7***	18.7***
Week 9	-	-	-	-	22.8	-	-	-	-	19.4
Week 13 (recovery Group 5)	13.8	13.6	13.3	15.5***	19.3***	13.0	12.8	12.5	13.2	15.8***
Week 17 (recovery)	14.4	-	-	12.8***	-	12.3	-	-	11.5	-

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

	Male					Female				
Daily Dose (mg/kg/day)[a]	**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Platelet Count (10^9/L)										
Week 4	884	883	854	552**	715	1100	1151	1084	481***	546*
Week 9	-	-	-	-	650	-	-	-	-	461
Week 13 (recovery Group 5)	900	872	823	197***	902	1209	1149	1035	672***	1099
Week 17 (recovery)	1037	-	-	939	-	1042	-	-	1044	-
White Blood Cell Count (10^9/L)										
Week 4	13.7	11.7	12.6	9.8***	9.3***	11.3	10.3	8.4**	7.1***	8.3*
Week 9	-	-	-	-	10.7	-	-	-	-	8.6
Week 13 (recovery Group 5)	13.5	11.0	12.3	10.1*	14.8	9.7	7.5	6.0***	5.9***	11.1
Week 17 (recovery)	11.9	-	-	15.5	-	6.5	-	-	8.1	-
Lymphocyte Count (10^9/L)										
Week 4	11.3	9.8	10.4	7.5***	5.0***	9.7	8.7	6.9**	5.7***	5.9***
Week 9	-	-	-	-	6.6	-	-	-	-	6.2
Week 13 (recovery Group 5)	11.1	9.0	9.8	7.4***	12.8	8.0	6.2*	4.8***	4.5***	8.1
Week 17 (recovery)	9.4	-	-	11.9	-	5.5	-	-	6.5	-
Clinical Chemistry - Week 4										
Aspartate Aminotransferase (IU/L)										
Week 4	92	90	88	101*	174***	89	86	87	103	125**
Week 9	-	-	-	-	155	-	-	-	-	173
Week 13 (recovery Group 5)	117	82	87	123	86	84	84	83	107**	81
Week 17 (recovery)	91	-	-	75*	-	108	-	-	87**	-
Alanine Aminotransferase (IU/L)										
Week 4	51	53	49	46*	98***	53	54	54	53	67
Week 9	-	-	-	-	78	-	-	-	-	67
Week 13 (recovery Group 5)	67	48	48	48	39	50	44	47	45	41
Week 17 (recovery)	50	-	-	43	-	49	-	-	43	-

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

	Male					Female				
Daily Dose (mg/kg/day)[a]	**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Alkaline Phosphatase (IU/L)										
Week 4	180	169	189	251**	228**	124	103	120	177***	169*
Week 9	-	-	-	-	176	-	-	-	-	135
Week 13 (recovery Group 5)	102	92	99	111	102	59	49	53	83**	60
Week 17 (recovery)	74	-	-	63	-	44	-	-	37	-
Total Cholesterol (mmol/L)										
Week 4	1.9	1.7	1.5**	1.3***	3.0***	2.0	2.1	1.9	1.7*	3.3***
Week 9	-	-	-	-	3.3	-	-	-	-	3.1
Week 13 (recovery Group 5)	2.0	1.7*	1.4***	1.3***	2.0	1.9	2.1	1.7	1.5*	2.2
Week 17 (recovery)	1.8	-	-	2.3	-	2.2	-	-	1.7	-
Urea (mmol/L)										
Week 4	4.7	4.8	4.1	4.9	6.9***	6.8	6.9	6.9	6.1	6.3
Week 9	-	-	-	-	4.2	-	-	-	-	4.8
Week 13 (recovery Group 5)	5.3	5.9	5.2	6.4*	5.8	7.0	6.8	6.6	7.2	8.5*
Week 17 (recovery)	5.8	-	-	6.3	-	6.6	-	-	5.7	-
Triglycerides (mmol/L)										
Week 4	0.75	0.70	0.86	2.77	10.01	0.83	0.80	0.67	2.88	10.81
Week 9	-	-	-	-	9.23	-	-	-	-	9.83
Week 13 (recovery Group 5)	1.27	0.98	1.58	2.44***	1.07	1.17	1.20	0.95	3.03*	0.65*
Week 17 (recovery)	1.16	-	-	1.38	-	1.01	-	-	0.81	-
Glutamate Dehydrogenase (IU/L)										
Week 4	6.4	6.3	6.9	10.6***	27.5***	6.9	6.2	12.4	16.8*	30.9***
Week 9	-	-	-	-	12.2	-	-	-	-	28.3
Week 13 (recovery Group 5)	6.6	9.4	11.3	9.3	4.5	6.8	10.6	11.1	8.6	4.5
Week 17 (recovery)	10.4	-	-	7.2	-	20.9	-	-	5.2	-

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

	Male					Female				
Daily Dose (mg/kg/day)[a]	**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Iron (umol/L)										
Week 4	50.6	53.6	50.9	37.3	13.5***	63.3	60.9	78.2	67.8	21.3**
Week 9	-	-	-	-	24.7	-	-	-	-	30.4
Week 13 (recovery Group 5)	41.1	48.2	61.3	42.0	54.1	57.0	59.9	73.1	68.4	78.8
Week 17 (recovery)	41.7	-	-	76.3***	-	80.9	-	-	81.8	-
Unsaturated Iron Binding Capacity (umol/L)										
Week 4	32.0	38.0	55.4	79.1	89.6	43.0	41.7	32.9	58.0	89.6
Week 9	-	-	-	-	81.3	-	-	-	-	81.3
Week 13 (Recovery Group 5)	61.9	54.9	64.5	78.3	32.2	57.5	54.2	41.5	52.1	9.6
Week 17 (Recovery)	57.8	-	-	4.3***	-	21.4	-	-	12.5	-
Organ Weights[d] (X Control):										
Terminal Necropsy										
Number of Animals:	**14**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Kidney	2.556 g	0.99X	0.95X	1.13X*	1.06X	1.506	1.01X	1.02X	1.11X***	1.14X***
Spleen	0.183%	0.91X	0.91X	1.33X**	1.19	0.213%	0.97X	0.94X	1.12X	1.28X***
Thymus	0.307 g	1.03X	1.04X	0.95X	1.08X	0.275 g	1.01X	0.88X	0.95X	1.32X***
Heart	0.306%	1.02X	0.95X	1.08X	1.29X**	0.966 g	1.02X	1.01X	1.02X	1.25X***
Recovery Necropsy										
Number of Animals:	**5**	**0**	**0**	**5**	**5**	**5**	**0**	**0**	**5**	**5**
Spleen	0.727 g	-	-	1.31X*	1.35X*	0.554 g	-	-	1.30X*	1.29X*
Thymus	0.056%	-	-	1.02X	1.48X*	0.210 g	-	-	1.06X	1.62X**

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

		Male					Female				
Daily Dose (mg/kg/day)[a]		**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Macroscopic Examination: Terminal Necropsy											
Number of Animals:		**14**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Heart	Large	0	0	0	3	0	0	0	0	0	0
	Firm	0	0	0	5	0	0	0	0	2	0
Lung	Dark	0	0	0	0	0	0	0	0	0	1
	Dark area	0	0	0	0	1	0	0	0	0	0
	Red area	0	0	0	0	1	0	0	0	0	0
	Pale area	0	0	0	0	1	0	0	0	0	0
Kidney	Dark	0	0	0	5	1	0	0	0	0	2
	Large	0	0	1	3	0	0	0	0	0	0
	Irregular surface	0	0	0	2	0	0	0	0	0	0
	Depressed area	0	1	0	1	1	1	0	0	1	0
	Depressed focus	0	0	0	0	0	0	0	0	0	1
Stomach	Dark focus	0	0	0	1	0	0	0	0	3	0
	Red focus	0	0	0	1	0	0	0	0	0	2
	Dark area	0	0	0	4	0	0	0	0	0	2
	Thick	0	0	0	3	2	0	0	0	0	7
	Irregular surface	0	0	0	1	4	0	0	0	0	9
	Depressed area	0	0	0	1	0	0	0	0	0	2
	Depressed focus	0	0	0	0	0	0	0	0	2	0
	Raised area	0	0	0	1	0	0	0	0	3	1
	Dark contents	0	0	0	3	2	0	0	0	0	5
Spleen	Large	0	0	0	3	0	0	0	0	0	0
Adrenals	Large	0	0	0	0	0	0	0	0	1	1
Liver	Mottled	0	1	7	5	2	0	0	0	1	5
	Large	0	0	0	1	0	0	0	0	0	0
	Pale	0	0	1	0	2	0	1	1	0	5
Cranial Cavity	Abnormal contents	0	0	0	3	0	0	0	0	0	0

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

		Male					Female				
Daily Dose (mg/kg/day)[a]		**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Whole Animal	Dark	0	0	0	4	0	0	0	0	3	0
	Red	0	0	0	3	3	0	0	0	6	4
Blood	Thick	0	0	0	4	0	0	0	0	0	0
	Dark	0	0	0	5	0	0	0	0	2	0
Pancreas	Dark	0	0	0	1	2	0	0	0	0	3
Mesenteric Lymph Nodes	Dark	0	0	0	0	0	0	0	0	0	1
Jejunum	Dark	0	0	0	1	0	0	0	0	0	0
Ileum	Dark	0	0	0	1	0	0	0	0	0	0
Caecum	Dark	0	0	0	1	0	0	0	0	0	0
Ovary	Dark	0	0	0	0	0	0	0	0	0	1
Thymus	Dark	0	0	0	1	0	0	0	0	1	3
Recovery Necropsy Number of Animals:		**5**	**0**	**0**	**5**	**5**	**5**	**0**	**0**	**5**	**5**
Spleen	Mottled	0	0	0	1	0	0	0	0	0	0
	Dark focus	0	0	0	1	0	0	0	0	0	0
Thymus	Red	0	0	0	1	0	0	0	0	0	0
Microscopic Examination: Terminal Necropsy: Heart (No. Examined):		**14**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Valvulopathy	Minimal	0	0	0	1	0	0	0	0	1	0
	Slight	0	0	0	3	0	0	0	0	0	0
	Moderate	0	0	0	1	0	0	0	0	0	0
Valvular thrombus	Present	0	0	0	4	0	0	0	0	0	0
Atrial thrombus	Present	0	0	0	1	0	0	0	0	0	1
Cardiomyopathy	Minimal	1	2	2	4	2	3	2	0	2	1
	Slight	0	0	0	0	1	0	0	0	0	0
Lungs (No. Examined):		**13**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Congestion	Present	0	0	1	0	0	2	0	0	2	4
Chronic passive congestion	Minimal	0	0	0	0	0	0	0	0	0	1

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

		Male					Female				
Daily Dose (mg/kg/day)[a]		**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Kidneys (No. Examined):		**14**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Infarct	Moderately severe	0	0	0	1	0	0	0	0	0	0
Pigment	Minimal	0	1	0	2	0	0	0	1	0	0
	Slight	0	0	0	1	0	0	0	0	0	1
	Moderate	0	0	0	1	0	0	0	0	0	0
Congestion	Present	1	0	0	6	2	0	0	0	0	4
Brain (No. Examined):		**14**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Focal degeneration of neuropil	Minimal	0	0	0	0	0	0	0	0	0	1
	Slight	0	0	0	1	0	0	0	0	0	0
Stomach (No. Examined):		**14**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Glandular erosion/ulceration	Minimal	0	0	0	4	1	0	0	0	5	4
	Slight	0	0	0	4	2	0	0	0	2	4
Submucosal inflammatory cell infiltrate											
	Minimal	2	2	0	10	4	0	0	0	9	7
	Slight	0	0	0	2	0	0	0	0	2	2
Congestion/haemorrhage	Minimal	0	0	0	8	3	0	0	0	3	5
	Slight	0	0	0	1	0	0	0	0	0	1
	Moderate	0	0	0	0	0	0	0	0	0	1
Vascular medial hypertrophy	Minimal	0	0	0	5	0	0	0	0	6	4
Femur (No. Examined):		**14**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Increased haemopoiesis	Minimal	3	0	0	13	3	1	0	1	8	10
Sternum with Marrow (No. Examined):		**14**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Increased haemopoiesis	Minimal	3	0	0	13	3	1	0	0	8	10
Spleen (No. Examined):		**14**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Increased haemopoiesis	Minimal	13	15	13	6	1	8	9	7	12	5
	Slight	1	0	0	6	3	7	5	7	1	4
	Moderate	0	0	0	1	0	0	1	0	0	0
	Moderately severe	0	0	0	0	0	0	0	0	0	1

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

		Male					Female				
Daily Dose (mg/kg/day)[a]		**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Adrenal (No. Examined):		**14**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Congestion	Present	0	0	0	0	1	0	0	0	1	3
Thymus (No. Examined):		**14**	**15**	**15**	**13**	**4**	**15**	**15**	**15**	**15**	**10**
Congestion	Present	0	0	0	3	0	1	0	1	3	6
Microscopic Examination:											
Recovery Necropsy:											
Heart (No. Examined):		**5**	**0**	**0**	**5**	**5**	**5**	**0**	**0**	**5**	**5**
Cardiomyopathy	Minimal	0	0	0	2	0	0	0	0	1	0
	Slight	0	0	0	0	1	0	0	0	0	0
Valvulopathy	Minimal	0	0	0	1	1	0	0	0	0	0
	Slight	0	0	0	0	0	0	0	0	0	2
Endocardial hyperplasia	Minimal	0	0	0	0	1	0	0	0	0	0
Valvular thrombus	Present	0	0	0	0	0	0	0	0	0	2
Atrial thrombus	Present	0	0	0	0	1	0	0	0	0	0
Kidney (No. Examined):		**5**	**0**	**0**	**5**	**5**	**5**	**0**	**0**	**5**	**5**
Focal nephropathy	Minimal	0	0	0	3	3	0	0	0	1	2
	Slight	0	0	0	1	0	0	0	0	0	0
Pigment	Minimal	0	0	0	2	1	0	0	0	3	1
	Slight	0	0	0	1	0	0	0	0	0	2
Cortical scar	Slight	0	0	0	0	1	0	0	0	0	1
Stomach (No. Examined):		**5**	**0**	**0**	**5**	**5**	**5**	**0**	**0**	**5**	**5**
Vascular medial hypertrophy	Minimal	0	0	0	1	0	0	0	0	0	0
Submucosal inflammatory cell infiltrate											
	Minimal	0	0	0	0	1	0	0	0	0	2
Femur (No. Examined):		**5**	**0**	**0**	**5**	**5**	**5**	**0**	**0**	**5**	**5**
Increased haemopoiesis	Minimal	0	0	0	2	1	0	0	0	1	1
Sternum and Marrow (No. Examined):		**5**	**0**	**0**	**5**	**5**	**4**	**0**	**0**	**5**	**5**
Increased haemopoiesis	Minimal	0	0	0	2	0	0	0	0	0	1

GSK1278863A: 13 Week Oral Toxicity Study in Male and Female Rats (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09057

		Male					Female				
Daily Dose (mg/kg/day)[a]		**0**	**0.8**	**4**	**20**	**100**	**0**	**0.8**	**4**	**20**	**100**
Spleen (No. Examined):		**5**	**0**	**0**	**5**	**5**	**5**	**0**	**0**	**5**	**5**
Haemopoiesis	Minimal	5	0	0	2	5	4	0	0	4	1
	Moderate	0	0	0	0	0	0	0	0	0	1
Pigment	Minimal	1	0	0	0	3	1	0	0	0	1
	Slight	3	0	0	2	2	4	0	0	2	3
	Moderate	0	0	0	3	0	0	0	0	3	1
Mineralisation	Minimal	0	0	0	2	0	0	0	0	0	0
Adrenal (No. Examined):		**5**	**0**	**0**	**5**	**5**	**5**	**0**	**0**	**5**	**5**
Cortical hypertrophy	Minimal	0	0	0	0	0	0	0	0	0	1
Thymus (No. Examined):		**5**	**0**	**0**	**5**	**5**	**5**	**0**	**0**	**5**	**5**
Congestion	Present	0	0	0	1	0	0	0	0	0	0

Key:

a = Doses expressed in terms of parent compound.

b = For controls, group means are presented. For test article-treated groups, change from control is shown. Statistical significance is based on actual data not change from control.

c = Group 5 were not dosed from Day 60 (Week 9).

d = For controls, group means are shown for organ weights adjusted to body weight or organ to body weight ratios. For test article-treated groups, change from control is shown. Statistical significance is based on actual data not change from control.

- = Not examined.

Statistical significance = * = p<0.05. ** = p<0.01. *** = p<0.001.

Table 8.5 GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat

Study Type: Repeat Dose Toxicity	**Report Title:** GSK1278863A: A 26-week Oral (Gavage) Toxicity Study in the Rat	**Test Article:** GSK1278863A (parent compound) **Batch No.:** NE-021129-Batch-01-2009
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** 26 weeks	**GSK Reference No.:** G10276
Initial Age: Approximately 7 weeks	**Route/Frequency:** Oral by gavage, once daily	**GSK Document Number:** 2011N126130 **Location in CTD:** m4.2.3.2
Date of First Dose: 01 February 2011	**Vehicle/Formulation:** 1% (w/v) Methylcellulose (400 cps) in ultra pure water	**Study in Compliance with GLP:** Yes

Data Collected: Toxicokinetics, clinical observations, body weight, food consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, serum cardiac troponin I, organ weights, macroscopic and microscopic pathology

Conclusion: GSK1278863A (vehicle, 0.8, 4 and 10 mg/kg/day as parent compound), was administered daily by oral gavage to male and females rats for up to 26 weeks. A dose of 10 mg/kg/day was associated with pharmacology-related increased erythroid hyperplasia in the bone marrow and increased splenic and liver extramedullary hematopoiesis, correlating with increases in red blood cell mass. Increased hematocrit resulted in adverse vascular lesions/thrombosis and secondary changes including hemorrhages and infarction affecting many tissues. These aforementioned changes contributed to deaths of males at 10 mg/kg/day and resulted in the early termination of surviving males in this dose group by Week 20. Additionally, gastric erosions were noted in males and females given 10 mg/kg/day. At 4 mg/kg/day, increases in circulating red cell mass parameters were of a lower magnitude than seen at 10 mg/kg/day and lacked any evidence of thrombotic events.

Since adverse thrombotic events and gastric erosions were limited to rats given 10 mg/kg/day, the no observed adverse effect level (NOAEL) was considered to be 4 mg/kg/day (mean $AUC_{(0\text{-}t)}$ 785 μg.h/mL, range 522 to 1118 and mean C_{max} 46.8 μg /mL, range 31.8 to 69.9 [gender averaged, based on Week 26 values]).

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10276

		Male				Female			
Daily Dose (mg/kg/day)		**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Numbers of Animals:	Main	12	12	12	12	12	12	12	12
	Toxicokinetic[a]	3	3	3	9	3	3	3	9
AUC_{0-t} (μg.h/mL)	Week 4	NC	173	639	941	NC	179	707	1034
	Week 13	NC	197	636	807	NC	258	857	1233
	Week 26	NC	208	607	NA[b]	NC	259	964	1377
C_{max} (μg/mL)	Week 4	NA	10.0	37.7	49.5	NA	11.0	40.9	58.5
	Week 13	NA	13.1	41.0	45.1	NA	15.3	50.8	71.4
	Week 26	NA	13.3	38.4	NA[b]	NA	15.7	55.3	75.0
Noteworthy Findings: Unscheduled Deaths[b]									
	Main	0	0	0	7	0	1	0	0
	Toxicokinetic	0	0	0	4	0	0	0	0
Clinical Observations		Skin reddening in rats given 10 mg/kg/day began as early as Week 6 in males and Week 7 in females and progressed until most individuals at that dose were affected by Week 12. Skin reddening also occurred in males given 4 or 0.8 mg/kg/day, starting at Weeks 10 and 11, respectively. A single female given 4 mg/kg/day (No. 3503) was also noted with transient red skin (both pinna and hindpaws) between Weeks 21 and 25. Other test article-related clinical signs were limited to severely affected males given 10 mg/kg/day that were either found dead or euthanized early. Clinical signs in these rats included a few instances of tremors, limited usage of limbs, abnormal gait and/or uncoordination and other findings reflecting their poor clinical condition (i.e., decreased activity, decreased muscle tone, suspected dehydration, hunched posture, erect/ungroomed fur, red liquid discharge from muzzle, thin, weak, prominent backbone, irregular breathing rate, breathing shallow, blue skin on the tail, and cold to touch).							

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10276

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Skin Red								
Number of observations	3	80	151	142	4	2	5	127
Number of animals Affected	1	10	12	12	1	1	1	10
Days from - to -	66 - 80	59 - 183	38 - 183	38 – 135[b]	164 – 183	164 – 171	143 – 171	45 – 183
Body Weight	Test article-related mean body weight effects were limited to decreased mean body weight gain for males given 10 mg/kg/day which was noticeable from approximately Week 10 until their early termination in Week 20.							
Absolute Body Weight Gain[c] (X control)								
Week 10 to 19 (Day 70 to 133)								
	110.8 g	1.14X	1.06X	0.74X	29.7 g	1.26X	1.25X	1.03X
Food Consumption	Test article-related food consumption effects were limited to high dose males given 10 mg/kg/day which was generally sporadic throughout the first seven weeks of the study but was consistently reduced (to 0.80X concurrent control values) from Week 8 onward until their early termination in Week 20.							
Ophthalmoscopy	There were no treatment-related ocular changes observed at Week 13, evidence of retinal vessel congestion was noted at Week 25 in five out of twelve female rats given 10 mg/kg/day							
Hematology								
Red blood cell counts (10^{12}/L)								
Week 4	8.353	8.666	8.485	9.688***	8.432	8.291	8.317	9.835***
Week 13	9.668	10.173	10.362	13.660***	9.043	8.848	9.369	12.610***
Week 26/27	9.295	9.883*	10.243***	NA[b]	8.357	8.509	8.577	10.753***
Hemoglobin (g/L)								
Week 4	160.3	164.3	167.9*	201.9***	160.9	159.0	159.6	193.4***
Week 13	167.8	170.0	181.8**	249.0***	159.3	156.4	163.2	231.8***
Week 26/27	166.2	173.3	190.8***	NA[b]	159.0	161.0	162.7	212.4***
Hematocrit (%)								
Week 4	48.63	50.26	50.32	60.52***	46.68	46.28	46.18	57.35***
Week 13	52.65	53.77	55.95	75.31***	48.15	47.13	48.70	68.84***
Week 26/27	49.48	52.06	56.43***	NA[b]	45.93	46.68	46.83	60.88***

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10276

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Red blood cell distribution width (%)								
Week 4	12.45	12.24	11.81*	13.45***	10.80	10.82	10.78	12.08***
Week 13	13.38	13.11	12.70	14.30*	11.88	11.71	11.69	12.73***
Week 26/27	13.59	13.58	12.84	NA[b]	11.67	11.55	11.88	12.73**
Reticulocyte counts (10^9/L)								
Week 4	379.17	360.98	352.81	560.62**	248.09	228.76	212.45	451.56**
Week 13	306.21	289.83	313.24	527.05***	264.85	247.65	222.85*	392.03***
Week 26/27	257.96	273.61	252.66	NA[b]	201.07	188.98	223.17	344.66**
Platelets counts (10^9/L)								
Week 4	1236.8	1219.2	1219.3	1028.1	1187.5	1294.8	1135.6	1040.0
Week 13	1150.6	1137.3	1019.5	597.8***	1190.8	1186.1	1022.6	912.5*
Week 26/27	1138.8	1076.9	942.3**	NA[b]	1032.6	1054.1	904.6	731.9***
Neutrophil counts (10^9/L)								
Week 4	1.343	1.894	1.242	2.172	1.303	1.204	1.071	1.128
Week 13	1.405	1.563	1.400	2.234*	0.861	0.883	0.940	1.134
Week 26/27	1.505	1.839	1.432	NA[b]	0.749	0.863	0.868	1.474
Lymphocyte counts (10^9/L)								
Week 4	11.468	10.600	9.287	9.467	7.793	6.553	6.808	5.746
Week 13	10.374	8.944	7.986	7.369*	5.342	4.088	4.938	4.468
Week 26/27	8.890	8.138	6.499*	NA[b]	3.667	4.784	3.498	4.066
Clinical Chemistry								
Cholesterol (mmol/L)								
Week 4	2.159	2.264	1.959	1.411***	2.408	2.265	2.314	1.874
Week 13	2.506	2.331	1.502***	1.425**	2.475	2.384	2.265	1.809*
Week 26/27	2.748	2.385	1.574***	NA[b]	2.911	2.930	2.329	2.019**
Triglyceride (mmol/L)								
Week 4	1.094	1.390	1.661	2.337***	0.688	0.758	1.057*	1.163*
Week 13	1.848	2.548*	2.717*	5.600***	1.302	1.122	1.926	2.257
Week 26/27	2.648	3.424	2.918	NA[b]	2.027	1.831	2.364	3.322*

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10276

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Glucose (mmol/L)								
Week 4	6.62	6.49	6.63	4.98***	5.66	5.94	6.55*	5.82
Week 13	7.03	6.33	5.79**	5.20	6.04	6.14	5.98	5.07***
Week 26/27	7.12	7.18	5.66*	NA[b]	6.12	5.91	6.20	5.61
Urea (mmol/L)								
Week 4	4.07	4.57	4.58	5.18	5.43	5.48	5.25	4.32
Week 13	4.77	5.11	4.56	5.22	6.22	5.58	5.01	5.00**
Week 26/27	4.43	4.78	4.33	NA[b]	5.51	5.15	4.81*	4.75*
Total protein (g/L)								
Week 4	65.3	66.4	66.8	65.8	69.4	72.3	72.2	71.6
Week 13	72.1	73.1	71.5	71.0	82.4	81.7	79.8	76.9*
Week 26/27	72.1	71.7	70.9	NA[b]	82.5	85.5	80.6	78.0
Albumin (g/L)								
Week 4	45.6	45.1	46.4	45.6	49.0	51.6	53.1**	52.5*
Week 13	45.3	45.6	46.6	47.0	57.9	57.9	56.6	54.2
Week 26/27	44.3	44.3	47.1**	NA[b]	59.1	61.1	58.0	54.9**
Calcium (mmol/L)								
Week 4	2.817	2.797	2.798	2.683***	2.786	2.739	2.755	2.739
Week 13	2.715	2.688	2.670	2.640	2.778	2.688	2.703	2.627**
Week 26/27	2.704	2.660	2.636	NA[b]	2.800	2.801	2.725	2.698
Potassium (mmol/L)								
Week 4	6.725	6.028	5.990	5.457***	5.892	5.390*	5.307*	4.988***
Week 13	6.157	6.033	5.279***	5.536	5.008	5.280	4.367**	4.473*
Week 26/27	5.501	5.529	5.331	NA[b]	4.576	4.480	4.208	4.558
Total iron (μg/dL)								
Week 4	279.1	247.2	346.4	351.1	303.1	294.8	369.9	379.7
Week 13	245.4	239.9	333.7***	452.0***	352.4	405.1	501.3**	344.0
Week 26/27	234.2	216.1	314.8*	NA[b]	397.3	491.1	544.9**	438.1

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10276

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Unsaturated iron binding capacity (μg/dL)								
Week 4	243.9	319.1	324.5	424.3***	157.9	207.2	197.8	264.3
Week 13	352.1	467.7**	419.8	340.0	181.4	160.2	142.4	299.9
Week 26/27	425.8	606.9*	532.8	NA[b]	160.4	123.1	132.4	330.3
Total iron binding capacity (μg/dL)								
Week 4	524.4	566.3	670.8***	775.3***	461.0	502.0	567.7***	644.0***
Week 13	597.5	707.6***	753.5***	792.0*	533.8	565.3	643.8***	649.4***
Week 26/27	660.0	823.0*	847.5***	NA[b]	557.7	614.2	677.3**	768.3***
Microscopic Examination: Main Study (number of animals)	12	12	12	12	12	12	12	12
Adrenal								
Thrombosis								
Minimal	0	0	0	2	0	0	0	0
Hemorrhage								
Slight	0	0	0	1	0	0	0	0
Moderate	0	0	0	3	0	0	0	0
Inflammation: vascular								
Minimal	0	0	0	1	0	0	0	0
Necrosis								
Minimal	0	0	0	1	0	0	0	0
Slight	0	0	0	1	0	0	0	0
Marked	0	0	0	1	0	0	0	0
Hypertrophy: cortical								
Minimal	0	0	0	1	0	0	0	0
Slight	0	0	0	5	0	0	0	0
Blood vessel								
Hemorrhage								
Moderate	0	0	0	1	0	0	0	0

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10276

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Bone – femur								
Ectopic tissue								
Minimal	0	0	0	1	0	0	0	0
Bone marrow								
Hyperplasia: erythroid								
Minimal	0	0	0	4	0	0	0	1
Slight	0	0	0	5	0	0	0	0
Thrombosis								
Moderate	0	0	0	1	0	0	0	0
Brain								
Thrombosis								
Minimal	0	0	0	1	0	0	0	1
Slight	0	0	0	3	0	0	0	0
Necrosis								
Moderate	0	0	0	1	0	0	0	0
Cecum								
Inflammation: vascular								
Minimal	0	0	0	1	0	0	0	0
Duodenum								
Inflammation: acute								
Slight	0	0	0	1	0	0	0	0
Hemorrhage								
Moderate	0	0	0	1	0	0	0	0
Eye								
Thrombosis								
Minimal	0	0	0	1	0	0	0	0
Fat								
Hemorrhage								
Slight	0	0	0	1	0	0	0	0

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10276

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Heart								
Hemorrhage								
Minimal	0	0	1	2	0	0	0	0
Slight	0	0	1	2	0	0	0	0
Infiltration: mixed cell								
Minimal	5	4	4	3	0	0	1	1
Slight	1	2	1	1	0	0	0	0
Degeneration: valvular								
Minimal	0	0	0	1	0	0	0	0
Moderate	0	0	0	3	0	0	0	0
Inflammation: subacute								
Minimal	0	0	0	2	0	0	0	0
Slight	0	0	0	5	0	0	0	0
Hyperplasia: endocardial								
Minimal	0	0	0	1	0	0	0	0
Slight	0	0	0	1	0	0	0	0
Degeneration and/or necrosis: myocardial								
Slight	0	0	0	1	0	0	0	0
Thrombosis: atrial/ventricular								
Minimal	0	0	0	2	0	0	0	0
Slight	0	0	0	1	0	0	0	0
Moderate	0	0	0	2	0	0	0	0
Marked	0	0	0	1	0	0	0	0
Thrombosis								
Slight	0	0	0	1	0	0	0	0

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10276

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Jejunum								
Hemorrhage								
Minimal	0	0	0	1	0	0	0	0
Slight	0	0	0	1	0	0	0	0
Inflammation: vascular								
Minimal	0	0	0	1	0	0	0	0
Kidney								
Cast: hyaline								
Minimal	0	0	0	2	1	1	1	1
Slight	0	0	0	3	1	0	0	0
Thrombosis								
Minimal	0	0	0	1	0	0	0	1
Slight	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	0
Marked	0	0	0	1	0	0	0	0
Inflammation: vascular								
Moderate	0	0	0	1	0	0	0	0
Marked	0	0	0	1	0	0	0	0
Deposits: pigment								
Slight	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	1
Necrosis								
Moderate	0	0	0	3	0	0	0	1
Marked	0	0	0	2	0	0	0	0
Hyaline droplet: tubular								
Minimal	0	0	0	3	0	0	0	0
Slight	0	0	0	2	0	0	0	0
Moderate	0	0	0	1	0	0	0	0

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10276

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Hemorrhage								
Slight	0	0	0	1	0	0	0	1
Liver								
Atrophy: hepatocellular								
Minimal	0	0	0	5	0	0	0	0
Hematopoiesis: extramedullary								
Minimal	0	0	0	1	0	0	0	3
Thrombosis								
Minimal	0	0	0	3	0	0	0	0
Lung								
Thrombosis								
Minimal	0	0	0	1	0	0	0	0
Slight	0	0	0	1	0	0	0	0
Hemorrhage								
Minimal	0	0	1	2	0	0	0	0
Moderate	0	0	0	2	0	0	0	0
Inflammation: vascular								
Minimal	0	0	0	3	0	0	0	0
Slight	0	0	0	1	0	0	0	0
Edema								
Minimal	0	0	0	1	0	0	0	0
Lymph node								
Hemorrhage								
Minimal	0	0	0	1	0	0	0	0
Moderate	0	0	0	3	0	0	0	0

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10276

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Erythrocytosis/ erythrophagocytosis								
Minimal	0	0	0	2	0	0	0	0
Lymph node mandibular								
Hemorrhage								
Minimal	0	0	0	3	0	0	0	0
Erythrocytosis/ erythrophagocytosis								
Minimal	0	3	2	1	0	0	0	0
Lymph node mesenteric								
Hemorrhage								
Moderate	0	0	0	1	0	0	0	0
Erythrocytosis/ erythrophagocytosis								
Minimal	1	0	0	2	0	0	0	1
Slight	0	0	0	4	0	0	0	0
Pancreas								
Inflammation: vascular								
Minimal	0	0	0	2	0	0	0	0
Hemorrhage								
Slight	0	0	0	1	0	0	0	0
Seminal vesicle								
Inflammation: vascular								
Minimal	0	0	0	1	NA	NA	NA	NA

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10276

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Spleen								
Hematopoiesis/extramedullary: increased								
Minimal	1	1	1	3	0	0	0	2
Slight	0	0	0	3	0	0	0	0
Moderate	0	0	0	1	0	0	0	0
Stomach								
Thrombosis								
Minimal	0	0	0	2	0	0	0	0
Erosion/ulceration: glandular mucosa								
Minimal	0	0	0	1	0	0	0	0
Slight	0	0	0	1	0	0	0	2
Moderate	0	0	0	1	0	0	0	0
Hemorrhage								
Minimal	1	0	0	2	0	0	0	1
Slight	0	0	0	4	0	0	0	0
Moderate	0	0	0	2	0	0	0	0
Inflammation: vascular								
Minimal	0	0	0	1	0	0	0	0
Testis								
Inflammation: vascular								
Minimal	0	0	0	3	NA	NA	NA	NA

GSK1278863A: 26 Week Oral (Gavage) Toxicity Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10276

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.8**	**4**	**10**	**0**	**0.8**	**4**	**10**
Thymus								
Hemorrhage								
Minimal	7	2	3	3	5	1	0	4
Slight	0	0	1	2	0	0	0	1
Moderate	0	0	0	5	0	0	0	1
Atrophy/necrosis: lymphoid								
Minimal	0	0	2	3	1	1	1	1
Slight	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	0
Whole Body								
Congestion								
Minimal	0	0	3	2	0	0	0	0
Slight	0	0	0	8	0	0	0	0
Moderate	0	0	0	2	0	0	0	0

Key:

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, NA = Not Applicable, NC = Not Calculated.

a = Additional toxicokinetic (TK) rats were added to the 10 mg/kg/day group to ensure toxicokinetics could be assessed appropriately as elevated hematocrits in previous studies have led to difficulty obtaining adequate plasma volume.

b = In view of the reduced survival rate, all remaining males given 10 mg/kg/day were prematurely euthanized in Week 20 (Day 135/134). The death on Day 22 of the female given 0.8 mg/kg/day was not considered test article-related.

c = For controls, group means are shown; for treated groups, X change as compared to controls.

Table 8.6 GSK1278863A: 14 Day Dermal Irritation Study in Rabbits

Study Type: Repeat-Dose Dermal Irritation	**Report Title:** GSK1278863A: 2-Week Dermal Irritation Study in Rabbits (GlaxoSmithKline Study No. L42845)	**Test Article:** GSK1278863A (parent compound) **Batch No.:** 111280742
Species/Strain: Rabbit/Hra:(NZW)SPF	**Duration of Exposure:** approximately 23 hours/day	**Study No.:** L42845
Initial Age: 5 months	**Route:** Dermal (occluded, non-abraded and abraded sites)	**GSK Document Number:** 2011N125481 **Location in CTD:** m4.2.3.2
Date of First Dose: 11 October 2011	**Vehicle/Formulation:** petrolatum/suspension	**Study in Compliance with GLP:** Yes

Data Collected: Toxicokinetics, clinical observations, body weight, food consumption, dermal irritation scores, hematology, macroscopic and microscopic (skin only) pathology

Conclusion: GSK1278863A formulations caused no dermal irritation. Treatment with GSK1278863A was associated with attenuation in the severity, pattern of distribution, and/or incidence of the skin microscopic changes (acanthosis, orthokeratotic hyperkeratosis, dermal mixed inflammatory cell infiltrate, and dermal edema) seen with the vehicle.

GSK1278863A: 14 Day Dermal Irritation Study in Rabbits (Continued)

		Male				
Dose (%)[1]		**0**	**0.5**	**1**	**2**	
Numbers of Animals:		3[2]	3[2]	3[2]	6[3]	
$AUC_{(0-t)}$ (ng.h/mL)					Non-Abraded Sites	Abraded Sites
	Day 1	NA	NA	NA	169[4]	219
	Day 14	NA	NA	NA	2492	3332
C_{max} (ng/mL)					Non-Abraded Sites	Abraded Sites
	Day 1	NA	NA	NA	23.4	22.3
	Day 14	NA	NA	NA	248	319
Noteworthy Findings		GSK1278863A formulations caused no dermal irritation.				

Key:

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

2 = Each animal had both non-abraded and abraded application sites.

3 = The first 3 animals in the group had non-abraded application sites, and the last 3 animals in the group had abraded application sites.

4 = N=1.

NA = Not applicable.

Table 8.7 GSK1278863A: 4 Week Oral (Capsule) Toxicity Study in Beagle Dogs

Study Type: Repeat Dose Toxicity	**Report Title:** GSK1278863A: 4 Week Oral (Capsule) Toxicity Study in Beagle Dogs	**Test Article:** GSK1278863A (parent compound) **Batch No.:** NE-021129-Batch-01-2007
Species/Strain: Dog/beagle	**Duration of Dosing:** Up to 29 days	**Study No.:** D42196
Initial Age: 18 months	**Route/Frequency:** Capsule, once daily	**GSK Document Number:** RD2007/01336
		Location in CTD: m4.2.3.2
Date of First Dose: 8 November 2007	**Vehicle:** Empty gelatin capsule	**Study in Compliance with GLP:** Yes

Data Collected: Toxicokinetics, clinical observations, body weight, food consumption, ophthalmoscopy, electrocardiography, hematology, coagulation, clinical chemistry, urinalysis, organ weights, macroscopic and microscopic pathology (including stage-dependent evaluation of spermatogenesis).

Conclusion: GSK1278863A (vehicle, 3, 30 or 90 mg/kg/day) was given orally to male and female dogs for up to 4 weeks. Dogs given 90 mg/kg/day did not tolerate GSK1278863A and were euthanized on Day 12 or Day 19. In association with poor gastrointestinal tolerability, stomach erosions/ulcers and hemorrhage were evident in these dogs. Emesis, loose/watery feces and body weight loss (generally stabilized with supplemental food) were noted in dogs given 30 mg/kg/day. Thymic lymphoid depletion (≥30 mg/kg/day) was considered secondary to stress. Dose- and time-dependent pharmacologically-related erythroid hyperplasia and peripheral erythrocytosis were observed in dogs given ≥3 mg/kg/day. Additional pharmacologically-related findings observed in dogs given ≥30 mg/kg/day included congestion (bone marrow), extramedullary hematopoiesis (spleen and liver), megakaryocytosis (lungs) and altered serum iron parameters. Based on the stomach erosions/ulcers in dogs given 90 mg/kg/day and the body weight losses in dogs given ≥30 mg/kg/day, the no observed adverse effect level (NOAEL) is 3 mg/kg/day (mean $AUC_{0\text{-}t}$ 20.8 μg.h/mL, range 10.6 to 30.3 μg.h/mL; mean C_{max} 2.23 μg/mL, range 1.00 to 3.15 μg/mL [gender-averaged based on Day 28 values]).

GSK1278863A: 4 Week Oral (Capsule) Toxicity Study in Beagle Dogs (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** D42196

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**3**	**30**	**90**	**0**	**3**	**30**	**90**
Numbers of Animals:		3	3	3	3	3	3	3	3
AUC_{0-24} (μg.h/mL):	Day 1	NA	19.5	82.7	180	NA	20.9	116	272
	Day 28	NA	18.2	88.3	NA[2]	NA	23.4	90.8	NA[2]
C_{max} (μg/mL):	Day 1	NA	1.87	6.64	12.7	NA	2.20	7.71	17.8
	Day 28	NA	1.86	6.57	NA[2]	NA	2.60	5.97	NA[2]
Noteworthy Findings:									
Unscheduled Deaths:		0	0	0	3[2]	0	0	0	3[2]
Clinical Observations:		Dogs given 90 mg/kg/day had the following clinical observations beginning on Day 1: fecal changes (mucoid, green, red, reduced and/or loose/watery), slight to moderate decreased activity, slight to moderate thinness, slight to moderate loss of skin elasticity, slight to moderate salivation, slight redness of the gums (one female only) and/or emesis. Beginning on Day 1, an increased incidence of loose/watery feces and emesis was observed in dogs given 30 mg/kg/day.							
Body Weight Gains (kg)[3]:	Days -1 to 7	0.203	-0.027	-0.453	-1.123	0.100	0.300	-0.493	-0.797
	Days 7 to 12	0.237	0.360	-0.083	-0.567	0.343	0.233	-0.230	-0.080
	Days 12 to 14	-0.110	0.003	-0.063	0.015	-0.070	-0.097	0.177	0.120
	Days 14 to 21	0.083	0.057	0.320	-0.655[4]	0.230	0.277	-0.030	-0.210[4]
	Days 21 to 27	0.033	0.157	0.180	NA	0.243	-0.053	-0.050	NA
	Days -1 to 27	0.447	0.550	-0.100	-1.960[4]	0.847	0.660	-0.627	-0.967[4]
Food Consumption (g/animal/day)[3,5]:									
	Days 1 to 8	293.9	1.01X	0.69X	0.36X	262.7	0.98X	0.61X	0.51X
	Days 8 to 15	299.9	1.00X	0.59X	0.43X	296.2	0.88X	0.36X	0.46X
	Days 15 to 22	283.3	1.06X	0.76X	90.5[6]	300.0	0.86X	0.39X	171.3[6]
	Days 22 to 29	239.0	1.17X	0.77X	NA[2]	253.0	0.86X	0.39X	NA[2]

GSK1278863A: 4 Week Oral (Capsule) Toxicity Study in Beagle Dogs (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** D42196

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**3**	**30**	**90**	**0**	**3**	**30**	**90**
Hematology:									
Hematocrit (L/L)	Week -1	0.510	0.537	0.530	0.527	0.517	0.507	0.500	0.470
	Week 1	0.473	0.547	0.583	0.653	0.507	0.537	0.557	0.607
	Week 2	0.467	0.553	0.633	0.680	0.527	0.587	0.630	0.643
	Week 3[7]	0.490	0.560	0.643	0.750	0.527	0.603	0.667	0.717
	Week 4	0.500	0.580	0.670	NA[2]	0.510	0.623	0.727	NA[2]
Hemoglobin (g/L)	Week -1	171.0	181.0	178.7	176.0	172.3	169.3	169.0	158.3
	Week 1	160.0	186.3	196.0	219.3	171.7	180.0	188.0	203.0
	Week 2	158.3	186.3	205.7	219.5	178.0	196.3	203.7	208.0
	Week 3[7]	165.0	190.0	208.0	238.0	179.0	201.3	212.3	222.7
	Week 4	168.3	195.7	215.0	NA[2]	174.0	207.0	228.0	NA[2]
Red blood cell count (x10^{12}/L)	Week -1	7.047	7.637	7.493	7.567	7.327	7.203	6.970	6.600
	Week 1	6.603	7.767	8.160	9.267	7.247	7.603	7.720	8.330
	Week 2	6.483	7.810	8.683	9.435	7.457	8.180	8.343	8.513
	Week 3[7]	6.773	7.927	8.840	10.565	7.473	8.420	8.927	9.433
	Week 4	7.003	8.310	9.427	NA[2]	7.293	8.833	9.740	NA[2]
Mean cell volume (fL)	Week -1	72.27	70.30	70.37	69.70	70.43	70.33	72.37	70.80
	Week 1	71.70	70.23	71.60	70.50	70.00	70.43	72.57	73.10
	Week 2	72.00	71.00	72.93	72.10	70.70	71.93	75.63	75.97
	Week 3[7]	72.07	70.93	72.73	71.05	70.70	71.63	75.03	75.63
	Week 4	70.83	70.03	71.23	NA[2]	69.97	70.47	74.73	NA[2]
Mean cell hemoglobin concentration (g/L)									
	Week -1	335.7	337.3	338.3	334.0	334.7	334.7	335.7	339.7
	Week 1	338.0	341.7	335.3	335.3	338.3	336.7	336.7	333.3
	Week 2	340.0	336.3	325.0	323.0	337.3	333.3	324.3	322.0
	Week 3[7]	338.3	338.7	323.7	317.5	338.0	334.0	319.0	313.3
	Week 4	339.7	336.0	320.7	NA[2]	340.7	332.3	314.3	NA[2]

GSK1278863A: 4 Week Oral (Capsule) Toxicity Study in Beagle Dogs (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** D42196

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**3**	**30**	**90**	**0**	**3**	**30**	**90**
Hematology (Continued):									
Red cell distribution width (%)	Week -1	13.00	13.17	13.30	13.17	13.63	13.00	12.93	13.00
	Week 1	13.07	13.97	16.03	17.57	13.77	14.17	16.27	18.07
	Week 2	13.03	13.60	15.93	15.35	13.77	14.27	16.73	17.87
	Week 3[7]	13.03	13.50	15.13	14.60	13.57	13.80	16.07	16.37
	Week 4	11.80	12.50	13.63	NA[2]	12.27	12.37	15.53	NA[2]
Reticulocytes (x10^9/L)	Week -1	40.07	50.07	58.13	70.97	55.53	57.87	51.17	52.83
	Week 1	48.93	107.00	211.73	332.80	89.33	144.43	227.23	354.80
	Week 2	41.23	65.07	217.03	253.30	92.03	130.50	338.03	386.00
	Week 3[7]	43.47	72.43	167.90	275.90	78.50	109.57	254.17	318.67
	Week 4	37.73	60.33	135.17	NA[2]	42.80	61.13	220.43	NA[2]
Platelets (x10^9/L)	Week -1	304.7	355.3	367.0	355.0	361.0	429.0	413.3	492.0
	Week 1	287.0	333.3	361.7	279.0	314.7	432.3	403.0	452.3
	Week 2	294.3	323.7	370.7	429.5	326.3	472.7	465.7	537.0
	Week 3[7]	317.7	338.7	474.7	359.0	348.7	424.3	435.0	629.0
	Week 4	319.3	347.7	435.7	NA[2]	326.0	412.0	495.7	NA[2]
White blood cell count (x10^9/L)	Week -1	8.300	6.400	7.477	8.387	8.740	8.743	8.017	8.787
	Week 1	9.373	9.300	16.110	16.017	8.583	11.667	12.833	16.030
	Week 2	8.113	6.297	11.160[8]	6.360[8]	8.240	10.693	9.157[8]	7.170[8]
	Week 3[7]	9.450	6.517	11.340[9]	10.250	8.153	9.317	9.713[9]	9.217[9]
	Week 4	8.243	6.730	11.330	NA[2]	7.990	8.263	11.197	NA[2]
Neutrophils (x10^9/L)									
	Week -1	5.350	3.790	4.563	5.377	5.447	4.973	4.557	5.200
	Week 1	5.723	5.947	10.277	11.370	5.063	7.097	7.753	11.133
	Week 2	4.787	3.420	7.093	3.480	4.473	6.213	4.307	3.383
	Week 3[7]	5.770	3.640	6.647	7.215	4.570	5.230	6.010	4.890
	Week 4	5.073	4.023	7.453	NA[2]	4.750	4.693	6.703	NA[2]

GSK1278863A: 4 Week Oral (Capsule) Toxicity Study in Beagle Dogs (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** D42196

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**3**	**30**	**90**	**0**	**3**	**30**	**90**
Hematology (Continued):									
Lymphocytes (x10^9/L)	Week -1	2.273	1.983	2.073	2.283	2.637	2.997	2.807	2.703
	Week 1	2.883	2.587	4.123	3.740	2.830	3.630	4.050	3.653
	Week 2	2.583	2.210	3.047	2.390	3.067	3.563	3.987	3.287
	Week 3[7]	2.853	2.170	3.373	2.180	2.953	3.263	3.003	3.377
	Week 4	2.473	2.053	2.940	NA[2]	2.533	2.910	3.523	NA[2]
Monocytes (x10^9/L)	Week -1	0.343	0.223	0.443	0.237	0.180	0.387	0.310	0.333
	Week 1	0.387	0.333	1.183	0.473	0.227	0.460	0.497	0.677
	Week 2	0.330	0.243	0.643	0.275	0.240	0.413	0.480	0.323
	Week 3[7]	0.377	0.253	0.877	0.390	0.223	0.397	0.353	0.427
	Week 4	0.287	0.200	0.423	NA[2]	0.263	0.267	0.440	NA[2]
Basophils (x10^9/L)	Week -1	0.040	0.043	0.060	0.050	0.057	0.067	0.053	0.057
	Week 1	0.053	0.047	0.063	0.080	0.070	0.090	0.103	0.147
	Week 2	0.047	0.037	0.153	0.055	0.087	0.133	0.113	0.067
	Week 3[7]	0.080	0.040	0.143	0.110	0.073	0.127	0.043	0.157
	Week 4	0.073	0.040	0.160	NA[2]	0.070	0.137	0.193	NA[2]
Clinical Chemistry:									
Iron (μmol/L)	Week -1	32.27	49.70	38.97	42.83	40.73	55.47	42.23	45.53
	Week 1	39.90	39.97	33.03	24.40	45.87	47.23	51.50	41.33
	Week 2	37.47	38.07	28.10	12.20	39.73	42.17	26.33	17.93
	Week 3[7]	31.77	37.20	19.57	10.00	39.03	43.47	36.67	34.63
	Week 4	36.97	40.47	16.27	NA[2]	46.13	58.60	26.97	NA[2]
Unsaturated iron binding capacity (μmol/L)									
	Week -1	45.3	40.0	43.7	41.3	37.0	46.7	55.0	56.3
	Week 1	49.0	49.0	46.3	48.0	45.0	50.7	48.3	43.7
	Week 2	53.0	47.3	44.0	55.0	48.3	53.7	58.3	49.3
	Week 3[7]	54.3	49.3	60.3	59.5	50.7	52.0	53.3	46.3
	Week 4	48.0	47.3	68.7	NA[2]	42.0	40.3	54.3	NA[2]

GSK1278863A: 4 Week Oral (Capsule) Toxicity Study in Beagle Dogs (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** D42196

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**3**	**30**	**90**	**0**	**3**	**30**	**90**
Clinical Chemistry (Continued):									
Total iron binding capacity (μmol/L)									
	Week -1	77.7	89.7	82.3	84.3	77.7	102.3	97.3	102.0
	Week 1	88.7	89.0	79.3	72.7	91.0	97.7	100.0	85.0
	Week 2	90.7	85.3	72.3	67.0	88.0	96.0	85.0	67.3
	Week 3[7]	86.0	86.7	79.7	69.5	89.7	95.3	90.0	81.0
	Week 4	85.0	88.0	85.0	NA[2]	88.0	99.0	81.3	NA[2]
Albumin (g/L)	Week -1	34.0	33.7	33.3	34.7	32.3	33.0	33.3	33.0
	Week 2	31.7	31.3	29.0	27.5	33.0	32.7	28.7	26.7
	Week 3	NA	NA	NA	30.0[2]	NA	NA	NA	29.0[2]
	Week 4	32.0	32.3	31.0	NA	33.3	34.7	28.7	NA
Glucose (mmol/L)	Week -1	5.193	4.770	5.233	6.380	5.190	4.987	4.903	5.090
	Week 2	4.907	4.777	3.497	4.275	5.430	4.650	4.547	3.743
	Week 3	NA	NA	NA	2.490[2]	NA	NA	NA	1.827[2]
	Week 4	5.400	4.673	4.603	NA	5.237	4.670	3.590	NA
Organ Weights[10]:									
Thymus									
Absolute (g)	Week 5	4.7463	1.42X	0.88X	0.59X[11]	5.9537	0.75X	0.52X	0.44X[11]
Relative to body weight (%)									
	Week 5	0.053	1.13X	1.08X	0.66X[11]	0.063	0.90X	0.63X	0.75X[11]
Microscopic Examination (Number of Animals):		**3**	**3**	**3**	**3[2]**	**3**	**3**	**3**	**3[2]**
Stomach									
Erosion/ulcer; pyloric region; multifocal	Moderate	0	0	0	2	0	0	0	1
Hemorrhage; pyloric region; mucosa; multifocal	Mild	0	0	0	2	0	0	0	1

GSK1278863A: 4 Week Oral (Capsule) Toxicity Study in Beagle Dogs (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** D42196

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**3**	**30**	**90**	**0**	**3**	**30**	**90**
Microscopic Examination (Continued) (Number of Animals):		**3**	**3**	**3**	**3[2]**	**3**	**3**	**3**	**3[2]**
Sternum - Bone Marrow									
Hyperplasia, erythroid	Minimal	0	2	0	0	0	1	0	0
	Mild	0	1	1	3	0	2	1	0
	Moderate	0	0	2	0	0	0	2	3
Congestion									
	Minimal	0	0	2	0	0	0	2	1
	Mild	0	0	1	1	0	0	1	0
	Moderate	0	0	0	2	0	0	0	2
Femur - Femoral Head									
Hyperplasia, erythroid	Minimal	0	2	0	0	0	0	0	0
	Mild	0	1	1	3	0	3	1	0
	Moderate	0	0	2	0	0	0	2	3
Congestion									
	Minimal	0	0	2	0	0	0	1	1
	Mild	0	0	1	2	0	0	2	1
	Moderate	0	0	0	1	0	0	0	1
Spleen									
Extramedullary hematopoiesis; increased; multifocal	Minimal	0	0	1	0	0	0	0	0
	Mild	0	0	1	0	0	0	0	0
	Moderate	0	0	1	1	0	0	3	2
	Marked	0	0	0	2	0	0	0	1
Liver									
Extramedullary hematopoiesis; multifocal	Minimal	0	0	1	2	0	0	3	1
	Mild	0	0	0	1	0	0	0	2

GSK1278863A: 4 Week Oral (Capsule) Toxicity Study in Beagle Dogs (Continued)

Study Type: Repeat Dose Toxicity | **Study No.:** D42196

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**3**	**30**	**90**	**0**	**3**	**30**	**90**
Microscopic Examination (Continued) (Number of Animals):		**3**	**3**	**3**	**3[2]**	**3**	**3**	**3**	**3[2]**
Lungs									
Megakaryocyte; multifocal	Minimal	0	0	2	2	0	0	1	2
	Mild	0	0	0	1	0	0	2	1
Thymus									
Lymphoid depletion	Minimal	0	0	1	1	0	0	1	0
	Mild	0	0	2	0	0	0	2	1
	Moderate	0	0	0	2	0	0	0	2

Key:

1 = Doses are expressed in terms of the parent compound.
2 = One male dog given 90 mg/kg/day was euthanized on Day 12; surviving dogs given 90 mg/kg/day were euthanized on Day 19 (Week 3).
3 = All dogs were offered longer access to pelleted food beginning on Day 8, and dogs given ≥30 mg/kg/day were offered canned food beginning on Day 9.
4 = For dogs given 90 mg/kg/day, body weight gain values are for Days 14 to 19, and absolute body weight gain values are from Days -1 to 19.
5 = Pelleted diet food consumption only. For controls, group means are shown; for test article-treated groups, change from control is shown.
6 = For dogs given 90 mg/kg/day, group means are shown for Days 15 to 19.
7 = Week 3 samples were collected on Day 19 from dogs given 90 mg/kg/day and on Day 21 from dogs given 0, 3 or 30 mg/kg/day.
8 = White blood cell counts were corrected for increased nucleated red blood cells for one male and one female given 30 mg/kg/day and one male and two females given 90 mg/kg/day.
9 = White blood cell counts were corrected for increased nucleated red blood cells for one male and two females given 30 mg/kg/day and one female given 90 mg/kg/day.
10 = For controls, group means are shown for absolute and/or relative weights. For test article-treated groups, change from control is shown.
11 = For animals given 90 mg/kg/day, organ weights were collected on Day 19 (Week 3).
NA = Not applicable.

Table 8.8 GSK1278863A: 13 Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 4 Week Recovery Period

Study Type: Repeat Dose Toxicity	**Report Title:** GSK1278863A: 13 Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 4 Week Recovery Period	**Test Article:** GSK1278863A (parent compound) **Batch No.:** NE-021129-BATCH-01-2009
Species/Strain: Beagle dog	**Duration of Dosing:** 13 weeks **Duration of Recovery:** 4 weeks	**GSK Reference No.:** G09058
Initial Age: 13 to 14 months	**Route/Frequency:** Oral by capsule, once daily	**GSK Document Number:** CD2009/00952 **Location in CTD:** m4.2.3.2
Date of First Dose: 20 April 2009	**Vehicle/Formulation:** Gelatine capsule	**Study in Compliance with GLP:** Yes

Data Collected: Clinical observations; body weights; food consumption measurements; haematology, coagulation, clinical chemistry and urinalysis results; ophthalmoscopic observations; electrocardiographic assessment; organ weights; and macroscopic and microscopic observations. Blood samples for toxicokinetic evaluations were taken on Days 1, 17 and in Weeks 7, 9, 11 and 13.

Conclusion: GSK1278863A (vehicle, 1, 3, 30 or 30/15 mg/kg/day) was given orally by capsule to male and female dogs once daily for up to 13 weeks. Due to reduced food consumption and progressive body weight loss in 4 of 6 female dogs given 30 mg/kg/day, the dose was reduced to 15 mg/kg/day on Day 17 for the high dose females. Dogs given 30/15 mg/kg/day were terminated early due to adverse clinical signs (convulsions, tremors, staggering, uncoordinated, circling, abnormal gait and prostration) attributed to increased blood viscosity and tissue hypoxia, especially within the central nervous system, as a consequence of increased red cell parameters caused by pharmacologically-mediated increased haemopoiesis. Substantial recovery of all effects was evident following a 4 week post-drug recovery period. Based on the effects at 30 mg/kg/day, the no observed adverse effect level (NOAEL) was 3 mg/kg/day (mean $AUC_{0\text{-}t}$ 19.1 μg.h/mL, mean C_{max} 2.34 μg/mL [gender-averaged based on Week 13 values]).

GSK1278863A: 13 Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09058

		Male				Female			
Daily Dose (mg/kg/day)[a]		**0**	**1**	**3**	**30**	**0**	**1**	**3**	**15/30**
Group		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Numbers of Animals:	Main	4	4	4	4	4	4	4	4
	Recovery	2	-	-	2	2	-	-	2
AUC_{0-24} (μg.h/mL):	Day 1	-	10.4	18.8	104	-	9.08	26.7	108
	Day 17	-	-	-	-	-	-	-	74.3
	Week 7	-	9.10	28.7	94.9	-	12.1	36.0	67.1
	Week 13	-	7.39	17.8	-	-	8.06	20.3	-
C_{max} (μg/mL):	Day 1	-	1.05	1.78	7.90	-	0.98	1.79	8.12
	Day 17	-	-	-	-	-	-	-	5.94
	Week 7	-	1.11	2.62	5.89	-	1.41	4.24	6.23
	Week 13	-	1.30	1.79	-	-	1.32	2.89	-
Noteworthy Findings:									
Unscheduled Deaths:		0	0	0	2	0	0	0	2
Decedent Findings:		Two males given 30 mg/kg/day were killed during Weeks 8 or 9, and 2 females given 30/15 mg/kg/day were killed during Weeks 10 or 11. Clinical signs of reaction to treatment included body tremors, staggering, uncoordinated/circling movement, prostrate, abnormal gait, sluggish/subdued mood, abnormal respiration, reddened abdomen, ears and mouth/gums and/or salivation. In addition, one male (Number 15) experienced a convulsive episode and was hypersensitive to touch and noise. All animals lost small amounts of body weight prior to euthanasia (3.8% to 9.1%).							
Mean Body Weight Gain Over Selected Intervals (X Control[b]) or (kg Change from Day 1):									
	Days 1 to 8	0.15 kg	0.27X	0.73X	-0.64 kg***	0.18 kg	0.33X	0.00 kg	-0.53 kg*
Gp 4F off-dose	Days 8 to 16	-	-	-	-	0.35 kg	1.11X	1.20X	2.03X
	Days 8 to 29	0.64 kg	0.56X	1.20X	0.63X	-	-	-	-
	Days 8 to 60	0.92 kg	0.90X	1.42X	0.32X	-	-	-	-
	Days 16 to 29	-	-	-	-	0.26 kg	0.88X	1.00X	0.08X
	Days 16 to 71	-	-	-	-	0.68 kg	1.18X	1.24X	0.78X

GSK1278863A: 13 Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09058

		Male				Female			
Daily Dose (mg/kg/day)[a]		**0**	**1**	**3**	**30**	**0**	**1**	**3**	**15/30**
Gp 4M recovery	Days 60 to 92	0.04 kg	6.50X	-0.12 kg	24.75X*	-	-	-	-
Gp 4F recovery	Days 71 to 99	-	-	-	-	0.12 kg	-	-	2.50X
	Days 1 to 92	1.10 kg	1.00X	1.17X	0.61X	1.35 kg	0.78X	1.07X	0.65X
Mean Food Consumption Over Selected Intervals (X Control[b]):									
	Week 1	2228 g	1.05X	1.06X	0.69X	1908 g	1.00X	0.81X	0.62X
Gp 4F off-dose	Weeks 2 to 3	-	-	-	-	2546 g	1.00X	0.83X	0.91X
	Weeks 2 to 4	2720 g	1.08X	1.07X	0.78X	-	-	-	-
	Weeks 2 to 8	2591 g	1.12X	1.08X	0.84X	-	-	-	-
	Weeks 3 to 10	-	-	-	-	2340 g	0.95X	0.81X	0.86X
Gp 4M recovery	Weeks 9 to 13	2334 g	1.20X	1.10X	1.14X	-	-	-	-
Gp 4F recovery	Weeks 11 to 14	-	-	-	-	2234 g	-	-	1.07X
	Weeks 1 to 13	2464 g	1.14X	1.09X	-	2293 g	0.95X	0.81X	-
Haematology:									
Red Blood Cell Count (10^{12}/L)									
Pre-treatment		7.10	7.18	6.94	7.18	7.11	7.02	7.21	7.25
Day 17		-	-	-	-	7.06	-	-	7.60*
Week 7		7.52	7.33	8.10	10.97***	7.16	7.42	7.86	9.81***
Week 9		-	-	-	11.81	-	-	-	-
Week 11		-	-	-	-	-	-	-	9.93
Week 13 (recovery Group 4M)		7.56	7.39	8.18	9.38**	6.88	7.12	8.07**	-
Week 14 (recovery)		-	-	-	-	6.77	-	-	8.44

GSK1278863A: 13 Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09058

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**1**	**3**	**30**	**0**	**1**	**3**	**15/30**
Reticulocyte Count (10^9/L)								
Pre-treatment	31.5	42.9	56.7	58.8	43.7	84.9	87.4	61.4
Day 17	-	-	-	-	70.8	-	-	50.7
Week 7	35.1	49.3	57.2	106.6***	52.2	50.2	53.4	99.7**
Week 9	-	-	-	112.6	-	-	-	-
Week 11	-	-	-	-	-	-	-	84.3
Week 13 (recovery Group 4M)	40.8	53.8	68.8	8.3	40.6	39.8	41.6	-
Week 14 (recovery)	-	-	-	-	27.4	-	-	9.6
Packed Cell Volume (%)								
Pre-treatment	48.8	49.3	48.3	50.2	48.2	49.3	49.8	49.5
Day 17	-	-	-	-	48.3	-	-	54.1**
Week 7	51.2	50.1	55.3	70.7***	47.9	50.9	53.8*	64.9***
Week 9	-	-	-	74.2	-	-	-	-
Week 11	-	-	-	-	-	-	-	65.8
Week 13 (recovery Group 4M)	53.3	52.1	57.5	58.7	47.6	50.4	56.2**	-
Week 14 (recovery)	-	-	-	-	44.7	-	-	55.3
Haemoglobin Concentration (g/dL)								
Pre-treatment	16.7	17.1	16.4	17.1	16.3	16.6	16.9	16.9
Day 17	-	-	-	-	16.2	-	-	17.4*
Week 7	18.0	17.5	19.2	23.9***	16.7	17.7	18.6*	21.9***
Week 9	-	-	-	24.2	-	-	-	-
Week 11	-	-	-	-	-	-	-	22.3
Week 13 (recovery Group 4M)	17.9	17.5	18.9	18.5	15.9	16.9	18.8**	-
Week 14 (recovery)	-	-	-	-	15.2	-	-	18.5

GSK1278863A: 13 Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G09058

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**1**	**3**	**30**	**0**	**1**	**3**	**15/30**
Red Cell Distribution Width (%)								
Pre-treatment	12.7	12.6	13.0	12.6	13.1	12.9	13.3	12.9
Day 17	-	-	-	-	13.3	-	-	15.2**
Week 7	13.1	12.8	13.3	14.9***	13.3	12.8	13.4	14.8**
Week 9	-	-	-	15.0	-	-	-	-
Week 11	-	-	-	-	-	-	-	14.0
Week 13 (recovery Group 4M)	12.4	12.3	12.9*	15.7	12.6	12.5	12.6	-
Week 14 (recovery)	-	-	-	-	13.4	-	-	12.7
Clinical Chemistry: Iron (umol/L)								
Pre-treatment	28.9	36.6	25.9	30.4	39.0	31.1	36.6	30.9
Day 17	-	-	-	-	32.7	-	-	38.1
Week 7	30.2	36.8	34.6	18.3	36.7	34.9	39.3	21.6*
Week 9	-	-	-	16.5	-	-	-	-
Week 13 (recovery Group 4M)	32.5	38.7	28.3	55.4***	33.2	38.1	48.4**	-
Week 14 (recovery)	-	-	-	-	32.6	-	-	52.1
Unsaturated Iron Binding Capacity (umol/L)								
Pre-treatment	33.2	27.9	37.4	34.0	26.8	40.4	31.7	37.1
Day 17	-	-	-	-	36.5	-	-	28.8
Week 7	32.2	29.1	31.3	56.6***	31.8	31.1	30.0	47.3*
Week 9	-	-	-	60.0	-	-	-	-
Week 13 (recovery Group 4M)	33.3	30.1	38.9	3.4***	38.7	34.4	25.9	-
Week 14 (recovery)	-	-	-	-	44.7	-	-	12.5

GSK1278863A: 13 Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G09058

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**1**	**3**	**30**	**0**	**1**	**3**	**15/30**
Urea (mmol/L)								
Pre-treatment	5.6	6.4	5.9	6.4	5.6	6.1	5.8	7.2
Day 17	-	-	-	-	6.7	-	-	9.5*
Week 7	5.6	7.4	6.1	5.3	5.5	6.1	6.0	6.3
Week 9	-	-	-	4.6	-	-	-	-
Week 11	-	-	-	-	-	-	-	8.7
Week 13 (recovery Group 4M)	6.6	7.1	6.8	7.5	5.8	6.4	6.5	-
Week 14 (recovery)	-	-	-	-	5.7	-	-	6.9
Triglycerides (mmol/L)								
Pre-treatment	0.44	0.38	0.54	0.59	0.43	0.64	0.58	0.70
Day 17	-	-	-	-	0.67	-	-	0.97
Week 7	0.43	0.47	0.65*	0.52	0.48	0.56	0.55	0.63
Week 9	-	-	-	0.46	-	-	-	-
Week 11	-	-	-	-	-	-	-	1.08
Week 13 (recovery Group 4M)	0.61	0.50	0.76	0.60	0.55	0.70	0.77	-
Week 14 (recovery)	-	-	-	-	0.66	-	-	0.67
Creatinine (umol/L)								
Pre-treatment	62	66	61	62	50	54	55	60
Day 17	-	-	-	-	50	-	-	62*
Week 7	63	66	62	71	58	55	59	68
Week 9	-	-	-	66	-	-	-	-
Week 11	-	-	-	-	-	-	-	79
Week 13 (recovery Group 4M)	64	60	60	60	49	54	61	-
Week 14 (recovery)	-	-	-	-	47	-	-	54

GSK1278863A: 13 Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09058

		Male				Female			
Daily Dose (mg/kg/day)[a]		**0**	**1**	**3**	**30**	**0**	**1**	**3**	**15/30**
Glucose (mol/L)									
Pre-treatment		4.9	5.6	5.4	5.4	5.2	5.4	5.3	5.5
Day 17		-	-	-	-	5.3	-	-	5.3
Week 7		5.9	5.8	5.9	4.1***	5.5	5.4	5.0	4.3***
Week 9		-	-	-	4.4	-	-	-	-
Week 13 (recovery Group 4M)		5.3	5.3	5.4	4.9	4.7	4.8	5.0	-
Week 14 (recovery)		-	-	-	-	5.0	-	-	5.0
Total cholesterol (mol/L)									
Pre-treatment		5.4	4.8	5.8	5.5	4.7	6.3	5.4	5.7
Day 17		-	-	-	-	5.3	-	-	5.9
Week 7		5.8	5.6	6.3	4.1*	5.3	6.6	6.0	5.3
Week 9		-	-	-	4.1	-	-	-	-
Week 13 (recovery Group 4M)		6.0	5.6	6.4	6.1	6.4	7.9	6.8	-
Week 14 (recovery)		-	-	-	-	7.2	-	-	7.4
Macroscopic Observations (Main Study):		Many tissues were reported as red or dark, often in animals given 30 or 30/15 mg/kg/day, and these correlated with congestion seen microscopically and also with clinical signs of red abdomen, ears and mouth/gums.							
(Number of Animals):		**4**	**4**	**4**	**2**	**4**	**4**	**4**	**2**
Skin + Subcutis	Red	0	0	0	2	0	0	1	2
Ear	Red	0	0	0	2	0	0	1	2
Oral Cavity	Red	0	0	0	2	0	0	1	2
Spleen	Dark area	0	0	0	0	0	1	1	0
	Dark	0	0	0	1	0	0	0	0
Stomach	Red	0	0	0	0	0	0	1	0
	Dark	0	0	0	2	0	0	0	0
Lung	Dark area	0	0	0	0	0	1	2	0

GSK1278863A: 13 Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09058

		Male				Female			
Daily Dose (mg/kg/day)[a]		**0**	**1**	**3**	**30**	**0**	**1**	**3**	**15/30**
Microscopic Examination (Main Study) (Number of Animals):		**4**	**4**	**4**	**2**	**4**	**4**	**4**	**2**
Liver									
Sinusoidal dilatation/congestion									
	Unremarkable	4	4	4	0	4	4	4	0
	Minimal	0	0	0	1	0	0	0	1
	Slight	0	0	0	1	0	0	0	0
	Moderate	0	0	0	0	0	0	0	1
Kidney									
Congestion	Unremarkable	4	4	4	0	4	4	4	0
	Minimal	0	0	0	1	0	0	0	0
	Slight	0	0	0	1	0	0	0	1
	Moderate	0	0	0	0	0	0	0	1
Brain									
Congestion	Unremarkable	4	4	4	0	4	4	4	0
	Slight	0	0	0	2	0	0	0	2
Macroscopic Observations (Recovery):		Findings of red or dark were occasionally reported in some tissues for dogs given 30 or 30/15 mg/kg/day. In one male previously given 30 mg/kg/day and one female given 30/15 mg/kg/day, oral cavity and/or ears and skin were reported as red, and these sometimes correlated with congestion seen microscopically, and also with the clinical signs of red mouth and/or ears and abdomen. In 2 males previously given 30 mg/kg/day, the bone marrow was reported as pale and correlated with the increase in marrow fat seen microscopically.							
(Number of Animals):		**2**	**0**	**0**	**2**	**2**	**0**	**0**	**2**
Skin + Subcutis	Red	0	-	-	1	0	-	-	0
Ear	Red	0	-	-	1	0	-	-	0
Oral Cavity	Red	0	-	-	1	0	-	-	1
Lung	Dark area	0	-	-	0	1	-	-	2
	Dark	1	-	-	0	1	-	-	0

GSK1278863A: 13 Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G09058

		Male				Female			
Daily Dose (mg/kg/day)[a]		**0**	**1**	**3**	**30**	**0**	**1**	**3**	**15/30**
Microscopic Examination (Recovery) (Number of Animals):		**2**	**0**	**0**	**2**	**2**	**0**	**0**	**2**
Femur + Marrow									
Marrow fat	Unremarkable	0	-	-	0	0	-	-	0
	Minimal	0	-	-	0	0	-	-	0
	Slight	1	-	-	0	0	-	-	0
	Moderate	1	-	-	0	2	-	-	0
	Moderately severe	0	-	-	2	0	-	-	2
Sternum + Marrow									
Marrow fat	Unremarkable	0	-	-	0	0	-	-	0
	Minimal	1	-	-	0	0	-	-	0
	Slight	0	-	-	0	1	-	-	0
	Moderate	1	-	-	0	1	-	-	0
	Moderately severe	0	-	-	2	0	-	-	2

Key:
a = Doses expressed in terms of parent.
b = For controls, group means are presented. For test article-treated groups, change from control is shown.
- = Not examined.
Statistical significance: * = p<0.05. ** = p<0.01. *** = p<0.001.

Table 8.9 GSK1278863A: A 3-Month Dermal Toxicity Study in the Minipig

Study Type: Repeat Dose Toxicity	**Report Title:** GSK1278863A: A 3-Month Dermal Toxicity Study in the Minipig	**Test Item/Article:** GSK1278863A (parent compound) **Batch No.:** 152389102
Species/Strain: Minipigs/Göttingen	**Duration of Dosing:** 91/92 days	**GSK Reference No.:** F70916G
Initial Age: 4 months	**Route/Frequency:** Dermal/once daily for approximately 21 hours	**GSK Document Number:** 2016N273683 **Location in CTD:** m4.2.3.2
Date of First Dose: 02 March 2016	**Vehicle/Formulation:** White Petrolatum, Batch 152394625	**Study in Compliance with GLP:** Yes

Data Collected: Formulation analysis, clinical observations, dermal scores, body weights, body weight changes, food consumption (qualitatively), electrocardiography (qualitative assessment of ~5 minute recording for wave form abnormalities and arrhythmia), ophthalmology, hematology, coagulation, clinical chemistry, urinalysis, and macroscopic and microscopic observations (limited to treated and untreated skin sites and tissue with macroscopic observations

Conclusion: GSK1278863 (vehicle, 5%, 10%, or 20% w/w; estimated achieved doses of 42, 84 or 168 mg/kg/day, respectively) was given dermally to male and female minipigs for 13 weeks. Pharmacologically-mediated minimal increases in red blood cell count, hemoglobin, and hematocrit were noted in males given 168 mg/kg/day. Dermal irritation was noted in all groups, including the petrolatum control group; however, during the second half of the study a test article-related increase in incidence and severity was seen in all test article-related groups and was characterized by involvement of more diffuse areas of the treatment site and onset of ulceration in Week 11. Microscopic changes at the application site of test article-treated animals were indistinguishable from those in the vehicle control group with the exception of 1 male given 168 mg/kg/day which had mild ulceration and an increased severity of epidermal hyperplasia.

Due to the presence of dermal observations of skin ulcerations in all test article-treated groups, a no-observed-adverse-effect level (NOAEL) for local irritation effects could not be identified. Systemic exposure in Week 13 at 42 mg/kg/day, the lowest dose tested, was: mean $AUC_{0\text{-}t}$ of 107 and 338 ng·h/mL and mean C_{max} of 7.29 and 27.5 ng/mL for males and females, respectively.

GSK1278863A: A 3-Month Dermal Toxicity Study in the Minipig (Continued)

Study Type: Repeat Dose Toxicity **Study No:** F70916G

	Male				Female			
Formulation Concentration (%, w/w)[a]	0	5	10	20	0	5	10	20
Estimated Achieved Daily Dose (mg/kg/day)[a]	0	42	84	168	0	42	84	168
Numbers of Animals:	4	4	4	4	4	4	4	4
$AUC_{(0-t)}$ (ng.h/mL) Week 4 (Day 28)	NC	205	336	704	NC	429	335	473
Week 13 (Day 91)	NC	107	475	1410	NC	388	397	1860
C_{max} (ng/mL) Week 4 (Day 28)	5.17[b]	23.7	23.4	66.9	2.15[b]	43.2	27.2	38.4
Week 13 (Day 91)	4.41[b]	7.29	28.5	143	2.46[b]	27.5	32.6	142
Noteworthy Findings								
Unscheduled Deaths	0	0	0	1[c]	0	0	0	1[c]
Dermal Irritation	Dermal irritation was noted in all groups, including the petrolatum control group, and included observations of very slight (Grade 1) to maximized (M-4) erythema, very slight (Grade 1) to severe (Grade 4) edema, eschar, eschar exfoliation, and blanching. The irritation generally started as focal pin point areas of erythema in some instances within the first week of dosing; however, the onset was generally variable and did not follow a dose-related trend. Although these findings gradually progressed in incidence and/or severity, the presentation and distribution remained generally comparable across GSK1278863-treated and vehicle groups for the first half of the study and were consistent with the petrolatum-based vehicle and/or procedural-related effects (hair clipping, semi-occlusive dressing). During the second half of the study the irritation in the GSK1278863-treated animals increased in incidence and severity compared to controls, progressed to more diffuse areas of the treatment site, and included areas of ulceration which were not seen to any degree in control animals. Ulceration was first seen in Week 11 and affected 1 of 4 males and 1 of 4 females given 42 mg/kg/day, 3 of 4 males and 1 of 4 females given 84 mg/kg/day, and 4 of 4 males and 1 of 4 females given 168 mg/kg/day.							

GSK1278863A: A 3-Month Dermal Toxicity Study in the Minipig (Continued)

Study Type: Repeat Dose Toxicity **Study No:** F70916G

	Male				Female			
Formulation Concentration (%, w/w)[a]	0	5	10	20	0	5	10	20
Hematology								
Red Blood Cell Counts (10^6/µL)	-	-	-	-	-	-	-	-
Baseline (Day –5)	8.13	8.52	8.36	8.19	8.29	8.16	8.23	8.01
End of Dosing Phase (Day 91)	9.13	8.27	8.96	10.43	9.33	9.04	8.91	9.65
Hemoglobin (g/dL)	-	-	-	-	-	-	-	-
Baseline (Day –5)	12.7	12.7	12.9	13.1	13.8	12.2	13.6	12.7
End of Dosing Phase (Day 91)	14.5	13.4	14.8	18.1	15.8	13.9	15.4	14.8
Hematocrit (%)	-	-	-	-	-	-	-	-
Baseline (Day –5)	40.5	41.1	40.9	42.1	43.3	38.8	42.9	40.1
End of Dosing Phase (Day 91)	43.3	41.6	44.6	55.2	47.9	41.9	46.3	44.6
Microscopic Observations								
Number of Animals Examined	4	4	4	4[d]	4	4	4	4[d]
Skin, Treated								
Ulceration								
mild	0	0	0	1	0	0	0	0
Hyperplasia, epidermal[e]								
minimal	2	2	0	1	0	2	2	1
mild	1	0	2	2	0	0	0	1
moderate	0	0	0	0	0	1	0	0
marked	0	0	0	0	0	0	0	0

GSK1278863A: A 3-Month Dermal Toxicity Study in the Minipig (Continued)

Key:

NC = Not calculated.

a = Estimated achieved doses and formulation concentration strengths are expressed in terms of the parent compound.

b = The concentrations of GSK1278863 in most samples collected from the control animals were above the limit of quantitation (0.100 ng/mL). Quantifiable control group concentrations ranged from 0.119 to 5.17 ng/mL for males and from 0.108 to 2.46 ng/mL for females. With the exception of several control group males having comparable concentrations to those measured in GSK1278863-treated males on Day 91, these control results were generally lower than the concentrations measured in animals at the low dose (42 mg/kg/day), and are therefore not expected to have any impact on the overall toxicokinetic interpretations.

c = Euthanized early with accidental injuries unrelated to the test article on Day 91 (male) and Day 43 (female).

d = Includes early euthanasia animals.

e = Minimal to moderate epidermal hyperplasia was also seen in untreated skin sites.

Table 8.10 GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Cynomolgus Monkey with a 4 Week Recovery Period

Study Type: Repeat Dose Toxicity	**Report Title:** GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Cynomolgus Monkey with a 4 Week Recovery Period	**Test Article:** GSK1278863A (parent compound) **Batch No.:** NE-021129-Batch-01-2009
Species/Strain: Cynomolgus monkeys, *Macaca Fascicularis* (Chinese origin)	**Duration of Dosing:** 13 weeks **Duration of Recovery:** 4 weeks	**GSK Reference No.:** G10005
Initial Age: 2.5-3 years at onset of dosing	**Route/Frequency:** Oral by gavage, once daily	**GSK Document Number:** 2010N108482 **Location in CTD:** m4.2.3.2
Date of First Dose: 23 February 2010	**Vehicle/Formulation:** 1% aqueous methylcellulose (400 cps @2%)	**Study in Compliance with GLP:** Yes

Data Collected: Toxicokinetics, clinical observations (including qualitative assessment of food consumption), body weight, ophthalmoscopy, electrocardiography, hematology, coagulation, clinical chemistry, urinalysis, organ weights, macroscopic and microscopic observations.

Conclusion: GSK1278863A was administered once daily by oral gavage to cynomolgus monkeys of Chinese origin for 13 weeks at 0 (vehicle control), 5, 20, and 100 mg/kg/day, followed by a 4-week recovery period. Test article-related changes consistent with pharmacologically-mediated increased erythropoiesis were seen in all dose groups and primarily included dose-dependent increases in red cell mass (red blood cells, hemoglobin, and hematocrit) and reticulocyte counts (which were seen at ≥20 mg/kg/day) at all dose levels along with increased bone marrow erythroid hypercellularity at ≥20 mg/kg/day. Two males given 100 mg/kg/day had unexpected reductions in red cell mass between sampling occasions and/or body weight loss, decreased thymic weight, thymic lymphoid atrophy and transient dark feces with an associated positive occult blood test. Collectively, the spectrum of findings in these two males was considered adverse. At the end of the 4-week recovery period, the majority of test article-related findings were either no longer evident or had demonstrated partial reversibility. Partial reversibility of pharmacologically-mediated increases in red cell mass is expected given the short duration of the recovery period and normal lifespan of circulating red blood cells in this species.

Based on the changes at 100 mg/kg/day, the No-Observable-Adverse-Effect-Level (NOAEL) was considered to be 20 mg/kg/day [$AUC_{0\text{-}t}$ = 14.8 μg.h/mL and C_{max} = 1.40 μg/mL (based on combined male and female mean values from Week 13)].

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Cynomolgus Monkey with a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10005

Daily Dose (mg/kg/day)[a]		Male 0	Male 5	Male 20	Male 100	Female 0	Female 5	Female 20	Female 100
Numbers of Animals:	Main	4	4	4	4	4	4	4	4
	Recovery	2	-	2	2	2	-	2	2
AUC_{0-t} (μg.h/mL)	Day 1	-	3.02	13.4	54.2	-	2.84	15.6	55.1
	Week 4	-	4.66	13.9	47.0	-	3.77	21.2	50.2
	Week 13	-	5.44	16.2	52.2	-	3.67	13.3	34.3
Cmax (μg/mL)	Day 1	-	1.00	1.98	5.02	-	0.887	2.30	4.60
	Week 4	-	0.898	1.89	3.96	-	0.914	2.55	4.00
	Week 13	-	0.753	1.43	3.85	-	0.762	1.38	2.83
Noteworthy Findings									
Clinical Observations		Test article-related clinical signs were limited to 100 mg/kg/day. Sporadic liquid and/or soft feces were observed in males and salivation was seen in males and females in this dose group. In addition, clinical signs of weakness and decreased activity were noted for one male (404) given 100 mg/kg/day on a single day at the end of the dosing period which was preceded by a week of numerous study-related procedures. Transient dark feces, a positive fecal occult blood test and dehydration were noted for one other male (403) in Week 8 only.							
Body Weight		Body weight effects were limited to one male (No. 404) given 100 mg/kg/day which had gradual body weight loss generally beginning in Week 9. By the end of the dosing period, the body weight for this male was decreased to approximately 0.87X its pretreatment value.							
Hematology[b]									
Red Blood Cells (10^{12}/ L)									
Baseline (Week -1)		5.44	5.56	5.71	5.55	5.62	5.53	5.29	5.19
Week 4		5.51	5.89	7.39	7.80	5.72	6.22	7.03	7.12
Week 8		5.41	6.00	8.06	8.52	5.68	6.35	7.69	8.80
Week 13 (end of treatment)		5.52	6.32	9.03	10.09	5.57	6.90	8.64	9.45
Week 17 (end of recovery)		5.88	-	7.99	8.72	5.75	-	7.33	9.16

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Cynomolgus Monkey with a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10005

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**5**	**20**	**100**	**0**	**5**	**20**	**100**
Hematology[b]								
Hemoglobin (g/L)								
Baseline (Week -1)	130.3	126.8	133.0	123.2	132.0	131.8	126.0	122.7
Week 4	128.7	134.0	171.2	167.4	136.0	147.5	170.7	172.2
Week 8	128.8	139.3	184.0	165.0	133.5	151.8	184.8	201.2
Week 13 (end of treatment)	129.8	147.0	197.5	182.3	126.7	159.8	200.2	212.5
Week 17 (end of recovery)	137.5	-	151.0	159.0	135.5	-	165.0	195.0
Hematocrit (%)								
Baseline (Week -1)	40.05	39.43	40.77	39.00	40.43	41.28	39.17	38.15
Week 4	40.40	42.93	55.65	57.18	42.52	47.93	55.60	57.43
Week 8	40.58	44.53	59.77	57.55	41.70	48.35	59.93	66.28
Week 13 (end of treatment)	40.12	45.18	63.35	63.85	39.70	50.93	65.67	70.03
Week 17 (end of recovery)	44.35	-	50.75	52.35	43.40	-	53.35	65.05
Red Cell Distribution Width (%)								
Baseline (Week -1)	13.47	13.15	13.32	13.03	13.02	12.20	12.67	13.13
Week 4	13.47	13.95	15.72	16.74	13.24	12.63	14.52	16.78
Week 8	13.02	12.88	14.13	15.83	12.65	12.03	13.33	15.15
Week 13 (end of treatment)	13.47	13.03	14.20	17.55	12.88	12.33	14.07	16.10
Week 17 (end of recovery)	13.70	-	15.75	18.45	13.65	-	12.50	16.70

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Cynomolgus Monkey with a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10005

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**5**	**20**	**100**	**0**	**5**	**20**	**100**
Hematology[b] (Continued)								
Reticulocyte Count (10^9/L)								
Baseline (Week -1)	67.45	48.93	58.93	57.05	60.53	51.68	81.23	64.95
Week 4	55.87	92.03	171.75	322.62	55.78	95.00	188.33	319.45
Week 8	66.98	53.38	139.00	289.05	49.30	68.30	119.08	237.92
Week 13 (end of treatment)	52.13	55.13	113.82	236.87	44.70	50.15	127.28	202.57
Week 17 (end of recovery)	51.60	-	16.70	12.60	41.85	-	14.55	12.15
Platelet Count (10^9/L)								
Baseline (Week -1)	472.3	423.0	461.7	420.3	407.7	481.0	438.5	419.0
Week 4	395.5	418.8	429.2	512.2	412.4	486.5	430.8	437.0
Week 8	390.0	368.8	366.7	523.7	413.5	424.5	356.0	322.7
Week 13 (end of treatment)	402.3	392.0	364.7	539.7	384.5	413.8	291.0	239.7 [168; 176]
Week 17 (end of recovery)	511.5	-	400.5	265.5	447.5	-	373.0	292.5
Mean Cell Volume (fL)								
Baseline (Week -1)	73.70	71.00	71.50	70.30	72.07	74.78	74.28	73.53
Week 4	73.37	72.98	75.28	73.30	74.38	77.18	79.17	80.55
Week 8	75.02	74.32	74.30	67.50	73.50	76.18	78.05	75.40
Week 13 (end of treatment)	72.67	71.50	70.45	63.25	71.30	73.93	76.08	74.20
Week 17 (end of recovery)	75.40	-	63.55	60.20	75.60	-	72.80	71.05

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Cynomolgus Monkey with a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10005

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**5**	**20**	**100**	**0**	**5**	**20**	**100**
Hematology[b] (Continued)								
Mean Cell Hemoglobin (pg)								
Baseline (Week -1)	24.03	22.85	23.32	22.22	23.52	23.80	23.97	23.60
Week 4	23.38	22.83	23.12	21.52	23.76	23.78	24.30	24.18
Week 8	23.78	23.33	22.90	19.35	23.53	23.88	24.12	22.88
Week 13 (end of treatment)	23.52	23.28	21.98	18.03	22.75	23.15	23.22	22.55
Week 17 (end of recovery)	23.45	-	18.85	18.25	23.60	-	22.50	21.30
Mean Cell Hemoglobin Concentration (g/L)								
Baseline (Week -1)	326.0	321.8	326.2	316.5	326.5	318.8	322.3	321.0
Week 4	319.0	312.5	307.5	293.2	319.4	308.3	307.0	300.3
Week 8	317.2	313.8	307.8	287.0	320.3	313.5	308.7	302.7
Week 13 (end of treatment)	323.7	325.3	312.0	284.7	319.3	313.3	305.3	303.3
Week 17 (end of recovery)	311.0	-	296.0	304.0	312.5	-	309.0	300.0
Clinical Chemistry[b]								
Triglycerides (mmol/L)								
Baseline (Week -1)	0.507	0.493	0.482	0.533	0.563	0.323	0.477	0.538
Week 4	0.650	0.590	0.663	0.503	0.682	0.630	0.357	0.388
Week 13 (end of treatment)	0.548	0.570	0.632	1.278	0.645	0.555	0.610	0.860
Week 17 (end of recovery)	0.460	-	0.820	0.570	0.590	-	0.600	0.470

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Cynomolgus Monkey with a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10005

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**5**	**20**	**100**	**0**	**5**	**20**	**100**
Clinical Chemistry[b] (Continued)								
Cholesterol (mmol/L)								
Baseline (Week -1)	4.122	3.208	3.800	4.218	3.593	4.190	3.823	3.828
Week 4	4.043	3.015	3.027	2.415	3.680	4.035	2.758	2.365
Week 13 (end of treatment)	3.775	2.695	2.772	2.353	3.483	3.808	3.085	2.185
Week 17 (end of recovery)	5.005	-	2.820	3.270	4.100	-	3.390	3.375
Total Protein (g/L)								
Baseline (Week -1)	72.7	69.0	74.5	77.0 [74]	73.7	76.3	77.5	78.8
Week 4	70.5	67.3	71.5	73.2 [62]	73.8	78.0	73.7	75.2
Week 13 (end of treatment)	68.8	64.8	73.2	69.0 [60]	71.7	73.3	75.7	75.0
Week 17 (end of recovery)	71.5	-	69.0	70.0	73.0	-	72.5	68.5
Albumin (g/L)								
Baseline (Week -1)	47.0	44.0	46.5	48.2 [43]	45.2	48.5	48.2	50.5
Week 4	46.2	42.5	43.5	41.7 [29]	44.2	48.0	43.7	44.0
Week 13 (end of treatment)	44.3	40.3	43.5	33.3 [16]	43.8	46.0	43.8	40.0
Week 17 (end of recovery)	45.0	-	41.0	39.5	44.5	-	41.5	43.0

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Cynomolgus Monkey with a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10005

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**5**	**20**	**100**	**0**	**5**	**20**	**100**
Clinical Chemistry[b] (Continued)								
Calcium (mmol/L)								
Baseline (Week -1)	2.530	2.528	2.615	2.652 [2.64]	2.487	2.618	2.632	2.643
Week 4	2.423	2.460	2.570	2.475 [2.35]	2.442	2.638	2.525	2.467
Week 13 (end of treatment)	2.467	2.435	2.548	2.446 [2.30]	2.433	2.558	2.605	2.473
Week 17 (end of recovery)	2.680	-	2.510	2.480	2.480	-	2.520	2.570
Phosphorus (mmol/L)								
Baseline (Week -1)	2.180	2.250	2.087	2.053 [2.26]	1.932	2.050	1.977	1.900
Week 4	2.227	2.303	2.270	2.072 [2.26]	2.093	2.368	2.035	1.948
Week 13 (end of treatment)	2.283	2.475	2.130	1.840 [1.08]	2.162	2.315	2.188	1.835
Week 17 (end of recovery)	2.420	-	2.395	2.010	1.930	-	2.015	2.145
Alanine Aminotransferase (U/L)								
Baseline (Week -1)	38.5	38.5	33.3	47.3	48.5	38.3	41.0	38.5
Week 4	47.3	44.8	44.7	61.8	50.7	49.0	43.5	58.7
Week 13 (end of treatment)	43.3	43.8	49.7	59.0 [89]	50.2	42.8	66.2	81.5 [113]
Week 17 (end of recovery)	50.5	-	29.5	54.0	70.0	-	38.5	41.0

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Cynomolgus Monkey with a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10005

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**5**	**20**	**100**	**0**	**5**	**20**	**100**
Clinical Chemistry[b] (Continued)								
Glutamate Dehydrogenase (U/L)								
Baseline (Week -1)	16.80	16.35	15.83	18.65	20.63	20.03	18.70	13.45
Week 4	24.73	21.58	20.67	31.48 [60.8]	21.82	35.13	23.62	19.93
Week 13 (end of treatment)	25.13	23.60	18.75	32.88	26.72	25.13	45.17 [117.5]	35.96 [53.7]
Week 17 (end of recovery)	26.85	-	20.75	45.05	36.40	-	25.90	16.05
Organ Weights[c]								
Thymus								
Absolute								
End of Treatment	3.6360g	0.89X	0.80X	0.49X	2.9150g	1.12X	0.99X	0.62X
End of Recovery	3.4820g	-	1.03X	1.12X	2.8550g	-	1.59X	1.16X
Relative to body weight								
End of Treatment	0.15463%	0.77X	0.76X	0.51X	0.12147%	1.12X	0.98X	0.64X

GSK1278863A: A 13 Week Oral Gavage Toxicity Study in the Cynomolgus Monkey with a 4 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10005

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**5**	**20**	**100**	**0**	**5**	**20**	**100**
Microscopic Examination – End of Treatment								
number of animals	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Bone marrow								
Erythroid hypercellularity	0	0	3	3	0	0	3	4
Minimal	0	0	0	0	0	0	1	0
Slight	0	0	1	1	0	0	2	0
Moderate	0	0	2	2	0	0	0	4
Lung								
Hemorrhage	0	0	0	3	1	0	1	2
Minimal	0	0	0	3	1	0	1	2
Thymus								
Lymphoid Atrophy								
Marked	0	0	0	1	0	0	0	0
Microscopic Examination – End of Recovery								
number of animals	**2**	**0**	**2**	**2**	**2**	**0**	**2**	**2**
	Test article-related microscopic findings noted in lung, bone marrow and thymus at the end of the dosing period were not evident in any animals at the end of the 4-week recovery period.							

Key:

- = Not examined or Not applicable.

a = Doses expressed in terms of parent compound.

b = Mean values for control and treated groups are presented for hematology and clinical chemistry data. For parameters where mean values were unaffected but individual animals exhibited test article-related changes, the individual values or range of values for the affected individuals are also presented in brackets.

c = For absolute and relative (to body weight) organ weight data, control group means are shown. For test article-treated groups, change as compared to mean control values (X control) is presented.

Table 8.11 GSK1278863A: 39 Week Oral (Gavage) Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period

Study Type: Repeat Dose Toxicity	**Report Title:** GSK1278863A: A 39 Week Oral (Gavage) Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period	**Test Item:** GSK1278863A (parent compound) **Batch No.:** NE-021129-Batch-01-2009
Species/Strain: Cynomolgus monkeys, *Macaca fascicularis* (Chinese origin)	**Duration of Dosing:** 39 weeks **Duration of Recovery:** 6 weeks	**GSK Reference No.:** G10277
Initial Age: 2.7 to 3.9 years old at onset of dosing	**Route/Frequency:** Oral by gavage, once daily	**GSK Document Number:** 2011N126131 **Location in CTD:** m4.2.3.2
Date of First Dose: 1 March 2011	**Vehicle/Formulation:** 1% w/v methylcellulose (400 cps) in ultra pure water	**Study in Compliance with GLP:** Yes

Data Collected: Toxicokinetics, clinical observations, body weight, food evaluation, ophthalmoscopy, electrocardiography, hematology, clinical chemistry, urinalysis, serum cardiac troponin I, organ weights, macroscopic and microscopic pathology.

Conclusion: GSK1278863A (vehicle, 3, 10 and 50 mg/kg/day, as parent compound) was administered daily by oral gavage to male and female cynomolgus monkey of Chinese origin for 39 weeks followed by a 6 week recovery period.

Pharmacologically-mediated changes including bone marrow erythroid hypercellularity with associated increases in red blood cell mass were observed at all doses, but were more pronounced at ≥10 mg/kg/day. Microscopic evidence of multi-organ congestion, gastric hemorrhage and erosions/ulcerations, mononuclear cell infiltrates in the choroid plexus (compatible with previous hemorrhage) and inflammation/active hemorrhage in the brainstem were noted at ≥10 mg/kg/day.

Findings at 3 mg/kg/day were limited to pharmacologically-mediated increased bone marrow erythroid cellularity and red blood cell mass. These changes were of lower magnitude and were not associated with secondary changes or other findings seen at higher doses; therefore, the no observed adverse effect level (NOAEL) for this study was considered to be 3 mg/kg/day (mean $AUC_{0\text{-}t}$ 3.49 μg.h/mL, range 1.67 to 5.83 and mean C_{max} 0.655 μg/mL, range 0.282 to 1.02 [gender averaged, based on Week 39 values]).

GSK1278863A: 39 Week Oral (Gavage) Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10277

Daily Dose (mg/kg/day)[a]		Male 0	Male 3	Male 10	Male 50	Female 0	Female 3	Female 10	Female 50
Numbers of Animals:	Main	4	4	4	4	4	4	4	4
	Recovery	2	-	-	2	2	-	-	2
AUC_{0-t} (µg.h/mL):	Day 1	NC	2.37	9.49	43.5	NC	3.46	12.4	50.7
	Week 4	NC	4.76	14.1	53.5	NC	2.51	14.1	50.0
	Week 26	NC	5.96	6.52	41.7	NC	2.68	13.0	43.7
	Week 39	NC	4.55[a]	7.76	30.2	NC	2.69	11.2	29.4
C_{max} (µg/mL):	Day 1	NC	0.771	1.66	5.15	NC	0.960	2.62	5.52
	Week 4	NC	1.80	1.78	4.76	NC	0.887	2.71	4.30
	Week 26	NC	1.03	1.01	2.62	NC	0.566	2.12	3.01
	Week 39	NC	0.829[a]	0.972	2.44	NC	0.524	1.62	2.72
Noteworthy Findings:									
Unscheduled Deaths:	Main	0	1[a]	0	0	0	0	0	0
	Recovery	0	-	-	0	0	-	-	0

Clinical Observations:	At 50 mg/kg/day, generalized cranial skin reddening, not associated to a lesion and/or a scab, was noted starting at Weeks 7 and 11 for males and females, respectively. These observations progressed until most males (5 out of 6) and all females were affected. The generalized reddening also affected other locations such as but not limited to: gums and/or mouth, forelimbs, hindlimbs, abdominal area and ventral thoracic and/or cervical region. All males and one female given 10 mg/kg/day were also affected starting at Week 15. Recovery study animals, which were all affected during the dosing period, showed signs of a complete recovery following the 6 week recovery period. Between Week 20 and 22 (Day 138 to Day 149), Female No. 453 given 50 mg/kg/day was observed with red skin at the right periorbital area and right eyelid, a partly closed right eye, soft swelling of the upper right eyelid and periorbital area and with right pupil constriction. Skin redness of the upper lip was also noted. Despite normal eye position, direct and consensual pupillary light reflexes, corneal reflex and nasal septum test, Female No. 453 had partly closed right eye (ptosis of the right upper eyelid) and anisocoria (mydriasis of the right pupil).

GSK1278863A: 39 Week Oral (Gavage) Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** G10277

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**3**	**10**	**50**	**0**	**3**	**10**	**50**
Absolute Body Weight Gain[b]:								
Main (Weeks 1 to 39)	0.75 kg	0.93X	0.60X	0.73X	0.45 kg	0.78X	0.22X	0.29X
Recovery (Weeks 39 to 45)	0.30 kg	-	-	1.00X	0.05 kg	-	-	9X
Ophthalmoscopy:	At the end of the dosing period (Week 39), the majority of monkeys given ≥10 mg/kg/day had congestion of the retinal vessels, including all 50 mg/kg/day monkeys (2/sex) retained throughout the recovery period. Hyperemia of the optic disc was also noted in the majority of monkeys given 50 mg/kg/day in Week 39, including 1 of 2 males and both females retained throughout the recovery period. By the end of the recovery period, retinal vessel congestion and optic disc hyperemia were either no longer evident or were reduced in severity in the previously affected animals.							
Hematology:								
Red blood cell count (10^{12}/L)								
Baseline (Week -1)	5.572	5.635	5.415	5.735	5.368	5.185	5.245	5.088
Week 4	5.687	6.323	7.323	7.978	5.758	5.888	6.748	7.767
Week 13	6.173	6.635	8.895	10.763	5.958	6.050	8.475	10.743
Week 26	5.625	6.078	8.870	10.183	5.405	5.798	8.035	9.995
Week 39 (end of dosing)	5.745	6.643	8.708	10.168	5.710	5.900	7.988	9.940
Week 45 (end of recovery)	5.740	-	-	7.705	5.655	-	-	7.720
Hemoglobin (g/L)								
Baseline (Week -1)	133.0	134.0	131.3	132.3	126.7	128.5	129.0	122.0
Week 4	135.0	147.5	175.5	175.5	135.2	142.5	164.5	183.3
Week 13	141.3	152.0	206.5	208.8	136.0	143.3	199.3	226.7
Week 26	139.7	147.5	220.3	229.3	131.5	146.0	204.3	241.5
Week 39 (end of dosing)	141.7	162.3	220.8	230.2	137.2	147.5	202.3	243.5
Week 45 (end of recovery)	142.5	-	-	182.0	135.0	-	-	172.0

GSK1278863A: 39 Week Oral (Gavage) Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10277

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**3**	**10**	**50**	**0**	**3**	**10**	**50**
Hematology (Continued):								
Hematocrit (%) Baseline (Week -1)	40.40	41.15	39.50	41.25	38.55	39.55	39.53	37.80
Week 4	40.77	45.40	55.65	58.02	41.22	44.65	52.10	59.62
Week 13	43.83	47.65	65.78	70.98	42.47	45.58	63.60	74.93
Week 26	41.77	44.18	66.05	72.27	39.25	44.60	61.40	73.17
Week 39 (end of dosing)	42.35	48.73	65.80	72.24	41.62	45.78	60.10	73.63
Week 45 (end of recovery)	44.95	-	-	58.50	42.95	-	-	54.25
Red blood cell distribution width (%)								
Baseline (Week -1)	12.85	12.63	13.23	12.72	12.50	12.60	12.88	12.93
Week 4	12.53	12.58	13.83	15.32	12.37	12.28	13.25	14.83
Week 13	12.38	12.40	13.25	16.60	12.18	12.23	12.70	14.10
Week 26	12.25	12.13	13.13	16.80	11.87	11.93	13.00	14.60
Week 39 (end of dosing)	12.33	12.57	12.83	15.66	11.87	11.90	12.63	14.17
Week 45 (end of recovery)	11.90	-	-	13.50	11.75	-	-	13.70
Reticulocyte count (10^9/L)								
Baseline (Week -1)	78.23	81.08	101.65	75.48	87.20	77.55	88.28	85.33
Week 4	52.02	67.07	225.33	344.55	65.45	55.03	167.75	350.85
Week 13	49.38	54.63	160.85	258.95	70.42	67.10	129.00	194.30
Week 26	58.35	67.98	160.73	263.85	76.65	52.50	141.03	200.07
Week 39 (end of dosing)	59.77	80.87	132.43	194.98	66.87	54.88	119.95	186.60
Week 45 (end of recovery)	54.20	-	-	18.95	39.50	-	-	21.25
Platelet count (10^9/L)								
Baseline (Week -1)	501.0	439.3	429.5	404.2	481.8	451.3	405.3	469.8
Week 4	401.3	399.0	421.5	505.8	456.2	440.3	385.8	444.8
Week 13	457.7	381.0	327.8	375.7	471.7	385.5	355.8	318.0
Week 26	448.5	379.8	327.0	300.3	459.2	398.5	314.3	262.8
Week 39 (end of dosing)	456.5	412.3	323.0	279.6	482.2	405.3	332.0	276.3
Week 45 (end of recovery)	538.0	-	-	310.5	481.5	-	-	367.0

GSK1278863A: 39 Week Oral (Gavage) Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10277

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**3**	**10**	**50**	**0**	**3**	**10**	**50**
Hematology (Continued):								
Lymphocyte count (10^9/L)								
Baseline (Week -1)	6.850	4.358	3.963	4.283	5.282	6.045	3.253	4.980
Week 4	5.188	5.018	3.210	3.702	5.032	6.308	3.005	4.335
Week 13	7.095	6.473	4.308	4.922	5.650	7.028	3.500	4.015
Week 26	6.645	6.085	4.225	4.420	5.283	5.830	3.228	3.313
Week 39 (end of dosing)	7.163	5.977	4.548	5.222	5.427	6.530	4.113	4.057
Week 45 (end of recovery)	6.535	-	-	6.500	4.955	-	-	7.675
Clinical Chemistry:								
Alkaline phosphatase (U/L)								
Baseline (Week -1)	509.8	606.0	549.5	693.0	326.2	435.3	352.3	407.5
Week 4	555.0	714.0	665.0	862.8	337.0	459.8	379.5	423.2
Week 13	616.2	765.8	806.0	1033.8	311.8	423.3	379.0	495.6
Week 26	585.3	558.8	825.0	1198.0	247.5	344.8	382.3	441.0
Week 39 (end of dosing)	690.0	629.3	832.0	1179.3	247.7	336.3	296.0	397.5
Week 45 (end of recovery)	501.5	-	-	797.5	218.5	-	-	337.0
Total bilirubin (μmol/L)								
Baseline (Week -1)	3.7	4.3	4.0	4.2	3.3	3.5	3.3	3.8
Week 4	3.8	3.5	4.3	5.7	3.7	2.8	4.5	3.8
Week 13	3.3	3.3	4.5	6.8	2.7	2.5	4.5	8.2
Week 26	3.2	2.8	6.5	9.0	2.5	2.5	5.0	10.7
Week 39 (end of dosing)	3.2	3.3	4.5	9.7	3.0	2.3	5.3	8.5
Week 45 (end of recovery)	4.0	-	-	7.5	4.0	-	-	6.5

GSK1278863A: 39 Week Oral (Gavage) Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10277

Daily Dose (mg/kg/day)[a]		Male 0	Male 3	Male 10	Male 50	Female 0	Female 3	Female 10	Female 50
Clinical Chemistry (Continued):									
Glucose (mmol/L)	Baseline (Week -1)	3.85	3.28	3.33	2.90	3.35	3.20	3.18	3.17
	Week 4	3.42	3.18	2.30	2.62	3.07	3.60	2.60	3.13
	Week 13	2.98	3.10	3.18	2.62	3.18	3.48	2.98	2.50
	Week 26	2.73	2.95	2.65	2.53	3.15	2.90	3.30	2.28
	Week 39 (end of dosing)	3.25	3.30	2.93	2.50	3.35	3.40	3.23	2.88
	Week 45 (end of recovery)	3.00	-	-	2.50	3.25	-	-	3.25
Total iron (μg/dL)									
	Baseline (Week -1)	158.0	160.5	134.5	109.8	139.8	135.8	136.8	114.3
	Week 4	131.2	157.0	80.3	41.2	130.3	153.5	102.5	63.8
	Week 13	133.5	173.0	153.8	64.2	136.0	134.3	138.0	81.3
	Week 26	112.8	151.5	180.3	103.0	123.2	146.3	162.5	118.0
	Week 39 (end of dosing)	149.8	156.0	175.0	129.0	141.7	195.0	171.3	176.8
	Week 45 (end of recovery)	160.0	-	-	223.0	144.5	-	-	263.5
Total iron binding capacity (μg/dL)									
	Baseline (Week -1)	429.5	390.8	379.0	381.5	386.5	398.8	392.5	376.0
	Week 4	387.0	392.3	421.0	544.0	352.7	389.5	428.8	514.2
	Week 13	332.3	345.3	384.5	508.0	325.0	334.0	395.0	513.3
	Week 26	305.2	309.0	480.8	405.5	292.5	324.3	398.5	444.0
	Week 39 (end of dosing)	361.2	364.3	416.3	374.0	337.3	358.5	408.3	519.5
	Week 45 (end of recovery)	370.0	-	-	232.0	327.5	-	-	NC

GSK1278863A: 39 Week Oral (Gavage) Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10277

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**3**	**10**	**50**	**0**	**3**	**10**	**50**
Clinical Chemistry (Continued):								
Unsaturated iron binding capacity (μg/dL)								
Baseline (Week -1)	271.5	230.3	244.5	271.7	246.7	263.0	255.8	261.7
Week 4	255.8	235.3	340.8	502.8	222.3	236.0	326.3	450.4
Week 13	198.8	172.3	230.8	443.8	189.0	199.8	257.0	432.0
Week 26	192.3	157.5	300.5	302.5	169.3	178.0	236.0	258.0
Week 39 (end of dosing)	211.3	208.3	241.3	259.0	195.7	163.5	237.0	342.8
Week 45 (end of recovery)	210.0	-	-	14.0	183.0	-	-	NC
Microscopic Examination - End of Dosing (Number of Animals):	**4**	**4[a]**	**4**	**4**	**4**	**4**	**4**	**4**
Bone Marrow								
Hypercellularity: Erhythroid								
Minimal	0	1	1	0	0	0	2	3
Slight	0	0	2	0	0	0	0	0
Moderate	0	0	0	4	0	0	0	1
Brain								
Inflammation: Subacute								
Slight	0	0	0	0	0	0	0	1
Infiltration: Choroid plexus								
Minimal	0	0	1	3	0	0	0	4
Slight	0	0	0	1	0	0	0	0
Kidney								
Deposits: Pigment Minimal	0	0	0	3	0	0	1	1
Moderate	0	0	0	1	0	0	0	0
Hyperthrophy/hyperplasia: Arteriolar Slight	0	0	0	1	0	0	0	0

GSK1278863A: 39 Week Oral (Gavage) Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10277

		Male				Female			
Daily Dose (mg/kg/day)[a]		**0**	**3**	**10**	**50**	**0**	**3**	**10**	**50**
Kidney Prussian Blue									
(Number of Animals):		**1**	**0**	**0**	**2**	**1**	**0**	**0**	**1**
Positive	Minimal	0	-	-	0	0	-	-	1
	Marked	0	-	-	1	0	-	-	0
Muscle Skeletal									
Degeneration/necrosis: Myofiber									
	Minimal	2	1	0	1	0	0	0	1
	Slight	0	0	0	1	0	0	0	0
Regeneration: Myofiber									
	Minimal	0	0	0	3	0	0	0	2
	Slight	0	0	0	1	0	0	0	0
Stomach									
Hemorrhage	Minimal	0	0	1	1	0	0	1	2
	Slight	0	0	1	1	0	0	0	0
Erosion/ulceration: Glandular mucosa									
	Minimal	0	0	0	2	0	0	0	0
Whole Body									
Congestion	Minimal	0	0	3	2	0	0	2	2
	Slight	0	0	0	2	0	0	1	2

GSK1278863A: 39 Week Oral (Gavage) Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10277

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**3**	**10**	**50**	**0**	**3**	**10**	**50**
Microscopic Examination - End of Recovery (Number of Animals):	**2**	**-**	**-**	**2**	**2**	**-**	**-**	**2**
Brain								
Infiltration: Choroid plexus								
Minimal	0	-	-	1	0	-	-	0
Kidney								
Deposits: Pigment Minimal	0	-	-	1	0	-	-	1
Slight	0	-	-	1	0	-	-	0
Liver								
Deposits: Pigment								
Slight	0	-	-	1	0	-	-	0
Muscle Skeletal								
Regeneration: Myofiber								
Minimal	0	-	-	2	1	-	-	0
Spleen								
Hematopoiesis/extramedullary: Increased								
Moderate	0	-	-	1	0	-	-	0
Deposits: Pigment								
Minimal	0	-	-	1	0	-	-	0
Stomach								
Hemorrhage								
Minimal	1	-	-	1	0	-	-	0

GSK1278863A: 39 Week Oral (Gavage) Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity | **GSK Reference No.:** G10277

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**3**	**10**	**50**	**0**	**3**	**10**	**50**
Whole Body								
Congestion								
Minimal	0	-	-	1	0	-	-	1

Key:

a = One male given 3 mg/kg/day was euthanized in a poor and deteriorating clinical condition in Week 38. Clinical pathology changes were consistent with protein loss and correlated with clinical signs of poor health status. In the absence of similar findings and/or mortality in higher dose groups, moribundity was considered unrelated to test article. As this decedent had microscopic changes that were similar to other animals in that dose group at the end of the dosing period, its microscopic findings are presented with findings from the end of the dosing period. N=3 for toxicokinetic parameters in Week 39 since this animal was euthanized prior to blood sampling.

b = For controls, group means are shown; for treated groups, X change as compared to controls.

- = Not examined/not applicable.

NC = Not calculated/Not Measured.

9. GENOTOXICITY: IN VITRO

Table 9.1 GSK1278863A: Bacterial Mutation Assay (Ames Test) with Salmonella typhimurium and Escherichia coli

Genotoxicity: In Vitro

Test for Induction of: Reverse mutation in bacterial cells

Report Title: GSK1278863A: Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

No. of Independent Assays: 2

Test Compound: GSK1278863A (parent compound)
Batch Number: NE-021129-Batch-01-2007
Covance Study No.: 2990/236
GSK Reference No.: V27887
GSK Document Number: WD2007/01575

Strain: *S. typhimurium* and *E. coli*

No. of Replicate Plates: 3 (6 vehicle control, 3 positive control)

Location in CTD: m4.2.3.3.1

Metabolising System: Aroclor-induced rat liver S9-mix containing 50 μL S9 fraction/plate (final)
Vehicles: Test Article: Dimethylformamide (DMF)
Positive Controls: Dimethylsulphoxide (DMSO) or water
Treatment: Plate incorporation for 3 days

GLP Compliance: Yes

Date of Treatment: November to December 2007

Cytotoxic Effects: Reduction in revertant numbers at 500 μg/plate for most *S. typhimurium* strains in the absence and/or presence of S9
Mutagenic Effects: Negative

Metabolic Activation	Test Compound	Concentration (μg/plate)[1]	Main Plate Incorporation (Ames) Test 1 Mean Number of Revertant Colonies Per Plate				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* pKM101
Without Activation	DMF	100 μL/plate	29	115	19	10	136
	GSK1278863	5	24	115	15	13	142
	GSK1278863	15	23	101	14	12	146
	GSK1278863	50	24	117	23	12	160
	GSK1278863	150	21	105	20	11	136
	GSK1278863	500	20[3]	62[3]	10[3]	9[3]	129[3]
	2-nitrofluorene	5	1472[2]	NT	NT	NT	NT
	Sodium azide	2	NT	966[2]	729[2]	NT	NT
	9-aminoacridine	50	NT	NT	NT	354[2]	NT
	4-nitroquinoline-1-oxide	2	NT	NT	NT	NT	1522[2]

Key:
1 = All concentrations are expressed in terms of parent compound.
2 = ≥2-fold increase in revertants for TA98, TA100 and WP2 *uvrA* (pKM101) and ≥3-fold increase for TA1535 and TA1537.
3 = Precipitation observed by eye on the test plates at the end of incubation.
NT = Not treated.

GSK1278863A: Bacterial Mutation Assay (Ames Test) with Salmonella typhimurium and Escherichia coli (Cont'd)

Genotoxicity: In Vitro

Report Title: GSK1278863A: Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

Test Compound: GSK1278863A

Batch Number: NE-021129-Batch-01-2007

Metabolic Activation	Test Compound	Concentration (μg/plate)[1]	Main Plate Incorporation (Ames) Test 1 Mean Number of Revertant Colonies Per Plate				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* pKM101
With Activation	DMF	100 μL/plate	31	112	16	14	184
	GSK1278863	5	24	118	15	13	179
	GSK1278863	15	40	119	17	9	179
	GSK1278863	50	36	96	15	15	172
	GSK1278863	150	24	111	13	14	185
	GSK1278863	500	22[3]	40[3]	9[3]	6[3]	185[3]
	Benzo[a]pyrene	10	373[2]	NT	NT	NT	NT
	2-aminoanthracene	5	NT	1468[2]	319[2]	125[2]	NT
	2-aminoanthracene	10	NT	NT	NT	NT	947[2]

Key:

1 = All concentrations are expressed in terms of parent compound.

2 = ≥2-fold increase in revertants for TA98, TA100 and WP2 *uvrA* (pKM101) and ≥3-fold increase for TA1535 and TA1537.

3 = Precipitation observed by eye on the test plates at the end of incubation.

NT = Not treated.

GSK1278863A: Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK1278863A: Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

Test Compound: GSK1278863A

Batch Number: NE-021129-Batch-01-2007

Metabolic Activation	Test Compound	Concentration (μg/plate)[1]	Main Plate Incorporation (Ames) Test 2 Mean Number of Revertant Colonies Per Plate				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* pKM101
Without Activation	DMF	100 μL/plate	22	98	14	9	155
	GSK1278863	5	21	89	12	9	196
	GSK1278863	15	20	94	13	7	154
	GSK1278863	50	22	96	11	7	215
	GSK1278863	150	20	96	9	8	182
	GSK1278863	500	11[3]	44[3]	6[3]	3[3]	149[3]
	2-nitrofluorene	5	1527[2]	NT	NT	NT	NT
	Sodium azide	2	NT	842[2]	665[2]	NT	NT
	9-aminoacridine	50	NT	NT	NT	462[2]	NT
	4-nitroquinoline-1-oxide	2	NT	NT	NT	NT	743[2]

Key:

1 = All concentrations are expressed in terms of parent compound.

2 = ≥2-fold increase in revertants for TA98, TA100 and WP2 *uvrA* (pKM101) and ≥3-fold increase for TA1535 and TA1537.

3 = Precipitation observed by eye on the test plates at the end of incubation.

NT = Not treated.

GSK1278863A: Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro **Report Title:** GSK1278863A: Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* **Test Compound:** GSK1278863A **Batch Number:** NE-021129-Batch-01-2007

Metabolic Activation	Test Compound	Concentration (μg/plate)[1]	Main Plate Incorporation (Ames) Test 2 Mean Number of Revertant Colonies Per Plate				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* pKM101
With Activation	DMF	100 μL/plate	35	111	19	14	190
	GSK1278863	5	31	105	18	19	179
	GSK1278863	15	33	108	14	16	169
	GSK1278863	50	27	123	22	13	183
	GSK1278863	150	27	98	13	14	165
	GSK1278863	500	18[3]	20[3]	14[3]	6[3]	146[3]
	Benzo[a]pyrene	10	373[2]	NT	NT	NT	NT
	2-aminoanthracene	5	NT	1549[2]	291[2]	146[2]	NT
	2-aminoanthracene	10	NT	NT	NT	NT	638[2]

Key:
1 = All concentrations are expressed in terms of parent compound.
2 = ≥2-fold increase in revertants for TA98, TA100 and WP2 *uvrA* (pKM101) and ≥3-fold increase for TA1535 and TA1537.
3 = Precipitation observed by eye on the test plates at the end of incubation.
NT = Not treated.

Table 9.2 GSK1278863A: In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus

Genotoxicity: In Vitro	**Report Title:** GSK1278863A: In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus	**Test Article:** GSK1278863A (parent compound) **Batch Number:** NE-021129-Batch-01-2007
Test for Induction of: Forward mutation at the $TK^{+/-}$ locus	**No. of Independent Tests:** 3	**Covance Study No.:** 2990/237 **GSK Ref No.:** V27888 **GSK Document Number:** WD2007/01578
Cell Type: L5178Y mouse lymphoma cells	**No. of Replicate Cultures:** 4 (vehicle); 2 (treatment and positive controls)	**Location in CTD:** m4.2.3.3.1

Metabolising System: Aroclor-induced rat liver S9-mix. Final concentration of S9 fraction in cultures = 2% v/v.

Vehicles: Test Article: Dimethylformamide (DMF) **Positive Controls:** Dimethylsulphoxide (DMSO)	**GLP Compliance:** Yes
Treatment: 3 hour treatment with and without S9-mix; treatment for 24 hours without S9-mix.	**Date of Treatment(s):** November to December 2007

Cytotoxic Effects: Relative total growth (RTG) was reduced to 17% at 70 μg/mL for 3 hour treatments in the absence of S9-mix, 11% at 70 μg/mL for 3 hour treatments in the presence of S9-mix and 17% at 30 μg/mL for 24 hour treatments in the absence of S9-mix.

Genotoxic Effects: Negative

GSK1278863A: In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus (Continued)

Genotoxicity: In Vitro

Report Title: GSK1278863A: In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus

Test Article: GSK1278863A
Batch Number: NE-021129-Batch-01-2007

Test Article	3 Hour Treatment -S9-Mix		3 Hour Treatment +S9-Mix		24 Hour Treatment -S9-Mix		
	Dose Level[1] (μg/mL)	Mean Relative Total Growth (%)	Mean Mutant Frequency ($x10^{-6}$)	Mean Relative Total Growth (%)	Mean Mutant Frequency ($x10^{-6}$)	Dose Level[1] (μg/mL)	Mean Relative Total Growth (%)	Mean Mutant Frequency ($x10^{-6}$)
Untreated controls[2]	0	118	73.95	128	71.85	0	304	74.17
DMF	0	100	63.57	100	73.79	0	100	93.62
GSK1278863	10	103	66.68	106	NE	5	100	68.52
GSK1278863	20	56	78.21	126	NE	10	79	75.17
GSK1278863	30	47	NE	110	71.12	20	43	75.75
GSK1278863	40	47	64.08	88	84.19	25	30	95.15
GSK1278863	50	43	NE	63	78.63	30	17	144.04
GSK1278863	60	37	79.31	37	84.85	NT	NT	NT
GSK1278863	70	17	77.24	11	82.33	NT	NT	NT
Methyl methane sulphonate	15	61	502.83	NT	NT	NT	NT	NT
Methyl methane sulphonate	NT	NT	NT	NT	NT	5	104	588.94
Benzo[a]pyrene	2	NT	NT	45	817.51	NT	NT	NT

Key:
1 = All concentrations are expressed in terms of parent compound.
2 = Untreated controls contained culture medium.
NE = Not evaluated for mutant frequency.
NT = Not tested.

Table 9.3 GSK2391220A (M2 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

Genotoxicity: In Vitro	**Report Title:** GSK2391220A (M2 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.	**Test article:** GSK2391220 (parent) **Batch Number:** H10694-011
Test for Induction of: Reverse mutation in bacterial cells	**No. of Independent Tests:** 2	**Study No:** V29664 **GSK Document No.:** 2011N120130
Strain: *S. typhimurium* and *E. coli*	**No. of Replicate Plates:** **Dose Range Plate Incorporation Test:** 2 (4 vehicle control, 2 positive control) **Main Plate Incorporation Test:** 3 (6 vehicle control, 2 positive control)	**Location in CTD:** m4.2.3.7.5

Metabolising System: Phenobarbital, 5-6 Benzoflavone-induced rat liver S9-mix containing 100 μL S9 fraction per mL

Vehicles Test article: Dimethyl sulphoxide (DMSO) **Positive Controls:** DMSO or Sterile Water **GLP Compliance:** Yes

Treatment: Plate incorporation for 3 days **Date of Treatment:** June , July 2011

Cytotoxic Effects: None

Mutagenic Effects: Not mutagenic

GSK2391220A (M2 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2391220A (M2 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2391220 (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Dose Range Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Without Activation	DMSO	100 μl/plate	98.3	19.3	17.5	34.0	102.8
	GSK2391220	50	113.0	23.0	13.0	32.0	98.0
	GSK2391220	150	103.0	24.5	16.5	26.5	95.0
	GSK2391220	500	112.0	20.5	18.0	29.0	101.5
	GSK2391220	1500	122.0	22.5	17.5	36.0	100.5
	GSK2391220	2500	126.0	27.5	24.0	35.5	99.5
	GSK2391220	5000	81.0[3]	20.5	17.5	22.5	94.0
	2-Nitrofluorene	1	NT	NT	NT	280.0[2]	NT
	Sodium azide	2	920.0[2]	1128.0[2]	NT	NT	NT
	9-Amino acridine	50	NT	NT	1226.0[2]	NT	NT
	4-Nitroquinoline-1-oxide	2	NT	NT	NT	NT	4151.5[2]

Key:
1 = Expressed in terms of parent compound.
2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.
3 = Slight precipitation observed by eye on the test plates at the end of incubation.
NT = Not tested.

GSK2391220A (M2 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2391220A (M2 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2391220 (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Dose Range Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
With Activation	DMSO	100 μl/plate	101.0	24.7	25.0	50.3	153.3
	GSK2391220	50	91.0	25.0	31.5	45.5	164.0
	GSK2391220	150	96.5	20.0	26.5	42.5	168.0
	GSK2391220	500	102.0	20.0	23.0	43.5	154.5
	GSK2391220	1500	81.5	20.0	23.5	35.0	167.5
	GSK2391220	2500	79.5	20.0	29.5	41.0	157.0
	GSK2391220	5000	96.5	24.0	14.5	51.0	144.5
	Benzo(a)pyrene	10	NT	NT	NT	396.5[2]	NT
	2-Aminoanthracene	5	3841.0[2]	485.0[2]	178.0[2]	NT	NT
	2-Aminoanthracene	10	NT	NT	NT	NT	1621.5[2]

Key:
1 = Expressed in terms of parent compound.
2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.
NT = Not tested.

GSK2391220A (M2 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2391220A (M2 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2391220A (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Main Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Without Activation	DMSO	100 μl/plate	106.7	18.8	9.5	30.7	117.5
	GSK2391220	150	108.0	21.3	13.0	27.0	113.0
	GSK2391220	500	109.3	19.3	11.7	29.3	103.7
	GSK2391220	1500	101.7	15.7	14.0	32.7	120.0
	GSK2391220	2500	113.0	19.7	16.7	43.3	103.7
	GSK2391220	5000	140.7	16.7	13.3	43.3	109.0
	2-Nitrofluorene	1	NT	NT	NT	259.5[2]	NT
	Sodium azide	2	980.5[2]	970.5[2]	NT	NT	NT
	9-Amino acridine	50	NT	NT	507.0[2]	NT	NT
	4-Nitroquinoline-1-oxide	2	NT	NT	NT	NT	4480.5[2]

Key:
1 = Expressed in terms of parent compound.
2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.
NT = Not tested.

GSK2391220A (M2 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2391220A (M2 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2391220A (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Main Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
With Activation	DMSO	100 μl/plate	74.8	17.0	38.2	49.0	187.8
	GSK2391220	150	78.0	14.3	23.0	39.7	179.0
	GSK2391220	500	75.0	17.3	32.7	40.3	181.3
	GSK2391220	1500	79.3	16.3	18.3	39.0	184.7
	GSK2391220	2500	87.3	20.7	23.3	42.7	151.3
	GSK2391220	5000	79.7	12.3	27.3	58.3	160.0
	Benzo(a)pyrene	10	NT	NT	NT	389.5[2]	NT
	2-Aminoanthracene	5	322.5[2]	88.0[2]	217.0[2]	NT	NT
	2-Aminoanthracene	10	NT	NT	NT	NT	1480.0[2]

Key:
1 = Expressed in terms of parent compound.
2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.
NT = Not tested.

Table 9.4 GSK2506104A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

Genotoxicity: In Vitro	**Report Title:** GSK2506104A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.	**Test article:** GSK2506104A (M3 metabolite of GSK1278863A) (parent) **Batch Number:** H10694-065
Test for Induction of: Reverse mutation in bacterial cells	**No. of Independent Tests:** 2	**Study No:** V29751 **GSK Document No.:** 2011N119269
Strain: *S. typhimurium* and *E. coli*	**No. of Replicate Plates:** **Dose Range Plate Incorporation Test:** 2 (4 vehicle control, 2 positive control **Main Plate Incorporation Test:** 3 (6 vehicle control, 2 positive control)	**Location in CTD:** m4.2.3.7.5

Metabolising System: Phenobarbital, 5-6 Benzoflavone-induced rat liver S9-mix containing 100 μL S9 fraction per mL

Vehicles Test article: Dimethyl sulphoxide (DMSO) **Positive Controls:** DMSO or Sterile Water **GLP Compliance:** Yes

Treatment: Plate incorporation for 3 days **Date of Treatment:** June 2011

Cytotoxic Effects: None

Mutagenic Effects: Not mutagenic

GSK2506104A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2506104A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2506104A (M3 metabolite of GSK1278863A) (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Dose Range Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Without Activation	DMSO	100 μl/plate	93.8	20.3	11.3	34.0	83.0
	GSK2506104	50	105.5	15.0	7.5	30.5	100.5
	GSK2506104	150	104.5	16.5	9.0	30.0	82.5
	GSK2506104	500	90.0	16.0	15.0	27.0	90.0
	GSK2506104	1500	109.5	14.0	14.0	22.5	91.0
	GSK2506104	2500	126.0	22.0	12.5	25.5	88.5
	GSK2506104	5000	107.5	15.5	9.5	24.0	76.5
	2-Nitrofluorene	1	NT	NT	NT	355.0[2]	NT
	Sodium azide	2	1025.5[2]	1023.0[2]	NT	NT	NT
	9-Aminoacridine	50	NT	NT	600.5[2]	NT	NT
	4NQO	2	NT	NT	NT	NT	4048.5[2]

Key:

1 = Expressed in terms of parent compound.

2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.

NT = Not tested.

GSK2506104A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2506104A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2506104A (M3 metabolite of GSK1278863A) (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Dose Range Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
With Activation	DMSO	100 μl/plate	70.3	15.3	22.0	34.3	156.3
	GSK2506104	50	80.5	14.0	18.0	43.5	122.5
	GSK2506104	150	89.5	16.0	19.5	49.0	148.0
	GSK2506104	500	81.5	20.5	12.0	38.0	145.5
	GSK2506104	1500	83.0	15.0	20.0	40.5	143.5
	GSK2506104	2500	87.0	13.0	19.0	42.0	149.5
	GSK2506104	5000	96.0	21.0	11.0[3]	34.0	138.0
	Benzo(a)pyrene	10	NT	NT	NT	421.5[2]	NT
	2-Aminoanthracene	5	1607.5[2]	354.5[2]	96.5[2]	NT	NT
	2-Aminoanthracene	10	NT	NT	NT	NT	2005.0[2]

Key:

1 = Expressed in terms of parent compound.

2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.

3 = Slight toxicity seen, i.e., slight thinning of the background lawn.

NT = Not tested.

GSK2506104A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2506104A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2506104A (M3 metabolite of GSK1278863A) (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Main Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Without Activation	DMSO	100 μl/plate	80.7	19.0	14.0	38.2	118.7
	GSK2506104	150	87.0	17.7	8.0	47.0	121.7
	GSK2506104	500	90.7	17.7	13.7	44.0	105.3
	GSK2506104	1500	96.7	21.7	16.0	34.3	125.7
	GSK2506104	2500	98.7	20.3	11.7	35.0	128.7
	GSK2506104	5000	91.7	16.3	13.7	34.3	123.3
	2-Nitrofluorene	1	NT	NT	NT	247.5[2]	NT
	Sodium azide	2	1021.5[2]	854.0[2]	NT	NT	NT
	9-Aminoacridine	50	NT	NT	814.0[2]	NT	NT
	4NQO	2	NT	NT	NT	NT	3526.0[2]

Key:
1 = Expressed in terms of parent compound.
2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.
NT = Not tested.

GSK2506104A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2506104A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2506104A (M3 metabolite of GSK1278863A) (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Main Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
With Activation	DMSO	100 μl/plate	70.7	19.8	38.0	61.7	188.3
	GSK2506104	150	62.3	17.3	33.7	53.7	188.3
	GSK2506104	500	69.0	23.7	42.7	55.7	220.3
	GSK2506104	1500	84.0	14.3	34.0	66.3	205.3
	GSK2506104	2500	77.3	16.7	41.3	53.3	180.7
	GSK2506104	5000	67.3	21.0	37.0	54.0	185.3
	Benzo(a)pyrene	10	NT	NT	NT	426.5[2]	NT
	2-Aminoanthracene	5	2737.0[2]	171.0[2]	152.5[2]	NT	NT
	2-Aminoanthracene	10	NT	NT	NT	NT	1932.0[2]

Key:
1 = Expressed in terms of parent compound.
2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.
NT = Not tested.

Table 9.5 GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

Genotoxicity: In Vitro	**Report Title:**	GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.	**Test article:** GSK2531403A (M3 metabolite of GSK1278863A) (parent) **Batch Number:** N19791-23P1
Test for Induction of: Reverse mutation in bacterial cells		**No. of Independent Tests:** 3	**Study No:** V29666 **GSK Document No.:** 2011N119441
Strain: *S. typhimurium* and *E. coli*		**No. of Replicate Plates:** **Dose Range Plate Incorporation Test:** 2 (4 vehicle control, 2 positive control **Main Plate Incorporation Tests:** 3 (6 vehicle control, 2 positive control)	**Location in CTD:** m4.2.3.7.5

Metabolising System: Phenobarbital, 5-6 Benzoflavone-induced rat liver S9-mix containing 100 μL S9 fraction per mL

Vehicles Test article: Dimethyl sulphoxide (DMSO) **Positive Controls:** DMSO or Sterile Water **GLP Compliance:** Yes

Treatment: Plate incorporation for 3 days **Date of Treatment:** June 2011

Cytotoxic Effects: None

Mutagenic Effects: Not mutagenic

GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2531403A (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Dose Range Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Without Activation	DMSO	100 μl/plate	94.3	17.3	9.5	18.5	82.0
	GSK2531403A	50	90.0	14.0	13.0	31.5	88.5
	GSK2531403A	150	90.5	19.0	12.5	21.0	86.0
	GSK2531403A	500	84.5	20.0	10.0	37.5[2]	94.0
	GSK2531403A	1500	77.0	18.5	12.0	29.0	95.5
	GSK2531403A	2500	83.0	24.5	10.5	36.5[2]	100.5
	GSK2531403A	5000	78.0[3]	15.0[3]	12.0[3]	24.5	99.0
	2-Nitrofluorene	1	NT	NT	NT	982.0[2]	NT
	Sodium azide	2	982.0[2]	1184.0[2]	NT	NT	NT
	9-Aminoacridine	50	NT	NT	839.5[2]	NT	NT
	4NQO	2	NT	NT	NT	NT	3970.5[2]

Key:

1 = Expressed in terms of parent compound.

2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.

3 = Slight toxicity seen, i.e., slight thinning of the background lawn.

NT = Not tested.

GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2531403A (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Dose Range Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
With Activation	DMSO	100 μl/plate	93.3	18.3	19.3	37.5	182.5
	GSK2531403A	50	80.0	19.5	19.5	43.5	135.0
	GSK2531403A	150	81.5	15.0	24.5	37.0	160.5
	GSK2531403A	500	73.0	17.0	24.5	38.0	159.0
	GSK2531403A	1500	77.0	18.5	25.0	48.5	148.5
	GSK2531403A	2500	81.5	21.5	21.5	35.5	137.5
	GSK2531403A	5000	71.5	9.5	23.0[3]	42.0	161.5
	Benzo(a)pyrene	10	NT	NT	NT	439.0[2]	NT
	2-Aminoanthracene	5	3389.0[2]	268.5[2]	95.0[2]	NT	NT
	2-Aminoanthracene	10	NT	NT	NT	NT	1797.0[2]

Key:

1 = Expressed in terms of parent compound.

2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.

NT = Not tested.

GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2531403A (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Main Plate Incorporation Test 1 Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Without Activation	DMSO	100 μl/plate	73.5	21.8	12.0	31.7	126.0
	GSK2531403A	150	95.3	17.0	15.3	33.0	116.3
	GSK2531403A	500	79.3	17.3	13.7	45.0	117.3
	GSK2531403A	1500	82.0	15.3	15.0	34.7	116.7
	GSK2531403A	2500	92.7	15.7	13.7	33.3	117.7
	GSK2531403A	5000	72.3	20.0	17.7	39.0	121.3
	2-Nitrofluorene	1	NT	NT	NT	334.5[2]	NT
	Sodium azide	2	949.5[2]	938.5[2]	NT	NT	NT
	9-Aminoacridine	50	NT	NT	797.5[2]	NT	NT
	4NQO	2	NT	NT	NT	NT	3540.0[2]

Key:

1 = Expressed in terms of parent compound.

2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.

NT = Not tested.

GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2531403A (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Main Plate Incorporation Test 1 Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
With Activation	DMSO	100 μl/plate	68.0	21.2	40.0	64.5	186.3
	GSK2531403A	150	67.3	16.3	33.3	52.7	173.3
	GSK2531403A	500	75.0	19.0	35.0	52.3	194.3
	GSK2531403A	1500	73.7	14.7	43.7	59.0	170.0
	GSK2531403A	2500	73.3	17.7	38.0	48.7	174.3
	GSK2531403A	5000	65.7	17.0	32.3	48.7	189.7
	Benzo(a)pyrene	10	NT	NT	NT	414.0[2]	NT
	2-Aminoanthracene	5	1927.0[2]	253.5[2]	147.5[2]	NT	NT
	2-Aminoanthracene	10	NT	NT	NT	NT	1835.0[2]

Key:
1 = Expressed in terms of parent compound.
2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.
NT = Not tested.

GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity:	**Report Title:**	**Test article:**
In Vitro	GSK2531403A (M3 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.	GSK2531403A (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Main Plate Incorporation Test 2 Mean Number of Revertant Colonies per Plate TA98
Without Activation	DMSO	100 μl/plate	25.7
	GSK2531403A	150	24.0
	GSK2531403A	500	25.0
	GSK2531403A	1500	24.0
	GSK2531403A	2500	24.0
	GSK2531403A	5000	32.3
	2-Nitrofluorene	1	312.5[2]

Key:
1 = Expressed in terms of parent compound.
2 = ≥ two fold increase in revertants for TA98.

Aug 08 2019 11:29:25

Table 9.6 GSK2487818A (M4 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

Genotoxicity: In Vitro

Report Title: GSK2487818A (M4 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2487818A

Batch Number: H10694-064

Test for Induction of: Reverse mutation in bacterial cells

No. of Independent Tests: 1

Study No: V30227

GSK Document No.: 2012N143001

Strain: *S. typhimurium* and *E. coli*

No. of Replicate Plates:
Plate Incorporation Test: 3 treatment plates (6 vehicle control plates, 2 positive control plates)

Location in CTD: m4.2.3.7.5

Metabolising System: Phenobarbital, 5-6 Benzoflavone-induced rat liver S9-mix containing 100 μL S9 fraction per mL

Vehicles Test article: Dimethyl sulfoxide (DMSO) **Positive Controls:** DMSO or Sterile Water

GLP Compliance: Yes

Treatment: Plate incorporation for 3 days in the presence and absence of S9-mix

Date of Treatment: June, 2012

Cytotoxic Effects: None

Mutagenic Effects: Not Mutagenic

GSK2487818A (M4 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2487818A (M4 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2487818A

Metabolic Activation	Test Article	Concentration[1] (μg/plate)	Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
With Activation	DMSO	100 μL/plate	120.3	20.7	17.0	40.8	110.0
	GSK2487818	50	137.7	24.0	22.7	45.7	127.3
	GSK2487818	150	128.0	17.7	30.0	34.7	110.0
	GSK2487818	500	130.0	19.3	24.0	46.3	141.0
	GSK2487818	1500	123.3	17.7	27.3	39.0	130.3
	GSK2487818	2500	118.3	15.3	26.3	46.0	131.0
	GSK2487818	5000	123.7	21.3	24.7	42.7	122.3
	Benzo(a)pyrene	10	NT	NT	NT	591.5[2]	NT
	2-Aminoanthracene	5	5309.5[2]	577.0[2]	362.5[2]	NT	NT
	2-Aminoanthracene	10	NT	NT	NT	NT	1856.5[2]

Key:
1 = Expressed in terms of parent compound.
2 = Positive control induced an unequivocal increase in revertant numbers.
NT = Not Tested.

GSK2487818A (M4 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2487818A (M4 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2487818A

Metabolic Activation	Test Article	Concentration[1] (μg/plate)	Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Without Activation	DMSO	100 μL/plate	105.0	20.3	10.8	23.5	70.0
	GSK2487818	50	111.0	20.3	9.3	28.3	84.3
	GSK2487818	150	117.7	18.7	14.7	27.0	79.3
	GSK2487818	500	95.3	21.7	18.3	27.0	79.0
	GSK2487818	1500	134.7	25.0	13.7	27.7	83.0
	GSK2487818	2500	110.0	15.7	11.3	27.3	72.3
	GSK2487818	5000	121.0	20.3	11.3	33.7	75.3
	2-Nitrofluorene	1	NT	NT	NT	412.0[2]	NT
	Sodium azide	2	1850.0[2]	1199.0[2]	NT	NT	NT
	9-Amino acridine	50	NT	NT	477.0[2]	NT	NT
	4-Nitroquinoline-1-oxide	2	NT	NT	NT	NT	4293.5[2]

Key:
1 = Expressed in terms of parent compound.
2 = Positive control induced an unequivocal increase in revertant numbers.
NT = Not Tested.

Table 9.7 GSK2506102A (M5 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

Genotoxicity: In Vitro	**Report Title:** GSK2506102A (M5 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with Salmonella typhimurium and Escherichia coli.	**Test article:** GSK2506102A **Batch Number:** TH04939-086
Test for Induction of: Reverse mutation in bacterial cells	**No. of Independent Tests:** 1	**Study No:** V30314G **GSK Document No.:** 2012N150862
Strain: *S. typhimurium* and *E. coli*	**No. of Replicate Plates:** **Plate Incorporation Test:** 3 treatment plates (6 vehicle control plates, 2 positive control plates)	**Location in CTD:** m4.2.3.7.5

Metabolising System: Phenobarbital, 5-6 Benzoflavone-induced rat liver S9-mix containing 100 μL S9 fraction per mL

Vehicles Test article: Dimethyl sulfoxide (DMSO) **Positive Controls:** DMSO or Sterile Water **GLP Compliance:** Yes

Treatment: Plate incorporation for 3 days in the presence and absence of S9-mix **Date of Treatment:** August-Sept, 2012

Cytotoxic Effects: None

Mutagenic Effects: Not Mutagenic

GSK2506102A (M5 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Metabolic Activation	Test article	Concentration[1] (μg/plate)	Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
With Activation	DMSO	100 μL/plate	135	17.7	31.5	43.2	141.8
	GSK2506102	50	135.7	20.0	31.7	57.0	149.3
	GSK2506102	150	131.7	24.7	34.0	35.3	145.0
	GSK2506102	500	143.3	20.0	29.3	48.7	140.3
	GSK2506102	1500	121.7	13.0	27.3	41.0	148.0
	GSK2506102	2500	140.0	18.7	31.7	37.7	147.3
	GSK2506102	5000	149.0	17.3	25.0	53.7	135.7
	Benzo(a)pyrene	10	NT	NT	NT	874.5[2]	NT
	2-Aminoanthracene	5	5488.0[2]	572.5[2]	326.5[2]	NT	NT
	2-Aminoanthracene	10	NT	NT	NT	NT	2341.5[2]

Key:
1 = Expressed in terms of parent compound
2 = Positive control induced an unequivocal increase in revertant numbers
NT = Not tested

GSK2506102A (M5 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Metabolic Activation	Test article	Concentration[1] (μg/plate)	Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Without Activation	DMSO	100 μL/plate	129.0	26.7	13.7	28.0	85.5
	GSK2506102	50	132.0	27.7	14.7	23.3	106.7
	GSK2506102	150	137.3	24.3	14.0	30.3	99.3
	GSK2506102	500	141.0	28.3	18.0	29.7	102.0
	GSK2506102	1500	145.3	25.3	11.3	25.3	99.0
	GSK2506102	2500	115.7	24.3	13.7	21.7	106.7
	GSK2506102	5000	136.0	23.7	11.0	30.3	96.0
	2-Nitrofluorene	1	NT	NT	NT	360.5[2]	NT
	Sodium azide	2	1804.5[2]	1332.5[2]	NT	NT	NT
	9-Amino acridine	50	NT	NT	264.5[2]	NT	NT
	4-Nitroquinoline-1-oxide	2	NT	NT	NT	NT	4910.5[2]

Key:

1 = Expressed in terms of parent compound

2 = Positive control induced an unequivocal increase in revertant

NT = Not tested

Table 9.8 GSK2531398A (M6 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

Genotoxicity: In Vitro	**Report Title:**	GSK2531398A (M6 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with Salmonella typhimurium and Escherichia coli	**Test article:** GSK2531398A(free base) **Batch Number:** TH05324-047
Test for Induction of: Reverse mutation in bacterial cells		**No. of Independent Tests:** 1	**Study No:** V30313G **GSK Document No.:** 2012N150330
Strain: *S. typhimurium* and *E. coli*		**No. of Replicate Plates:** **Plate Incorporation Test:** 3 treatment plates (6 vehicle control plates, 2 positive control plates)	**Location in CTD:** m4.2.3.7.5

Metabolising System: Phenobarbital, 5-6 Benzoflavone-induced rat liver S9-mix containing 100 μL S9 fraction per mL

Vehicles Test article: Dimethyl sulfoxide (DMSO) **Positive Controls:** DMSO or Sterile Water	**GLP Compliance:** Yes
Treatment: Plate incorporation for 3 days in the presence and absence of S9-mix	**Date of Treatment:** August/September 2012

Cytotoxic Effects: None

Mutagenic Effects: Not Mutagenic

GSK2531398A (M6 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Metabolic Activation	Test article	Concentration[1] (μg/plate)	Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
With Activation	DMSO	100 μL/plate	121.8	15.0	28.0	36.3	140.0
	GSK2531398	50	116.0	14.3	23.3	37.0	148.0
	GSK2531398	150	109.3	16.0	26.3	32.7	140.7
	GSK2531398	500	116.0	17.0	33.7	40.3	130.3
	GSK2531398	1500	122.0	14.3	29.3	37.7	117.7
	GSK2531398	2500	131.7	15.7	34.0	44.7	134.7
	GSK2531398	5000	151.3	17.0	31.7	56.0	127.3
	Benzo(a)pyrene	10	NT	NT	NT	898.5[2]	NT
	2-Aminoanthracene	5	6017.5[2]	601.5[2]	251.0[2]	NT	NT
	2-Aminoanthracene	10	NT	NT	NT	NT	2269.5[2]

Key:

1 = Expressed in terms of parent compound

2 = Positive control induced an unequivocal increase in revertant numbers

NT = Not tested

GSK2531398A (M6 metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Metabolic Activation	Test article	Concentration[1] (μg/plate)	Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Without Activation	DMSO	100 μL/plate	115.7	22.8	10.2	24.7	84.3
	GSK2531398	50	111.3	23.0	8.3	27.3	105.3
	GSK2531398	150	124.7	18.0	9.7	20.7	91.3
	GSK2531398	500	141.3	17.7	12.0	26.0	83.3
	GSK2531398	1500	120.0	33.7	10.3	20.0	88.3
	GSK2531398	2500	116.3	23.7	12.7	24.3	78.3
	GSK2531398	5000	118.3	19.0	14.7	32.3	100.0
	2-Nitrofluorene	1	NT	NT	NT	469.0[2]	NT
	Sodium azide	2	1724.5[2]	1075.5[2]	NT	NT	NT
	9-Amino acridine	50	NT	NT	448.5[2]	NT	NT
	4-Nitroquinoline-1-oxide	2	NT	NT	NT	NT	5971.0[2]

Key:

1 = Expressed in terms of parent compound

2 = Positive control induced an unequivocal increase in revertant numbers

NT = Not tested

Table 9.9 GSK2531401A (M13 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

Genotoxicity: In Vitro	**Report Title:**	GSK2531401A (M13 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.	**Test article:** GSK2531401A (parent) **Batch Number:** N19791-24P1
Test for Induction of: Reverse mutation in bacterial cells		**No. of Independent Tests:** 2	**Study No:** V29665 **GSK Document No.:** 2011N120131
Strain: *S. typhimurium* and *E. coli*		**No. of Replicate Plates:** **Dose Range Plate Incorporation Test:** 2 (4 vehicle control, 2 positive control) **Main Plate Incorporation Test:** 3 (6 vehicle control, 2 positive control)	**Location in CTD:** m4.2.3.7.5

Metabolising System: Phenobarbital, 5-6 Benzoflavone-induced rat liver S9-mix containing 100 μL S9 fraction per mL

Vehicles Test article: Dimethyl sulphoxide (DMSO) **Positive Controls:** DMSO or Sterile Water **GLP Compliance:** Yes

Treatment: Plate incorporation for 3 days **Date of Treatment:** June, 2011

Cytotoxic Effects: Slight thinning of background lawn in some strains as indicated

Mutagenic Effects: Not mutagenic

GSK2531401A (M13 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2531401A (M13 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2531401A (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Dose Range Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Without Activation	DMSO	100 μl/plate	113.3	21.0	15.0	29.0	85.3
	GSK2531401	50	101.5	18.5	12.5	33.0	97.0
	GSK2531401	150	106.0	21.0	18.5	27.5	92.0
	GSK2531401	500	116.5	14.5	11.0	34.0	95.5
	GSK2531401	1500	91.5	22.0	16.0	27.5	99.5
	GSK2531401	2500	110.5	19.5	15.5	28.0	100.5
	GSK2531401	5000	88.0[3]	18.5[3]	12.5	28.0	92.0
	2-Nitrofluorene	1	NT	NT	NT	448.0[2]	NT
	Sodium azide	2	918.5[2]	1072.5[2]	NT	NT	NT
	9-Amino acridine	50	NT	NT	1076.0[2]	NT	NT
	4-Nitroquinoline-1-oxide	2	NT	NT	NT	NT	4330.0[2]

Key:
1 = Expressed in terms of parent compound.
2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.
3 = Slight toxicity seen, i.e., slight thinning of the background lawn.
NT = Not tested.

GSK2531401A (M13 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2531401A (M13 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2531401A (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Dose Range Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
With Activation	DMSO	100 μl/plate	82.8	19.3	19.8	42.0	139.3
	GSK2531401	50	64.0	16.0	18.5	43.0	150.0
	GSK2531401	150	78.5	19.5	16.0	36.0	161.0
	GSK2531401	500	86.5	16.0	18.0	38.0	143.5
	GSK2531401	1500	89.5	19.0	23.0	60.5	139.0
	GSK2531401	2500	65.5	12.5	15.0	30.0	149.5
	GSK2531401	5000	64.5[3]	11.0	15.5[3]	46.0	147.0
	Benzo(a)pyrene	10	NT	NT	NT	401.5[2]	NT
	2-Aminoanthracene	5	3608.0[2]	347.5[2]	216.0[2]	NT	NT
	2-Aminoanthracene	10	NT	NT	NT	NT	1503.5[2]

Key:

1 = Expressed in terms of parent compound.

2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.

3 = Slight toxicity seen, i.e., slight thinning of the background lawn.

NT = Not tested.

GSK2531401A (M13 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2531401A (M13 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2531401A (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Main Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Without Activation	DMSO	100 μl/plate	124.7	17.7	17.2	32.0	123.5
	GSK2531401	150	119.7	19.0	9.7	30.0	120.0
	GSK2531401	500	103.7	14.7	10.3	30.0	124.3
	GSK2531401	1500	99.0	17.0	11.0	36.7	123.3
	GSK2531401	2500	110.3	9.3	8.0	40.7	114.3
	GSK2531401	5000	92.0[3]	11.0[3]	6.0	37.7	119.7
	2-Nitrofluorene	1	NT	NT	NT	255.5[2]	NT
	Sodium azide	2	909.5[2]	1101.0[2]	NT	NT	NT
	9-Amino acridine	50	NT	NT	689.0[2]	NT	NT
	4-Nitroquinoline-1-oxide	2	NT	NT	NT	NT	4468.0[2]

Key:

1 = Expressed in terms of parent compound.

2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.

3 = Slight toxicity seen, i.e., slight thinning of the background lawn.

NT = Not tested.

GSK2531401A (M13 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Genotoxicity: In Vitro

Report Title: GSK2531401A (M13 Metabolite of GSK1278863A): Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*.

Test article: GSK2531401A (parent)

Metabolic Activation	Test Article	Dose Level[1] (μg/plate)	Main Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
With Activation	DMSO	100 μl/plate	78.5	17.7	16.7	41.3	189.8
	GSK2531401	150	100.3	14.3	18.7	49.0	146.3
	GSK2531401	500	91.0	17.3	20.3	35.3	159.3
	GSK2531401	1500	73.7	9.7	15.3	44.0	152.7
	GSK2531401	2500	86.3	12.7	18.7	42.0	196.7
	GSK2531401	5000	66.3[3]	18.3	12.3	34.3	180.0
	Benzo(a)pyrene	10	NT	NT	NT	385.5[2]	NT
	2-Aminoanthracene	5	314.5[2]	89.5[2]	88.0[2]	NT	NT
	2-Aminoanthracene	10	NT	NT	NT	NT	1708.5[2]

Key:

1 = Expressed in terms of parent compound.

2 = ≥ two fold increase in revertants for TA98, TA100 and WP2*uvr*A(pKM101) and ≥ three fold increase for TA1535 and TA1537.

3 = Slight toxicity seen, i.e.. slight thinning of the background lawn.

NT = Not tested.

Table 9.10 GSK2531401A (M13 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus

Study Type: Genetic Toxicology In Vitro	**Report Title:** GSK2531401A (M13 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus	**Test Article:** GSK2531401 (tri-oxygenated M13 metabolite of GSK1278863A)
Test for Induction of: Forward mutation at the $TK^{+/-}$ locus	**No. of Independent Tests:** 3	**Study No:** V29742 **Document No:** 2011N120224
Cell Type: L5178Y Mouse Lymphoma Cells	**No. of Replicate Cultures:** 4 (vehicle); 2 (treatment and positives)	**Location in CTD:** m4.2.3.7.5

Metabolising System: Phenobarbital –5,6-Benzoflavone -induced rat liver S9-mix containing 1% v/v S9-fraction (final)

Vehicles	**Test Article:** Dimethyl sulfoxide	**Positive Controls:** Dimethyl sulfoxide	**GLP Compliance:** Yes

Treatment: 3hr treatments in the presence and absence of S9-mix; 24hr treatment in the absence of S9-mix

Date of Treatment(s): June to July, 2011

Cytotoxic Effects: Reduction in Relative Total Growth (RTG)

Genotoxic Effects: Not genotoxic (3 hr treatment in the absence of S9-mix). Weakly genotoxic (3 hr treatment in the presence of S9-mix and 24 hr treatment in the absence of S9-mix, at single highly cytotoxic concentrations only)

GSK2531401A (M13 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus (Continued)

Study Type: Genetic Toxicology In Vitro **Study No:** V29742

Test Article	Concentration[1] µg/mL	3 hr Treatment -S9-mix		3 hr Treatment +S9-mix		24 hr Treatment -S9-mix	
		Mean Relative Total Growth (%)	Mean Mutant Frequency ($x10^{-6}$)	Mean Relative Total Growth (%)	Mean Mutant Frequency ($x10^{-6}$)	Mean Relative Total Growth (%)	Mean Mutant Frequency ($x10^{-6}$)
Dimethyl sulfoxide	0	99.72	135.55	99.29	112.89	100.10	89.59
GSK2531401	40	NT	NT	70.40	121.76	NT	NT
GSK2531401	60	NT	NT	63.28	134.48	NP	NP
GSK2531401	100	NP	NP	NP	NP	73.44	135.84
GSK2531401	120	NT	NT	40.57	210.44	NT	NT
GSK2531401	140	NT	NT	28.76	188.87	NT	NT
GSK2531401	160	NT	NT	11.91	265.64[3]	NT	NT
GSK2531401	200	99.92	113.39	NP	NP	NP	NP
GSK2531401	250	64.54	189.90	NT	NT	72.33	119.53
GSK2531401	300	40.75	186.13	NP	NP	NP	NP
GSK2531401	340	23.82	205.37	NT	NT	NT	NT
GSK2531401	350	NT	NT	NT	NT	33.05	193.08
GSK2531401	380	9.69	238.66	NT	NT	NT	NT
GSK2531401	425	NT	NT	NT	NT	17.38	252.89[3]
Methyl methane sulphonate	20	47.43	1010.69[2]	NT	NT	NT	NT
Methyl methane sulphonate	5	NT	NT	NT	NT	71.64	611.23[2]
Dimethyl benzanthracene	1	NT	NT	33.35	1368.52[2]	NT	NT

Key:

1 = Expressed in terms of parent compound.

2 = Positive control induced an acceptable response.

3 = Mean mutant frequency exceeds the sum of the mean vehicle control mutant frequency plus the Global Evaluation Factor (126 x 10^{-6}). Statistically significant trend (Spearman's rank correlation coefficient). Significant to the 1% level.

NT = Not Tested.

NP = Not plated.

Table 9.11 GSK2391220A (M2 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus

Study Type: Genetic Toxicology In Vitro

Report Title: GSK2391220A (M2 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus

Test Article: GSK2391220A (di-oxygenated M2 metabolite of GSK1278863A)

Batch Number: H11454-120-1A

Test for Induction of: Forward mutation at the $TK^{+/-}$ locus

No. of Independent Tests: 3

Study No: V29807
Document Number: 2011N124122

Cell Type: L5178Y Mouse Lymphoma Cells

No. of Replicate Cultures: 3 hr treatment in the presence of S9-mix: 2 (vehicle controls, treatment and positive controls). 3 hr treatment in the absence of S9-mix and 24 hr treatment in the absence of S9-mix: 4 (vehicle controls); 2 (treatment and positive controls)

Location in CTD: m4.2.3.7.5

Metabolising System: Phenobarbital –5,6-Benzoflavone -induced rat liver S9-mix containing 1% v/v S9-fraction (final)

Vehicles **Test Article:** DMSO **Positive Controls:** DMSO **GLP Compliance:** Yes

Treatment: 3 hr treatments in the presence and absence of S9-mix; 24 hr treatment in the absence of S9-mix

Date of Treatment(s): Aug to Sept 2011

Cytotoxic Effects: Reduction in Relative Total Growth (RTG) for the 3 and 24 hr treatments in the absence of S9-mix only

Genotoxic Effects: Not Genotoxic

GSK2391220A (M2 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus (Continued)

Study Type: Genetic Toxicology In Vitro **Study No:** V29807

Test Article	Concentration[1] µg/mL	3 hr Treatment +S9-mix		3 hr Treatment -S9-mix		24 hr Treatment -S9-mix	
		Mean Relative Total Growth (%)	Mean Mutant Frequency ($x10^{-6}$)	Mean Relative Total Growth (%)	Mean Mutant Frequency ($x10^{-6}$)	Mean Relative Total Growth (%)	Mean Mutant Frequency ($x10^{-6}$)
Dimethyl sulfoxide	0	99.91	89.01	99.95	92.37	99.56	83.18
GSK2391220	200	109.24	88.09	NP	NP	NP	NP
GSK2391220	600	NP	NP	103.06	79.70	NP	NP
GSK2391220	800	NP	NP	NP	NP	102.43	79.97
GSK2391220	900	NP	NP	NT	NT	80.34	110.75
GSK2391220	1000	91.38	128.44	104.26	125.33	NP	NP
GSK2391220	1025	NP	NP	NT	NT	36.10	121.26
GSK2391220	1100	NP	NP	87.56	135.22	20.04	99.71
GSK2391220	1150	96.60	105.92	NP	NP	15.41	128.05
GSK2391220	1200	NP	NP	99.85	103.97	NP	NP
GSK2391220	1250	107.04	104.79	NP	NP	NP	NP
GSK2391220	1278.4	107.56	119.40	87.68	134.35	NP	NP
Methyl methane sulphonate	20	NT	NT	41.33	810.47[2]	NT	NT
Methyl methane sulphonate	5	NT	NT	NT	NT	75.71	671.48[2]
Dimethylbenzanthracene	1	25.51	2136.18[2]	NT	NT	NT	NT

Key:
1 = Expressed in terms of parent compound.
2 = Positive control induced an acceptable response.
NT = Not Tested.
NP = Not Plated.

Table 9.12 GSK2506104A (M3 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus

Study Type: Genetic Toxicology In Vitro	**Report Title:** GSK2506104A (M3 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus	**Test Article:** GSK2506104A (a di-oxygenated enantiomeric M3 metabolite of GSK1278863A) **Batch Number**: H10694-065
Test for Induction of: Forward mutation at the TK locus	**No. of Independent Tests:** 3	**Study No:** V29760 **Document No:** 2011N118972
Cell Type: L5178Y Mouse Lymphoma Cells	**No. of Replicate Cultures:** 4 (vehicle controls); 2 (treatment and positive controls)	**Location in CTD:** m4.2.3.7.5

Metabolising System: Phenobarbital –5,6-Benzoflavone -induced rat liver S9-mix containing 1% v/v S9-fraction (final concentration)

Vehicles	**Test Article:** Dimethyl sulfoxide	**Positive Controls:** Dimethyl sulfoxide	**GLP Compliance:** Yes

Treatment: 3 hr treatments in the presence and absence of S9-mix; 24 hr treatment in the absence of S9-mix

Date of Treatment(s): June-July, 2011

Cytotoxic Effects: None (3 hr treatments), Reduction in Relative Total Growth (24 hr treatment)

Genotoxic Effects: Not Genotoxic

GSK2506104A (M3 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus (Continued)

Study Type: Genetic Toxicology In Vitro **Study No:** V29760

Test Article	Concentration[1] µg/mL	3 hr Treatment +S9-mix		3 hr Treatment -S9-mix	
		Mean Relative Total Growth (%)	Mean Mutant Frequency (x10^{-6})	Mean Relative Total Growth (%)	Mean Mutant Frequency (x10^{-6})
Dimethyl sulfoxide	0	99.97	109.66	99.89	100.32
GSK2506104	500	113.62	NS	144.57	69.87
GSK2506104	1000	112.61	104.68	131.76	79.26
GSK2506104	1300	112.15	86.73	94.18	NS
GSK2506104	1400	104.38	116.63	120.51	92.39
GSK2506104	1466	95.85	94.61	116.99	118.19
Methyl methane sulphonate	20	NT	NT	29.73	1379.00[2]
Dimethylbenzanthracene	1	27.89	1186.41[2]	NT	NT

Key:
1 = Expressed in terms of parent compound.
2 = Positive control induced an acceptable response.
NT = Not Tested.
NS = Not Scored.

GSK2506104A (M3 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus (Continued)

Study Type: Genetic Toxicology In Vitro **Study No:** V29760

Test Article	Concentration[1] µg/mL	24 hr Treatment -S9-mix	
		Mean Relative Total Growth (%)	Mean Mutant Frequency ($x10^{-6}$)
Dimethyl sulfoxide	0	100.07	89.43
GSK2506104	800	99.77	87.92
GSK2506104	1080	73.40	95.34
GSK2506104	1160	34.71	126.63
GSK2506104	1200	27.00	143.83
GSK2506104	1280	13.88	145.53
Methyl methane sulphonate	5	82.02	711.08[2]

Key:
1 = Expressed in terms of parent compound.
2 = Positive control induced an acceptable response.

Aug 08 2019 11:29:25

Table 9.13 GSK2531403A (M3 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus

Study Type: Genetic Toxicology In Vitro

Report Title: GSK2531403A (M3 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus

Test Article: GSK2531403A (a di-oxygenated M3 metabolite of GSK1278863A)

Batch Number: H12344-38-1B

Test for Induction of: Forward mutation at the TK locus

No. of Independent Tests: 3

Study No: V29743

Document No: 2011N120944

Cell Type: L5178Y Mouse Lymphoma Cells

No. of Replicate Cultures: 3 hr treatments: 4 (vehicle controls); 2 (treatment and positive controls). 24 hr treatment: 3 (vehicle controls); 2 (treatment and positive controls).

Location in CTD: m4.2.3.7.5

Metabolising System: Phenobarbital –5,6-Benzoflavone -induced rat liver S9-mix containing 1% v/v S9-fraction (final concentration)

Vehicles **Test Article:** Dimethyl Sulfoxide (DMSO) **Positive Controls:** DMSO **GLP Compliance:** Yes

Treatment: 3 hr treatments in the presence and absence of S9-mix; 24 hr treatment in the absence of S9-mix

Date of Treatment(s): Aug-Sept, 2011

Cytotoxic Effects: Reduction in Relative Total Growth (RTG) for the 24 hr treatment in the absence of S9-mix only

Genotoxic Effects: Not Genotoxic

GSK2531403A (M3 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus (Continued)

Study Type: Genetic Toxicology In Vitro **Study No:** V29743

Test Article	Concentration[1] μg/mL	3 hr Treatment +S9-mix		3 hr Treatment -S9-mix	
		Mean Relative Total Growth (%)	Mean Mutant Frequency (x10^{-6})	Mean Relative Total Growth (%)	Mean Mutant Frequency (x10^{-6})
Dimethyl Sulfoxide	0	100.03	92.02	96.96	86.25
GSK2531403	500	101.37	125.72	107.17	94.76
GSK2531403	1200	118.04	90.08	94.45	140.62
GSK2531403	1400	108.49	84.04	82.92	133.40
GSK2531403	1600	120.57	83.63	85.48	121.60
GSK2531403	1711	99.06	97.86	93.64	111.84
Methyl methanesulphonate	20	NT	NT	38.86	734.64[2]
Dimethylbenzanthracene	1	51.10	704.67[2]	NT	NT

Key:
1 = All concentrations are expressed in terms of parent compound.
2 = Positive control induced an acceptable response.
NT = Not Tested.

GSK2531403A (M3 metabolite of GSK1278863A): In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus (Continued)

Study Type: Genetic Toxicology In Vitro **Study No:** V29743

Test Article	Concentration[1] μg/mL	24 hr Treatment -S9-mix	
		Mean Relative Total Growth (%)	Mean Mutant Frequency (x10^{-6})
Dimethyl Sulfoxide	0	99.98	91.16
GSK2531403	500	104.75	80.93
GSK2531403	1000	68.89	108.23
GSK2531403	1100	50.01	97.10
GSK2531403	1200	25.52	164.38
GSK2531403	1300	12.39	200.72
Methyl methanesulphonate	5	73.07	702.46[2]

Key:
1 = All concentrations are expressed in terms of parent compound.
2 = Positive control induced an acceptable response.

10. GENOTOXICITY: IN VIVO

Table 10.1 GSK1278863A: Oral Bone Marrow Micronucleus Assay in Rats

Genetic Toxicology: In Vivo

Test for Induction of: Structural chromosomal damage and/or aneuploidy

Species/Strain: Rat:(Hsd:SD)
Approximate Age: 8 weeks at time of dosing

Cells Evaluated: Polychromatic erythrocytes (PCEs)
No. of Cells Analysed/Animal: 4000 PCEs
Special Features: None

Report Title: GSK1278863A: Oral Bone Marrow Micronucleus Assay in Rats

Treatment Schedule: Two doses 24 hours apart (vehicle & test compound). Positive control dosed once only.
Sampling Time: 24 hours after final dose
Method of Administration: Oral
Dose Volume: 10 mL/kg
Vehicle/Formulation: 1% methylcellulose w/v in deionized water (400 cps)

Test Article: GSK1278863A (parent compound)
Batch Number: NE-021129-Batch-01-2007
PCS-MTL Study No.: 961787
GSK Reference No.: R27886
GSK Document No.: WD2007/01574
Location in CTD: m4.2.3.3.2

GLP Compliance: Yes

Date of Dosing: December 2007

Toxic/Cytotoxic Effects: Decrease in group mean % PCE; clinical signs included fur staining and soft/liquid feces with mucoid material. Following dosing on Day 2, suspected dehydration (lack of skin elasticity during skin pinch) was seen at 1000 mg/kg/day (slight to moderate) and 2000 mg/kg/day (slight to severe). Group mean body weight loss of approximately 10% and 12%, for males treated at 1000 and 2000 mg/kg/day, respectively.
Genotoxic Effects: Small (2-fold) increase in micronuclei at 2000 mg/kg/day, considered to be the result of increased levels of erythropoiesis, cell division and enucleation; not considered to be a direct genotoxic effect.
Evidence of Exposure: Mean plasma concentration (range 112.3 to 119.2 μg/mL) as well as clinical signs and body weight loss detailed above.

Test Compound	Dose[1] (mg/kg/day)	Number of Animals Analysed[2]	Group Mean % PCE[3]	Group Mean MPCE[4,5]
Vehicle	0	6M	46.4	2.2
GSK1278863	1000	6M	24.3	2.7
GSK1278863	2000	6M	23.4	4.3[6]
Cyclophosphamide	20	3M	43.2	38.4[6]

GSK1278863A: Oral Bone Marrow Micronucleus Assay in Rats (Cont'd)

Key:

1 = All doses/concentrations are expressed in terms of parent compound.
2 = M = Male.
3 = Average of both slide reading occasions.
4 = 4000 PCEs analysed in total.
5 = Group mean number of micronucleated polychromatic erythrocytes (MPCEs) per 2000 PCEs analyzed.
6 = Outside group mean historical control range micronucleated PCEs/2000 PCEs (range 0.28 to 4.02). Results from both slide reading occasions were combined for statistical analysis; p value <0.05 considered significant (Fisher's exact test).

Table 10.2 GSK1278863A: Induction of Chromosome Aberrations in the Bone Marrow of Treated Rats

Study Type: Genetic Toxicology In Vivo

Report Title: GSK1278863A: Induction of chromosome aberrations in the bone marrow of treated rats

Test Article: GSK1278863A

Batch Number: NE-021129-BATCH-01-2009

Test for Induction of: Structural chromosome aberrations

Treatment Schedule: Single dose

Covance Study No.: 8256269

GSK Reference No.: R29957

GSK Document No.: 2012N133264

Species/Strain: Rat: Han Wistar

Sampling Time: 16 or 42 hrs after single administration

Location in CTD: m4.2.3.3.2

Approximate Age: 8 to 9 weeks at time of dosing

Method of Administration: Oral (gavage)

Dose volume: 10 mL/kg

Cells Evaluated: Bone Marrow Lymphocytes

Vehicle/Formulation: 1%(w/v) Methylcellulose (400 cps. @2%) / Suspension

GLP Compliance: Yes

No. of Cells Analysed/Animal: Metaphase analysis was not performed.

Date of Dosing: December 2011

Special Features: None.

Toxic/Cytotoxic Effects: Marked reductions in bone marrow lymphocyte Mitotic Index in treated versus controls at the 16 hour sample time. Mortality observed in 2/6 animals dosed at 2000 mg/kg for the 42 hour sample time (on Day 2). Clinical signs of piloerection noted in all GSK1278863 treated animals with decreased activity also noted in 6 animals (2000 mg/kg) on Day 2.

Genotoxic Effects: Analysis of chromosome aberrations was not conducted due to marked reductions in bone marrow lymphocyte MI (16 hour sample) and mortality (42 hour sample).

Evidence of Exposure: Mean plasma concentration at 1000 mg/kg : 108.8 μg/mL (range 99.18 to 118.4 μg/mL). Mean plasma concentration at 2000 mg/kg: 99.49 μg/mL (range 90.38 to 114.9 μg/mL. Reduction in group mean Mitotic Index in all treated rats compared to concurrent vehicle control at the 16 hour sample time. Mortality observed at 2000 mg/kg on Day 2 for the 42 hour sample time.

GSK1278863A: Induction of Chromosome Aberrations in the Bone Marrow of Treated Rats (Continued)

Test Article	Dose[1] (mg/kg/day)	No. of Animals Analysed	Sampling Time (hours)	Mitotic Index (MI)	Cytotoxicity (% Reduction in MI Compared to Control Value)
Vehicle control	0	6M	16	8.6	-
GSK1278863	500	6M	16	1.7	80
GSK1278863	1000	6M	16	3.5	59
GSK1278863	2000	6M	16	1.5	83
Cyclophosphamide	35	6M	16	2.0	77

Key:
1 = All doses/concentrations are expressed in terms of parent compound.
M = Male.

GSK1278863A: Induction of Chromosome Aberrations in the Bone Marrow of Treated Rats (Continued)

Study Type: Genetic Toxicology In Vivo

Report Title: GSK1278863A: Induction of chromosome aberrations in the bone marrow of treated mice

Test Article: GSK1278863A

Batch Number: NE-021129-BATCH-01-2009

Test article	Dose[1] (mg/kg/day)	No. of Animals Analysed	Sampling Time (hours)	Mitotic Index (MI)	Cytotoxicity (% Reduction in MI Compared to Control Value)
Vehicle control	0	6M	42	8.2	-
GSK1278863	2000	4M	42	8.9	0

Key:
1 = Expressed in terms of parent compound.
M = Male.

Table 10.3 GSK1278863A: Oral Comet Assay in Rats

Study Type: Genetic Toxicology In Vivo

Report Title: GSK1278863A: Oral Comet Assay in Crl:CD(SD) Rats

Test Article: GSK1278863A (parent compound)
Batch No: NE-021129-Batch-01-2009
Study No: R30069
GSK Document No.: 2012N139517

Test for Induction of: DNA strand breaks measured as Comets

Treatment Schedule: Two doses, approximately 21-22 hours apart (vehicle & test article)
Positive control and satellite bioanalysis animals dosed once only

Species/Strain: Rat: Crl:CD(SD)
Approximate Age: 9-10 Weeks
Cells Evaluated: Single cell suspensions prepared from liver
No. of Cells Analysed/Organ/Animal: 150 cells
Special Features: None

Sampling Time: 3-4 hours after last dose
Method of Administration: Oral, by gavage
Vehicle/Formulation: Suspensions in 1% w/v aqueous methylcellulose (400 cps. @ 2%)

Location in CTD: m4.2.3.3.2

GLP Compliance: Yes

Date of Dosing: April 2012

Toxic/Cytotoxic Effects: No evidence of excessive toxicity observed in the cells examined.
Genotoxic Effects: None
Evidence of Exposure: Analysis of plasma from satellite animals demonstrated detectable circulating levels of GSK1278863, 2 hours after dosing 250, 500 or 1000 mg/kg/day (250 mg/kg group mean: 112 μg/mL, range: 109 to 114 μg/mL; 500 mg/kg group mean: 111 μg/mL, range: 107 to 114 μg/mL; 1000 mg/kg group mean: 107 μg/mL, range: 101 to 114 μg/mL) in male rats.

Test Article	Dose[1] (mg/kg/day)	No. of Animals[2]	Liver % Tail Intensity (i.e. % Tail DNA)[3]
Vehicle control	0	5M	1.34 (0.43)
GSK1278863	250	5M	1.21 (0.32)
GSK1278863	500	5M	1.19 (0.48)
GSK1278863	1000	5M	1.28 (0.36)
Positive control[4]	250	3M	13.70 (1.72)

Key:
1 = All doses are expressed in terms of parent compound.
2 = M = Male.
3 = Figures in parenthesis = standard deviation.
4 = Positive control = Ethyl methane sulphonate (EMS) produced a clear unequivocal positive response.

Table 10.4 GSK2531401A: Intravenous Liver Comet Assay in Mice

Study Type: Genetic Toxicology In Vivo

Test for Induction of: DNA strand breaks measured as Comets

Species/Strain: Mouse: Crl:CD1(Icr)
Approximate Age: 7 to 10 Weeks
Cells Evaluated: Single cell suspensions prepared from liver
No. of Cells Analysed/Organ/Animal: 150 cells

Report Title: GSK2531401A: Intravenous Liver Comet Assay in Crl:CD1(Icr) Mice
Treatment Schedule: Two doses, 21 hours apart (vehicle & test article)
Positive control & satellite bioanalysis animals dosed once only
Sampling Time: 3 hours after last dose
Method of Administration: Intravenous bolus
Vehicle/Formulation: Solutions in 0.9%(w/v) Aqueous Sodium Chloride, final formulation adjusted to pH 7.0±0.2

Test Article: GSK2531401A (parent)
Batch No: H11451-114-A1
Study No: M29835
GSK Document No.: 2011N124885

Location in CTD: m4.2.3.7.5

GLP Compliance: Yes

Date of Dosing: September, October & November 2011

Special Features: None
Toxic/Cytotoxic Effects: No evidence of excessive toxicity observed in the cells examined.
Genotoxic Effects: Equivocal at 200 mg/kg/day. Reproducibly negative at 100 and 25 mg/kg/day

Evidence of Exposure: Analysis of plasma from satellite male mice demonstrated detectable circulating levels of GSK2531401, 3 to 5 mins after dosing 200 mg/kg/day (mean 1150 μg/mL; range 989 to1310 μg/mL) in Study 1. Analysis of plasma from satellite male mice demonstrated detectable circulating levels of GSK2531401, 3 to 5 mins after dosing 25, 100 or 200 mg/kg/day (mean 170; range 155 to 198 μg/mL, 604; range 521 to 658 μg/mL or 1260 μg/mL; range 985 to 1450 μg/mL, respectively) in Study 2.

GSK2531401A: Intravenous Liver Comet Assay in Mice (Continued)

Study Type: Genetic Toxicology In Vivo - Comet **Study No:** M29835 (**Study 1**)

Test Article	Dose[1] (mg/kg/day)	No. of Animals[2]	Liver Group Tail Moment[3] (arbitrary unit)	Liver % Tail DNA[3]
Vehicle control	0	5M	0.31 (0.10)	1.52 (0.40)
GSK2531401	100	4M[4]	0.22 (0.10)	1.08 (0.41)
GSK2531401	200	5M	0.53 (0.19)[6]	2.43 (0.10)[6]
Positive control[5]	300	5M	4.49 (0.63)	14.52 (1.26)

Key:

1 = All doses are expressed in terms of parent compound.

2 = M = Male.

3 = Figures in parenthesis = standard deviation.

4 = 1 animal died during the dosing procedure on Day 1.

5 = Positive control = Ethyl methane sulphonate (EMS) produced a clear unequivocal positive response.

6 = Exceeds the upper limit of group mean historical vehicle control range tail moment (0.15 to 0.36) & % tail DNA (0.85 to 1.88) & statistically significant increase in DNA damage observed ($p<0.05$), with no indication of excessive toxicity seen (Bartlett's test; upper linear contrasts)

.

GSK2531401A: Intravenous Liver Comet Assay in Mice (Continued)

Comet data for Study 2 were invalidated and not presented.

Study Type: Genetic Toxicology In Vivo - Comet **Study No:** M29835 (**Study 3**)

Test Article	Dose[1] (mg/kg/day)	No. of Animals[2]	Liver Group Tail Moment[3] (arbitrary unit)	Liver % Tail DNA[3]
Vehicle control	0	5M	0.11 (0.04)	0.91 (0.30)
GSK2531401	25	5M	0.12 (0.03)	1.05 (0.28)
GSK2531401	100	5M	0.14 (0.04)	1.15 (0.26)
GSK2531401	200	6M	0.32 (0.11)	2.36 (0.84)
Positive control[4]	300	3M	4.76 (1.03)	21.18 (1.87)

Key:
1 = All doses are expressed in terms of parent compound.
2 = M = Male.
3 = Figures in parenthesis = standard deviation.
4 = Positive control = Ethyl methane sulphonate (EMS) produced a clear unequivocal positive response.

GSK2531401A: Intravenous Liver Comet Assay in Mice (Continued)

Study Type: Genetic Toxicology In Vivo - Comet **Study No:** M29835 (**Study 4**)

Test Article	Dose[1] (mg/kg/day)	No. of Animals[2]	Liver Group Tail Moment[3] (arbitrary unit)	Liver % Tail DNA[3]
Vehicle control	0	5M	0.20 (0.04)	1.51 (0.40)
GSK2531401	25	5M	0.17 (0.09)	1.18 (0.62)
GSK2531401	100	5M	0.12 (0.07)	0.94 (0.56)
GSK2531401	200	6M	0.15 (0.04)	1.17 (0.36)
Positive control[4]	300	3M	2.94 (0.57)	13.70 (1.53)

Key:
1 = All doses are expressed in terms of parent compound.
2 = M = Male.
3 = Figures in parenthesis = standard deviation.
4 = Positive control = Ethyl methane sulphonate (EMS) produced a clear unequivocal positive response.

Table 10.5 GSK2531401A (M13 metabolite of GSK1278863A): Induction of Chromosome Aberrations in the Bone Marrow of Treated Mice

Study type: Genetic Toxicology In Vivo

Report Title: GSK2531401A (M13 metabolite of GSK1278863A): Induction of chromosome aberrations in the bone marrow of treated mice

Test Article: GSK2531401

Batch Number: H11451-114-A1

Test for Induction of: Structural chromosome aberrations

Treatment Schedule: Single dose

Covance Study No.: 8255732

GSK Reference No.: M29910

GSK Document No.: 2012N132787

Species/Strain: Crl:CD1 (ICR)

Sampling Time: 16 or 42 hrs after single administration

Location in CTD: m4.2.3.7.5

Approximate Age: 8 to 10 weeks at time of dosing

Method of Administration: Vehicle & test article: Intravenous infusion(flow rate, 0.5 mL/min). Positive control: Intravenous bolus injection
Dose volume: 5 mL/kg

Cells Evaluated: Bone Marrow Lymphocytes

Vehicle/Formulation: 0.9% (w/v) aqueous sodium chloride with pH adjusted to 7.0

GLP Compliance: Yes

No. of Cells Analysed/Animal: 200 metaphase cells / animal (where possible)

Date of Dosing: December 2011

Special Features: None.

Toxic/Cytotoxic Effects: Slight dose-related decrease in mitotic index (MI) in treated versus controls (up to 31% reduction in MI at 200 mg/kg only, for the 16 hour sample). No reduction in MI noted at the 42 hour sample.

Genotoxic Effects: Not Genotoxic.

Evidence of Exposure: Mean plasma concentration at 100 mg/kg 329 μg/mL (range 313 to 362 μg/mL). Mean plasma concentration at 200 mg/kg 437 μg/mL (range 369 to 487 μg/mL).

GSK2531401A (M13 metabolite of GSK1278863A): Induction of Chromosome Aberrations in the Bone Marrow of Treated Mice (Continued)

Test article	Dose[1] (mg/kg)	No. of Animals Analysed[2]	Sampling Time (hours)	Mitotic Index (MI)	Cytotoxicity (% reduction in MI compared to control value)	Aberrant Cells (excluding gaps) Mean %
Vehicle control	0	5M	16	5.4	-	0.40
GSK2531401	25	5M	16	4.8	11%	0.20
GSK2531401	100	5M	16	4.5	17%	0.42
GSK2531401	200	6M	16	3.7	31%	0.17
Cyclophosphamide	40	5M	16	1.9	65%	20.6*

Key:
1 = Expressed in terms of parent compound.
2 = M = Male
* Statistically significant ($p \leq 0.001$) as measured by 2x2 contingency chi-square analysis

GSK2531401A (M13 metabolite of GSK1278863A): Induction of Chromosome Aberrations in the Bone Marrow of Treated Mice (Continued)

Test article	Dose[1] (mg/kg)	No. of Animals Analysed[2]	Sampling Time (hours)	Mitotic Index (MI)	Cytotoxicity (% reduction in MI compared to control value)	Aberrant Cells (excluding gaps) Mean %
Vehicle control	0	5M	42	5.9	-	0.50
GSK2531401	100	5M	42	5.8	5%	0.20
GSK2531401	200	6M	42	6.9	0%	0.33

Key:
1 = Expressed in terms of parent compound.
2 = M = Male

11. CARCINOGENICITY

Table 11.1 GSK1278863A: A 2-Year Carcinogenicity Study in Mice

Study Type: Carcinogenicity	**Report Title:** GSK1278863A: A 2-Year Carcinogenicity Study in Mice	**Test Items:** GSK1278863A (Batch No./Lot No. 8863B3B001/132377077), GSK2391220A (M2; Batch No. H11454-120-1A), GSK2506104A (M3; Batch Nos. N26923-17P1 and ES2553-60), and GSK2531401A (M13; Batch No. H11451-114-A1)
Species/Strain: Mice/Crl:CD1 (ICR)	**Duration of Dosing:** 104 weeks	**GSK Reference No.:** M70585G
Initial Age: 7 weeks	**Route/Frequency:** Oral by gavage, once daily; Subcutaneous injection, once daily	**GSK Document Number:** 2014N221714 **Location in CTD:** m4.2.3.4.1
Date of First Dose: 25 Nov 2014	**Vehicle/Formulation:** Oral formulation (GSK1278863A): 1% (w/v) methyl cellulose (400 cP@ 2%) / 0.2% Tween 80 (v/v) / 5 mM NaOH in Ultra Pure Water, pH 6 (± 0.2) Subcutaneous formulation (M2, M3 and M13; Metabolite cocktail): Aqueous 25 mM phosphate buffer, pH7.4 (± 0.2)	**Study in Compliance with GLP:** Yes

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Data Collected: Toxicokinetics, clinical observations including mass palpation, body weight, food consumption, ophthalmoscopy, hematology (limited to hematocrit in the control group and test item-dosed group given 3 mg/kg/day + metabolites), macroscopic and microscopic pathology. Transcriptomic evaluation of erythropoietin (Epo) and vascular endothelial growth factor (VEGF) mRNA expression on select tissues (kidney, liver, lung, spleen and mesenteric lymph node) collected from satellite animals (control and test item-dosed groups given GSK1278863 + metabolites only) in Week 26 was also performed as a non-GLP assessment.

Basis for high dose selection: Based on adverse ischemia-related histopath findings and/or increased hematocrit at >6 mg/kg/day in 13-week studies, a GSK1278863 high dose of 3 mg/kg/day was selected. This dose is the highest dose considered tolerable for this 2-year study. Furthermore, literature indicates that estrogen has an inhibitory effect on EPO production in female rats [Peschle, 1972]. Therefore, due to similarity of estrous cycles between rats and mice, and because a proportion of female mice will pass into reproductive senescence (persistent anestrus) during this study, further increases in Hct in females given 3 mg/kg/day may be expected later in the course of this 2-year study.

These metabolite doses were selected as they were anticipated to yield systemic exposures (AUC) in mice equivalent to those obtained for each respective metabolite at the maximum human recommended dose (MHRD).

Conclusion: GSK1278863A (parent compound) was administered to mice at 0 (oral vehicle/reference item), 0.2, 0.8, or 3 mg/kg/day once daily for a minimum of 104 weeks by oral gavage with subcutaneous injection of 0 (subcutaneous vehicle/reference item) or 2.0 mg/kg/day GSK2391220 (M2), 2.5 mg/kg/day GSK2506104 (M3) and 1.3 mg/kg/day GSK2531401 (M13). An additional group received 0.8 mg/kg/day GSK1278863 by once daily oral gavage + once daily subcutaneous injection of the subcutaneous reference item (no metabolites).

There were no test item-related neoplastic microscopic findings.

Non-neoplastic pharmacologically-mediated microscopic changes included increased incidence/severity of hematopoiesis in the spleen and/or liver and whole body congestion in all test item-treated groups. These changes were accompanied by increased mean hematocrit at 3 mg/kg/day + metabolites, and dose-dependent increased incidence of skin reddening of the extremities in all test-item treated groups with a more pronounced incidence in groups that received the metabolites. Females given 3 mg/kg/day + metabolites had a slightly increased incidence of degeneration of the sciatic nerve and an increased incidence of myelopoiesis in the bone marrow. Increased vascular/perivascular inflammation consistent with polyarteritis, was seen in numerous tissues, most notably reproductive tracts and accessory glands, urinary tract, digestive tract, heart, aorta and thymus, of both sexes at all doses except males given 0.8 mg/kg/day without the metabolites. There was also an increased incidence of hemorrhage at the injection site at all doses of males and females receiving subcutaneous metabolites associated with increased pigmentation of splenic macrophages, hepatic Kupffer cells and/or kidney tubules. In the thymus, there was an increased incidence of lymphoid hyperplasia in females at all doses.

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A Metabolite cocktail (M2, M3, M13)	Male 0	Male 0.2	Male 0.8	Male 0.8	Male 3	Female 0	Female 0.2	Female 0.8	Female 0.8	Female 3
		0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Numbers of Animals: Main		60	60	60	60	60	60	60	60	60	60
Toxicokinetic		12	51	0	51	51	12	51	0	51	51
$AUC_{(0-24)}$ (µg.h/mL) GSK1278863	Week 4	NC	13.8	-	49.1	145	NC	22.3	-	82.7	278
	Week 26	NC	13.1		43.2	141	NC	28.1		92.8	335
M2:	Week 4	NC	1.05	-	1.02	1.27	NC	1.25	-	1.08	1.26
	Week 26	NC	1.24		1.53	1.50	NC	1.95		1.87	1.86
M3:	Week 4	NC	1.27	-	1.23	1.52	NC	1.34	-	1.14	1.37
	Week 26	NC	1.46		1.86	1.79	NC	2.02		1.95	1.98
M13:	Week 4	NC	0.979	-	0.913	1.18	NC	0.983	-	0.916	1.01
	Week 26	NC	1.08		1.37	1.29	NC	1.48		1.42	1.40
C_{max} (µg/mL) GSK1278863	Week 4	NQ	0.987	-	3.92	10.6	NQ	1.42	-	5.31	17.0
	Week 26	NQ	0.935		3.83	10.2	NQ	1.76		6.02	19.5
M2:	Week 4	NQ	2.37	-	2.11	2.69	NQ	2.73	-	2.51	2.41
	Week 26	NQ	3.39		3.79	4.00	NQ	3.60		4.61	3.83
M3:	Week 4	NQ	2.82	-	2.45	3.14	NQ	3.20	-	2.86	2.87
	Week 26	NQ	4.06		4.56	4.70	NQ	3.89		5.50	4.57
M13:	Week 4	NQ	2.01	-	1.53	1.96	NQ	1.88	-	1.98	1.82
	Week 26	NQ	2.37		2.71	2.83	NQ	2.58		3.12	2.57
Noteworthy Findings											
Pre-terminal Death/Euthanasia											
Main		26	27	28	32	27	31	33	28	24	34
Toxicokinetic		0	0	0	0	2	0	0	0	1	0
Terminal Euthanasia		34	33	32	28	33	29	27	32	36	26
Survival (%) Week 104		57	55	53	47	55	48	45	53	60	43

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

		Male					Female				
Daily Dose (mg/kg/day)[a]	**GSK1278863A**	0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Clinical Observations											
Skin Red											
Number of observations		28	487	111	685	983	23	1108	105	1802	3542
Number of animals		7	52	13	55	54	9	57	20	60	60
Hematology [b]											
Hematocrit (%)											
Week 26		46.85	-	-	-	55.70***	49.05	-	-	-	73.05***
Week 39		42.07	-	-	-	52.70**	45.40	-	-	-	70.80***
Week 52		46.00	-	-	-	53.22**	46.28	-	-	-	71.00***
Neoplastic lesions (Not Test Item-related)											
Adipose tissue (no. examined)		1	4	2	5	6	10	8	5	6	9
M-malignant lymphoma		0	0	0	1	1	5	1	4	2	6
M-bronchioloalveolar carcinoma		0	0	0	2	0	0	1	0	1	0
M-leiomyosarcoma		0	1	0	0	0	0	0	1	0	0
M-histiocytic sarcoma		0	0	0	0	0	1	2	0	0	0
B-hemangioma		0	2	0	0	0	0	0	0	1	0
M-adenocarcinoma		0	0	1	0	0	0	0	0	0	0
Artery, Aorta (no. examined)		60	60	60	60	60	59	58	59	60	60
M-malignant lymphoma		2	2	4	2	0	14	5	9	5	8
M-bronchioloalveolar carcinoma		1	1	0	0	2	0	1	0	1	0
M-histiocytic sarcoma		0	0	0	0	0	1	1	1	1	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female			
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Body cavity, abdominal (no. examined)		2	1	0	1	0	3	2	0	1	1
M-malignant lymphoma		1	0	0	0	0	1	0	0	0	0
M-malignant granular cell tumor		1	0	0	0	0	0	0	0	0	0
M-bronchioloalveolar carcinoma		0	0	0	0	0	0	0	0	1	0
M-histiocytic sarcoma		0	0	0	0	0	1	1	0	0	0
M-fibrosarcoma		0	0	0	0	0	0	1	0	0	0
Body cavity, nasal (no. examined)		60	60	60	60	60	60	60	60	60	60
M-malignant lymphoma		1	1	0	1	0	5	3	4	1	2
M-myxosarcoma		1	0	0	0	0	0	0	0	0	0
B-adenoma		1	0	0	0	0	0	0	0	0	0
M-osteosarcoma		0	0	0	0	0	0	0	0	0	1
B-hemangioma		0	1	0	0	0	0	0	0	0	0
Body cavity, oral (no. examined)		0	0	1	0	0	0	0	1	0	0
M-squamous cell carcinoma		0	0	1	0	0	0	0	1	0	0
Bone (no. examined)		0	0	0	1	1	0	0	1	0	0
M-osteosarcoma		0	0	0	0	1	0	0	1	0	0
M-bronchioloalveolar carcinoma		0	0	0	1	0	0	0	0	0	0
Bone, femur (no. examined)		59	60	59	60	60	60	59	60	60	60
M-osteosarcoma		0	0	0	0	1	1	0	1	0	1
M-malignant lymphoma		1	1	0	2	0	4	3	2	2	1
Body cavity, thoracic (no. examined)		0	0	0	0	2	2	0	3	3	1
M-bronchioloalveolar carcinoma		0	0	0	0	2	0	0	2	1	0
M-histiocytic sarcoma		0	0	0	0	0	0	0	0	1	0
M-osteosarcoma		0	0	0	0	0	1	0	0	0	0
M-malignant lymphoma		0	0	0	0	0	1	0	0	1	1

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Bone sternum (no. examined)		60	60	60	60	60	60	60	60	60	60
M-malignant lymphoma		1	2	0	2	0	11	5	8	3	2
M-bronchioloalveolar carcinoma		0	0	0	0	1	0	0	0	0	0
M-histiocytic sarcoma		0	0	0	0	0	1	1	1	0	0
M-osteosarcoma		1	0	0	0	1	1	0	0	0	1
Bone marrow (no. examined)		60	60	60	60	60	60	60	60	60	60
M-malignant lymphoma		2	2	7	1	0	9	5	7	4	1
M-hemangiosarcoma		3	0	0	2	0	2	0	0	0	1
M-histiocytic sarcoma		0	1	0	1	0	3	2	2	1	3
M-malignant granulosa cell tumor		0	0	0	0	0	0	0	0	0	1
Brain (no. examined)		60	60	60	60	60	60	60	60	60	60
B-benign meningioma		0	0	0	0	0	0	0	0	0	1
M-malignant lymphoma		1	1	2	1	0	5	4	5	4	2
M-pars distalis carcinoma		0	0	0	0	1	1	0	1	0	0
M-histiocytic sarcoma		0	0	0	0	0	1	0	0	0	0
Cervix (no. examined)		-	-	-	-	-	59	56	60	60	60
M-leiomyosarcoma		-	-	-	-	-	1	0	1	0	1
M-histiocytic sarcoma		-	-	-	-	-	4	1	0	1	1
M-malignant lymphoma		-	-	-	-	-	14	7	10	4	4
M-bronchioloalveolar carcinoma		-	-	-	-	-	0	0	0	1	0
M-adenocarcinoma		-	-	-	-	-	0	0	0	0	1
M-squamous cell carcinoma		-	-	-	-	-	0	0	0	1	0
Ear (no. examined)		0	0	0	0	1	0	0	0	0	0
B-papilloma		0	0	0	0	1	0	0	0	0	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female			
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Epididymis (no. examined)		60	60	60	60	60	-	-	-	-	-
M-histiocytic sarcoma		0	0	0	1	0	-	-	-	-	-
M-malignant lymphoma		2	3	7	3	0	-	-	-	-	-
M-hemangiosarcoma		0	1	0	0	0	-	-	-	-	-
B-interstitial (leydig) cell adenoma		1	0	1	0	1	-	-	-	-	-
M-fibrosarcoma		0	0	1	0	0	-	-	-	-	-
Esophagus (no. examined)		60	60	60	60	60	60	59	60	60	60
M-malignant lymphoma		2	1	1	2	0	6	3	3	1	1
M-bronchioloalveolar carcinoma		0	0	0	1	0	0	0	1	0	0
M-myxosarcoma		1	0	0	0	0	0	0	0	0	0
Eye (no. examined)		60	60	60	60	60	60	59	60	60	60
M-malignant lymphoma		1	1	1	3	0	8	4	5	4	2
Gallbladder (no. examined)		59	59	59	59	60	60	60	59	59	58
M-malignant lymphoma		2	2	2	1	1	11	6	6	3	3
B-adenoma		3	2	6	3	2	1	1	2	2	4
M-bronchioloalveolar carcinoma		0	0	0	0	0	0	0	0	1	0
M-leiomyosarcoma		0	1	0	0	0	0	0	1	0	0
M-histiocytic sarcoma		0	0	0	0	0	2	2	0	0	1
M-fibrosarcoma		0	0	0	0	0	0	1	0	0	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

		Male					Female				
Daily Dose (mg/kg/day)[a]	**GSK1278863A**	0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Gland, Adrenal (no. examined)		60	60	60	60	60	60	60	60	60	60
B-benign pheochromocytoma		1	2	2	0	0	0	0	0	0	0
M-malignant pheochromocytoma		0	0	0	1	1	0	0	0	0	0
B-benign subcapsular adrenal tumor type b		2	0	0	0	3	0	0	0	0	0
B-benign subcapsular adrenal tumor mixed type		2	2	4	0	1	0	0	0	1	0
B-benign subcapsular adrenal tumor type a		0	0	1	1	0	0	2	0	1	0
M-malignant lymphoma		2	2	4	2	0	11	7	7	5	5
M-bronchioloalveolar carcinoma		0	0	0	0	0	0	0	0	1	0
M-histiocytic sarcoma		0	0	0	0	0	1	2	0	1	0
M-leiomyosarcoma		0	0	0	0	0	0	0	1	0	0
M-malignant subcapsular adrenal tumor type b		0	0	1	2	0	0	0	0	0	0
M-malignant subcapsular adrenal tumor mixed type		0	0	2	2	1	0	0	0	0	0
M-malignant subcapsular adrenal tumor type a		0	0	0	0	0	0	2	1	1	0
M-fibrosarcoma		0	0	0	0	0	0	1	0	0	0
Gland, clitoral (no. examined)		-	-	-	-	-	59	59	60	60	60
M-malignant lymphoma		-	-	-	-	-	6	5	5	2	0
Gland, harderian (no. examined)		60	60	60	60	60	60	60	60	60	60
B-adenoma		8	14	9	10	10	4	7	12	7	2
M-adenocarcinoma		1	0	0	1	1	0	0	0	1	0
M-malignant lymphoma		1	1	1	2	0	6	6	6	3	4
M-leiomyosarcoma		0	0	0	0	0	0	0	1	0	0
M-histiocytic sarcoma		0	0	0	0	0	0	3	0	0	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Gland, lacrimal (no. examined)		0	1	0	0	0	0	0	0	3	2
M-malignant lymphoma		0	1	0	0	0	0	0	0	1	0
M-malignant granulosa cell tumor		0	0	0	0	0	0	0	0	0	1
Gland, mammary (no. examined)		9	15	12	11	17	60	59	60	60	60
M-adenocarcinoma		0	0	0	0	0	1	3	1	2	2
M-malignant lymphoma		1	0	0	0	0	14	4	7	7	2
Gland, parathyroid (no. examined)		57	58	55	55	58	57	55	53	54	58
M-malignant lymphoma		1	1	2	0	0	2	1	5	0	0
Gland, pituitary (no. examined)		60	60	58	59	60	59	60	60	60	60
M-malignant craniopharyngioma		0	0	0	0	0	0	0	0	1	0
M-malignant lymphoma		0	0	0	0	0	1	5	2	1	0
M-pars distalis carcinoma		0	0	0	0	1	1	0	1	0	0
B-pars distalis adenoma		1	1	2	1	1	1	2	1	6	2
Gland, preputial (no. examined)		60	60	60	60	60	-	-	-	-	-
M-malignant lymphoma		2	2	4	2	0	-	-	-	-	-
M-histiocytic sarcoma		0	0	0	1	0	-	-	-	-	-
Gland, prostate (no. examined)		60	60	60	60	60	-	-	-	-	-
M-malignant lymphoma		2	4	6	3	0	-	-	-	-	-
Gland salivary, mandibular (no. examined)		60	60	60	60	60	60	60	60	60	60
M-malignant lymphoma		2	2	5	2	0	8	4	8	4	2
M-myxosarcoma		1	0	0	0	0	0	0	0	0	0
M-histiocytic sarcoma		0	0	0	0	0	1	0	0	0	0
Gland salivary, parotid (no. examined)		60	60	60	60	60	60	60	60	60	60
M-malignant lymphoma		2	1	4	2	0	9	4	6	3	1
M-histiocytic sarcoma		0	1	0	0	0	0	0	0	0	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Gland salivary, sublingual (no. examined)		60	60	59	58	58	59	60	60	60	58
M-malignant lymphoma		1	1	2	2	0	3	6	4	3	2
M-myxosarcoma		1	0	0	0	0	0	0	0	0	0
M-histiocytic sarcoma		0	0	0	0	0	1	0	0	0	0
Gland, seminal vesicle (no. examined)		60	60	60	60	60	-	-	-	-	-
B-adenoma		0	0	2	0	0	-	-	-	-	-
M-adenocarcinoma		0	0	0	0	2	-	-	-	-	-
M-malignant granular cell tumor		1	0	0	0	0	-	-	-	-	-
M-malignant lymphoma		3	3	6	3	1	-	-	-	-	-
M-leiomyosarcoma		1	1	0	1	0	-	-	-	-	-
M-bronchioloalveolar carcinoma		0	0	0	1	0	-	-	-	-	-
M-osteosarcoma		0	0	0	0	1	-	-	-	-	-
M-sarcoma		0	0	0	1	0	-	-	-	-	-
Gland thyroid (no. examined)		60	60	60	60	60	60	59	60	60	60
B-follicular cell adenoma		0	0	0	0	1	0	0	0	0	0
M-malignant lymphoma		2	1	4	3	0	7	3	7	4	1
M-myxosarcoma		1	0	0	0	0	0	0	0	0	0
Head (no. examined)		0	1	0	0	0	0	0	0	1	0
M-malignant craniopharyngioma		0	0	0	0	0	0	0	0	1	0
Heart (no. examined)		60	60	60	60	60	60	60	60	60	60
M-hemangiosarcoma		0	0	0	0	0	0	1	0	0	0
M-malignant lymphoma		2	2	4	2	0	15	9	10	8	5
M-bronchioloalveolar carcinoma		0	1	0	2	1	0	0	1	1	0
M-histiocytic sarcoma		0	0	0	0	0	2	2	2	1	0
M-osteosarcoma		0	0	0	0	0	1	0	0	0	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Hemolymphoreticular tissue (no. examined)		60	60	60	60	60	60	60	60	60	60
M-histiocytic sarcoma		0	1	0	1	0	4	3	2	3	3
M-malignant lymphoma		4	8	10	3	2	21	17	18	15	15
Kidney (no. examined)		60	60	60	60	60	60	60	60	60	60
M-histiocytic sarcoma		0	1	0	0	0	3	3	0	1	2
M-malignant lymphoma		1	3	6	2	1	15	9	10	4	8
B-lipoma		1	1	0	0	0	0	0	0	0	0
M-bronchioloalveolar carcinoma		0	0	0	2	0	0	0	0	1	0
M-leiomyosarcoma		0	0	0	0	0	0	0	1	0	0
M-osteosarcoma		0	0	0	0	0	0	0	1	0	0
M-tubular cell carcinoma		1	0	2	0	0	0	0	0	0	0
B-tubular cell adenoma		0	0	0	0	0	0	0	0	1	0
Larynx (no. examined)		60	60	60	60	60	60	59	60	60	60
M-malignant lymphoma		2	1	2	1	0	8	6	6	3	2
M-myxosarcoma		1	0	0	0	0	0	0	0	0	0
M-squamous cell carcinoma		0	2	0	0	0	0	0	0	0	0
Large intestine, cecum (no. examined)		60	60	60	60	60	60	60	60	60	60
M-leiomyosarcoma		0	0	1	0	0	0	0	1	0	0
M-malignant lymphoma		0	0	1	1	0	6	2	4	2	3
M-histiocytic sarcoma		0	0	0	0	0	2	0	0	0	0
Large intestine, colon (no. examined)		60	60	60	60	60	60	60	60	60	60
M-malignant lymphoma		1	1	0	0	0	4	1	2	1	4
Large intestine, rectum (no. examined)		58	58	59	60	58	59	59	60	60	60
M-malignant lymphoma		1	1	0	1	0	7	2	7	2	4
M-histiocytic sarcoma		0	0	0	0	0	1	1	0	1	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Liver (no. examined)		60	60	60	60	60	60	60	60	60	60
M-hepatocellular carcinoma		4	9	12	6	7	0	1	0	0	1
B-hepatocellular adenoma		7	3	9	2	4	0	0	0	0	0
M-malignant lymphoma		3	3	6	2	0	14	11	9	5	7
M-hemangiosarcoma		2	3	2	0	3	2	0	0	1	1
M-histiocytic sarcoma		0	1	0	1	0	4	3	1	2	2
M-bronchioloalveolar carcinoma		0	0	0	1	0	0	0	0	1	0
M-adenosquamous carcinoma		0	0	0	0	1	0	0	0	0	0
M-leiomyosarcoma		0	0	0	0	0	0	0	1	0	0
M-osteosarcoma		0	0	0	0	0	0	0	2	0	0
M-fibrosarcoma		0	0	0	0	0	0	1	0	0	0
M-malignant granulosa cell tumor		0	0	0	0	0	0	0	0	0	1
Lung (no. examined)		60	60	60	60	60	60	60	60	60	60
M-histiocytic sarcoma		0	1	0	1	0	3	2	2	1	2
M-bronchioloalveolar carcinoma		19	15	21	19	20	9	12	9	11	7
B-bronchioloalveolar adenoma		10	13	11	12	9	8	5	8	12	12
M-malignant granulosa cell tumor		1	0	0	0	0	0	0	0	0	0
M-malignant lymphoma		1	3	6	3	0	15	12	12	7	6
M-adenosquamous carcinoma		0	0	0	0	1	0	0	0	0	0
M-adenocarcinoma		0	0	0	0	0	0	0	0	0	1
M-osteosarcoma		0	0	0	0	0	1	0	2	0	0
M-sarcoma		0	0	0	0	0	1	0	0	0	0
M-fibrosarcoma		0	0	0	0	0	0	1	0	0	0
M-hepatocellular carcinoma		0	1	0	0	0	0	0	0	0	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female			
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Lymph node (no. examined)		9	9	14	13	15	22	21	14	10	18
M-malignant lymphoma		0	3	4	3	0	11	9	7	3	8
M-histiocytic sarcoma		0	0	0	0	0	4	2	0	1	3
M-endometrial stromal sarcoma		0	0	0	0	0	0	1	0	0	0
M-bronchioloalveolar carcinoma		1	1	0	2	1	0	1	1	2	0
M-leiomyosarcoma		0	0	0	0	0	0	0	1	0	0
M-fibrosarcoma		0	0	0	0	0	0	1	0	0	0
M-malignant granular cell tumor		0	0	0	0	0	0	0	0	0	1
M-hemangiosarcoma		0	0	0	0	0	0	0	0	1	0
Lymph node mandibular (no. examined)		59	58	59	54	58	57	59	59	57	58
M-malignant lymphoma		2	3	3	2	0	10	9	10	6	5
M-histiocytic sarcoma		0	1	0	0	0	1	2	0	1	2
M-malignant granular cell tumor		0	0	0	0	0	0	0	0	0	1
Lymph node, mesenteric (no. examined)		60	60	59	60	60	60	59	60	59	59
M-malignant lymphoma		2	4	5	3	1	15	9	11	9	8
M-histiocytic sarcoma		0	1	0	0	0	4	2	0	0	3
M-bronchioloalveolar carcinoma		0	0	0	0	0	0	0	0	1	0
M-hemangiosarcoma		0	1	0	0	0	0	0	0	1	0
M-fibrosarcoma		0	0	0	0	0	0	1	0	0	0
M-osteosarcoma		1	0	0	0	0	0	0	0	0	0
B-hemangioma		0	0	0	0	0	0	1	0	1	0
Muscle, diaphragm (no. examined)		0	0	0	1	0	0	0	0	0	0
M-malignant lymphoma		0	0	0	1	0	0	0	0	0	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Muscle, skeletal (no. examined)		59	60	59	59	59	60	58	60	59	60
M-fibrosarcoma		0	0	0	0	0	0	0	0	1	0
M-malignant granular cell tumor		1	0	0	0	0	0	0	0	0	0
M-malignant lymphoma		2	1	1	2	0	10	3	6	4	1
M-hemangiosarcoma		0	1	0	0	0	0	0	1	0	0
M-bronchioloalveolar carcinoma		0	1	0	2	0	0	0	0	1	0
M-leiomyosarcoma		0	0	0	0	0	0	0	1	0	0
Nerve, optic (no. examined)		60	58	58	57	60	59	57	58	59	57
M-malignant lymphoma		1	0	0	0	0	0	0	0	0	0
Nerve, sciatic (no. examined)		60	60	60	60	60	60	60	59	60	60
M-malignant lymphoma		1	1	2	1	0	6	4	5	4	2
Ovary (no. examined)		-	-	-	-	-	59	60	60	60	60
B-cystadenoma		-	-	-	-	-	2	1	1	2	2
B-benign granulosa cell tumor		-	-	-	-	-	2	0	0	0	1
M-malignant granulosa cell tumor		-	-	-	-	-	0	0	0	0	1
M-malignant lymphoma		-	-	-	-	-	14	8	11	6	5
M-bronchioloalveolar carcinoma		-	-	-	-	-	0	0	0	1	0
M-hemangiosarcoma		-	-	-	-	-	0	0	0	2	0
M-histiocytic sarcoma		-	-	-	-	-	2	3	0	1	2
M-leiomyosarcoma		-	-	-	-	-	0	0	1	0	0
M-fibrosarcoma		-	-	-	-	-	0	1	0	0	0
B-benign mixed sex cord stromal tumor		-	-	-	-	-	0	2	2	2	0
B-luteoma		-	-	-	-	-	0	1	1	1	0
Oviduct (no. examined)		-	-	-	-	-	2	1	2	3	2
M-malignant lymphoma		-	-	-	-	-	1	0	0	0	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Pancreas (no. examined)		60	60	60	60	60	59	60	60	60	60
M-hemangiosarcoma		0	0	0	0	1	0	0	0	0	0
M-malignant lymphoma		2	1	5	2	1	10	5	9	6	5
M-bronchioloalveolar carcinoma		0	0	0	0	0	0	0	0	1	0
M-leiomyosarcoma		0	1	0	0	0	0	0	0	0	0
M-histiocytic sarcoma		0	0	0	0	0	2	2	0	1	0
B-islet cell adenoma		0	0	0	0	0	0	0	2	0	1
M-fibrosarcoma		0	0	0	0	0	0	1	0	0	0
Pericardium (no. examined)		0	1	0	1	0	1	0	0	0	0
M-malignant lymphoma		0	0	0	0	0	1	0	0	0	0
Site injection (no. examined)		60	60	60	60	60	60	60	60	60	60
M-fibrosarcoma		0	0	1	2	0	0	0	1	1	0
M-malignant lymphoma		2	1	5	2	1	13	8	11	6	4
M-adenocarcinoma		0	0	0	0	0	0	0	0	0	1
M-malignant mast cell tumor		0	0	0	0	0	0	0	0	0	1
M-histiocytic sarcoma		0	0	0	0	0	0	0	0	0	1
Site, uncertain primary (no. examined)		0	0	1	0	0	0	0	1	0	0
M-adenocarcinoma		0	0	1	0	0	0	0	0	0	0
M-osteosarcoma		0	0	0	0	0	0	0	1	0	0
Skin (no. examined)		60	60	60	60	60	60	59	59	60	60
B-papilloma		0	1	0	0	0	0	0	1	0	0
B-benign basal cell tumor		1	0	1	0	0	0	0	0	0	0
M-malignant lymphoma		2	3	6	2	0	9	6	7	5	2
M-histiocytic sarcoma		0	0	0	0	0	1	0	0	0	0
M-bronchioloalveolar carcinoma		0	0	0	1	0	0	0	0	0	0
B-sebaceous cell adenoma		1	0	1	0	0	0	0	0	0	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Small intestine, duodenum (no. examined)		60	60	60	58	60	60	60	60	60	60
B-adenoma		1	2	1	0	0	0	0	1	0	0
M-adenocarcinoma		1	0	0	1	0	0	0	0	1	0
M-malignant lymphoma		1	0	0	0	0	3	2	3	1	0
M-histiocytic sarcoma		0	0	0	0	0	0	2	0	0	0
Small intestine, ileum (no. examined)		60	59	59	60	60	60	60	60	60	60
M-malignant lymphoma		1	0	1	0	0	4	3	1	1	1
M-histiocytic sarcoma		0	0	0	0	0	1	0	0	0	1
Small intestine, jejunum (no. examined)		58	60	60	60	59	59	60	60	60	60
M-adenocarcinoma		1	0	0	0	1	1	0	1	0	1
M-malignant lymphoma		1	0	3	0	0	5	4	1	0	0
M-histiocytic sarcoma		0	1	0	0	0	0	0	0	0	0
Spinal cord, lumbar (no. examined)		60	60	60	60	60	60	59	60	60	60
M-malignant astrocytoma		1	0	0	0	0	0	0	0	0	0
M-malignant lymphoma		1	0	1	0	0	5	5	3	2	0
Spleen (no. examined)		60	60	60	60	60	60	60	60	60	60
M-hemangiosarcoma		1	1	0	3	1	2	2	0	2	1
M-malignant lymphoma		2	5	8	2	0	19	14	13	10	9
M-histiocytic sarcoma		0	1	0	1	0	3	3	0	1	2
M-leiomyosarcoma		0	1	0	0	0	0	0	1	0	0
M-fibrosarcoma		0	0	0	0	0	0	1	0	0	0
M-osteosarcoma		0	0	0	0	0	0	0	0	0	1

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Stomach (no. examined)		60	60	60	60	60	60	60	60	60	60
B-adenoma		0	1	0	1	0	0	0	0	1	0
M-malignant lymphoma		1	1	3	1	1	11	6	7	4	4
M-bronchioloalveolar carcinoma		0	0	0	0	0	0	0	0	1	0
M-histiocytic sarcoma		0	0	0	0	0	2	1	0	0	1
B-papilloma		0	0	1	1	0	0	0	0	0	0
M-squamous cell carcinoma		1	0	1	1	0	0	0	0	0	0
M-fibrosarcoma		0	0	0	0	0	0	1	0	0	0
Subcutis (no. examined)		3	2	2	1	1	1	3	3	2	0
M-myxosarcoma		1	0	0	0	0	0	0	0	0	0
M-hemangiosarcoma		1	2	1	1	0	0	0	1	0	0
M-Rhabdomyosarcoma		0	0	0	0	0	0	0	1	0	0
M-fibrosarcoma		0	0	0	0	0	0	3	0	2	0
M-sarcoma		0	0	0	0	0	1	0	0	0	0
M-malignant schwannoma		0	0	0	0	0	0	0	1	0	0
B-hemangioma		1	0	0	0	0	0	0	0	0	0
Tail (no. examined)		0	0	0	0	0	0	0	1	0	1
M-osteosarcoma		0	0	0	0	0	0	0	1	0	0
Testis (no. examined)		60	60	60	60	60	-	-	-	-	-
B-interstitial (leydig) cell adenoma		1	5	0	0	1	-	-	-	-	-
M-malignant lymphoma		1	0	1	2	0	-	-	-	-	-
M-histiocytic sarcoma		0	0	0	1	0	-	-	-	-	-
M-adenocarcinoma		0	0	0	0	1	-	-	-	-	-

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Thymus (no. examined)		58	60	59	60	58	59	60	60	60	59
M-malignant lymphoma		2	4	6	3	2	20	17	17	14	15
M-bronchioloalveolar carcinoma		2	1	0	0	1	0	0	2	1	0
M-histiocytic sarcoma		0	1	0	0	0	3	2	2	1	1
M-malignant granulosa cell tumor		0	0	0	0	0	0	0	0	0	1
Tongue (no. examined)		60	60	60	60	60	60	59	60	60	60
M-malignant lymphoma		1	0	3	2	0	7	4	5	3	0
M-squamous cell carcinoma		0	1	0	0	0	0	0	0	0	0
Trachea (no. examined)		59	60	58	60	60	59	59	60	60	60
M-histiocytic sarcoma		0	0	0	0	0	0	0	1	0	0
M-malignant lymphoma		2	2	2	2	0	9	5	5	2	1
M-myxosarcoma		1	0	0	0	0	0	0	0	0	0
Ureter (no. examined)		1	3	2	2	5	2	2	2	2	2
M-malignant lymphoma		0	0	1	0	0	2	0	2	1	0
M-histiocytic sarcoma		0	0	0	0	0	0	1	0	0	0
M-transitional cell carcinoma		0	0	0	0	0	0	1	0	0	0
Urinary bladder (no. examined)		60	59	60	60	60	59	59	58	60	59
M-leiomyosarcoma		0	0	0	0	0	0	0	1	0	0
M-malignant lymphoma		1	1	4	3	0	14	8	8	7	8
M-histiocytic sarcoma		0	1	0	0	0	0	1	0	0	1
M-fibrosarcoma		0	0	0	0	0	0	1	0	0	0
M-adenocarcinoma		0	0	0	0	0	0	0	0	0	1

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female			
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Uterus (no examined)		-	-	-	-	-	59	60	60	60	60
M-histiocytic sarcoma		-	-	-	-	-	3	3	0	2	2
B-leiomyoma		-	-	-	-	-	1	1	2	1	1
M-leiomyosarcoma		-	-	-	-	-	3	1	3	4	1
M-endometrial stromal sarcoma		-	-	-	-	-	0	1	0	0	1
M-adenocarcinoma		-	-	-	-	-	1	0	0	0	2
M-malignant lymphoma		-	-	-	-	-	13	8	11	6	5
M-bronchioloalveolar carcinoma		-	-	-	-	-	0	0	0	1	0
M-hemangiosarcoma		-	-	-	-	-	3	3	2	3	3
B-benign granular cell tumor		-	-	-	-	-	0	0	1	0	0
B-hemangioma		-	-	-	-	-	0	1	1	1	0
M-fibrosarcoma		-	-	-	-	-	0	1	0	0	0
B-polyp glandular		-	-	-	-	-	6	2	3	5	3
B-endometrial stromal polyp		-	-	-	-	-	1	4	0	2	1
Vagina (no. examined)		-	-	-	-	-	59	58	58	60	60
M-malignant lymphoma		-	-	-	-	-	10	3	5	3	5
M-leiomyosarcoma		-	-	-	-	-	0	1	0	1	0
M-fibrosarcoma		-	-	-	-	-	0	1	0	0	0
M-squamous cell carcinoma		-	-	-	-	-	0	0	1	0	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Macroscopic Examination											
Spleen (no. examined)		60	60	60	60	60	60	60	60	60	60
enlargement		9	22	13	19	17	27	33	29	29	38
Injection site - left dorsal thoracic (no. examined)		60	60	60	60	60	60	60	60	60	60
Focus; dark		15	19	11	21	26	19	25	20	22	24
Injection site - right dorsal thoracic (no. examined)		60	60	60	60	60	60	60	60	60	60
Focus; dark		14	29	10	28	36	8	29	21	35	29
Injection site - left scapular (no. examined)		60	60	60	60	60	60	60	60	60	60
Focus; dark		16	21	8	17	22	10	19	21	20	26
Injection site - right scapular (no. examined)		60	60	60	60	60	60	60	60	60	60
Focus; dark		14	35	13	26	29	11	27	20	24	23
Whole animal (no. examined)		60	60	60	60	60	60	60	60	60	60
Discoloration; dark		0	1	0	3	6	1	1	1	3	2
Test Item-related Non-Neoplastic Findings											
Bone marrow (no. examined)		60	60	60	60	60	60	60	60	60	60
Increased myelopoiesis											
mild		3	3	0	1	3	1	2	1	5	4
moderate		1	1	0	2	1	4	1	1	1	10
marked		1	2	1	3	1	1	3	2	1	6
severe		1	3	1	2	2	3	1	3	0	0

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

		Male					Female				
Daily Dose (mg/kg/day)[a]	**GSK1278863A**	0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Injection Site (no. examined)		60	60	60	60	60	60	60	60	60	60
Hemorrhage											
minimal		14	22	11	23	21	9	20	12	15	16
mild		4	15	4	15	16	9	17	10	18	16
moderate		4	6	1	4	4	2	6	5	10	6
marked		2	1	0	0	0	0	1	0	5	2
Kidney (no. examined)		60	60	60	60	60	60	60	60	60	60
Pigmentation; tubular											
minimal		0	0	0	0	0	0	0	1	1	5
mild		0	0	0	0	0	0	1	0	0	0
moderate		0	0	0	0	0	0	1	0	0	1
Liver (no. examined)		60	60	60	60	60	60	60	60	60	60
Increased hematopoiesis											
minimal		0	1	2	2	0	2	6	4	3	7
mild		1	0	0	0	2	4	3	2	2	3
moderate		0	0	0	1	1	1	0	1	1	1
marked		0	1	0	0	0	0	0	1	0	0
Pigmentation; kupffer cell											
minimal		10	11	6	19	21	11	23	11	24	24
mild		1	2	0	2	6	2	0	4	2	14
moderate		0	0	0	0	0	0	2	0	0	2
Nerve, Sciatic (no. examined)		60	60	60	60	60	60	60	59	60	60
Degeneration											
minimal		1	7	7	3	5	5	3	0	3	9
mild		1	0	0	0	0	0	0	1	1	1

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

Daily Dose (mg/kg/day)[a]	GSK1278863A	Male					Female				
		0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Spleen (No. examined)		60	60	60	60	60	60	60	60	60	60
Increased hematopoiesis											
minimal		8	12	13	14	14	10	11	10	14	7
mild		6	7	4	8	12	2	12	9	10	12
moderate		4	7	4	15	7	4	5	4	6	7
marked		1	2	1	4	6	3	6	4	6	11
severe		2	8	2	4	8	6	9	8	5	10
Pigmentation; macrophage											
minimal		6	14	6	11	18	20	29	24	40	31
mild		0	0	1	1	1	1	4	0	4	15
moderate		0	0	0	0	0	0	0	0	0	1
Thymus (no. examined)		58	60	59	60	58	59	60	60	60	59
Hyperplasia; lymphoid											
minimal		0	0	2	2	0	0	0	4	2	4
mild		2	1	1	3	1	6	7	4	3	5
moderate		4	7	6	1	1	6	9	11	9	8
marked		1	2	0	1	0	1	4	4	3	3
severe		2	0	0	2	0	0	2	0	2	0
Vasculature[c] (no. examined)		60	60	60	60	60	60	60	60	60	60
Vascular/perivascular inflammation											
minimal		13	18	9	6	14	13	14	17	10	14
mild		6	8	7	15	13	4	13	7	16	12
moderate		2	9	0	2	3	4	3	3	8	8
marked		0	1	0	2	0	1	4	2	2	6

GSK1278863A: A 2-Year Carcinogenicity Study in Mice (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** 2014N221714

		Male					Female				
Daily Dose (mg/kg/day)[a]	**GSK1278863A**	0	0.2	0.8	0.8	3	0	0.2	0.8	0.8	3
	Metabolite cocktail (M2, M3, M13)	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3	0	2/2.5/1.3	0	2/2.5/1.3	2/2.5/1.3
Whole Animal (no. examined)		3	16	11	27	14	3	5	5	11	19
Congestion											
minimal		3	14	6	21	9	3	5	3	11	9
mild		0	2	5	6	3	0	0	2	0	6
moderate		0	0	0	0	2	0	0	0	0	4

Key:

** p < 0.01;*** p < 0.001, Statistical significance is based on actual data not change.

- = Not examined/Not applicable; NC = Not calculable; NQ = not quantifiable (below the lower limit of quantification); B= Benign; M= Malignant

a = Doses are expressed in terms of parent compound, GSK1278863, or its metabolites [GSK2391220 (M2), GSK2506104 (M3) and GSK2531401 (M13)]. The oral reference item was 1% (w/v) methyl cellulose (400 cP@ 2%) / 0.2% Tween 80 (v/v) / 5 mM NaOH in Ultra Pure Water, pH 6 (± 0.2). The subcutaneous reference item was aqueous 25 mM phosphate buffer, pH7.4 (± 0.2).

b = Hematology evaluation was limited to n=10/sex/group given 0 mg/kg/day (reference item) and 3 mg/kg/day + metabolites and included hematocrit only.

c = Vasculature findings were most prominent in the male and female reproductive tracts and accessory glands, urinary tract, digestive tract, heart, aorta and thymus, although were also sporadically noted in other tissues.

Table 11.2 GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats

Study Type: Carcinogenicity	**Report Title:** GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats	**Test Item:** GSK1278863A (parent compound) **Batch No.:** 8863B3B001
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** Up to 95 weeks for males and for 99 weeks for females. Last dose given: males at 4 mg/kg/day (Day 631/Week 91); all other males (Day 670/Week 96); females (Day 700/Week 100)	**GSK Reference No.:** R70375G
Initial Age: 7 weeks	**Route/Frequency:** Oral by gavage, once daily	**GSK Document Number:** 2014N196080 **Location in CTD:** m4.2.3.4.1
Date of First Dose: 03 April 2014	**Vehicle/Formulation:** 1% (w/v) methyl cellulose (400 cP@ 2%) with 0.2% Tween 80 (v/v) with 5 mM NaOH in Ultra Pure Water, pH 6 (± 0.2)	**Study in Compliance with GLP:** Yes

Data Collected: Toxicokinetics, clinical observations, body weight, food consumption, ophthalmoscopy, hematology (limited to red blood cell counts, hematocrit, hemoglobin, and absolute reticulocyte counts), macroscopic and microscopic pathology, and transcriptomic evaluation of erythropoietin (Epo) and vascular endothelial growth factor (VEGF) mRNA expression.

Basis for high dose selection: High doses of 4 mg/kg/day and 7 mg/kg/day were selected for males and females, respectively. These were the lowest respective doses at which clear pharmacodynamic effects (statistically significant increase in mean hematocrit) were identified in prior studies. In a prior 26-Week study, males did not tolerate 10 mg/kg/day and while 10 mg/kg/day was tolerated by females, the marked hematocrit increases (1.23X to 1.43X control) observed were considered unsustainable for more prolonged administration based on the mortality observed in male rats at comparable hematrocrit values.

Conclusion: Administration of GSK1278863A by oral gavage to Sprague-Dawley rats for 90 to 99 weeks at doses of 0.02, 0.1, 0.8 and at 4 mg/kg/day (in males) or 7 mg/kg/day (in females) did not result in any test item-related neoplastic microscopic findings. Non-neoplastic changes were limited to erosion/ulceration of the glandular stomach and pharmacologically-mediated increases in red blood cell mass parameters at 4 (males) and 7 (females) mg/kg/day, and progressive cardiomyopathy in males and females given ≥0.8 mg/kg/day and atrial thrombosis along with thrombosis with or without an infarct or segmental necrosis of various tissues in males at 4 mg/kg/day. The progressive cardiomyopathy and atrial thrombosis likely contributed to the increased mortality seen in males given 4 mg/kg/day.

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

		Male					Female				
Daily Dose (mg/kg/day)[a]		0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Numbers of Animals:	**Main**	70	70	70	70	70	70	70	70	70	70
	Toxicokinetic[b]	6	3	6	3	9	6	3	6	3	9
$AUC_{(0-t)}$ (µg.h/mL)	Week 4	NC	5.01	31.2	182	844	NC	7.03	26.4	213	1270
	Week 26	NC	6.53	42.8	242	889	NC	10.4[c]	38.9	306	1430
C_{max} (µg/mL)	Week 4	NQ	0.335	2.16	12.3	54.9	NQ	0.473	1.87	13.8	75.0
	Week 26	NQ	0.398	2.67	17.5	58.0	NQ	0.569	2.60	18.5	83.5
Noteworthy Findings											
Terminal Euthanasia (TE): Number of Surviving Rats [Week of TE][d]		20 [97]	17 [97]	17 [97]	16 [97]	15 [94]	20 [100]	21 [100]	20 [100]	27 [100]	30 [100]
Survival at Terminal Euthanasia (%)[d]		29	24	24	23	21[e]	29	30	29	39	43
Decedents		50	53	53	54	55	50	49	50	43	40
Most Common Cause of Demise											
Number Examined		50	53	53	54	55	50	49	50	43	40
Undetermined		13	14	9	19	21	3	1	2	2	1
Accidental (including gavage accident)		0	0	1	0	0	0	0	0	1	0
Neoplastic											
Pituitary gland		12	10	12	8	6	28	27	22	14	14
Mammary gland		1	0	0	0	0	9	13	13	8	11
Non-neoplastic											
Progressive cardiomyopathy		5	3	4	9	10	0	0	0	1	0
Atrial thrombosis		0	0	0	1	4	0	0	0	0	0
Clinical Observations											
Red skin											
Number of observations		590	708	735	610	1398	521	664	543	596	967
Number of animals		50	62	59	54	58	41	56	52	47	60

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Hematology[f]										
Red blood cells (10^{12}/L)										
Week 26	8.97	--	--	9.07	10.24†††	8.11	--	--	8.01	9.44**
Week 39	8.86	--	--	8.75	10.96†††	7.82	--	--	7.78	9.37**
Week 52	8.78	--	--	8.98	11.31†††	7.74	--	--	7.62	9.40**
Hemoglobin (g/L)										
Week 26	156	--	--	164	188†††	151	--	--	154	183***
Week 39	155	--	--	159	203***	148	--	--	153	187***
Week 52	151	--	--	160	204***	145	--	--	148	182***
Hematocrit (%)										
Week 26	47.1	--	--	49.6	57.2†††	43.6	--	--	44.9	53.1***
Week 39	46.8	--	--	47.9	61.3***	42.8	--	--	43.9	53.2***
Week 52	47.4	--	--	49.8	63.1***	43.1	--	--	43.7	54.3***
Reticolocytes (10^{9}/L)										
Week 26	235.0	--	--	204.1	238.5	157.2	--	--	163.3	206.2†
Week 39	222.5	--	--	204.2	236.4	147.0	--	--	142.6	223.4**
Week 52	229.9	--	--	201.5	249.4	153.5	--	--	150.4	225.9**
Transcriptomics [g]	mRNA expression for erythropoietin (Epo) and vascular endothelial growth factor (VEGF) was interrogated in selected frozen samples (kidney, liver, lung, mesenteric lymph node, and spleen) from male and female rats given 0 (reference item), 0.1, 4 (males only) or 7 (females only) mg/kg/day for 26 weeks. There were no test-item related changes in VEGF expression. Epo expression in liver was increased (approximately 250X control mean) in rats given 4 mg/kg/day.									

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Microscopic Examination: Neoplastic lesions (without consideration of cause or relevance)										
Adipose tissue (no.examined)	5	6	7	4	3	3	5	2	6	8
M-histiocytic sarcoma	1	0	1	1	0	0	0	1	0	1
M-large granular lymphocytic leukemia	0	0	2	0	0	0	0	0	0	0
M-malignant mesothelioma	0	0	0	1	0	0	0	0	0	0
B-benign hibernoma	1	0	0	0	0	0	0	0	0	0
M-stromal sarcoma	0	0	0	0	0	1	0	0	0	0
M-malignant lymphoma	0	0	0	0	0	0	1	0	0	0
M-liposarcoma	0	0	0	0	0	0	0	0	1	0
M-acinar adenocarcinoma	0	0	0	0	0	0	0	0	1	0
Adrenal gland (no.examined)	70	70	70	70	70	70	70	70	70	70
B-benign pheochromocytoma; unilateral	6	7	6	4	1	2	2	1	0	3
B-benign pheochromocytoma; bilateral	1	0	0	0	0	0	0	1	0	0
M-cortical carcinoma; unilateral	0	1	0	0	0	0	0	0	0	0
B-cortical adenoma; unilateral	1	1	1	1	0	0	2	3	1	2
B-cortical adenoma; bilateral	0	0	0	0	0	0	0	1	0	0
B-benign complex pheochromocytoma; unilateral	0	0	0	1	0	0	0	0	0	0
M-malignant pheochromocytoma; unilateral	2	1	1	1	0	0	1	2	0	1
M-malignant pheochromocytoma; bilateral	0	0	0	0	0	0	0	0	0	1
M-malignant lymphoma; bilateral	0	0	1	0	0	0	0	0	1	0
M-large granular lymphocytic leukemia; unilateral	0	0	1	0	0	0	0	0	0	0
M-large granular lymphocytic leukemia; bilateral	0	0	1	1	0	0	0	0	1	1
M-histiocytic sarcoma; unilateral	0	0	0	0	0	0	0	0	0	2
M-histiocytic sarcoma; bilateral	0	0	0	0	0	0	0	1	0	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Aorta (no.examined)	70	70	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	0	0	0	0	0	0	0	0	0	1
M-large granular lymphocytic leukemia	0	0	0	0	0	0	0	0	1	0
Body cavity, abdominal (no.examined)	2	0	1	0	1	0	0	0	2	1
M-histiocytic sarcoma	1	0	1	0	0	0	0	0	0	0
M-stromal sarcoma	0	0	0	0	0	0	0	0	1	0
B-lipoma	0	0	0	0	0	0	0	0	1	0
Body cavity, cranial (no.examined)	0	0	0	0	0	0	0	0	1	0
M-large granular lymphocytic leukemia	0	0	0	0	0	0	0	0	1	0
Body cavity, nasal (no.examined)	70	70	70	70	70	70	70	70	70	70
M-malignant lymphoma	1	1	0	0	0	0	0	0	1	0
M-granulocytic leukemia	1	0	0	0	0	0	0	0	0	0
M-histiocytic sarcoma	0	0	1	0	0	0	0	0	0	0
M-squamous cell carcinoma	0	1	1	0	0	0	0	0	1	1
M-large granular lymphocytic leukemia	2	1	3	1	0	0	0	0	1	1
B-adenoma	0	1	0	0	0	0	0	0	1	0
M-malignant astrocytoma	0	0	0	0	0	1	0	0	0	0
Body cavity, oral (no.examined)	0	1	2	0	0	1	0	5	1	0
M-squamous cell carcinoma	0	0	2	0	0	0	0	5	1	0
M-osteosarcoma	0	0	0	0	0	1	0	0	0	0
Body cavity, thoracic (no.examined)	1	1	0	1	0	1	0	0	0	0
M-histiocytic sarcoma	1	0	0	0	0	0	0	0	0	0
M-malignant thymoma	0	0	0	1	0	0	0	0	0	0
M-paraganglioma	0	1	0	0	0	0	0	0	0	0
M-c-cell carcinoma	0	0	0	0	0	1	0	0	0	0
Bone (no.examined)	3	0	1	2	0	1	0	0	2	3
M-large granular lymphocytic leukemia	2	0	1	1	0	0	0	0	1	1
M-malignant lymphoma	1	0	0	0	0	0	0	0	0	0
M-sarcoma; not otherwise specified	0	0	0	0	0	0	0	0	1	1
M-osteosarcoma	0	0	0	0	0	1	0	0	0	0
M-malignant meningioma	0	0	0	0	0	0	0	0	0	1

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Bone, femur (no.examined)	70	70	70	70	70	70	70	70	70	69
M-granulocytic leukemia	1	0	0	0	0	0	0	0	0	0
M-hemangiosarcoma	1	0	0	0	0	1	0	0	0	0
M-large granular lymphocytic leukemia	2	0	2	1	0	0	0	0	0	1
M-histiocytic sarcoma	0	2	0	0	0	0	0	0	0	0
M-malignant lymphoma	0	1	0	0	0	0	0	0	1	0
Bone, sternum (no.examined)	70	70	70	70	70	70	70	70	70	70
M-malignant lymphoma	0	1	0	0	0	0	0	0	0	0
M-large granular lymphocytic leukemia	2	1	2	1	0	0	0	0	0	1
M-granulocytic leukemia	1	0	0	0	0	0	0	0	0	0
Bone marrow (no.examined)	70	70	70	70	70	70	70	70	70	70
M-malignant lymphoma	1	1	0	0	0	0	0	1	1	0
M-granulocytic leukemia	1	0	0	0	0	0	0	0	0	0
M-histiocytic sarcoma	2	1	2	0	0	1	0	0	0	1
M-large granular lymphocytic leukemia	2	1	3	1	0	0	0	0	1	1
M-malignant pheochromocytoma	0	0	1	0	0	0	0	0	0	0
Brain (no.examined)	70	70	70	70	70	70	69	70	70	70
M-malignant astrocytoma	1	3	2	0	0	1	0	1	1	1
M-malignant meningioma	1	0	1	1	1	0	0	0	0	1
M-histiocytic sarcoma	0	1	0	0	0	0	0	0	0	0
M- carcinoma, pars distalis	1	0	1	1	1	0	1	1	1	0
M-malignant lymphoma	0	1	0	0	0	0	0	0	0	0
M-large granular lymphocytic leukemia	1	0	2	1	0	0	0	0	1	1
M-fibrosarcoma	0	0	0	1	0	0	0	0	0	0
M-malignant granular cell tumor	0	0	0	0	0	0	0	0	0	1
M-malignant oligodendroglioma	0	0	0	0	0	0	1	0	0	1
Cervix (no.examined)	-	-	-	-	-	70	69	70	70	70
M-histiocytic sarcoma	-	-	-	-	-	1	0	1	0	1
M-malignant lymphoma	-	-	-	-	-	0	0	0	1	0
M-stromal sarcoma	-	-	-	-	-	1	0	0	1	0
B-endometrial stromal polyp	-	-	-	-	-	0	0	0	0	1
M-large granular lymphocytic leukemia	-	-	-	-	-	0	0	0	1	1
M-acinar adenocarcinoma	-	-	-	-	-	0	0	0	1	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Epididymis (no.examined)	70	70	70	70	70	-	-	-	-	-
M-large granular lymphocytic leukemia; bilateral	1	0	1	1	0	-	-	-	-	-
Esophagus (no.examined)	70	70	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	0	0	0	0	0	0	0	0	0	1
Eye (no.examined)	70	68	70	69	69	70	70	70	69	70
M-histiocytic sarcoma; unilateral	0	1	0	0	0	0	0	0	0	0
M-malignant lymphoma; bilateral	0	0	1	0	0	0	0	0	1	0
M-large granular lymphocytic leukemia; bilateral	1	0	2	1	0	0	0	0	0	1
B-benign melanoma; unilateral	0	0	0	0	0	0	0	0	1	0
M-fibrosarcoma; unilateral	0	0	0	0	0	0	0	0	1	0
Harderian gland (no.examined)	70	70	70	70	69	70	70	70	69	70
M-malignant lymphoma; bilateral	0	0	1	0	0	0	0	0	1	0
M-large granular lymphocytic leukemia; bilateral	1	0	2	1	0	0	0	0	1	1
M-fibrosarcoma; unilateral	0	0	0	0	0	0	0	0	1	0
Head (no.examined)	1	0	0	2	1	0	0	1	1	0
M-sarcoma; not otherwise specified	0	0	0	1	0	0	0	1	1	0
M-fibrosarcoma	0	0	0	1	0	0	0	0	0	0
Heart (no.examined)	70	70	70	70	70	70	70	70	70	70
M-malignant mesothelioma	0	0	0	1	0	0	0	0	0	0
M-large granular lymphocytic leukemia	2	0	2	1	0	0	0	0	1	0
M-histiocytic sarcoma	0	1	0	0	0	0	0	0	0	0
M-malignant lymphoma	0	0	1	0	0	0	0	0	0	0
M-malignant thymoma	0	0	0	1	0	0	0	0	0	0
M-adenocarcinoma; mammary gland	0	0	0	0	0	0	0	0	0	1
M-adenosquamous carcinoma; mammary gland	0	0	0	0	0	0	1	0	0	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Hemolymphoreticular tissue (no.examined)	70	70	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	3	2	2	2	0	1	0	1	0	3
M-granulocytic leukemia	1	0	0	0	0	0	0	0	0	0
M-malignant lymphoma	2	1	1	0	0	0	1	1	2	0
M-large granular lymphocytic leukemia	2	1	3	1	0	0	0	0	1	1
Joint (no.examined)	12	11	7	5	5	5	9	8	6	9
M-large granular lymphocytic leukemia	0	0	0	1	0	0	0	0	0	0
Kidney (no.examined)	70	70	70	70	70	70	70	70	70	70
B-amphophilic vacuolar adenoma; unilateral	0	0	1	0	0	0	1	0	0	0
B-amphophilic vauolar adenoma; bilateral	1	0	2	1	3	0	0	1	0	0
M-histiocytic sarcoma; unilateral	0	0	1	0	0	0	0	1	0	1
M-histiocytic sarcoma; bilateral	1	1	0	1	0	0	0	0	0	1
M-granulocytic leukemia; bilateral	1	0	0	0	0	0	0	0	0	0
M-large granular lymphocytic leukemia; bilateral	2	1	2	1	0	0	0	0	1	1
M-malignant lymphoma; bilateral	1	1	1	0	0	0	0	1	1	0
M-liposarcoma; unilateral	0	1	0	0	0	0	0	0	0	1
M-acinar adenocarcinoma; bilateral	0	0	0	0	0	0	0	0	1	0
Lacrimal gland (no.examined)	12	11	10	14	9	0	0	0	0	0
M-large granular lymphocytic leukemia	0	0	1	0	0	0	0	0	0	0
Larynx (no.examined)	70	70	70	70	69	70	70	70	70	70
M-malignant lymphoma	0	1	0	0	0	0	0	0	1	0
M-large granular lymphocytic leukemia	2	0	2	1	0	0	0	0	1	0
M-c-cell carcinoma	0	0	1	0	0	0	0	0	0	0
M-fibrosarcoma	0	0	0	0	0	0	0	0	0	1
Large intestine, cecum (no.examined)	70	70	69	70	70	70	70	70	70	70
M-malignant lymphoma	1	0	1	0	0	0	0	0	0	0
M-large granular lymphocytic leukemia	0	0	2	1	0	0	0	0	0	0
M-histiocytic sarcoma	0	0	0	0	0	0	0	1	0	0
M-stromal sarcoma	0	0	0	0	0	0	0	0	1	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Large intestine, colon (no.examined)	70	70	69	70	70	70	70	70	70	70
M-large granular lymphocytic leukemia	0	0	2	1	0	0	0	0	0	0
M-malignant lymphoma	0	0	1	0	0	0	0	0	0	0
M-histiocytic sarcoma	0	0	0	0	0	0	0	1	0	1
Large intestine, rectum (no.examined)	70	70	70	70	70	70	70	70	70	70
M-malignant lymphoma	1	0	1	0	0	0	0	0	1	0
M-histiocytic sarcoma	0	1	0	0	0	1	0	0	0	1
M-large granular lymphocytic leukemia	0	0	2	0	0	0	0	0	0	0
Liver (no.examined)	70	70	70	70	70	70	70	70	70	70
B-hepatocellular adenoma	3	2	0	0	0	1	0	0	0	0
M-malignant lymphoma	1	1	1	0	0	0	1	1	1	0
M-large granular lymphocytic leukemia	2	1	3	1	0	0	0	0	1	1
M-granulocytic leukemia	1	0	0	0	0	0	0	0	0	0
B-cholangioma	0	1	0	0	1	0	0	0	0	0
M-histiocytic sarcoma	1	1	2	2	0	1	0	0	0	2
M-Islet cell carcinoma	1	1	1	0	0	0	0	0	0	0
B-hemangioma	0	0	0	0	1	0	0	0	0	0
M-malignant thymoma	0	0	0	1	0	0	0	0	0	0
M-ductal cell adenocarcinoma	1	0	0	0	0	0	0	0	0	0
M-malignant astrocytoma	0	0	0	0	0	1	0	0	0	0
M-malignant pheochromocytoma	0	0	0	0	0	0	0	1	0	0
M-acinar adenocarcinoma	0	0	0	0	0	0	0	0	1	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Lung (no.examined)	70	70	70	70	70	70	70	70	70	70
M-hemangiosarcoma	1	0	0	0	0	0	0	0	0	0
M-histiocytic sarcoma	3	2	1	1	0	1	0	0	0	2
M-malignant mesothelioma	0	0	0	1	0	0	0	0	0	0
M-bronchioloalveolar carcinoma	0	1	0	0	0	0	0	0	0	0
M-large granular lymphocytic leukemia	2	0	2	1	0	0	0	0	1	1
B-bronchioloalveolar adenoma	2	0	0	1	0	0	0	0	0	1
M-malignant lymphoma	2	1	1	0	0	0	0	1	1	0
M-c-cell carcinoma	0	0	1	1	0	0	0	0	0	1
M-malignant melanoma	0	0	1	0	0	0	0	0	0	0
M-malignant thymoma	0	0	0	1	0	0	0	0	0	0
M-acinar adenocarcinoma	0	0	0	0	0	0	0	0	1	0
M-adenocarcinoma; mammary gland	0	0	0	0	0	0	0	0	0	3
M-malignant basal cell tumor	0	0	0	0	0	1	0	0	0	0
M-adenosquamous carcinoma; mammary gland	0	0	0	0	0	0	1	0	0	0
M-sarcoma; not otherwise specified	0	0	0	0	0	0	0	1	0	0
M-epithelioma; cystic keratinizing	0	0	0	0	0	0	0	0	1	0
M-malignant pheochromocytoma	0	0	0	0	0	0	0	1	0	0
M-squamous cell carcinoma	0	0	0	0	0	0	0	1	0	0
Lymph node (no.examined)	17	14	16	8	7	17	21	17	16	19
M-malignant lymphoma	1	0	0	0	0	0	1	1	1	0
M-granulocytic leukemia	1	0	0	0	0	0	0	0	0	0
M-large granular lymphocytic leukemia	2	0	0	0	0	0	0	0	1	0
M-histiocytic sarcoma	1	2	2	0	0	1	0	1	0	3
M-c-cell carcinoma	1	0	1	0	0	1	0	0	0	1
M-malignant mesothelioma	0	0	0	1	0	0	0	0	0	0
M-paraganglioma	0	1	0	0	0	0	0	0	0	0
M-stromal sarcoma	0	0	0	0	0	0	0	0	1	0
B-hemangioma	0	0	0	0	0	0	1	0	0	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Lymph node, mandibular (no.examined)	70	70	70	70	69	70	70	70	68	70
M-large granular lymphocytic leukemia; unilateral	0	0	0	0	0	0	0	0	1	0
M-large granular lymphocytic leukemia; bilateral	2	0	2	1	0	0	0	0	0	1
M-malignant lymphoma; bilateral	1	0	0	0	0	0	0	0	0	0
M-histiocytic sarcoma; bilateral	1	0	1	0	0	0	0	0	0	0
M-c-cell carcinoma	0	0	1	0	0	0	0	0	0	0
M-malignant astrocytoma	0	0	0	0	0	1	0	0	0	0
M-squamous cell carcinoma; unilateral	0	0	0	0	0	0	0	1	0	0
M-fibrosarcoma; bilateral	0	0	0	0	0	0	0	0	1	0
Lymph node, mesenteric (no.examined)	70	70	69	69	70	70	70	70	70	70
M-malignant lymphoma	1	0	1	0	0	0	1	1	1	0
M-large granular lymphocytic leukemia	2	0	2	1	0	0	0	0	1	1
M-histiocytic sarcoma	0	0	2	0	0	0	0	1	0	2
M-hemangiosarcoma	0	1	0	1	0	0	1	0	0	0
B-hemangioma	1	1	1	0	1	0	1	0	0	0
B-benign neuroendocrine cell tumor; not otherwise specified	0	0	0	0	0	0	0	0	0	1
Mammary gland (no.examined)	65	56	63	62	63	70	69	70	70	70
B-fibroadenoma	1	4	0	3	8	41	48	41	50	54
Stats: fibroadenoma Pairwise comparisons	-	ns	ns	ns	p≤0.01	-	ns	ns	ns	p≤0.05
B-adenoma	1	0	3	1	1	14	13	17	15	16
M-adenocarcinoma	2	0	0	0	0	9	4	8	2	10
M-large granular lymphocytic leukemia	1	0	1	1	0	0	0	0	0	1
M-adenosquamous carcinoma	0	0	0	0	0	0	2	2	1	1
M-malignant lymphoma	0	0	0	0	0	0	0	1	1	0
Meninges (no.examined)	2	1	2	2	1	0	0	0	1	1
M-malignant meningioma	0	0	0	1	0	0	0	0	0	0
M-malignant lymphoma	1	0	0	0	0	0	0	0	0	0
M-large granular lymphocytic leukemia	1	0	1	1	0	0	0	0	1	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Muscle, skeletal (no.examined)	69	70	68	68	70	70	70	70	70	70
M-fibrosarcoma	1	0	1	0	0	0	0	0	1	0
M-malignant schwannoma	0	0	0	1	0	0	0	0	0	0
M-hemangiosarcoma	1	0	0	0	0	0	0	0	0	1
M-histiocytic sarcoma	0	1	0	0	0	1	0	0	0	1
M-large granular lymphocytic leukemia	1	0	2	1	0	0	0	0	1	0
M-sarcoma; not otherwise specified	0	0	0	0	0	0	0	1	0	0
M-acinar adenocarcinoma	0	0	0	0	0	0	0	0	1	0
Nerve, optic (no.examined)	70	68	68	69	69	70	70	70	70	70
M-large granular lymphocytic leukemia; bilateral	0	0	0	0	0	0	0	0	1	0
Nerve, sciatic (no.examined)	70	70	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	0	1	0	0	0	1	0	0	0	1
M-large granular lymphocytic leukemia	1	0	2	1	0	0	0	0	0	0
M-malignant lymphoma	0	0	0	0	0	0	0	0	1	0
Ovary (no.examined)	-	-	-	-	-	70	70	70	70	70
M-acinar adenocarcinoma; bilateral	-	-	-	-	-	0	0	0	1	0
B-benign granulosa cell tumor; unilateral	-	-	-	-	-	0	1	0	0	1
M-malignant mesothelioma; unilateral	-	-	-	-	-	1	0	0	0	0
M-histiocytic sarcoma; unilateral	-	-	-	-	-	0	0	0	0	1
M-histiocytic sarcoma; bilateral	-	-	-	-	-	0	0	1	0	0
M-malignant lymphoma; bilateral	-	-	-	-	-	0	0	0	1	0
M-large granular lymphocytic leukemia; bilateral	-	-	-	-	-	0	0	0	1	1
Oviduct (no.examined)	-	-	-	-	-	0	0	0	1	0
M-malignant lymphoma; bilateral	-	-	-	-	-	0	0	0	1	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Pancreas (no.examined)	70	70	70	70	70	70	70	70	70	70
M-Islet cell carcinoma	3	3	2	2	0	0	1	0	1	0
M-histiocytic sarcoma	1	0	1	0	0	0	0	1	0	1
B-Islet cell adenoma	6	2	9	4	5	0	3	3	2	1
B-acinar adenoma	1	1	1	1	0	0	1	2	0	0
M-large granular lymphocytic leukemia	2	0	2	1	0	0	0	0	0	1
M-malignant lymphoma	0	0	1	0	0	0	1	1	0	0
M-ductal cell adenocarcinoma	1	0	0	0	0	0	0	0	0	0
M-liposarcoma	0	0	0	0	0	0	0	0	1	0
M-acinar adenocarcinoma	0	0	0	0	0	0	0	0	1	0
Parathyroid gland (no.examined)	69	64	64	66	67	67	67	64	68	63
B-adenoma; unilateral	2	1	1	0	0	0	0	0	1	0
B-adenoma; bilateral	0	0	0	0	1	0	0	0	0	0
M-large granular lymphocytic leukemia; bilateral	1	0	0	0	0	0	0	0	0	0
Pericardium (no.examined)	0	0	0	1	0	0	0	0	0	0
M-malignant mesothelioma	0	0	0	1	0	0	0	0	0	0
Pharynx (no.examined)	0	2	1	1	0	1	0	0	0	0
M-large granular lymphocytic leukemia	0	0	0	1	0	0	0	0	0	0
M-osteosarcoma	0	0	0	0	0	1	0	0	0	0
Pituitary gland (no.examined)	70	70	70	70	68	70	70	70	70	70
B-adenoma, pars distalis	22	23	27	21	17	51	44	38	39	41
B-adenoma, pars intermedia	0	0	0	1	0	0	0	0	0	0
M-carcinoma, pars distalis	1	0	1	1	1	0	1	1	1	0
M-malignant lymphoma	1	1	0	0	0	0	0	0	1	0
M-malignant meningioma	1	0	0	0	1	0	0	0	0	0
M-large granular lymphocytic leukemia	2	0	2	1	0	0	0	0	1	1
M-squamous cell carcinoma	0	0	0	0	0	0	0	1	0	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Preputial/clitoral gland (no.examined)	70	70	70	70	70	69	70	70	70	70
M-large granular lymphocytic leukemia	1	0	1	0	0	0	0	0	1	1
B-squamous cell papilloma	1	0	0	0	0	0	1	0	0	0
M-malignant lymphoma	0	0	0	0	0	0	0	0	1	0
M-adenocarcinoma	0	0	0	0	0	1	0	2	0	1
M-squamous cell carcinoma	0	0	0	0	0	0	0	0	1	0
Prostate gland (no.examined)	70	70	70	70	70	-	-	-	-	-
M-histiocytic sarcoma	1	1	1	0	0	-	-	-	-	-
M-large granular lymphocytic leukemia	2	0	2	1	0	-	-	-	-	-
M-malignant lymphoma	1	0	1	0	0	-	-	-	-	-
Salivary gland, mandibular (no.examined)	70	70	70	70	69	70	70	70	69	70
M-large granular lymphocytic leukemia	0	0	2	1	0	0	0	0	0	0
Salivary gland, parotid (no.examined)	69	69	70	70	69	69	70	70	69	70
M-large granular lymphocytic leukemia	1	0	2	1	0	0	0	0	0	0
M-fibrosarcoma	0	0	0	0	0	0	0	0	1	0
Salivary gland, sublingual (no.examined)	70	70	70	69	68	70	70	70	69	70
M-large granular lymphocytic leukemia	0	0	2	1	0	0	0	0	0	0
Seminal vesicle gland (no.examined)	70	70	70	70	70	-	-	-	-	-
M-histiocytic sarcoma; unilateral	0	1	0	0	0	-	-	-	-	-
M-large granular lymphocytic leukemia; bilateral	0	0	1	0	0	-	-	-	-	-
M-malignant lymphoma; unilateral	0	0	1	0	0	-	-	-	-	-

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Skin (no.examined)	70	70	70	70	70	70	69	70	70	70
B-squamous cell papilloma	2	3	3	5	2	0	0	0	0	0
M-malignant melanoma	0	0	1	0	0	0	0	0	0	0
B-benign melanoma	0	0	0	0	0	0	0	1	0	0
B-benign hair follicule tumor	1	0	0	0	0	0	0	0	0	0
B-fibroma	1	0	0	0	0	0	0	0	0	0
M-malignant basal cell tumor	0	1	0	0	0	1	0	0	0	0
B-benign basal cell tumor	1	0	0	0	0	0	0	0	0	0
M-squamous cell carcinoma	0	0	3	2	0	1	0	0	0	0
M-histiocytic sarcoma	0	1	0	0	0	0	0	0	0	0
B-keratoacanthoma	9	3	6	1	3	2	1	0	2	2
M-large granular lymphocytic leukemia	0	0	0	1	0	0	0	0	0	0
B-sebaceous cell adenoma	0	0	0	0	1	0	0	0	0	0
Small intestine, duodenum (no.examined)	70	70	70	70	70	70	70	70	70	70
M-adenocarcinoma	0	0	0	0	1	0	0	0	0	0
M-acinar adenocarcinoma	0	0	0	0	0	0	0	0	1	0
M-histiocytic sarcoma	0	0	0	0	0	0	0	1	0	1
M-malignant lymphoma	0	0	0	0	0	0	0	1	0	0
Small intestine, ileum (no.examined)	70	70	69	70	70	70	70	70	70	70
M-large granular lymphocytic leukemia	1	0	0	0	0	0	0	0	1	0
M-malignant lymphoma	0	0	1	0	0	0	0	0	0	0
M-histiocytic sarcoma	0	0	0	0	0	0	0	0	0	2
Small intestine, jejunum (no.examined)	69	70	70	70	70	69	70	70	69	70
M-leiomyosarcoma	0	0	1	0	0	0	1	0	0	0
M-malignant lymphoma	0	0	1	0	0	0	0	1	1	0
M-large granular lymphocytic leukemia	1	0	2	0	0	0	0	0	0	0
M-adenocarcinoma	0	0	0	0	0	0	1	0	0	0
B-leiomyoma	0	0	0	0	0	0	0	1	2	1
M-stromal sarcoma	0	0	0	0	0	0	0	0	1	0
Spinal cord, lumbar (no.examined)	70	70	70	70	70	70	70	70	70	70
M-malignant astrocytoma	0	0	1	0	0	1	0	0	0	0
M-large granular lymphocytic leukemia	1	0	0	0	0	0	0	0	0	0
M-malignant lymphoma	0	0	0	0	0	0	0	0	1	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Spleen (no.examined)	70	70	70	70	70	70	70	70	70	70
M-hemangiosarcoma	0	0	0	0	2	0	0	0	0	0
B-hemangioma	0	0	0	0	0	1	0	0	0	0
M-malignant lymphoma	1	1	1	0	0	0	1	1	1	0
M-large granular lymphocytic leukemia	2	1	3	1	0	0	0	0	1	1
M-granulocytic leukemia	1	0	0	0	0	0	0	0	0	0
M-histiocytic sarcoma	1	1	2	1	0	0	0	1	0	3
M-fibrosarcoma	0	0	0	0	0	0	0	1	0	0
M-acinar adenocarcinoma	0	0	0	0	0	0	0	0	1	0
Stomach (no.examined)	70	70	70	70	70	70	70	70	70	70
B-adenoma	0	0	0	0	2	0	0	0	1	0
M-histiocytic sarcoma	0	0	1	0	0	0	0	0	0	2
M-malignant lymphoma	0	0	1	0	0	0	1	1	1	0
M-large granular lymphocytic leukemia	0	0	2	0	0	0	0	0	1	0
B-squamous cell papilloma	0	1	0	0	0	0	0	0	0	1
M-acinar adenocarcinoma	0	0	0	0	0	0	0	0	1	0
Subcutis (no.examined)	16	17	17	15	10	10	13	13	12	14
M-fibrosarcoma	0	3	2	3	3	2	1	1	3	3
M-histiocytic sarcoma	1	0	0	1	0	1	0	0	0	2
B-fibroma	9	9	9	9	6	3	4	8	4	5
B-lipoma	3	1	1	3	0	3	4	0	2	2
M-liposarcoma	0	1	0	0	0	0	0	1	0	0
M-large granular lymphocytic leukemia	0	0	1	0	0	0	0	0	1	0
M-sarcoma; not otherwise specified	1	0	0	0	0	0	0	1	1	0
B-benign schwannoma	0	0	3	0	1	0	1	1	0	1
M-malignant schwannoma	0	0	0	1	0	0	1	1	1	0
M-hemangiosarcoma	0	0	0	0	0	0	0	0	0	1
M-osteosarcoma	0	0	0	0	0	2	0	0	0	0
Tail (no.examined)	4	2	4	3	1	1	1	1	2	0
B-squamous cell papilloma	1	0	0	0	0	0	0	0	0	0
M-liposarcoma	1	0	0	0	0	0	0	0	0	0
M-squamous cell carcinoma	0	0	1	0	0	0	0	0	0	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Testis (no.examined)	70	70	70	70	70	-	-	-	-	-
B-hemangioma; unilateral	0	0	0	0	1	-	-	-	-	-
B-interstitial (leydig) cell adenoma; unilateral	1	2	1	1	0	-	-	-	-	-
M-large granular lymphocytic leukemia; bilateral	1	0	0	0	0	-	-	-	-	-
Thymus (no.examined)	70	69	70	70	69	69	70	70	70	69
M-malignant lymphoma	1	1	0	0	0	0	0	1	1	0
M-malignant thymoma	0	0	0	0	0	0	0	0	1	1
B-benign thymoma	0	0	1	0	0	0	0	3	0	0
M-histiocytic sarcoma	1	1	1	0	0	0	0	0	0	1
M-large granular lymphocytic leukemia	2	0	2	1	0	0	0	0	1	1
Thyroid gland (no.examined)	70	69	70	70	70	70	70	70	70	70
B-follicular cell adenoma; unilateral	1	2	1	2	0	1	1	0	2	0
B-follicular cell carcinoma; unilateral	0	0	0	0	0	0	1	0	0	0
M-c-cell carcinoma; unilateral	6	1	3	1	0	2	1	2	0	2
M-c-cell carcinoma; bilateral	0	0	0	0	1	0	0	0	0	0
B-c-cell adenoma; unilateral	3	5	8	8	5	4	3	4	5	4
Stats: c-cell adenoma Pairwise comparisons	-	ns	ns	p≤0.05	ns	-	-	-	-	-
B-c-cell adenoma; bilateral	0	1	0	0	0	1	0	0	0	0
M-large granular lymphocytic leukemia; unilateral	0	0	0	0	0	0	0	0	1	0
M-large granular lymphocytic leukemia; bilateral	1	0	2	1	0	0	0	0	0	1
M-fibrosarcoma; unilateral	0	0	0	0	0	0	0	0	0	1
Tongue (no.examined)	70	70	70	69	69	70	70	70	70	70
M-large granular lymphocytic leukemia	0	0	1	1	0	0	0	0	0	0
M-squamous cell carcinoma	0	0	0	0	0	0	0	1	0	0
Trachea (no.examined)	70	70	70	70	70	70	70	70	70	70
M-large granular lymphocytic leukemia	0	0	2	0	0	0	0	0	0	0
M-histiocytic sarcoma	0	0	0	0	0	0	0	0	0	1

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Urinary bladder (no.examined)	70	70	69	70	70	70	70	70	70	70
B-squamous cell papilloma	1	0	0	0	0	0	0	0	0	0
M-large granular lymphocytic leukemia	2	0	2	1	0	0	0	0	0	0
M-histiocytic sarcoma	0	0	0	0	0	1	0	1	0	1
M-malignant lymphoma	0	0	0	0	0	0	0	0	1	0
M-stromal sarcoma	0	0	0	0	0	0	0	0	1	0
Uterus (no.examined)	-	-	-	-	-	70	70	70	70	70
M-histiocytic sarcoma	-	-	-	-	-	0	0	1	0	0
M-leiomyosarcoma	-	-	-	-	-	0	0	0	0	1
M-endometrial stromal sarcoma	-	-	-	-	-	0	1	0	0	0
B-endometrial stromal polyp	-	-	-	-	-	1	2	7	2	6
Stats: endometrial stromal polyp										
Pairwise comparisons	-	-	-	-	-	-	ns	p≤0.05	ns	ns
M-adenocarcinoma	-	-	-	-	-	0	0	1	0	0
M-acinar adenocarcinoma	-	-	-	-	-	0	0	0	1	0
B-polyp; unilateral, glandular	-	-	-	-	-	1	0	1	0	0
M-large granular lymphocytic leukemia	-	-	-	-	-	0	0	0	1	1
B-benign granular cell tumor	-	-	-	-	-	0	0	0	0	1
Vagina (no.examined)	-	-	-	-	-	70	70	70	70	70
M-histiocytic sarcoma	-	-	-	-	-	1	0	0	0	1
M-malignant lymphoma	-	-	-	-	-	0	0	0	1	0
M-stromal sarcoma	-	-	-	-	-	1	0	0	1	0
M-large granular lymphocytic leukemia	-	-	-	-	-	0	0	0	1	0
Macroscopic Examination (number of animals)	70	70	70	70	70	70	70	70	70	70
Stomach										
focus; depressed	7	8	11	15	20	9	4	8	9	28
focus; dark	13	2	4	4	16	7	8	3	7	17
thick	11	12	11	11	17	8	9	5	8	21
Heart										
mass	1	0	1	1	3	0	0	0	0	1
nodule	0	1	0	0	2	0	0	0	0	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Test Item-related Non-Neoplastic Findings										
Stomach (no.examined)	70	70	70	70	70	70	70	70	70	70
Erosion/ulceration; glandular										
minimal	1	4	2	3	4	2	3	3	3	8
mild	1	1	1	0	6	0	0	0	1	10
moderate	0	0	0	0	1	0	0	0	0	1
Heart (no.examined)	70	70	70	70	70	70	70	70	70	70
Cardiomyopathy; progressive										
minimal	33	38	29	32	25	21	29	30	38	33
mild	24	22	23	22	26	3	3	7	6	10
moderate	7	5	9	9	12	0	0	0	1	1
marked	0	0	0	1	1	0	0	0	0	0
Thrombosis; atrial										
minimal	1	1	0	0	1	0	0	0	0	0
mild	0	0	1	1	3	0	0	0	0	1
moderate	0	0	0	0	2	0	0	0	0	0
marked	0	0	0	0	1	0	0	0	0	0

GSK1278863A: A 2-Year Oral (Gavage) Carcinogenicity Study in Rats (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R70375G

	Male					Female				
Daily Dose (mg/kg/day)[a]	0	0.02	0.1	0.8	4	0	0.02	0.1	0.8	7
Various tissues (no.examined)	70	70	70	70	70	70	70	70	70	70
Thrombosis (except atrial thrombosis seen in the heart)										
minimal	1	0	0	1	3	0	0	1	0	0
mild	0	2	0	1	1	0	0	0	0	0
moderate	1	1	0	1	3	0	0	0	0	0

Key:
-- Not Examined/not applicable NC = Not calculable NQ = Not quantifiable ns= Not statistically significant M = malignant B = Benign
** p ≤0.01, *** p≤0.001 (Dunn)
† p≤0.05, ††† p≤0.001 (Dunnett)

a. Doses are expressed in terms of the parent compound.
b. Additional toxicokinetic (TK) rats were added to the 0, 0.1 and 4 (males)/7(females) mg/kg/day groups to allow collection of tissues for transcriptomic assessment. Additional TK rats were added to the 4 (males)/7(females) mg/kg/day group to ensure toxicokinetics could be assessed appropriately as elevated hematocrits in previous studies have led to difficulty obtaining adequate plasma volume.
c. n=2; female No. 2573 in the 0.02 mg/kg/day group did not have a blood sample collected at 24 hours postdose during Week 26 and therefore was excluded from mean $AUC_{0\text{-}t}$ calculations.
d. The intended duration of dosing was for minimally 104 weeks; however, due to low survival, males given 4 mg/kg/day were taken off dose from Week 91 (last dose given on Day 631) and were terminated starting in Week 94 (Day 653). In addition, due to low survival in the controls, all remaining male groups were taken off dose in Week 96 (last dose given on Day 670) and were terminated starting in Week 97 (Day 679). Similarly, due to low survival in controls, all female groups were terminated starting in Week 100 (Day 698). Dosing was continuous for these females until the day prior to their scheduled euthanasia.
e. Statistically significant decreased survivability in males at 4 mg/kg/day when compared to control males (pairwise groups comparisons, p-value = 0.0131).
f. Hematology evaluation was limited to n=10/sex/group given 0 (reference item), 0.8 and 4(males)/7 (females) mg/kg/day and included only total red blood cells, hematocrit, hemoglobin and reticulocyte counts.
g. Selected tissues (kidney, liver, lung, mesenteric lymph node, and spleen) from satellite animals (reference item, 0.1, and 4/7 mg/kg/day groups) following 26 weeks of dosing were used for transcriptomic evaluation of erythropoietin (Epo) and vascular endothelial growth factor (VEGF) mRNA expression. Due to its investigative nature and utilization of non-standard technologies the transcriptomics portion of this study was excluded from compliance with the US FDA GLP regulations and was therefore conducted as a non-GLP element of this study.

12. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: NONPIVOTAL STUDIES

Table 12.1 Reproductive and Developmental Toxicity: Nonpivotal Studies

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Rat (Sprague Dawley)	Oral[a] (gavage)	25 days (GD 6 to LD 6)	0[a], 10[d], 40[e], 40[f], 60[b], 60[c]	5F (pregnant)	In the initial phase, GSK1278863A was administered once daily by oral gavage at 0 or 60 mg/kg/day (Groups 2 and 3), along with twice daily subcutaneous injection of a cocktail formulation containing the three major circulating human metabolites (M2; GSK2391220A, M3; GSK2506104A and M13; GSK2531401A) at doses of 2.5, 3.2 and 1.8 mg/kg/day (Group 2), respectively, or 7.5, 9.6 and 5.4 mg/kg/day (Group 3), respectively. In an extension phase, GSK1278863A was administered once daily by oral gavage at 0 (Group 4), 10 (Group 5) or 40 mg/kg/day (Groups 6 and 7) along with twice daily subcutaneous injection of a cocktail formulation containing the three metabolites (M2, M3 and M13) at doses of 2.5, 3.2 and 1.8 mg/kg/day, respectively (Groups 5 and 7). Test article-related effects at 40 and 60 mg/kg/day included decreased mean maternal body weight gain during late gestation with correlating decreased mean food consumption; and at 60 mg/kg/day included severely decreased mean body weight gain/body weight loss along with decreased food consumption during the lactation period. At 40 mg/kg/day, there was an increase in body weight gain during lactation. There were effects on pup body weight from birth to PND 7 at ≥40 mg/kg/day. At 60 mg/kg/day, F1 offspring viability was decreased, resulting in a decreased litter size by LD 7.	2016N305715 (R71028N)

Reproductive and Developmental Toxicity: Nonpivotal Studies (Continued)

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Rabbits (Dutch Belted)	Oral (gavage)	13 days (Days 7 to 19 pc)	4, 30, 60, 125, 250	3 or 4F (pregnant)	Groups of pregnant rabbits (3 or 4/group) were given 0, 4, 30, 60, 125, and 250 mg/kg/day daprodustat once daily between Days 7 to 19 post coitum (pc) by oral gavage. All rabbits given 250 mg/kg/day and one rabbit given 125 mg/kg/day were euthanized on Days 12 and 20 pc, respectively, due to body weight loss and reduced food consumption. For the remaining rabbits, body weight loss was observed at 125 mg/kg/day and reductions in body weight gains were observed at ≥4 mg/kg/day. In all groups, a dose-related reduction in the amount of food consumed occurred. At ≥30 mg/kg/day, pharmacologically-mediated increases in erythropoiesis were observed.	CD2008/01041 (D08169)

Key:

a = Groups 1 and 4, and 6 given oral and subcutaneous (SC) vehicle

b = Group 2 given 60 mg/kg/day parent and Metabolite cocktail - 2.5, 3.2, and 1.8 mg/kg/day (for GSK2391220 [M2], GSK2506104 [M3] or GSK2531401A [M13], respectively).

c = Group 3 given 60 mg/kg/day parent and Metabolite cocktail - 7.5, 9.6, and 5.4 mg/kg/day (for GSK2391220 [M2], GSK2506104 [M3] or GSK2531401A [M13], respectively).

d = Group 5 given 10 mg/kg/day parent and Metabolite cocktail - 2.5, 3.2, and 1.8 mg/kg/day (for GSK2391220 [M2], GSK2506104 [M3] or GSK2531401A [M13], respectively).

e = Group 6 given 40 mg/kg/day parent and SC vehicle.

f = Group 7 given 40 mg/kg/day parent and Metabolite cocktail - 2.5, 3.2, and 1.8 mg/kg/day (for GSK2391220 [M2], GSK2506104 [M3] or GSK2531401A [M13], respectively).

13. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: FERTILITY AND EARLY EMBRYONIC DEVELOPMENT TO IMPLANTATION (PIVOTAL)

Table 13.1 GSK1278863A: Oral (Gavage) Once Daily Male Fertility Study in the Crl:CD(SD) Rat

Study Type: Reproductive and Developmental Toxicology - Fertility and General Reproduction

Report Title: GSK1278863A: Oral (Gavage) Once Daily Male Fertility Study in the Crl:CD(SD) Rat

Test Article: (Lot No.): GSK1278863A (parent compound)
Batch No.: NE-021129-Batch-01-2009

Design Similar to ICH 4.1.1: Yes

Duration of Male Dosing: 28 days prior to co-habitation, through co-habitation to Days 56 to 59 of study (DS 56 to 59)

Study No.: AFA00831
GSK Reference No.: G09059

Species/Strain: Rat/Crl:CD(SD)

Initial Age: 71 days (males); 65 days (females)

Route/Frequency: Oral, once daily

Location in CTD: m4.2.3.5.1

Day of Sperm/Plug Present: Day 0 pc

GSK Document Number: CD2009/00389

Date of First Dose: 5 May 2009

Day of C-Section: Day 20 pc

GLP Compliance: Yes

Special Features: None

Method of Administration: Gavage

No Observed Adverse Effect Level:
F_0 Reproductive Effects: 20 mg/kg
F_1 Litters: 20 mg/kg

Vehicle/Formulation: 1.0% aqueous methylcellulose/ suspension

Data Collected: Treated F_0 males: Mortality, clinical observations, body weight, food consumption, mating, fertility, necropsy and male reproductive organ weights, testicular and epididymal sperm counts and sperm motility; untreated F_0 females: Clinical observations, body weight, corpora lutea and uterine weight; F_1 litters: Implantations, resorptions, live and dead fetuses, fetal weight, sex, and placental and fetal external morphology.

Conclusion: At 20 mg/kg/day, mortality was observed, as well as increased incidences of salivation and gross lesions, particularly evidence of gastrointestinal irritation. There were no test article-related effects on male reproductive organ weights, mating, fertility or gonadal function at any dose tested. Therefore, the male NOAEL for reproductive effects was 20 mg/kg/day.

GSK1278863A: Oral (Gavage) Once Daily Male Fertility Study in the Crl:CD(SD) Rat (Continued)

Study Type: Reproductive and Developmental Toxicology - Fertility and General Reproduction	**Study No.:** AFA00831			
Daily Dose (Males; mg/kg)	**0 (Vehicle)**	**0.8**	**4.0**	**20.0**
Males:				
No. Rats/Group	25	25	25	25
No. Died or Euthanized Moribund	2	1	0	2[a]
Clinical Observations:				
Slight salivation	0	2	0	15
Necropsy Observations:				
Stomach: Dark red or red pitted areas	0	0	0	20
Stomach: Walls thick	0	0	0	11
Stomach: Mucosal surface, fundic region, dark red or black areas	0	0	0	3
Duodenum: White foci	0	0	0	3
Liver: Dark red lobes	0	1	0	21
Kidneys: Dark red	0	0	0	8
Ureters: Bilaterally dilated	0	0	0	1
Urinary bladder: Walls thick	0	0	0	1
Adipose: Red or dark red	0	0	0	3
Muscle: Dark red	0	0	0	1
Connective tissue: Dark red	0	0	0	1
Body Weight Gain [Days 1 to 56 of study][b]	126.0 g	1.02X	0.96X	1.01X
Food Consumption [Days 22 to 28 of study][b]	28.0 g	0.99X	0.97X	0.97X
Food Consumption [Days 49 to 56 of study][b]	23.9 g	1.03X	1.00X	0.98X
Mean No. Days Needed to Mate	2.1	1.8	2.1	1.9
Mating Index[c]	100	100	100	100
Fertility Index[d]	100.0	95.8	100.0	92.0
Sperm:				
Sperm count (cauda epididymal)	176.2	183.1	174.6	169.6
Sperm motility	378.1	408.0	391.0	456.9
Sperm density	1496.06	1579.40	1466.15	1438.50

GSK1278863A: Oral (Gavage) Once Daily Male Fertility Study in the Crl:CD(SD) Rat (Continued)

Study Type: Reproductive and Developmental Toxicology - Fertility and General Reproduction	**Study No.:** AFA00831			
Daily Dose (Males; mg/kg)	**0 (Vehicle)**	**0.8**	**4.0**	**20.0**
Organ Weights:				
Seminal vesicles[b]	1.9896 g	0.93X	0.88X*	0.79X**
Seminal vesicles (relative to tbw) (%)	0.376	0.348	0.333*	0.296**
Prostate[b]	1.2354 g	0.98X	0.94X	0.86X**
Prostate (relative to tbw) (%)	0.231	0.225	0.222	0.201**
Females:				
No. Mated Females Evaluated	23	24	25	25
No. Died or Euthanized Moribund	-	-	-	-
Gestation Body Weight Gain [Days 0 to 20 pc][b]	165.4 g	1.02X	1.02X	0.98X
No. of Females Sperm-Positive	23	24	25	25
No. of Pregnant Females	23	23	25	23
No. of Pregnant Females Evaluated	23	23	25	23
Mean No. Corpora Lutea	15.3	15.8	15.8	16.4
Mean No. Implantations	14.9	15.4	15.1	15.7
Mean % Pre-Implantation Loss	2.8	2.2	4.1	3.9
Mean Total Post-Implantation Loss - No. (%)	4.7	4.3	5.0	5.5
Mean No. of Live Fetuses	14.2	14.7	14.3	14.9
Mean Fetal Body Weight (g) - Male	3.77	3.76	3.86	3.81
Mean Fetal Body Weight (g) - Female	3.59	3.56	3.68	3.63
% Live Males	50.0	44.2	48.4	43.2
External Fetal Malformations or Variations:				
No. fetuses (ratio, %)	-	-	-	-
No. litters (ratio, %)	-	-	-	-

Key: * = Statistical significance ($p \leq 0.05$) or ** = Statistical significance ($p \leq 0.01$) is based on raw data (not on the change from controls).
a = Males 16196 and 16200 were euthanized due to adverse clinical observations on Days of Study 53 and 54, respectively.
b = For controls, group means are shown. For treated groups, change from controls is shown.
c = Mating index = (Number mated/Total number co-habited) x 100.
d = Fertility index = (Number pregnant/Number mated) x 100.
pc = post coitum. tbw = Terminal body weight. - = No noteworthy findings.

Table 13.2 GSK1278863A: Oral Female Fertility and Early Embryonic Development Study in Rats

Study Type: Reproductive and Developmental Toxicology

Report Title: GSK1278863A: Oral Female Fertility and Early Embryonic Development Study in Rats

Test Article: GSK1278863 (parent compound)
Batch No.: NE-021129-Batch-01-2007

Design Similar to ICH 4.1.1: Yes

Duration of Dosing: 2 weeks prior to mating, during mating and up to gestation Day 6, inclusive

GSK Reference No.: G08250
GSK Document No.: CD2009/00236
CRO Study No.: WIL-472259

Species/Strain: Rat/[Crl:CD(SD)]

Initial Age: Approximately 9 weeks

Route/Frequency: Oral, once daily

Location in CTD: m4.2.3.5.1

Day of Sperm/Plug Present: Gestation Day 0

Date of First Dose: 27 October 2008

Day of Laparohysterectomy: Gestation Day 20

GLP Compliance: Yes[a]

Special Features: None

Method of Administration: Gavage

No Observed Adverse Effect Level:
F_0 Reproductive Effects: 7 mg/kg
F_1 Litters: 7 mg/kg

Vehicle/Formulation: 1% (w/v) aqueous methylcellulose/ suspension

Data Collected: Females: Survival, clinical observations, body weight, food consumption, estrous cycle, mating, fertility, conception, necropsy, corpora lutea and uterine weight; Litters: Implantations, resorptions, live and dead fetuses, fetal weight, sex, and placental and fetal external morphology.

Conclusion: At 100 mg/kg/day, a single female was euthanized on study Day 17 due to excessive body weight loss, and lower mean body weight gains and reduced food consumption were observed throughout the treatment period. Based on the lower mean number of corpora lutea and implantation sites and higher mean litter proportion of post-implantation loss, which collectively resulted in lower mean number of live fetuses at 100 mg/kg/day, the no observed adverse effect level (NOAEL) for female fertility and early embryonic development in rats is 7 mg/kg/day.

GSK1278863A: Oral Female Fertility and Early Embryonic Development Study in Rats (Continued)

Study Type: Reproductive and Developmental Toxicology	**GSK Reference No.:** G08250			
Dose (mg/kg/day)	**0 (Control)**	**2**	**7**	**100**
Mated Females:				
No. Animals/Group	25	25	25	25
No. Died or Euthanized Moribund	0	0	0	1
Clinical Observations (Total Occurrence/No. of Animals):				
Red material around mouth[b]	0	0	0	7/6
Red material around nose[b]	6/6	2/2	7/6	17/10
Clear material around mouth[b]	0	0	0	46/23
Necropsy Observations	-	-	-	-
Pre-Mating Body Weight Gain (Days 0 to 14; X Control)[c]	15 g	0.87X	0.80X	0.20X*
Gestation Body Weight Gain (Days 0 to 7; X Control)[c]	29 g	1.00X	1.07X	0.72X*
Gestation Post-Treatment Body Weight Gain (Days 7 to 10; X Control)[c]	15 g	0.93X	1.00X	1.80X*
Gestation Post-Treatment Body Weight Gain (Days 7 to 14; X Control)[c]	37 g	0.95X	1.00X	1.32X*
Pre-Mating Food Consumption (Days 7 to 14; X Control)[c]	20 g/animal/day	1.00X	1.00X	0.85X*
Gestation Food Consumption (Days 0 to 7; X Control)[c]	24 g/animal/day	1.00X	1.04X	0.88X*
Gestation Post-Treatment Food Consumption (Days 7 to 20; X Control)[c]	27 g/animal/day	1.00X	1.00X	1.07X*
Mean No. of Times in Estrus/15 Days of Treatment	3.6	3.5	3.5	3.4
Mean No. Days Needed to Mate	2.7	2.4	2.4	2.5
Mating Index (%)[d]	100.0	100.0	100.0	100.0
Fertility Index (%)[e]	100.0	100.0	100.0	100.0
Conception Index (%)[f]	100.0	100.0	100.0	100.0
No. of Females Mated	25	25	25	24
No. of Pregnant Females	25	25	25	24
No. of Pregnant Females Evaluated[g]	25	25	25	24
Mean No. Corpora Lutea	16.2	16.8	16.1	14.0+
Mean No. Implantations	15.2	14.9	15.0	12.9+
Mean Pre-Implantation Loss (% Per Litter)	6.5	10.9	6.0	7.5
Mean Total Post-Implantation Loss - No. (% Per Litter)	3.6	7.2	3.8	11.2+
Mean Gravid Uterine Weight	84.1	80.3	83.6	68.6+
Mean No. Live Fetuses	14.6	14.0	14.4	11.5+

GSK1278863A: Oral Female Fertility and Early Embryonic Development Study in Rats (Continued)

Study Type: Reproductive and Developmental Toxicology	**GSK Reference No.:** G08250			
Dose (mg/kg/day)	**0 (Control)**	**2**	**7**	**100**
Live Males (% Per Litter)	53.0	53.2	52.4	46.7
Mean Fetal Body Weight (g) - Males	3.7	3.8	3.8	3.9
Mean Fetal Body Weight (g) - Females	3.6	3.5	3.6	3.6
External Fetal Malformations	-	-	-	-
External Fetal Developmental Variations:	-	-	-	-

Key:

a = Test article characterization was conducted under Good Manufacturing Practices (GMPs).

b = Noted during the daily examinations, within 15 minutes of and/or 1 hour following dose administration.

c = For controls, group means are shown. For treated groups, magnitude of change (in treated groups relative to control group) is calculated as the treated mean divided by the control mean. Statistical significance ($p<0.05$) is based on raw data (not on the changes from controls).

d = Mating index = (Number mated/Total number co-habited) x 100.

e = Fertility index = (Number pregnant/Total number co-habited) x 100.

f = Conception index = (Number pregnant/Number mated) x 100.

g = At the gestation Day 20 laparohysterectomy.

* = Significantly different from the control group $p<0.05$ (parametric analysis).

+ = Significantly different from the control group $p<0.05$ (non-parametric analysis).

- = No noteworthy findings.

CRO = Contract research organization.

14. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: EFFECTS ON EMBRYOFETAL DEVELOPMENT (PIVOTAL)

Table 14.1 GSK1278863A: Oral (Gavage) Once Daily Embryofetal Development Study in the Crl:CD(SD) Rat

Study Type: Reproductive and Developmental Toxicology - Embryofetal Development

Report Title: GSK1278863A: Oral (Gavage) Once Daily Embryofetal Development Study in the Crl:CD(SD) Rat

Test Article: (Lot No.): GSK1278863A (parent compound).
Batch No.: NE-021129-Batch-01-2009

Design Similar to ICH 4.1.3: Yes

Duration of Dosing: Days 6 to 17 pc

Study No.: AFA00832

Day Sperm/Plug Present: Day 0 pc

Route/Frequency: Oral, once daily

GSK Reference No.: G09060

Species/Strain: Rat/Crl:CD(SD)

Day of C-Section: Day 21 pc

Location in CTD: m4.2.3.5.2

Initial Age: 65 days

Method of Administration: Gavage

GSK Document Number: CD2009/00388

Date of First Dose: 3 May 2009

Vehicle/Formulation: 1.0% aqueous methylcellulose/ suspension

GLP Compliance: Yes

Special Features: None

No Observed Adverse Effect Level:

F_1 Litters: 7 mg/kg

Data Collected: F_0 females: Mortality, clinical observations, body weight, food consumption, necropsy, gravid uterine weight and corpora lutea; F_1 litters: Implantations, resorptions, live and dead fetuses, fetal weight, sex, and placental and fetal morphology (external, visceral and skeletal).

Conclusion: Maternal toxicity (salivation and reduced food intake coupled with decreased body weight gains) occurred at 60 mg/kg/day. Increases in post-implantation loss associated with a slight decrease in mean litter size along with rib variations (shortened 13th rib and slight reduction in the average number of ossified rib pairs and thoracic vertebrae) occurred in the fetuses at this maternally toxic dose. No overt malformations or other test article-related variations occurred at any dose level tested. Therefore, the no observed adverse effect level (NOAEL) for rat embryofetal development is 7 mg/kg/day.

GSK1278863A: Oral (Gavage) Once Daily Embryofetal Development Study in the Crl:CD(SD) Rat (Continued)

Study Type: Reproductive and Developmental Toxicology - Embryofetal Development		**Study No.:** AFA00832			
Daily Dose (mg/kg)		**0 (Vehicle)**	**0.5**	**7**	**60**
Dams:	**No. Animals/Group**	22	22	22	22
	No. Pregnant	20	19	17	20
	No. Pregnant Evaluated	20	19	16	20
	No. Euthanized Moribund	1[a]	0	0	0
	No. Delivered and Euthanized	0	0	1[b]	0
	No. with Total Resorption of Litter	0	0	0	1
	Clinical Observations				
	Excess salivation	-	-	-	10
	Body Weight Gain [Days 6 to 18 pc][c]	90.6 g	1.02X	1.04X	0.78X**
	Body Weight Gain [Days 18 to 21 pc][c]	60.6 g	1.00X	0.93X	0.81X*
	Food Consumption [Days 9 to 12 pc][c,d]	24.8 g	1.02X	0.98X	0.82X**
	Necropsy Observations	-	-	-	-
	Mean No. Corpora Lutea	14.9	15.9	15.1	14.3
	Mean No. Implantations	14.6	14.8	14.6	14.2
	Mean % Pre-Implantation Loss	1.8	6.0	3.0	0.4
Litters:	**No. Litters Evaluated[e]**	20	19	16	19
	Mean No. Live Fetuses	14.4	14.4	14.1	12.2
	Mean Total Post-Implantation Loss - No. (%)[f]	2.1	2.8	3.3	13.7
	Mean Fetal Body Weight (g) - Males	5.68	5.74	5.74	5.55
	Mean Fetal Body Weight (g) - Females	5.40	5.43	5.37	5.19
	% Male Fetuses	46.1	49.6	48.7	47.9

GSK1278863A: Oral (Gavage) Once Daily Embryofetal Development Study in the Crl:CD(SD) Rat (Continued)

Study Type: Reproductive and Developmental Toxicology - Embryofetal Development	**Study No.:** AFA00832			
Daily Dose (mg/kg)	**0 (Vehicle)**	**0.5**	**7**	**60**
Test Article-Related Fetal Malformations or Variations:				
13th rib - short (fetuses; litters)	-	-	-	8**; 4
Rib pairs (mean ossification sites per fetus per litter)	13.11	13.07	13.02	13.00*
Thoracic vertebrae (mean ossification sites per fetus per litter)	13.16	13.09	13.02	13.00*
Test Article-Related Visceral Anomalies	-	-	-	-
Test Article-Related Skeletal Anomalies	-	-	-	-

Key:

a = Female 655 euthanized due to a gavage error.

b = Female 639 delivered on Day 20 pc.

c = For controls, group means are shown. For treated groups, change from controls is shown.

d = Representative interval chosen for food consumption. All food consumption intervals in the 60 mg/kg/day dose group during Days 6 to 18 pc were statistically significant ($p \leq 0.01$).

e = Method of fetal evaluation (external, visceral, skeletal).

f = Includes values for dams with all early resorptions.

* = Statistical significance ($p \leq 0.05$). ** = Statistical significance ($p \leq 0.01$) is based on raw data (not on the change from controls).

- = No noteworthy findings.

Table 14.2 GSK1278863A: Oral (Stomach Tube) Once Daily Embryofetal Development Study in the Dutch Belted Rabbit

Study Type: Reproductive and Developmental Toxicology - Embryofetal Development

Report Title: GSK1278863A: Oral (Stomach Tube) Once Daily Embryofetal Development Study in the Dutch Belted Rabbit

Test Article: GSK1278863A (parent compound)

Batch No.: NE-021129-Batch-01-2009

Design Similar to ICH 4.1.3: Yes

Duration of Dosing: Days 7 to 19 pc

Study No.: AFA00833

Day of Mating: Day 0 post coitum (pc)

Route/Frequency: Oral, once daily

GSK Reference No.: G09061

Species/Strain: Dutch Belted Rabbit/Haz:(DB)SPF

Day of C-Section: Day 29 pc

Location in CTD: m4.2.3.5.2

Initial Age: 6.5 months

Method of Administration: Stomach tube

GSK Document Number: CD2009/00390

Date of First Dose: 4 May 2009

Vehicle/Formulation: 1.0% aqueous methylcellulose/suspension

GLP Compliance: Yes

Special Features: Toxicokinetics

No Observed Adverse Effect Level:

F_1 Litters: 60 mg/kg

Data Collected: F_0 females: Mortality, clinical observations, body weight, food consumption, toxicokinetics, necropsy and corpora lutea; F_1 litters: Implantations, resorptions, live and dead fetuses, fetal weight, sex, and placental and fetal morphology (external, visceral and skeletal).

Conclusion: Maternal toxicity included reduced body weight gain at all doses and abortion at 60 mg/kg/day. There were no test article-related effects on embryofetal development at any dose; therefore, the no observed adverse effect level (NOAEL) for rabbit embryofetal development is 60 mg/kg/day, the highest dose tested; the mean AUC_{0-24} was 197 μg.h/mL and the mean C_{max} was 11.8 μg/mL at this dose.

GSK1278863A: Oral (Stomach Tube) Once Daily Embryofetal Development Study in the Dutch Belted Rabbit (Continued)

Study Type: Reproductive and Developmental Toxicology - Embryofetal Development		**Study No.:** AFA00833			
Daily Dose (mg/kg)		**0 (Vehicle)**	**4**	**30**	**60**
	Toxicokinetics:				
	AUC (μg.h/mL)	-	22.8	133	197
	C_{max} (μg/mL)	-	1.49	9.24	11.8
	No. Animals/Group	22	22	22	22
	No. Pregnant	21	22	21	22
	No. Pregnant Evaluated	20	21	21	19
	No. Euthanized Moribund	1	1	0	1
	No. Aborted or Naturally Delivered	0	0	0	2
	No. with Total Resorption of Litter	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight Gain [Days 7 to 20 pc][a]	0.12 kg	0.67X	0.75X	0.58X
	Body Weight Gain [Days 20 to 29 pc][a]	0.12 kg	0.83X	0.67X**	0.67X**
	Food Consumption [Days 7 to 20 pc][a]	60.5 g	1.0X	0.93X	0.95X
	Mean No. Corpora Lutea	7.9	7.2	8.3	7.4
	Mean No. Implantations	7.8	6.6*[b]	7.4	6.5*[b]
	Mean % Pre-Implantation Loss	1.7	8.9	9.9	12.7
Litters:	**No. Litters Evaluated[c]**	20	21	21	19
	Mean No. Live Fetuses	7.2	6.0*[b]	5.8*[b]	5.7*[b]
	Mean Total Post-Implantation Loss - No. (%)	6.8	7.6	19.5**[b]	10.6
	Mean Fetal Body Weight (Grams) - Males	38.47	39.16	39.68	39.38
	Mean Fetal Body Weight (Grams) - Females	37.95	38.17	38.10	37.65
	% Male Fetuses	50.0	40.4	43.2	49.8
	Test Article-Related Fetal Malformations or Variations:	-	-	-	-

Key: * = Statistical significance ($p \leq 0.05$) is based on raw data. ** = Statistical significance ($p \leq 0.01$) is based on raw data. - = No noteworthy findings.
a = For controls, group means are shown. For treated groups, change from controls is shown.
b = Not considered test article-related.
c = Method of fetal evaluation (external, visceral, skeletal).

Table 14.3 GSK1278863A: Oral Study to Determine Concentrations of GSK1278863 and its Metabolites in Rabbit Plasma

Study Type: Reproductive and Developmental Toxicology

Report Title: GSK1278863A: Oral Study to Determine Concentrations of GSK1278863 and its Metabolites in Rabbit Plasma (GlaxoSmithKline Study No. G12109)

GSK Document Number: 2012N140611
Study No. G12109

Design Similar to ICH 4.1.3. No

GLP Compliance: Yes

Location in CTD: m4.2.3.5.2

Species: Rabbit
Strain: Dutch Belted rabbit/[Haz:(DB)SPF

Day Sperm/Plug Present: Day 0 post coitum (Day 0 pc)

Initial Age (at arrival): approximately 6 months

Test Article GSK1278863A (Lot/ or Batch No.): Batch Number: NE-021129-Batch-01-2009

Vehicle: 1% methylcellulose (400 cps @ 2%)

Formulation: Suspension

Date of First Dose: 25-Jun-2012

Method of Administration: Gavage
Route/Frequency: Oral, once daily

Duration of Dosing: Day 7 to 11 pc

Day of C-Section: Day 12 pc

Special Study Features:

Data Collected: Mated female rabbits: mortality, clinical observations, body weight, and pregnancy status. Blood samples for the toxicokinetic phase were collected from mated female rabbits in each group at nominal times of 0.5, 2, 4, 8 and 24 hours after dosing on study Day 11 pc (after 5 daily doses).

Conclusion: Systemic exposure, as defined by mean AUC_{0-t} and C_{max} values, was at least 16-fold higher for GSK1278863 than any of the metabolites.

GSK1278863A: Oral Study to Determine Concentrations of GSK1278863 and its Metabolites in Rabbit Plasma (Continued)

Study Type: Reproductive and Developmental Toxicology

Daily Dose (mg/kg) 60 mg/kg/day GSK1278863 Analyte	Control	GSK1278863	GSK2391220 (M2)	GSK2531403 (M3)	GSK2499166 (M4)	GSK2531399 (M5)	GSK2531398 (M6)	GSK2531400 (M13)
Does:								
Toxicokinetics: AUC (μg.hr/mL)	…	188	11.7	2.69	1.37	0.594	0.210	0.194
No. Animals	2	4	…	…	…	…	…	…
No. Pregnant	2	4	…	…	…	…	…	…
No. Pregnant Evaluated	2	4	…	…	…	…	…	…
No. Found Dead or Euthanized Moribund	0	0	…	…	…	…	…	…
Body Weight (Day 11 pc) (kg)	1.94	1.0X	…	…	…	…	…	…
No. with Total Resorption of Litter	0	0	…	…	…	…	…	…

15. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: EFFECTS ON PRE- AND POST-NATAL DEVELOPMENT INCLUDING MATERNAL FUNCTION (PIVOTAL)

Table 15.1 GSK1278863A + metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: Oral Gavage and Subcutaneous Injection Pre- and Postnatal Development Study in Rats

Study Type: Reproductive and Developmental Toxicology

Report Title: GSK1278863A + metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: Oral Gavage and Subcutaneous Injection Pre- and Postnatal Development Study in Rats

Test Article: GSK1278863A/ HIF-prolyl hydroxylase inhibitor / Metabolite cocktail, consisting of M2 (GSK2391220), M3 (GSK2506104) and M13 (GSK2531401)
Lot/Batch No.: GSK1278863: 8863B3B007 (152388719); GSK2391220A (M2): H11454-120-1A; GSK2506104A (M3): ES2553-60; GSK2531401A (M13): H111451-114-A
Study No. 20118760
GSK Reference No. R71242G

Design similar to ICH 4.1.2.? Yes

Duration of Dosing: Main study: GD 6 to LD 20
TK Rats: GD 6 to GD 9 or to LD 21 (6 main study female rats/group that had blood samples collected on LD 21)

Species/Strain: Rat/Sprague-Dawley [Crl:CD(SD)]
Initial Age: 10 weeks

Day of Mating: GD 0

Method of Administration/Frequency: Oral Gavage Once daily (GSK1278863) or subcutaneous Twice Daily (metabolites)

Location in CTD: m4.2.3.5.3

Date of First Dose: 18 July 2017
Special Features: Toxicokinetic evaluation on GD 9 and LD 21 (F_0 dams) and on PND 10 (F_1 pups)

Vehicle/Formulation: Oral suspension: 1% (w/v) aqueous methylcellulose (400 cps @ 2%)
Metabolite Cocktail (subcutaneous): Aqueous 25 mM Phosphate Buffer, pH 7.4/ Solution

GSK Document Number: 2018N365151

GLP Compliance: Yes

No Observed Adverse-Effect Level:
F_0 Females: 7 mg/kg
F_1: 7 mg/kg

Litters Culled/Not Culled: Not Culled

GSK1278863A + metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: Oral Gavage and Subcutaneous Injection Pre- and Postnatal Development Study in Rats (Cont'd)

Data Collected: F_0 females: mortality, clinical observations, body weight, food consumption, parturition, toxicokinetics (GD 9 and LD 21), and necropsy; F_1 offspring: survival, gender, external morphology, clinical observations, body weight, plasma concentrations (PND 10), physical landmarks of physical development (vaginal opening in females and balano-preputial skin fold separation in males), neurobehavioral function (startle reflex, Morris water maze, motor activity), reproductive function, necropsy and femur length; F_2 litters: survival, gender, external morphology, clinical observations and body weight.

Conclusion: There was decreased F_0 body weight gain and food consumption late in gestation and in lactation at 40 mg/kg/day GSK1278863 + metabolites. There was increased pup death from PND 2 to 5, which manifest as decreased litter size, decreased viability and lactation indices and decreased pup weight up to PND 7 at 40 mg/kg/day GSK1278863 + metabolites. There was a decrease in F_1 female gestation and lactation body weight at 40 mg/kg/day GSK1278863 + metabolites. The no observed adverse effect level (NOAEL) for maternal (F_0) reproductive function as well as effects on pre- and postnatal development of the offspring in rats is 7 mg/kg/day + metabolites, based on the reduced viability of F_1 pups at 40 mg/kg/day GSK1278863 + metabolites. At this dose level, F_0 AUCs were 855 and 613 µg.h/mL for GSK1278863 on GD 9 and LD 21 and 2.50/2.24, 2.47/2.28 and 1.94/1.64 µg.h/mL for metabolites M2 (GSK2391220), M3 (GSK2506104) and M13 (GSK2531401), respectively, on GD 9/LD 21 respectively. F_1 plasma concentrations on PND 10 for male and female pups at 7 mg/kg/day GSK1278863 + metabolites ranged from 18600 to 38500 ng/mL for GSK1278863 and from 3.51 to 17.9, 0.407 to 3.32 and not quantified to 1.21 ng/mL for metabolites M2 (GSK2391220), M3 (GSK2506104) and M13 (GSK2531401), respectively.

Study Type: Genetic Toxicology In Vitro	**Study Number:** 20118760			
Daily Subcutaneous Dose metabolite cocktail [GSK2391220A (M2); GSK2506104A (M3): GSK2531401A (M13)] mg/kg/day [dosed as 1.25, 1.8 and 0.9 mg/kg/dose BID every 6 hrs]	**0/0/0**	**2.5, 3.2, 1.8**	**2.5, 3.2, 1.8**	**2.5, 3.2, 1.8**
Daily Oral Dose (mg/kg/day) GSK1278863	**0 (Control)**	**0.8**	**7**	**40**
F_0 Females:				
No. Assigned	24	24	24	24
Unscheduled Euthanasia	1[a]	0	0	2[b]
Found Dead	0	0	0	1[c]
No. Pregnant	23	23	22	24
No. Pregnant Survivors to Term	23	23	22	23

GSK1278863A + metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: Oral Gavage and Subcutaneous Injection Pre- and Postnatal Development Study in Rats (Cont'd)

Toxicokinetics (AUC_{0-t}) µg.h/mL				
GD 9 (F_0)				
GSK1278863	NQ	146	855	2240
GSK2391220 (M2)	NQ	2.65	2.50	2.51
GSK2506104 (M3)	NQ	2.73	2.47	2.36
GSK2531401 (M13)	NQ	2.16	1.94	1.88
LD 21 (F_0)				
GSK1278863	NQ	98.4	613	1620
GSK2391220 (M2)	NQ	2.72	2.24	3.03
GSK2506104 (M3)	NQ	2.91	2.28	2.90
GSK2531401 (M13)	NQ	2.15	1.64	2.16
Clinical Observations	-	-	-	-
Gestation Body Weight Change GD 6 to 10^d	22.8g	1.05X	1.10X	1.11X
Gestation Body Weight Change GD 6 to 14^d	51.4g	1.02X	1.10X	1.11X
Gestation Body Weight Change GD 6 to 18^d	102.1g	1.04X	1.09X	1.09X
Gestation Body Weight Change GD 6 to 21^d	155.8g	1.02X	1.03X	0.93X
Lactation Body Weight Change LD 1 to 4^d	17.0g	1.05X	0.92X	0.62X
Lactation Body Weight Change LD 1 to 8^d	30.0g	1.10X	1.08X	1.12X
Lactation Body Weight Change LD 1 to 12^d	41.6g	1.06X	1.15X	1.19X
Lactation Body Weight Change LD 1 to 16^d	50.4g	0.88X	0.92X	1.13X
Lactation Body Weight Change LD 1 to 21^d	49.9g	0.83X	0.98X	1.15X
Gestation Food Consumption GD 6 to 10^d	44.2g	1.11X	1.04X	1.01X
Gestation Food Consumption GD 10 to 14^d	48.3g	1.03X	1.03X	1.01X
Gestation Food Consumption GD 14 to 18^d	52.4g	1.04X	1.03X	0.97X
Gestation Food Consumption GD 18 to 21^d	25.6g	1.02X	0.94X	0.84X**
Lactation Food Consumption LD 1 to 4^d	32.4g	1.06X	1.05X	0.91X
Lactation Food Consumption LD 4 to 8^d	51.1g	1.02X	1.04X	0.88X**

GSK1278863A + metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: Oral Gavage and Subcutaneous Injection Pre- and Postnatal Development Study in Rats (Cont'd)

Lactation Food Consumption LD 8 to 12[d]	67.0g	0.99X	1.02X	0.91X
Lactation Food Consumption LD 12 to 14[d]	76.2g	1.01X	1.05X	0.90X
Mean Duration of Gestation (days)	22.4	22.5	22.6	22.4
Mean No. of Implantations	13.6	13.8	13.4	13.0
Average Pup Delivery Time (min)	10.57	9.41	11.92	13.53[e]
Necropsy Observations	-	-	-	-
F_1 Litters: No. Viable Litters at Birth (Day 1)	22	23	22	23
(Preweaning) No. Viable Litters at Weaning (Day 21)	22	23	22	23
Mean No. Live Pups Born/Litter	12.4	12.9**[f]	12.9**[f]	11.7
Mean No. Stillborn Pups Born/Litter	0.4	0.1**[f]	0.0**[f]	0.4
Pup Sex Ratio on PND 1 (% Males)	50.3	44.9	50.4	48.0
Viability Index (% Survival PND 1 to 4)	98.2	98.3	97.5	86.6**
Lactation Index (% Survival PND 4 to 21)	100.0	100.0	100.0	98.5**
Pups found dead, euthanized or presumed cannibalized PND 2-4 ratio (%)	4/273 (1.5)	3/294 (1.0)	4/280 (1.4)	33/259 (12.7)**
Pups found dead, euthanized or presumed cannibalized PND 5-7 ratio (%)	0/269 (0.0)	0/291 (0.0)	0/276 (0.0)	3/226 (1.3)**
Mean live litter size PND 4	12.2	12.6	12.5	10.3**[g]
Pup Weight/Litter on PND 1 (g)	7.0	6.8	7.0	6.3
Pup Weight/Litter on PND 4 (g)	10.2	10.0	10.2	8.9
Pup Weight/Litter on PND 7 (g)	15.1	15.0	15.3	13.6*
Pup Weight/Litter on PND 21 (g)	41.2	41.5	42.4	40.9
Clinical Observations PND 1 to 21 (number of pups/number of litters)				
Dehydration (skin turgor)	0	0	0	18/3
Cold to touch	0	1/1	0	15/2

GSK1278863A + metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: Oral Gavage and Subcutaneous Injection Pre- and Postnatal Development Study in Rats (Cont'd)

Plasma concentrations ng/mL				
PND 10 (F_1) males				
GSK1278863	h	4590-9310	19300-31700	40000-44600
GSK2391220 (M2)	h	1.31-2.93	4.01-17.9	8.15-51.1
GSK2506104 (M3)	NQ	0.491-1.39	0.407-3.32	0.553-7.29
GSK2531401 (M13)	NQ	NQ-0.595	0.203-1.21	NQ-4.05
PND 10 (F_1) females				
GSK1278863	NQ	3570-7830	18600-38500	36500-59500
GSK2391220 (M2)	NQ	0.754-6.07	3.51-12.7	7.38-24.1
GSK2506104 (M3)	NQ	0.324-2.94	0.480-1.81	0.434-4.59
GSK2531401 (M13)	NQ	NQ-1.30	NQ-1.17	NQ-2.63
F_1 Males (Postweaning): No. Evaluated (Subset 1)	22	23	22	21
Mean Body Weight PND 22 (Subsets 1 and 2)[d]	44.6g	1.01X	1.02X	0.95X
Mean Body Weight PND 106 (Subset 1)[d]	560.7 g	1.03X	1.02X	0.99X
Mean Body Weight Gain PND 22-29 (Subset 1 and 2)[d]	44.7 g	1.05X	1.03X	0.91X**
Mean Body Weight Gain PND 22-71 (Subset 1 and 2)[d]	384.6 g	1.03X	1.01X	1.00X
Mean Age of Balano-Preputial Separation (days, subsets 1 and 2)	43.0	42.8	43.3	43.3
Sensory Function (Startle reflex)	-	-	-	-
Motor Activity	-	-	-	-
Learning and Memory (Passive Avoidance)	-	-	-	-
Mean No. Days in Cohabitation	2.4	2.4	2.6	2.5
No. of Males that Mated	21	22	22	21
No. of Fertile Males	17	17	21	19
Clinical Observations (number of rats)				

GSK1278863A + metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: Oral Gavage and Subcutaneous Injection Pre- and Postnatal Development Study in Rats (Cont'd)

Localized swelling along the surface of the abdomen (Subsets 1 and 2) PND 71 and up	0	0	0	3[i]
Femur Length (Subset 2) (mm)	38.5	38.6	38.5	38.2
Necropsy Findings (Subset 2)	-	-	-	-
F_1 Females (Postweaning): No. Evaluated (Subset 1)	22	23	22	21
Mean Body Weight PND 22 (Subsets 1 and 2)[d]	42.4g	1.00X	1.01X	0.95X
Mean Body Weight PND 89[d]	270.3 g	1.04X	1.04X	1.06X
Mean Body Weight Gain[d] PND 22 to 29 (Subset 1 and 2)	38.7 g	1.01X	1.02X	0.92X**
Mean Body Weight Gain[d] PND 22 to 71 (Subset 1 and 2)	207.6 g	1.01X	1.04X	1.03X
Mean Age of Vaginal Patency (Subsets 1 and 2) (days)	32.0	32.0	32.5	32.9**[j]
Sensory Function (Startle Reflex)	-	-	-	-
Motor Activity	-	-	-	-
Learning and Memory (Morris Water Maze)	-	-	-	-
Mean No. of Estrous Cycles Premating	2.27	2.30	2.14	2.33
No. of Females With Confirmed Mating Dates	22	23	22	21
Mean Gestation Body Weight[d] GD 21	461.9 g	0.98X	1.00X	0.93X
Mean Gestation Body Weight Gain[d] GD 0-21	183.2 g	1.02X	0.98X	0.90X
Mean Lactation Body Weight[d] LD 7	356.9 g	0.97X	1.02X	0.93X
Mean Lactation Body Weight[d] LD 1 to 7	19.3 g	0.76X	0.99X	0.25X*
No. of Pregnant Females	19	18	21	19
Clinical Observations (number of rats)				
Localized swelling along the surface of the abdomen (Subsets 1 and 2) PND 53 and up	0	0	0	5[i]
Femur Length, Subset 2 (mm)	34.2	34.8	34.7	34.1
Necropsy Findings (Subset 2)	-	-	-	-
Mean Duration of Gestation (days)	22.8	22.7	22.5	22.4
Average Pup Delivery Time (min)	12.9	15.8	12.8	13.1

GSK1278863A + metabolites [GSK2391220A (M2), GSK2506104A (M3) and GSK2531401A (M13)]: Oral Gavage and Subcutaneous Injection Pre- and Postnatal Development Study in Rats (Cont'd)

Mean No. of Implantations	16.7	16.9	16.5	15.3
F_2 Litters: No. Evaluated	19	18	21	19
Mean No. Live Pups Born/Litter	15.4	15.7	14.8	13.8
Mean No. Stillborn Pups Born/Litter	0.0	0.0	0.1	0.1
Viability Index (% survival PND 1-4)	98.6	98.6	98.7	96.6
Lactation Index (% Survival PND 0-7)	99.3	98.9	99.0	100.0
Pup Sex Ratio on PND 1 (% males)	49.8	46.2	44.2	47.0
Pup Weight/Litter PND 1 (g)	6.8	6.3	6.6	6.6
Pup Weight/Litter PND 7 (g)	13.4	13.0	13.9	13.5*
Clinical Observations	-	-	-	-

Key:
- = No noteworthy findings. GD = Gestation Day LD = Lactation Day PND = Postnatal Day NQ = Not Quantifiable (<0.200 ng/ml)

a. F_0 female 3419 euthanized on GD 23 due to delivery complications.
b. F_0 female 3485 was euthanized due to dosing trauma on LD 14; F_0 female 3480 euthanized due to delivery complications on LD 2 – neither of these were considered test article-related
c. F_0 female 3490 found dead on GD 21 after body weight loss on GD 18-20. Not considered test article-related as deaths did not occur in other studies at 60 mg/kg/day.
d. For controls, group means are shown. For treated groups, change from controls is shown.
e. Not considered test article-related as there was no statistical significance.
f. Statistical difference for N (%). Not considered test article-related as no dose response and treated groups had less pup death than controls.
g. Similar statistically significant decreases in surviving pups/litter and litter size (0.82-0.83X controls) were observed on PND 7, 14 and 21 at 40 mg/kg/day GSK1278863 + metabolites compared to controls.
h. 3 male control pups has quantifiable concentrations of GSK1278863 (212 – 2510 ng/mL) at 3 hrs post the first maternal dose on PND 10. One of these pups (3401/2) also had 0.903 ng/mL of M2 at 3 hrs. These maternal animals did not have quantifiable concentrations of GSK1278863 as measured on LD 21, and the values reported were lower than values observed in 0.8 mg/kg/day GSK1278863 + metabolites pups, therefore were not considered to have affected interpretation of these results.
i. Significance of this finding is not known; was not observed at necropsy in the animals that had gross necropsy, no other test article-related effects in these animals.
j. Not considered test article-related as within historical control values of the laboratory (30.1-35.3 days)

*= Statistical significance ($p \leq 0.05$), ** = statistical significance ($p \leq 0.01$) based on raw data (not on the change from controls)

16. STUDIES IN JUVENILE ANIMALS

No Juvenile Toxicity studies with daprodustat have been completed

17. LOCAL TOLERANCE: NONPIVOTAL STUDIES

Table 17.1 Local Tolerance Studies

Species/ Strain	Route (Vehicle/Formulation)	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
SkinEthic reconstructed human corneal model	In vitro	30 mg of powder	NA	No Noteworthy Findings	2012N133177 (41101688)
SkinEthic reconstructed human epidermal model	In vitro	25 mg of powder	NA	Daproustat was considered to be a mild-moderate irritant.	2012N133176 (41101687)
EpiDerm™ skin tissue	In vitro	0.2%	NA	Daprodustat in all formulations had no effects on cell viability in this model	2012N152037
Mouse (CBA/Ca)	Dermal	10%, 25%, 50% 10%	1F 5F	Daprodustat was considered to be a non-sensitiser under the conditions of the test.	2013N163877 (41204918)

18. LOCAL TOLERANCE: PIVOTAL STUDIES

Table 18.1 GSK1278863A: Local Lymph Node Assay in the Mouse

Study Type: Local Lymph Node Assay

Report Title: GSK1278863A: Local Lymph Node Assay in the Mouse

Test Article: GSK1278863A
Batch No.: 091214093

Species/Strain: Female mouse CBA/CaCrl

Duration of Dosing: 3 days

GSK Reference No.: G11248

Initial Age: 8 to 9 weeks

Route/Frequency: Topical application to the ears once daily for 3 consecutive days

GSK Document Number: 2012N132983
Location in CTD: m4.2.3.6

Date of First Dose: 11 January 2012

Vehicle/Formulation: Petrolatum

Study in Compliance with GLP: Yes

Data Collected: Clinical observations, body weight, disintegrations per minute (DPM), stimulation indices (SI)

Conclusion: GSK1278863A applied topically to both ears of mice at concentrations up to 2% w/w for 3 consecutive days was not a contact sensitiser under the conditions of this study.

Study Type: Local Lymph Node Assay | **GSK Reference No.:** G11248

Group	**1**	**2**	**3**	**4**	**5**	**6**
Test Article	AOO	Placebo (Petrolatum)	GSK1278863 in Petrolatum	GSK1278863 in Petrolatum	GSK1278863 in Petrolatum	Hexyl cinnamaldehyde in AOO
Concentration % (w/w)	0	0	0.5	1.0	2.0	25 (v/v)
Number of animals	5	5	5	5	5	5
Mean DPM	172	129	153	160	251	3850
SI	N/A	N/A	1.18	1.24	1.95	22.33

Key:
AOO Acetone/olive oil (4:1 v/v)
N/A Not applicable

Table 18.2 GSK1278863A and GSK1278863A Ointments at 0 (placebo), 5, 10 or 20% w/w: Assessment of Ocular Irritation using the Bovine Corneal Opacity and Permeability Assay with Validation of an Analytical Method for the Petrolatum Based Ointments

Study Type: In Vitro

Report Title: GSK1278863A and GSK1278863A Ointments at 0 (placebo), 5, 10 or 20% w/w: Assessment of Ocular Irritation using the Bovine Corneal Opacity and Permeability Assay with Validation of an Analytical Method for the Petrolatum Based Ointments.

Test Articles: GSK1278863A (parent compound) and GSK1278863A 0 (placebo), 5, 10 and 20% w/w ointments
Batch No for parent: 152389102

Test System: Bovine cornea

Duration of Incubation: 4 hours (parent) or 10 minutes (ointments)

Formulation/Vehicle (ointments): 0, 5, 10 or 20% w/w in White Ultima Petroleum

Donor Animal Age Range:

Approximately18 months

Route/Frequency: In vitro (direct)

GSK Reference No.: V31530G

Experiments:	Date of Assay:	Positive Control:
1. GSK1278863A (parent compound)	27 April 2016	20% w/v imidizole
2. Placebo ointment	09 May 2016	Dimethyl formamide (DMF)
3. GSK1278863A 5, 10 and 20% w/w ointments	11 May 2016	Dimethyl formamide

GSK Document Number: 2016N293568

Location in CTD: m4.2.3.6

Study in Compliance with GLP: Yes

Data Collected: Corneal opacity using an opacitometer, permeability using a spectrophotometer; visual observations of corneal condition.

Conclusion: GSK1278863A (parent compound) produced an In Vitro Irritancy Score of 22.81. No prediction can be made in respect of the potential of GSK1278863A (parent compound) to cause eye irritation

GSK1278863A ointments at 0 (placebo), 5, 10 and 20% w/w, in petrolatum, produced In Vitro Irritancy Scores of 1.31, 3.03, 1.64 and 0.80, respectively and do not requiring classification for eye irritation.

The assay was considered valid as the assay acceptance criteria were met.

GSK1278863A and GSK1278863A Ointments at 0 (placebo), 5, 10 or 20% w/w: Assessment of Ocular Irritation using the Bovine Corneal Opacity and Permeability Assay with Validation of an Analytical Method for the Petrolatum Based Ointments (Continued)

Group	GSK1278863A (parent compound)	Placebo *	GSK1278863A Ointment	GSK1278863A Ointment	GSK1278863A Ointment
Dose Concentration % w/w	100	0	5	10	20
Volume of Formulation (µL)	750 (mg)	750	750	750	750
Experiment	1	2	3	3	3
Number of Corneas	3	3	3	3	3
Mean Corrected Corneal Opacity Score[a]	19.0	1.3	2.7	1.7	0.7
Mean Corneal Permeability (OD_{490})[b]	0.254	-0.001	0.024	-0.002	0.009
Calculated IVIS[c]	22.81	1.31	3.03	1.64	0.80
Negative Controls	Negative control was 0.9% w/v sodium chloride solution for each experiment and gave scores of 0 for mean corrected opacity, mean corneal permeability and calculated IVIS for each experiment.				
Positive Controls	Experiment 1: Positive control was 20% w/v imidizole. The mean corrected opacity, mean corneal permeability and calculated IVIS were 43.3, 1.022 and 58.66 respectively. Experiment 2: Positive control was dimethyl formamide (DMF). The mean corrected opacity, mean corneal permeability and calculated IVIS were 65.7, 0.503 and 73.21 respectively. Experiment 3: Positive control was (DMF). The mean corrected opacity, mean corneal permeability and calculated IVIS were 43.3, 0.336 and 48.37 respectively.				

Key:

* Placebo ointment - (vehicle for test article ointments)

a Individual scores corrected for mean opacity score in negative controls

b Optical density at 490 nm corrected for background opacity and negative control OD490 values

c A substance that induces an IVIS of >55 is defined as corrosive or severe irritant and an IVIS of ≤3 is defined as not requiring classification (OECD 437).

19. OTHER TOXICITY STUDIES

Table 19.1 Other Toxicity Studies

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Studies with Daprodustat						
Rat (Sprague Dawley)	In vitro	NA	0.5, 1, 2 mg/mL	NA	GSK1278863 at concentrations of 0.5, 1.0 and 2.0 mg/mL in vehicle (12% Cavitron™/0.5% NaCl in 20 mM phosphate buffer, pH 7.6) and vehicle alone was evaluated in an in vitro whole blood assay using rat erythrocytes. GSK1278863 at a concentration of 2.0 mg/mL in vehicle was haemolytic when added to rat blood. GSK1278863 at a concentration of 1.0 mg/mL in vehicle or vehicle alone were minimally haemolytic, and a concentration of 0.5 mg/mL in vehicle was not haemolytic when added to rat blood.	CD2008/01038 (I08189)
Human[a]	In vitro	NA	0.0488, 0.0952, 0.1818 mg/ mL	NA	The hemolytic potential of GSK1278863 formulations at concentrations of 48.8, 95.2 and 181.8 μg/mL in respective vehicles (containing ethanol/tromethamine buffer) and vehicles alone were evaluated in an in vitro whole blood assay using human erythrocytes. GSK1278863 at concentrations ≤181.8 μg/mL in ethanol/tromethamine buffer or vehicles alone did not produce hemolysis when added to human blood.	2012N131637 (G11256)

Other Toxicity Studies (Cont'd)

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Studies with Daprodustat						
Rat (Sprague Dawley)	IV (infusion)	14 days	20, 40	6M	Daprodustat was given once daily to rats (6 males/group) for 14 days as a 4 hour intravenous infusion at 0 (vehicle), 20 and 40 mg/kg/day. At 20 and 40 mg/kg/day most rats showed decreased activity immediately post dose beginning between Days 7 and 9 of dosing. Decreased overall body weight gain was present at 40 mg/kg/day, while body weight gain at 20 mg/kg/day was generally comparable to control with the exception of the last measurement interval for which body weight gain was decreased. Microscopic observations of erosions/ulcers, hemorrhage and mixed cell infiltrate in the glandular portion of the stomach were seen at generally similar incidence and severity in rats given 20 and 40 mg/kg/day and correlated with macroscopic changes of depressed areas, dark areas or foci and thickening in the stomach wall, respectively.	CD2008/01740 (I08185)

Other Toxicity Studies (Cont'd)

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Studies with Daprodustat						
Rat (Sprague Dawley)	Oral (gavage)	14 days	60	6M	Groups of male rats (6/group) were given 0 or 60 mg/kg/day daprodustat once daily for 14 consecutive days by oral gavage. Mean hemoglobin concentration for rats given 60 mg/kg/day was increased (1.35X) compared to control mean value on Day 15. Mean plasma glucose values for samples processed and analyzed immediately were decreased (0.83X and 0.75X control means for samples collected in lithium heparin and sodium fluoride, respectively), indicating that decreased glucose concentrations observed in this study are the result of an in vivo effect of daprodustat administration.	2012N135152 (I12031)
Studies with Metabolite						
Human	In vitro	NA	0.01 to 1000 μM	NA	GSK2531401A (M13 metabolite of daprodustat) did not exhibit any inhibitory activity on human Topoisomerase II relaxation over the requested test concentration range of 0.01 to 1000 μM. Etoposide (positive control) showed significant inhibition over the same concentration range with an average IC50 of 80.4 μM.	2011N130337

Other Toxicity Studies (Cont'd)

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. (Study No.)
Studies with Daprodustat						
Human	In vitro	NA	2 to 2000 μM	NA	GSK2531401A (M13 metabolite of daprodustat) did not produce any detectable inhibition of human topoisomerase II alpha activity up to 2 mM, the highest concentration tested. Suramin, the positive control, inhibited human topoisomerase II alpha activity with an IC_{50} = 23.62 μM.	2012N139337

Key:
a = Study was conducted to full GLP compliance.