2.6.7.4 Toxicology: Drug Substance

2.6.7.4.1 List of Tapinarof Batches Used in Nonclinical Toxicology Studies

Batch No.	Drug Substance					Test Article: tapinarof	
	Synthetic Route	Purity (%)	Known Impurities (%)	Unknown Impurities[a] (%)	Total Impurities (%)	Report Number	Type of Study
Proposed Specification:	-	98.0 - 102.0	NGT 0.15%	NGT 0.15%	NGT 1.0%		
[redacted]*	A	99.3	RS#3[b] = 0.39 RS#5[c] = 0.11	RRT 0.89 = 0.07 RRT 1.68 = 0.07 RRT 1.81 = 0.07	0.71	20[redacted]N163816 20[redacted]N163817 20[redacted]N163815 20[redacted]N178086	Repeat Dose Toxicity Repeat Dose Toxicity Repeat Dose Toxicity Local Tolerance
[redacted]**	B	99.2	NR	RRT 0.52 = 0.06 RRT 1.04 = 0.53 RRT 1.23 = 0.06	0.65	20[redacted]N163550 20[redacted]N164986 20[redacted]N166805 20[redacted]N163449 20[redacted]N170816 20[redacted]N173392 20[redacted]N166805 20[redacted]N182130 20[redacted]N166695 20[redacted]N178148 20[redacted]N189059 20[redacted]N163009	Single-Dose Toxicity Repeat Dose Toxicity Repeat Dose Toxicity Repeat Dose Toxicity Genotoxicity Genotoxicity Genotoxicity Juvenile Toxicity Reproductive Toxicity Reproductive Toxicity Reproductive Toxicity Local Tolerance
[redacted]***	B	94.9	GSK3234979A = 1.71	RRT 0.53 = 0.21 RRT 0.87 = 0.17 RRT 0.98 = 0.08 RRT 1.04 = 0.20 RRT 1.06 = 0.24 RRT 1.07 = 0.17 RRT 1.09 = 0.06 RRT 1.22 = 0.16 RRT 1.23 = 0.87 RRT 1.3 = 0.18 RRT 1.36 = 0.06 RRT 1.42 = 0.18	4.29	20[redacted]N184562	Repeat Dose Toxicity
[redacted]	C	99.9	NR	NR	0.07	20[redacted]N241812	Repeat Dose Toxicity
[redacted]**	B	99.8	NR	RRT 1.11 = 0.16	0.2	20[redacted]N163819	Repeat Dose Toxicity

タピナロフ
2.6.7 毒性試験の概要表

Batch No.	Drug Substance					Test Article: tapinarof	
	Synthetic Route	Purity (%)	Known Impurities (%)	Unknown Impurities[a] (%)	Total Impurities (%)	Report Number	Type of Study
Proposed Specification:	-	98.0 - 102.0	NGT 0.15%	NGT 0.15%	NGT 1.0%		
						20[redacted]N163820	Repeat Dose Toxicity
[redacted]	B	99.5	NR	NR	<0.05	20[redacted]N172520 20[redacted]N211242 20[redacted]N211697 20[redacted]N235202	Repeat Dose Toxicity Reproductive Toxicity Juvenile Toxicity Local Tolerance
[redacted]**	B	98.2	NR	RRT 0.52 = 0.08 RRT 0.59 = 0.06 RRT 0.77 = 0.13 RRT 0.98 = 0.05 RRT 1.06 = 0.06 RRT 1.07 = 0.09 RRT 1.13 = 0.25 RRT 1.22 = 0.08 RRT 1.23 = 0.14	0.93	20[redacted]N160460	Repeat Dose Toxicity
[redacted]**	B	98.7	NR	RRT 1.04 = 0.1 RRT 1.22 = 0.05 RRT 1.23 = 0.08	0.24	20[redacted]N167695 20[redacted]N175734 20[redacted]N175645 20[redacted]N172520 20[redacted]N175961	Repeat Dose Toxicity Repeat Dose Toxicity Repeat Dose Toxicity Repeat Dose Toxicity Local Tolerance
[redacted]	B	99.9	NR	RRT 1.278 = 0.06	0.06	20[redacted]N204716 20[redacted]N235202	Repeat Dose Toxicity Local Tolerance
[redacted]**	B	94.8	NR	RRT 0.41 = 0.06 RRT 0.45 = 0.16 RRT 0.47 = 0.07 RRT 0.5 = 0.07 RRT 0.53 = 0.24 RRT 0.59 = 0.24 RRT 0.72 = 0.19 RRT 0.78 = 1.22 RRT 0.82 = 0.05 RRT 0.82 = 0.17 RRT 0.92 = 0.19 RRT 0.95 = 0.14	3.40	20[redacted]N158999	Single-Dose Toxicity

タピナロフ
2.6.7 毒性試験の概要表

Batch No.	Drug Substance					Test Article: tapinarof	
	Synthetic Route	Purity (%)	Known Impurities (%)	Unknown Impurities[a] (%)	Total Impurities (%)	Report Number	Type of Study
Proposed Specification:	-	98.0 - 102.0	NGT 0.15%	NGT 0.15%	NGT 1.0%		
				RRT 1.06 = 0.19 RRT 1.07 = 0.17 RRT 1.07 = 0.13 RRT 1.23 = 0.12			
[redacted]*	A	99.6	RS#3[b] = 0.15 RS#5[c] = 0.14	NR	<0.5	20[redacted]N172052 20[redacted]N163814 20[redacted]N163815 20[redacted]N172054 20[redacted]N163810 20[redacted]N172055 20[redacted]N163830 20[redacted]N163832 20[redacted]N163833 20[redacted]N163834	Single-Dose Toxicity Single-Dose Toxicity Repeat Dose Toxicity Repeat Dose Toxicity Repeat Dose Toxicity Repeat Dose Toxicity Local Tolerance Local Tolerance Local Tolerance Local Tolerance
[redacted]*	A	99.5	GSK3087165A = 0.12	NR	0.12	20[redacted]N172052 20[redacted]N163814 20[redacted]N172054 20[redacted]N163810 20[redacted]N172055 20[redacted]N163822 20[redacted]N163824 20[redacted]N163826 20[redacted]N163830 20[redacted]N163832 20[redacted]N163833 20[redacted]N163834	Single-Dose Toxicity Single-Dose Toxicity Repeat Dose Toxicity Repeat Dose Toxicity Repeat Dose Toxicity Genotoxicity Genotoxicity Genotoxicity Local Tolerance Local Tolerance Local Tolerance Local Tolerance
[redacted]	B	99.5	GSK3087165A = 0.12	NR	0.12	20[redacted]N221246 20[redacted]N221820	Repeat Dose Toxicity Repeat Dose Toxicity
[redacted]	B	99.9	NR	NR	<0.05	20[redacted]N244027	Reproductive Toxicity
[redacted]†	C	99.7	NR	NR	<0.05	20[redacted]N254469 20[redacted]N299302 20[redacted]N278677	Repeat Dose Toxicity Repeat Dose Toxicity Juvenile Toxicity
[redacted]†	C	99.9	NR	<0.05	<0.05	20[redacted]N368233	Reproductive Toxicity

Batch No.	Drug Substance					Test Article: tapinarof	
	Synthetic Route	Purity (%)	Known Impurities (%)	Unknown Impurities[a] (%)	Total Impurities (%)	Report Number	Type of Study
Proposed Specification:	-	98.0 - 102.0	NGT 0.15%	NGT 0.15%	NGT 1.0%		
						DMVT-505-9001 DMVT-505-9002 DMVT-505-9003	Carcinogenicity Carcinogenicity Repeat Dose Toxicity
[redacted]†	C	100.2	NR	NR	<0.05	DMVT-505-9002	Carcinogenicity

a. Unknown impurities with % Area <0.05 are not reported in this table.
b. RS#3 = RRT 0.83; 4, 4'-diisopropyl-3, 3', 5, 5'-tetrahydroxylstilbene.
c. RS#4 = RRT 1.13; 5-dihydroxyl-4-isopropyl-2-methylstilbene.
* = The synthetic route for these batches is not relevant to the synthetic route outlined in Figure 1 of Section 3.2.S.2.2.; ** = For the indicated studies, the same synthetic route was used to prepare the nonclinical batches and the clinical batch; *** = Route B batch spiked with impurities; † = Route C batches represent the commercial synthetic route and process provided in Section 3.2.S.2.2.

2.6.7.5 Toxicology: Single-Dose Toxicity

2.6.7.5.1 Non-Pivotal Single Dose Studies

Single Dose Toxicity				Test Article: tapinarof			
Species/ Strain	**Method of Administration (Vehicle/ Formulation)**	**Concentration and/or Dose (mg/kg)**	**Gender and No. per Group**	**Observed Maximum Nonlethal Dose (mg/kg)**	**Approximate Lethal Dose (mg/kg)**	**Noteworthy Findings**	**Report Number/ Location in CTD**
Rat (WH)	Oral, Subcutaneous	0, 10	3M	≥10	Unknown	• No noteworthy findings	20[redacted]N158999/ 4.2.3.1-1
Rat (SD)	Dermal (Formulation A)	8% (480 mg/kg)	6M/6F	≥480	Unknown	• 8% cream was well tolerated. • Mild transient skin irritation was observed at the application site.	20[redacted]N172052/ 4.2.3.1-2
Rabbit (NZW)	Dermal (Formulation A)	8% (640 mg/kg)	6M/6F	≥640	Unknown	• 8% cream was well tolerated. • Mild transient skin irritation was observed at the application site.	20[redacted]N163814/ 4.2.3.1-3

F = female; WH = Wistar Han [Crl:WI(Han)]; M = male; NZW = New Zealand White [Crl:KBL(NZW)BR]; SD = Sprague-Dawley Rats [Crl:CD(SD)]

2.6.7.6 Toxicology: Repeated-Dose Toxicity (Nonpivotal Studies)

2.6.7.6.1 Non-Pivotal Dermal Administration Studies

Nonpivotal Studies					Test Article: tapinarof		
Species/ Strain	**Method of Administration (Vehicle/ Formulation)**	**Duration of Dosing**	**Concentration and/or Dose (mg/kg/day)**	**Gender and No. Per Group**	**NOAEL (mg/kg)**	**Noteworthy Findings**	**Report Number/ Location in CTD**
Mouse							
Mouse (CD-1)	Dermal (Formulation E)	7-Day	1%, 2%, 4% (0.2 g/mouse)	4M 15M[TK]	ND[a]	• Skin: very slight erythema (1 high dose animal) • Clinical pathology: minor treatment-related changes • Liver: increased weight (not dose related)	20[redacted]N175645/ 4.2.3.2-1
Rat							
Rat (SD)	Dermal (Formulation A)	7-Day	0%, 1%, 4%, 8% (0, 60, 240, 480)	4M/4F	ND[a]	• Clinical pathology: minor treatment-related changes (slightly increased WBC, neutrophils, lymphocytes, monocytes; highest at mid-dose)	20[redacted]N172054/ 4.2.3.2-4
Rat (WH)	Dermal (Formulation E)	7-Day	1%, 2%, 4% (10, 20, 40)	4M 3M[TK]	ND[a]	• Skin: inflammation/irritation at application site • Adrenals: zona fasciculata hypertrophy (high dose) • Clinical pathology: increased serum triglycerides (dose related)	20[redacted]N175734/ 4.2.3.2-5
Rabbit							
Rabbit (NZW)	Dermal (Formulation E)	7-14-Day	0, 80, 320, 640	2M/2F	ND[a]	• Body weight: loss in one high dose female • Skin: loss of elasticity (all groups); erythema (mid and high dose animals); fissuring (1 mid dose female, all high dose animals) • Clinical pathology: mild increases in alanine aminotransferase (ALT) • Liver: enlarged and friable (3 high dose animals); prominent globular pattern and off-white infiltrates in parenchyma (2 high dose animals, correlated with increased ALT); pale (1 high dose animal)	20[redacted]N172055/ 4.2.3.2-8
Rabbit (DB)	Dermal (Formulation F)	7-Day	0%, 0.5%, 1%, 3% (2 g/kg)	3F	ND[a]	• Skin: erythema (all groups); irritation (slightly higher for active groups); dry/flaking skin (mid and high dose); edema/epidermal hyperplasia/hyperkeratosis (dose-related)	20[redacted]N221820/ 4.2.3.2-9

Nonpivotal Studies					Test Article: tapinarof		
Species/ Strain	**Method of Administration (Vehicle/ Formulation)**	**Duration of Dosing**	**Concentration and/or Dose (mg/kg/day)**	**Gender and No. Per Group**	**NOAEL (mg/kg)**	**Noteworthy Findings**	**Report Number/ Location in CTD**
Minipig							
Göttingen Minipig	Dermal (Formulation D)	7-Day	0%, 1%, 2%, 4% (20, 40, 80)	1M/1F	ND[a]	• No noteworthy findings	20[redacted]N163449/ 4.2.3.2-11
Göttingen Minipig	Dermal (Formulations E, F, and Miglyol/ Kolliwax blend)	7-Day	0%, 2%	3M	ND[a]	• Skin: edema (all groups); perivascular inflammatory cell infiltrate (Miglyol/Kolliwax blend groups); epidermal hypertrophy/hyperplasia (all active groups)	20[redacted]N204716/ 4.2.3.2-12

a. No adverse findings in some or all groups, but a NOAEL was not described in the report.
CD-1 = Crl:CD1®(ICR); DB = Dutch Belted [Haz:(DB)SPF]; F = female; WH = Wistar Han [Crl:WI(Han)]; ND = not determined; M = male, NZW = New Zealand White [Crl:KBL(NZW)BR]; SD = Sprague Dawley Rats [Crl:CD(SD) BR]; TK = toxicokinetic

2.6.7.6.2 Non-Pivotal Subcutaneous Administration Studies

Nonpivotal Studies					**Test Article: tapinarof**		
Species/ Strain	**Method of Administration (Vehicle/ Formulation)**	**Duration of Dosing**	**Doses (mg/kg/day)**	**Gender and No. Per Group**	**NOAEL (mg/kg)**	**Noteworthy Findings**	**Report Number/** Location in CTD
Rat (WH)	Subcutaneous	7-Day	0, 3, 10, 30	4M/4F 3M/3F[TK]	ND[a]	• Skin: inflammation at injection site (all groups, increased severity in active groups) • Skin: bacterial colonization in dermis (all groups, increased severity in active groups) • Thymus: decreased cellularity (high dose, males) • Liver: hepatocellular microvesicular vacuolation (active groups, females) • Clinical pathology: evidence of inflammation (not dose related)	20[redacted]N160460/ 4.2.3.2-19
Rat (WH)	Subcutaneous	7-Day	0, 200, 500, 1000	5M/5F 6M/6F[TK]	ND[b]	• Mortality:2 high dose males on Days 2 and 3 • Skin/Injection site: thickening, discoloration, scabs, atonia, blanching, edema, erythema, eschar, fissuring (all active groups, some mild findings in control group) • Hematology: increased neutrophils, prothrombin time; decreased red blood cells (RBC), hemoglobin, reticulocytes, mean corpuscular volume, mean corpuscular hemoglobin (active groups) • Clinical Chemistry: increased AST, ALP, cholesterol, globulin; decreased ALT, sodium, albumin, A/G ratio (active groups) • Liver: increased weight (absolute and % body weight, all active groups); periportal hepatocyte vacuolation (low dose animals were the only ones analyzed, increased incidence in females)	20[redacted]N163819/ 4.2.3.2-20
Rat (WH)	Subcutaneous (30% aqueous Captisol®, corn oil, olive oil, peanut oil)	7-Day	0, 30	3M	ND[a]	• Skin: dermal/subcutaneous hemorrhage/edema (Captisol® or olive oil active groups) • Panniculus muscle necrosis (Captisol® active groups) • Thymus: decreased lymphocyte cellularity (all groups) • Liver: increased weight (Captisol® and olive oil active groups)	20[redacted]N164986/ 4.2.3.2-21

a. A NOAEL was not described in the report.
b. Due to adverse findings in all groups, a NOAEL could not be determined.
F = female; WH = Wistar Han [Crl:WI(Han)]; M = male; ND = not determined; TK = toxicokinetic

2.6.7.7 Toxicology: Repeated-Dose Toxicity (Pivotal Studies)

2.6.7.7.1 Dermal Administration

2.6.7.7.1.1 Mouse

2.6.7.7.1.1.1 14-Day Dermal Toxicity Study in Mice [Report 20[redacted]N184562]

Report Title:	**GSK2894512A: A 14-Day Dermal Toxicity Study in Mice**							
Species/ Strain:	CD-1 Mouse	**Duration of Dosing:**	14 days		**Test Article (Batch No.):**	tapinarof ([redacted])		
Initial Age:	7 weeks	**Duration of Postdose:**	NA		**Report No.**	20[redacted]N184562		
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Dermal once daily unoccluded for ~23 hours		**Location in CTD:**	4.2.3.2-2		
Vehicle/Formulation:	Cream, Formulation E				**GLP Compliance:**	Yes		
Special Features: Dermal assessment of dosing site								
No Observed Adverse Effect Level: 4% tapinarof cream (Formulation E; 220-330 mg/kg/day)								
Daily Dose (%)	**0**		**1**		**2**		**4**	
Daily Dose (mg/kg/day)	**0 (Control)**		**60-80**		**110-160**		**220-330**	
Numbers of Animals: Main TK	**M:10 M:6**	**F:10 F:6**	**M:10 M:30**	**F:10 F:30**	**M:10 M:30**	**F:10 F:30**	**M:10 M:30**	**F:10 F:30**
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Day 1	NQ	NQ	78.1	174	266	766	1250	1650
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Day 14	NQ	NQ	58.7	126	185	221	821	854
Toxicokinetics: C_{max} (ng/mL), Day 1	NQ	NQ	14.9	51.5	69.1	292	218	313
Toxicokinetics: C_{max} (ng/mL), Day 14	NQ	NQ	18.4	40.7	57.6	128	207	186
Noteworthy Findings:	No test article-related findings in clinical observations, dermal scores, body weights, food consumption, clinical pathology, organ weights, or macroscopic and microscopic observations							
Died or Sacrificed Moribund	0	0	0	0	0	0	1[a]	0

a. This animal was euthanized moribund on Day 2. Based on pathology findings in this animal and the lack of findings in any other animal on the study, this animal was considered to have had an underlying condition unrelated to the test article.
F = female; M = male; NQ = not quantifiable (samples were BLQ)

2.6.7.7.1.1.2 13-Week Dermal Toxicity Study in Mice [Report 20[redacted]N241812]

Report Title:	**GSK2894512A: A 13-Week Dermal Toxicity Study in Mice**							
Species/ Strain:	CD-1 mouse	**Duration of Dosing:**	91/92 days		**Test Article (Batch No.):**	tapinarof ([redacted])		
Initial Age:	7 weeks	**Duration of Postdose:**	NA		**Report No.**	20[redacted]N241812		
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Dermal once daily unoccluded for ~23 hours		**Location in CTD:**	4.2.3.2-3		
Vehicle/Formulation:	Cream, Formulation F				**GLP Compliance:**	Yes		
Special Features: Dermal assessment of dosing site								
No Observed Adverse Effect Level: ≥3% tapinarof cream (Formulation F; 164-206 mg/kgday)								
Daily Dose (%)	**0**		**0.5**		**1**		**3**	
Daily Dose (mg/kg/day)	**0**	**0**	**28**	**33**	**56**	**65**	**164**	**206**
Numbers of Animals: Main **TK**	**M:12** **M:3**	**F:12** **F:3**	**M:12** **M:18**	**F:12** **F:18**	**M:12** **M:18**	**F:12** **F:18**	**M:12** **M:18**	**F:12** **F:18**
Toxicokinetics: $AUC_{(0\text{-}t)}$ (ng.h/mL), Day 91	NC	NC	22.4	34.5	53.0	92.8	498	518
Toxicokinetics: C_{max} (ng.h/mL), Day 91	NQ	NQ	4.50	11.1	27.5	20.5	151	152
Noteworthy Findings:	No test article-related findings in clinical observations, dermal scores, body weights, food consumption, ophthalmology, clinical pathology, organ weights, or macroscopic and microscopic observations							
Died or Sacrificed Moribund:								
Main	0	0	0	0	0	0	0	0
Toxicokinetic	0	0	0	0	1[a]	0	0	0

a. One toxicokinetic male (Animal No. 3190) given 1% tapinarof was found dead on Day 31 of the study. Gross pathology findings were limited to an irregular surface on the left kidney. There were no abnormal clinical signs present in this animal prior to mortality, and no effects on body weight or body weight gain were noted in this animal. The specific cause of death was not identified; however, this early death was considered to be unrelated to the test article, as no mortality was observed in mice given 3% tapinarof with markedly (>2-fold) higher systemic exposure (AUC and C_{max}).

F = female; M = male; NC = not calculable; NQ = not quantifiable [samples were below the limit of quantitation (0.3 ng/mL)]

2.6.7.7.1.2 Rat

2.6.7.7.1.2.1 28-Day Repeated Dose Dermal Toxicity Study of WBI 1001 in Sprague Dawley Rats [Report 20[redacted]N163810]

Report Title:	**28-Day Repeated Dose Dermal Toxicity Study of WBI-1001 in Sprague-Dawley Rats**				
Species/ Strain:	Sprague Dawley Rat	**Duration of Dosing:**	28 days	**Test Article (Batch No.):**	tapinarof ([redacted])
Initial Age:	8-9 weeks	**Duration of Postdose:**	NA	**Report No.**	20[redacted]N163810
Date of First Dose:	[redacted]-[redacted]-20[redacted]	**Method of Administration:**	Dermal once daily, occluded for 6 hours; half of animals had abraded skin	**Location in CTD:**	4.2.3.2-6
Vehicle/Formulation:	Cream, Formulation A			**GLP Compliance:**	No
Special Features: Dermal assessment of dosing site					
No Observed Adverse Effect Level: 4% tapinarof cream (Formulation A; 240 mg/kg/day)					

Daily Dose (%)	**0**		**1**		**4**		**8**	
Daily Dose (mg/kg/day)	**0 (Control)**		**60**		**240**		**480**	
Number of Animals: Main TK	**M:10 M:8**	**F:10 F:8**	**M:10 M:16**	**F:10 F:16**	**M:10 M:16**	**F:10 F:16**	**M:10 M:16**	**F:10 F:16**
Toxicokinetics: AUC_{last} (ng.h/mL), Day 1	NQ	NQ	NC	NC	614	1022	1592	1368
Toxicokinetics: AUC_{last} (ng.h/mL), Day 28	NQ	NQ	194	1122	1544	2633	2411	1840
Toxicokinetics: C_{max} (ng/mL), Day 1	NQ	NQ	NC	NC	48	107	68	113
Toxicokinetics: C_{max} (ng/mL), Day 28	NQ	NQ	49.8	198	182	241	152	98
Noteworthy Findings:	No noteworthy findings in body weights, food consumption, ophthalmoscopy, coagulation, serum chemistry, or macroscopic observations							
Died or Sacrificed Moribund	0	0	2[a]	0	1[a]	0	0	0
Dermal Observations (No. of Rats)[b]								
Dryness	--	--	--	--	9	10	6	8
Erythema	--	--	--	--	7	10	5	8
Hyperkeratosis	--	--	--	--	7	10	4	6
Fissures	--	--	--	--	2	9	1	1
Hematology								
Hemoglobin (g/L)	150	152	148	152	145	138*	141*	141*
Hematocrit (%)	43.6	43.1	43.0	43.1	41.9	39.6*	40.9*	40.7*
Red blood cells ($x10^{12}$/L)	7.85	7.98	7.90	8.03	7.77	7.16*	7.53	7.63
WBC (10^9/L)	5.33	3.77	5.16	4.32	8.70*	6.89*	6.93	5.30

Daily Dose (%)	**0**		**1**		**4**		**8**	
Daily Dose (mg/kg/day)	**0 (Control)**		**60**		**240**		**480**	
Number of Animals: Main	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**
TK	**M:8**	**F:8**	**M:16**	**F:16**	**M:16**	**F:16**	**M:16**	**F:16**
Neutrophils (10^9/L)	0.98	0.47	0.78	0.62	2.62*	1.92*	1.63	0.84
Monocytes (10^9/L)	0.08	0.04	0.08	0.08	0.17*	0.17*	0.20*	0.11*
Organ Weights[c]								
Liver (g)	9.989	5.769	0.99X	1.03X	0.96X	1.11X	1.10X	1.15X**
Liver (% body weight)	2.716	2.681	1.03X	1.06X	1.07X	1.16X**	1.15X**	1.13X**
Histopathology [d]								
Skin Application Site								
Hyperplasia								
Minimal	--	3	6	1	2	1	2	3
Mild	--	--	1	--	1	3	4	3
Moderate	--	--	--	--	5	4	--	2
Marked	--	--	--	--	1	1	--	--
Severe	--	--	--	--	--	--	--	--
Liver								
Hepatic Vacuolation								
Minimal	3	2	--[e]	NA	--	5	4	2
Mild	--	--	--[e]	NA	--	--	1	4
Thymus								
Atrophy								
Minimal	--	--	--[e]	NA	--[f]	NA	2	3
Mild	1	--	--[e]	NA	--[f]	NA	2	--
Lymph Node, Axillary								
Paracortical Hyperplasia	NA	NA	NA	NA	NA	3[g]	NA	2[g]

a. Deaths were attributed to dosing procedure and were not test article-related.
b. Skin reactions peaked in severity during the 3rd week of dosing, after which reactions subsided.
c. For controls, group means are shown. For test article treated groups, change from control is shown. Statistical significance is based on actual data not change from control data.
d. Grades of skin responses were greater on those sites that had been abraded before application of the test article.
e. Only 2 males examined (unscheduled deaths).
f. Only 1 male examined (unscheduled death).
g. Tissue examined in these animals only based upon macroscopic observation of enlarged axillary lymph node(s).
* = Statistically significant difference from control group ($p < 0.05$); ** = Statistically significant difference from control group ($p < 0.01$); -- = no noteworthy findings; F = female; M = male; NA = not applicable; NQ = not quantifiable (samples were BLQ)

2.6.7.7.1.2.2 13-Week Dermal Toxicity Study of DMVT-505 (tapinarof) in Rats [Report DMVT-505-9003]

Report Title:	**A 13-Week Dermal Toxicity Study of DMVT-505 (Tapinarof) in Rats**				
Species/Strain:	Rat/Wistar Han	**Duration of Dosing:**	91 days, QD	**Test Article (Batch No.):**	tapinarof ([redacted])
Initial Age at First Dose:	7 weeks	**Duration of Postdose:**	None	**Report No.**	DMVT-505-9003
Date of First Dose:	[redacted] 20[redacted]	**Method of Administration:**	Topical	**Location in CTD:**	4.2.3.2-7
Vehicle/Formulation:	DMVT-505 Placebo - Propylene glycol, Diethylene glycol monoethyl ether, Polysorbate 80, Medium chain triglycerides, Non-ionic emulsifying wax, Polyoxyl stearyl ether-2, Polyoxyl stearyl ether-20, Benzoic acid, Butylated hydroxytoluene, Sodium citrate, Citric acid monohydrate, Edetate disodium, and Purified water (Cream, Formulation F)			**GLP Compliance:**	Yes
Special Features: None					
No Observed Adverse Effect Level: 3% DMVT-505 Cream, Formulation F					

Daily Dose (%)	**0 (Control)**		**0.5**		**1.5**		**3**	
Sex	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
No. of Animals								
Toxicology	12	12	12	12	12	12	12	12
Toxicokinetics	3	3	6	6	6	6	6	6
Toxicokinetics								
DMVT-505								
AUC_{0-24} (pg.hr/mL)								
Day 1	BLLOQ	BLLOQ	1360 ± 1010	2090 ± 694	9990 ± 1090	8580 ± 1650	19700 ± 1390	22300 ± 1580
Day 29	BLLOQ	BLLOQ	776 ± 338	2100 ± 1250	7400 ± 1060	9060 ± 1250	14800 ± 3100	15800 ± 4290
Day 91	BLLOQ	BLLOQ	3720 ± 3040	985 ± 485	7610 ± 1580	3710 ± 396	11300 ± 1250	10600 ± 247
C_{max} (pg/mL)								
Day 1	BLLOQ	BLLOQ	227 ± 60.8	258 ± 30.7	1230 ± 639	817 ± 159	1940 ± 382	1930 ± 453
Day 29	BLLOQ	BLLOQ	198 ± 37.5	341 ± 151	595 ± 66.3	584 ± 99.3	799 ± 262	993 ± 470
Day 91	BLLOQ	BLLOQ	317 ± 317	190 ± 84.7	1800 ± 526	470 ± 210	1510 ± 399	983 ± 290
DMVT-505 Sulfate								
AUC_{0-24} (pg.hr/mL)								
Day 1	BLLOQ	BLLOQ	NP	NP	NP	NP	NP	NP
Day 29	BLLOQ	BLLOQ	NP	NP	NP	NR	NR	NP
Day 91	BLLOQ	BLLOQ	NP	NP	NR	NR	548 ± 130	NR
C_{max} (pg/mL)								
Day 1	BLLOQ	BLLOQ	NP	NP	NP	NP	NP	NP

Daily Dose (%)	0 (Control)		0.5		1.5		3	
Sex	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Day 29	BLLOQ	BLLOQ	NP	NP	NP	64.7 ± 64.7	19.1 ± 9.88	NP
Day 91	BLLOQ	BLLOQ	NP	NP	15.2 ± 15.2	7.17 ± 7.17	47.4 ± 8.26	17.2 ± 17.2
Noteworthy Findings:								
Died or Euthanized Moribund[a]								
Toxicology	0	1	0	0	0	2	0	0
Toxicokinetics	0	0	1	0	1	0	0	0
Body Weight (%)	--	--	--	--	--	--	--	--
Food Consumption (%)[b,c]	25.17g	19.78g	-11.53**	-8.52	-17.27**	-13.23*	-11.81**	-12.59*
Clinical Observations	--	--	--	--	--	--	--	--
Dermal Scores	--	--	--	--	--	--	--	--
Ophthalmoscopy	--	--	--	--	--	--	--	--
Hematology	--	--	--	--	--	--	--	--
Coagulation	--	--	--	--	--	--	--	--
Clinical Chemistry	--	--	--	--	--	--	--	--
Urinalysis	--	--	--	--	--	--	--	--
Organ Weights (%)	--	--	--	--	--	--	--	--
Gross Pathology	--	--	--	--	--	--	--	--
Histopathology – Terminal (No. of animals)[d]	12	11	12	12	12	10	12	12
Liver								
Necrosis, hepatocellular	1	0	3	1	2	0	2	1
Minimal	1	0	3	1	2	0	2	1
Fibrosis	1	1	0	2	8	3	1	2
Minimal	1	1	0	2	8	3	1	2
Inflammation, mixed cell	1	1	3	4	4	2	0	2
Minimal	1	1	3	4	4	2	0	1
Mild	0	0	0	0	0	0	0	1
Pigmented macrophage	0	0	0	3	1	3	0	1
Minimal	0	0	0	3	1	2	0	1
Mild	0	0	0	0	0	1	0	0

a. No cause of death was evident grossly or microscopically for the 0% toxicity female and one of the 1.5% toxicity females. At necropsy, the body of the other 1.5% toxicity female was pale, there was dark fluid in the abdomen, and a mass microscopically identified as a large hematoma on the capsular surface of the liver was found. Collectively, these findings suggested that the cause of moribundity in this rat was exsanguination due to liver rupture. As there were no test article related clinical signs and these early deaths occurred in control and mid-dose animals with no early deaths in high-dose animals, these deaths were considered to be most likely related to the wrapping procedure. One 0.5% toxicokinetic male and one 1.5% toxicokinetic male were both euthanized moribund on Day 91; these deaths were attributed to complications arising from the blood collection procedure.
b. At end of dosing period. For controls, group means are shown. For other groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
c. Considered non-adverse due to the lack of correlation to changes in body weights.
d. Considered most likely to have been due to the wrapping procedure and not an effect of DMVT-505.
GLP = Good Laboratory Practice; BLLOQ = Below the lower limit of quantitation (< 100 pg/mL for DMVT-505 and < 20.0 pg/mL for DMVT-505 sulfate); NP = Due to DMVT-505 sulfate generally not quantifiable in plasma, TK analysis could not be performed; NR = Not reported because there were less than 3 quantifiable concentrations at consecutive time points; -- = no noteworthy findings; * = $p < 0.05$ Dunnett; ** = $p < 0.01$ Dunnett

2.6.7.7.1.3 Rabbit

2.6.7.7.1.3.1 28-Day Repeated Dose Dermal Toxicity Study of WBI-1001 in New Zealand Albino Rabbits[Report 20[redacted]N163815]

Report Title:	**28-Day Repeated Dose Dermal Toxicity Study of WBI-1001 in New Zealand Albino Rabbits**				
Species/ Strain:	NZW Rabbit	**Duration of Dosing:**	28 days	**Test Article (Batch No.):**	tapinarof ([redacted])
Initial Age:	10 weeks	**Duration of Postdose:**	NA	**Report No.**	20[redacted]N163815
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Dermal once daily, occluded for 6 hours; half of animals had abraded skin	**Location in CTD:**	4.2.3.2-10
Vehicle/Formulation:	Cream, Formulation A			**GLP Compliance:**	No
Special Features:					
No Observed Adver	Dermal assessment of dosing sitese **Effect Level:**	**1% tapinarof cream (Formulation A; 80 mg/kg/day)**			

Daily Dose (%)	**0**		**1**		**3**		**4**		**6**	
Daily Dose (mg/kg/day)	**0 (Control)**		**80**		**225[a]**		**320[a]**		**480**	
Number of Animals: Main	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**
TK	**M:2**	**F:2**	**M:4**	**F:4**	**M:4**	**F:4**	**M:0**	**F:0**	**M:4**	**F:4**
Toxicokinetics: AUC_{last} (ng.h/mL), Day 1	NQ	NQ	857	437	1790	2121	NA	NA	4305	3055
Toxicokinetics: AUC_{last} (ng.h/mL), Day 28	NQ	NQ	422	1888	1900	2026	9213	2362	3949	22,044
Toxicokinetics: C_{max} (ng/mL), Day 1	NQ	NQ	131.6	47.9	237.9	244.2	NA	NA	475.7	323.8
Toxicokinetics: C_{max} (ng/mL), Day 28	NQ	NQ	34.2	215.6	114.3	157.8	696.4	199.4	178.6	3499
Noteworthy Findings:	No noteworthy findings in food consumption or ophthalmoscopy									
Died or Sacrificed Moribund	0	0	0	1[b]	0	0	0	0	1[b]	0
Body Weight (Day 28)	2.8	2.8	0.93X	0.96X	0.89X*	0.93X	0.96X	0.93X	0.86X**	0.86X*
Dermal Observations (No. of Animals)										
Dryness	--	--	--	1	4	4	4	4	4	4
Loss of Elasticity	--	--	--	1	4	4	4	4	4	4
Erythema/Edema	--	--	--	1	4	4	4	4	4	4
Fissures	--	--	--	0	3	3	4	1	3	4
Hematology										
Hemoglobin (g/L)	130	131	123	125	131	119	122	122	119	112*
Platelets (10^9/L)	499	459	434	438	464	467	513	450	742*	649
White Blood Cells (10^9/L)	7.99	6.82	7.80	6.64	7.19	6.78	7.16	7.80	9.37	7.03
Neutrophils (10^9/L)	2.00	2.13	1.48	1.78	1.48	1.96	2.64	2.23	4.17	2.70
Coagulation										

Daily Dose (%)	**0**		**1**		**3**		**4**		**6**	
Daily Dose (mg/kg/day)	**0 (Control)**		**80**		**225[a]**		**320[a]**		**480**	
Number of Animals: Main	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**
TK	**M:2**	**F:2**	**M:4**	**F:4**	**M:4**	**F:4**	**M:0**	**F:0**	**M:4**	**F:4**
Fibrinogen (g/L)	3.80	2.74	3.39	3.06	3.48	3.32	4.99	2.80	4.41	6.07
Serum Chemistry										
ALT (u/L)	41	46	46	45	40	52	55	39	58	69
Bilirubin (µmol/L)	5.8	7.4	4.7	4.9	5.5	5.2	6.2	5.6	8.6	5.8
Triglycerides (mmol/L)	0.81	0.58	1.03	0.91	1.13	1.40	1.82	1.11	2.83*	3.03*
Cholesterol (mmol/L)	≤1.16	≤1.16	≤1.22	≤1.18	≤1.27	1.46	≤1.48	1.37	2.11	2.31
Globulin (g/L)	19	17	17	17	16*	16	18	15	19	20
Organ Weights[c]										
Liver										
Absolute	57 g	56 g	0.97X	1.13X	1.07X	1.04X	1.27X	1.17X	1.58X**	1.41X
Relative to Body Weight	2.082%	2.064%	1.03X	1.17X	1.20X	1.20X	1.36X	1.26X	1.87X**	1.75X**
Relative to Brain Weight	576%	558%	0.96X	1.24X	1.13X	1.08X	1.34X	1.19X	1.65X**	1.52X*
Histopathology										
Skin Application Site										
Epidermal Hyperplasia/ Hyperkeratosis										
Minimal	4	2	1	1	--	--	1	--	--	--
Mild	--	1	1	1	1	1	1	3	--	--
Moderate	--	--	--	--	3	3	1	1	2	3
Marked	--	--	--	--	--	--	1	--	2	1
Liver										
Necrosis/Inflammation, Multifocal										
Minimal	--	--	--	--	--	--	--	--	--	1
Mild	--	--	--	1	1	--	--	--	2	--
Moderate	--	--	--	--	--	--	--	--	--	1
Hepatocellular hypertrophy/ regeneration										
Minimal	--	--	--	1	--	2	--	3	--	--
Mild	--	--	--	--	2	1	--	--	4	3
Moderate	--	--	--	--	--	--	--	--	--	1
Cholangiolar proliferation, multifocal/ cholangitis										
Minimal	2	1	1	--	--	--	1	--	2	1
Mild	--	1	--	--	1	1	1	--	1	--
Moderate	--	--	--	--	--	--	--	--	--	1

Daily Dose (%)	0		1		3		4		6	
Daily Dose (mg/kg/day)	0 (Control)		80		225[a]		320[a]		480	
Number of Animals: Main	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
TK	M:2	F:2	M:4	F:4	M:4	F:4	M:0	F:0	M:4	F:4
Thymus[d]										
Cortical atrophy										
Minimal	--	--	NA	NA	NA	NA	NA	NA	--	1
Mild	--	--	NA	NA	NA	NA	NA	NA	1	0

a. Mid dose new batch group (cGMP production batch) and mid dose old batch group (non GMP production) were intended to be identical with the exception that the new batch was manufactured under cGMP conditions. These two groups were used for comparison purposes as the range finding study in rabbits which preceded this study was conducted on the old batch. However, the potency of the 4% cream (cGMP API), was only 70% of its intended potency (i.e., 3%).
b. Euthanized due to distress during blood collection procedure, not test article related.
c. For controls, group means are shown. For test article treated groups, change from control is shown. Statistical significance is based on actual data not change from control data.
d. Only examined in control and high dose, and only in 3 females given 480 mg/kg/day.
* Statistically significant difference when compared to the control group ($p < 0.05$); ** Statistically significant difference when compared to the control group ($p < 0.01$); -- = no noteworthy findings; F = female; M = male; NA = not applicable; NQ = not quantifiable [samples were below the lower limit of quantitation (LLOQ); < 2 ng/mL]

2.6.7.7.1.4 Minipig

2.6.7.7.1.4.1 28-Day Dermal Toxicity Study Followed by a 14-Day Recovery Period in the Göttingen Minipig [Report 20[redacted]N163816]

Report Title:	**A 28-Day Dermal Toxicity Study Followed by a 14-Day Recovery Period in the Göttingen Minipig**				
Species/ Strain:	Göttingen minipig	**Duration of Dosing:**	28 days	**Test Article:**	tapinarof
Initial Age:	3-4 months	**Duration of Postdose:**	14 days	**Report No.**	20[redacted]N163816
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Dermal once daily, occluded for 6 hours	**Location in CTD:**	4.2.3.2-13
Vehicle/Formulation:	Cream, Formulation B			**GLP Compliance:**	No
Special Features: Dermal assessment of dosing site; Electrocardiography					
No Observed Adverse Effect Level: 6% tapinarof cream (Formulation B; 87 mg/kg/day)					

Daily Dose (%)	**0**		**1.5**		**3**		**6**	
Daily Dose (mg/kg/day)	**0 (Control)**		**23**		**44**		**87**	
Number of Animals Main Recovery	**M:3 M:2**	**F:3 F:2**	**M:3 M:0**	**F:3 F:0**	**M:3 M:0**	**F:3 F:0**	**M:3 M:2**	**F:3 F:2**
Toxicokinetics: $AUC_{(last)}$ (ng.h/mL), Day 1	NC	3.82	NQ	0.98	NQ	NC	1.36	1.18
Toxicokinetics: $AUC_{(last)}$ (ng.h/mL), Day 28	3.71	87.35	11.10	6.38	33.55	30.78	91.83	75.56
Toxicokinetics: C_{max} (ng/mL), Day 1	NC	0.31	NQ	0.39	NQ	NC	0.54	0.42
Toxicokinetics: C_{max} (ng/mL), Day 28	0.58	6.06	1.06	1.23	3.84	2.98	6.79	3.76
Noteworthy Findings:	No test article-related findings in body weights, food consumption, ophthalmoscopy, electrocardiography, clinical pathology, organ weights, or macroscopic observations.							
Dermal Observations (No. of Findings)								
Reddening	--	--	--	--	--	--	Slight increase in incidence and frequency	
Erythema, Very Slight	1	--	1	1	2	2	2	4
Erythema, Slight	--	1	--	--	--	--	1	2
Erythema, Moderate	--	--	--	--	--	--	--	1
Desquamation, Moderate	--	--	--	--	--	--	--	1
Histopathology: Number Evaluated	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**
Skin, Epidermal Orthokeratotic Hyperkeratosis, Minimal	--	--	3	2	2	--	3	2
Post-dose Histopathology: Number Evaluated	**M:2**	**F:2**	**M:0**	**F:0**	**M:0**	**F:0**	**M:2**	**F:2**

Daily Dose (%)	0		1.5		3		6	
Daily Dose (mg/kg/day)	0 (Control)		23		44		87	
Number of Animals Main Recovery	M:3 M:2	F:3 F:2	M:3 M:0	F:3 F:0	M:3 M:0	F:3 F:0	M:3 M:2	F:3 F:2
Skin, Epidermal Orthokeratotic Hyperkeratosis, Minimal	--	--	NA	NA	NA	NA	2	1
Abscess	--	--	NA	NA	NA	NA	--	1

-- = no noteworthy findings; F = female; M = male; NA = not applicable, NC = not calculated; NQ = not quantifiable [samples were below the limit of quantitation (< 1.0 ng/mL)]

2.6.7.7.1.4.2 Toxicity Study by Dermal Administration to Göttingen Minipigs for 28 Days [Report 20[redacted]N167695]

Report Title:	**GSK2894512A: Toxicity Study by Dermal Administration to Göttingen Minipigs for 28 Days**							
Species/ Strain:	Göttingen minipig	**Duration of Dosing:**	28 days		**Test Article (Batch No.):**	tapinarof ([redacted])		
Initial Age:	approximately 4 months	**Duration of Postdose:**	NA		**Report No.**	20[redacted]N167695		
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Dermal once daily, semi-occluded for ~23 hours		**Location in CTD:**	4.2.3.2-14		
Vehicle/Formulation:	Cream, Formulation D				**GLP Compliance:**	No		
Special Features: Dermal assessment of dosing site; Electrocardiography Due to dose volume reduction from 2 to 1 mL/kg, doses of 17, 36, or 74 mg/kg/day were decreased by approximately 50% to 9, 18, or 37 mg/kg/day, respectively, starting on Day 15 (males), Day 14 (females) and Day 10 (a replacement control female).								
No Observed Adverse Effect Level: 4% tapinarof cream (Formulation D; 74/37 mg/kg/day)								
Daily Dose (%)	**0**		**1**		**2**		**4**	
Daily Dose (mg/kg/day)	**0**		**17/9**		**36/18**		**74/37**	
Number of Animals	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Day 1	NQ	NQ	0.847	6.22	4.02	3.87	11.4	18.0
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Day 28	NQ	NQ	2.18	3.98	4.06	9.54	11.5	41.0
Toxicokinetics: C_{max} (ng/mL), Day 1	NQ	NQ	0.329	1.65	0.468	0.906	1.34	4.00
Toxicokinetics: C_{max} (ng/mL), Day 28	NQ	NQ	0.451	0.328	0.508	1.48	1.35	4.02
Noteworthy Findings:	No test article-related findings in clinical observations, dermal observations, body weight, food consumption, ophthalmoscopy, electrocardiography, clinical pathology, organ weights, or macroscopic and microscopic observations							

F = female; M = male; NQ = not quantifiable [samples were below the limit of quantitation (< 0.1 ng/mL)]

2.6.7.7.1.4.3 28-Day Dermal Toxicity Study in Göttingen Minipigs [Report 20[redacted]N221246]

Report Title:	**GSK2894512A: A 28-Day Dermal Toxicity Study in Göttingen Minipigs**							
Species/ Strain:	Göttingen minipig	**Duration of Dosing:**	28 days		**Test Article (Batch No.):**	tapinarof ([redacted])		
Initial Age:	4 to 5 months	**Duration of Postdose:**	NA		**Report No.**	20[redacted]N221246		
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Dermal, twice daily, approximately 10 hours apart, semi-occluded for ~20 hours per day		**Location in CTD:**	4.2.3.2-15		
Vehicle/Formulation:	Cream, Formulation F				**GLP Compliance:**	Yes		
Special Features: Dermal assessment of dosing site; Electrocardiography; Quantitative skin analysis								
No Observed Adverse Effect Level: 3% tapinarof cream (Formulation F; 60 mg/kg/day)								
Daily Dose (%)	**0 (Control)**		**0.5**		**1**		**3**	
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**20**		**60**	
Number of Animals	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Day 1	NQ	NQ	NA	NR	NQ	NQ	NR	NR
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Day 28	NQ	NQ	NA	NR	NQ	NQ	NR	4.84
Toxicokinetics: C_{max} (ng/mL), Day 1	NQ	NQ	NA	NR	NQ	NQ	0.376	0.408
Toxicokinetics: C_{max} (ng/mL), Day 28	NQ	NQ	NA	0.395	NQ	NQ	0.845	0.830
Skin Concentration (Day 29, ng/g)								
Epidermis/Upper Epidermis	NA	NA	4830	2540	3950	2270	10,000	6530
Lower Dermis	NA	NA	166	NQ	615	305	3660	3.04
Noteworthy Findings:	No test article-related findings in clinical observations, dermal observations, body weight, food consumption, ophthalmoscopy, electrocardiography, clinical pathology, organ weights, or macroscopic and microscopic observations							

F = female; M = male; NA = not applicable; NQ = not quantifiable [samples were below the limit of quantitation (< 0.3 ng/mL for plasma and 0.25 ng/mL for skin)]; NR = not reportable due to limited data

2.6.7.7.1.4.4 13-Week Dermal Toxicity and Toxicokinetic Study with WBI 1001 in Minipigs with a 4-Week Recovery [Report 20[redacted]N163817]

Report Title:	**13-Week Dermal Toxicity and Toxicokinetic Study with WBI-1001 in Minipigs with a 4-Week Recovery**				
Species/ Strain:	Göttingen minipig	**Duration of Dosing:**	**13 weeks**	**Test Article (Batch No.):**	tapinarof ([redacted])
Initial Age:	4 to 5 months	**Duration of Postdose:**	**4 weeks**	**Report No.**	20[redacted]N163817
Date of First Dose:	[redacted]-[redacted]-20[redacted]	**Method of Administration:**	Dermal twice daily 6 hours apart, occluded for 6 hours	**Location in CTD:**	4.2.3.2-16
Vehicle/Formulation:	Cream, Formulation C			**GLP Compliance:**	No
Special Features: Dermal assessment of dosing site; Electrocardiography					
No Observed Adverse Effect Level: **4% tapinarof cream (Formulation C; 72-94 mg/kg/day)**					

Daily Dose (%)	**0**		**1**		**2**		**4**	
Daily Dose (mg/kg/day)	**0 (Control)**		**18-28**		**36-56**		**72-94**	
Number of Animals: Main	**M:5**	**F:5**	**M:5**	**F:5**	**M:5**	**F:5**	**M:5**	**F:5**
Recovery	**M:2**	**F:2**	**M:2**	**F:2**	**M:2**	**F:2**	**M:2**	**F:2**
Toxicokinetics: $AUC_{(0-24)}$ (ng.h/mL), Day 1	NQ	NQ	3.32	3.36	10.52	8.20	20.74	21.59
Toxicokinetics: $AUC_{(0-24)}$ (ng.h/mL), Day 28	NQ	NQ	21.31	25.10	53.36	38.26	216.76	196.11
Toxicokinetics: $AUC_{(0-24)}$ (ng.h/mL), Day 91	NQ	NQ	12.72	16.80	22.82	16.75	100.93	96.76
Toxicokinetics: C_{max} (ng/mL), Day 1	NQ	NQ	0.29	0.29	0.81	0.60	1.31	1.22
Toxicokinetics: C_{max} (ng/mL), Day 28	NQ	NQ	1.25	1.32	4.14	2.42	14.39	18.33
Toxicokinetics: C_{max} (ng/mL), Day 91	NQ	NQ	0.80	2.24	2.11	1.68	7.77	6.48
Noteworthy Findings:	No test article-related findings in clinical observations, dermal observations, body weight, food consumption, ophthalmoscopy, electrocardiography, clinical chemistry, organ weights, or macroscopic and microscopic observations							
Died or Sacrificed Moribund	0	0	0	0	0	0	0	1[a]
Hematology								
Neutrophils (E3/µL)								
Day 91	2.12	2.90	3.15	2.46	4.11*	4.28	4.34*	3.22
Recovery Day 32	3.66	1.73	2.15	2.60	2.64	3.96	3.30	4.74
Eosinophils (E3/µL)								
Day 91	0.12	0.36	0.11	0.17	0.09	0.13*	0.11	0.06*
Recovery Day 32	0.12	0.21	0.23	0.34	0.18	0.30	0.13	0.12
Monocytes (E3/µL)								
Day 91	0.32	0.46	0.34	0.35	0.29	0.36	0.29	0.20*
Recovery Day 32	0.35	0.24	0.32	0.51	0.45	0.49	0.52	0.37

Daily Dose (%)		0		1		2		4	
Daily Dose (mg/kg/day)		0 (Control)		18-28		36-56		72-94	
Number of Animals:	Main	M:5	F:5	M:5	F:5	M:5	F:5	M:5	F:5
	Recovery	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2

a. Clinical signs for this animal prior to death were limited to a single observation of vomitus on Day 43 and frequent observations of discolored skin at the dosing site. The cause of death was undetermined but due to the absence of clinical or pathological effects it was not considered test article-related.
* Statistically significant difference when compared to the control group ($p < 0.05$)
F = female; M = male; NQ = not quantifiable [samples were below the limit of quantitation (<0.1 ng/mL)]

2.6.7.7.1.4.5 A 13-Week Dermal Toxicity Study in Göttingen Minipigs [Report 20[redacted]N172520]

Report Title:	**A 13-Week Dermal Toxicity Study in Göttingen Minipigs**				
Species/ Strain:	Göttingen minipigs	**Duration of Dosing:**	13 weeks	**Test Article (Batch No.):**	tapinarof ([redacted])
Initial Age:	3 to 4 months	**Duration of Postdose:**	NA	**Report No.**	20[redacted]N172520
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Dermal, Groups 1, 2 and 3 once daily; Groups 4 and 5 twice daily ~10 hours apart; semi-occluded for ~23 hours	**Location in CTD:**	4.2.3.2-17
Vehicle/Formulation:	**Cream, Formulation E**			**GLP Compliance:**	Yes
Special Features: Electrocardiography					
No Observed Adverse Effect Level: 4% tapinarof cream (Formulation E; 76.2 mg/kg/day)					

Daily Dose (%)	**0 (Control)**		**0.1**		**1**		**2**		**4**	
Daily Dose (mg/kg/day)	**0 (Control)**		**0.9**		**9.7**		**38.4**		**76.2**	
Number of Animals	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Day 1	NQ	NQ	NR	NR	0.526	0.723	4.13	11.7	6.42	6.90
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Week 4	NQ	NQ	NR	NR	0.499	2.39	4.11	17.5	11.7	35.9
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Week 13	NQ	NQ	0.213	3.84	2.03	4.40	17.9	18.8	34.4	37.7
Toxicokinetics: C_{max} (ng/mL), Day 1	NQ	NQ	NQ	NQ	0.355	0.405	0.936	1.76	0.982	0.631
Toxicokinetics: C_{max} (ng/mL), Week 4	NQ	NQ	NQ	NQ	0.237	0.489	0.935	3.26	1.59	15.7
Toxicokinetics: C_{max} (ng/mL), Week 13	NQ	NQ	0.194	0.538	0.327	1.16	2.87	2.05	6.48	7.79
Noteworthy Findings:	No test article-related findings in clinical observations, dermal observations, body weight, food consumption, ophthalmoscopy, electrocardiography, clinical pathology, organ weights, or macroscopic and microscopic observations									

F = female; M = male; NQ = not quantifiable [samples were below the limit of quantitation (<0.1 ng/mL)]; NR = not reported due to insufficient data to calculate the parameter

2.6.7.7.1.4.6 Toxicity Study by Dermal Administration to Göttingen Minipigs for 9 Months Followed by a 1 Month Off Dose Period [Report 20[redacted]N299302]

Report Title:	**Toxicity Study by Dermal Administration to Göttingen Minipigs for 9 Months Followed by a 1-Month Off-Dose Period**							
Species/ Strain:	Göttingen minipigs	**Duration of Dosing:**	9 months (39 weeks)		**Test Article (Batch No.):**	tapinarof ([redacted])		
Initial Age:	4 to 5 months	**Duration of Postdose:**	1 month (4 weeks)		**Report No.**	20[redacted]N299302		
Date of First Dose:	[redacted]-20[redacted] (M) [redacted]-20[redacted] (F)	**Method of Administration:**	Dermal, twice daily, semi-occluded for ~20 hours		**Location in CTD:**	4.2.3.2-18		
Vehicle/Formulation:	Cream, Formulation F				**GLP Compliance:**	Yes		
Special Features: Electrocardiography								
No Observed Adverse Effect Level: 3% tapinarof cream (Formulation F; 60 mg/kg/day)								
Daily Dose (%)	**0**		**0.5**		**1**		**3**	
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**20**		**60**	
Number of Animals Main **Recovery**	**M:4** **M:2**	**F:4** **F:2**	**M:4** **M:0**	**F:4** **F:0**	**M:4** **M:0**	**F:4** **F:0**	**M:4** **M:2**	**F:4** **F:2**
Toxicokinetics: C_{max} (ng/mL), Week 5	NQ	NQ	0.130	0.0995	0.262	0.477	0.582	0.386
Toxicokinetics: C_{max} (ng/mL), Week 26	NQ	NQ	0.0976	0.116	0.911	0.137	0.366	0.366
Toxicokinetics: C_{max} (ng/mL), Week 39	NQ	NQ	0.106	0.182	0.224	0.267	0.455	0.964
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Week 5	NQ	NQ	1.01	0.328	2.61	2.27	6.80	4.65
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Week 26	NQ	NQ	0.558	1.26	5.70	1.43	4.44	3.78
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Week 39	NQ	NQ	0.436	1.21	1.65	1.84	4.65	5.61
Skin Concentration (ng/g)								
Terminal: Epidermis/Upper Dermis	NQ	NQ	10,000	14,500	57,200	54,400	110,000	44,300
Lower Dermis	NQ	NQ	110	516	667	874	367	362
Off-dose: Epidermis/Upper Dermis	NQ	NQ	NA	NA	NA	NA	84,700	99,500
Lower Dermis	NQ	NQ	NA	NA	NA	NA	215	154
Noteworthy Findings:	No test article-related findings in clinical observations, body weight, food consumption, ophthalmoscopy, electrocardiography, clinical pathology, organ weights, or macroscopic and microscopic observations							
Died or Sacrificed Moribund	0	0	0	0	0	0	0	1[a]

a. One female given 60 mg/kg/day was found dead soon after 1 hr post-dose TK bleed in Week 5 (Day 35). The cause of the death was considered incidental and related to the TK bleed procedure.

--= no noteworthy findings; F = female; M = male; NA = not applicable; NQ = not quantifiable [samples were below the limit of quantitation (< 0.04 ng/mL for plasma and < 1 ng/mL for skin)]

2.6.7.7.2 Subcutaneous Administration

2.6.7.7.2.1 Rat

2.6.7.7.2.1.1 4-Week Subcutaneous Toxicity Study and Bone Marrow Micronucleus Assay in Rats [Report 20[redacted]N166805]

Report Title:	**4-Week Subcutaneous Toxicity Study and Bone Marrow Micronucleus Assay in Rats**				
Species/Strain:	Rat/Wistar Han	**Duration of Dosing:**	4 weeks	**Test Article (Batch No):**	tapinarof ([redacted])
Initial Age:	8 weeks	**Duration of Postdose:**	NA	**Report No.**	20[redacted]N166805
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Subcutaneous injection, once daily	**Location in CTD:**	4.2.3.2-22
Vehicle/Formulation:	30% Captisol® /Solution			**GLP Compliance:**	Yes
Special Features: Bone marrow micronucleus assessment (see results in 2.6.7.9.2)					
No Observed Adverse Effect Level: 30 mg/kg/day					

Daily Dose (mg/kg/day)	**0 (Control)**		**1**		**6**		**30**	
Number of Animals: Main TK	**M:10 M:3**	**F:10 F:3**	**M:10 M:3**	**F:10 F:3**	**M:10 M:3**	**F:10 F:3**	**M:10 M:3**	**F:10 F:3**
Toxicokinetics: C_{max} (ng/mL), Day 1	NA	NA	48.8	19.2	203	155	1160	872
Toxicokinetics: C_{max} (ng/mL), Day 28	NA	NA	27.5	24.4	278	132	1100	673
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Day 1	NA	NA	71.1	44.8	461	413	3500	2610
Toxicokinetics: $AUC_{(0-t)}$ (ng.h/mL), Day 28	NA	NA	54.4	48.0	543	358	3060	2140
Noteworthy Findings:	No noteworthy findings observed in body weight, food consumption, ophthalmoscopy, coagulation, clinical chemistry, or macroscopic observations							
Clinical Observations	Beginning as early as Day 5, slight scabbing was noted at the dose sites of males given 1 mg/kg/day and females given 1 or 6 mg/kg/day. Slight to moderate scabbing at the dose sites was noted at a higher incidence in males and females given 30 mg/kg/day.							
Hematology								
Hemoglobin (g/L)	153.7	146.9	155.1	144.9	151.9	141.2**	146.7**	140.6**
Red blood cell distribution width (%)	10.63	10.63	10.47	10.65	11.02	10.55	11.36**	10.94
Reticulocytes ($x10^9$/L)	201.64	201.43	188.56	231.78	221.15	205.53	242.02**	241.24**
White blood cell count ($x10^9$/L)	5.794	4.305	6.087	3.942	7.543**	4.625	7.561*	5.363
Neutrophil count ($x10^9$/L)	0.916	0.621	0.914	0.567	1.205*	0.594	1.357**	0.734
Lymphocyte count ($x10^9$/L)	4.556	3.486	4.898	3.185	6.003*	3.825	5.849*	4.400*
Eosinophil count ($x10^9$/L)	0.098	0.067	0.068	0.059	0.089	0.048*	0.060**	0.041*

Daily Dose (mg/kg/day)	0 (Control)		1		6		30	
Number of Animals: Main TK	**M:10 M:3**	**F:10 F:3**	**M:10 M:3**	**F:10 F:3**	**M:10 M:3**	**F:10 F:3**	**M:10 M:3**	**F:10 F:3**
Basophil count (x10^9/L)	0.010	0.007	0.012	0.005	0.018*	0.006	0.014*	0.011
Large unstained cell count (x10^9/L)	0.016	0.014	0.016	0.010	0.025	0.014	0.038**	0.027
Urinalysis								
Volume (mL)	15.30	17.50	11.25	11.25	14.05	14.90	25.90**	19.20
pH	5.95	6.20	5.90	5.85	6.00	5.90	6.50**	6.40
Specific gravity	1.0145	1.0115	1.0203	1.0183	1.0181	1.0130	1.0094*	1.0109
Organ Weights[a]								
Liver								
Absolute	7.9455 g	5.8037 g	0.95X	0.96X	1.00X	1.06X	1.08X	1.13X**
Relative	2.659%	2.849%	0.97X	0.99X	1.03X	1.04X*	1.09X**	1.13X**
Thymus								
Absolute	0.3865 g	0.4314 g	1.08X	0.97X	0.89X	0.92X	0.88X	0.82X*
Relative	0.130%	0.212%	1.11X	1.00X	0.92X	0.91X	0.89X	0.82X*
Histopathology								
Injection Site								
Degeneration/Necrosis; Panniculus Muscle								
Minimal	4	4	3	6	3	4	2	3
Mild	--	--	--	--	--	--	1	3
Moderate	--	--	--	--	--	--	--	1
Exudate; Epidermis; Serocellular								
Minimal	--	1	--	4	--	2	--	1
Mild	--	--	--	--	--	--	2	--
Moderate	--	--	--	--	--	--	2	--
Hemorrhage/Edema; Subcutis								
Minimal	2	8	--	3	3	1	--	--
Mild	7	--	10	5	6	9	1	4
Moderate	1	--	--	2	1	--	9	6
Hyperplasia; Epidermis								
Minimal	1	2	--	2	--	1	2	2
Mild	--	--	--	--	--	1	2	1
Moderate	--	--	--	--	--	--	2	--

Daily Dose (mg/kg/day)	0 (Control)		1		6		30	
Number of Animals: Main TK	**M:10 M:3**	**F:10 F:3**	**M:10 M:3**	**F:10 F:3**	**M:10 M:3**	**F:10 F:3**	**M:10 M:3**	**F:10 F:3**
Inflammatory Cell Infiltrate; Dermis; Mixed Cell								
Minimal	1	--	--	--	--	--	2	3
Mild	--	--	--	--	--	--	1	--
Inflammatory Cell Infiltrate; Subcutis								
Minimal	1	7	--	2	--	--	--	--
Mild	9	3	9	8	7	10	1	6
Moderate	--	--	1	--	3	--	7	4
Marked	--	--	--	--	--	--	2	--
Ulcer, Epidermis								
Minimal	--	--	--	--	--	1	--	2
Mild	--	--	--	--	--	--	1	2

a. For controls, group means are shown for absolute and/or relative weights. For test article treated groups, change from control is shown. Statistical significance is based on actual data not change from control data.
* = Statistically significant difference from control group ($p < 0.05$); ** = Statistically significant difference from control group ($p < 0.01$); -- = no noteworthy findings; F = female; M = male; NA = not applicable

2.6.7.7.2.1.2 13-Week Subcutaneous Injection Toxicity and Toxicokinetic Study with WBI-1001 in Rats with a 4-Week Recovery Phase [Report 20[redacted]N163820]

Report Title:	**13-Week Subcutaneous Injection Toxicity and Toxicokinetic Study with GSK2894512A in Rats with a 4-Week Recovery Phase**				
Species/ Strain:	Sprague Dawley rat	**Duration of Dosing:**	13 weeks	**Test Article (Batch No.):**	tapinarof ([redacted])
Initial Age:	6-8 weeks	**Duration of Postdose:**	4 weeks	**Report No.**	20[redacted]N163820
Date of First Dose:	[redacted]-[redacted]-20[redacted]	**Method of Administration:**	Subcutaneous injection, once daily	**Location in CTD:**	4.2.3.2-23
Vehicle/Formulation:	Propylene glycol /Solution			**GLP Compliance:**	No
Special Features: Anti-keyhole limpet hemocyanin IgM and IgG					
No Observed Adverse Effect Level: **not established** due to dermal lesions observed in all groups including control animals					

Daily Dose (mg/kg/day)	**0 (Control)**		**3**		**10**		**40**	
Number of Animals **Main** **Recovery** **TK**	**M:10** **M:5** **M:3**	**F:10** **F:5** **F:3**	**M:10** **M:0** **M:9**	**F:10** **F:0** **F:9**	**M:10** **M:5** **M:9**	**F:10** **F:5** **F:9**	**M:10** **M:5** **M:9**	**F:10** **F:5** **F:9**
Toxicokinetics: C_{max} (ng/mL), Day 1	NQ	NQ	73.77	65.42	213.90	145.59	225.94	382.36
Toxicokinetics: C_{max} (ng/mL), Day 14	NQ	NQ	49.25	25.66	117.05	116.00	190.19	148.92
Toxicokinetics: C_{max} (ng/mL), Day 91	NQ	NQ	30.56	32.71	71.39	83.59	295.74	264.29
Toxicokinetics: AUC_{0-t} (ng.h/mL), Day 1	NQ	NQ	189.77	183.82	550.42	642.31	1608.83	2447.42
Toxicokinetics: AUC_{0-t} (ng.h/mL), Day 14	NQ	NQ	93.21	95.45	345.36	375.35	1813.73	1561.29
Toxicokinetics: AUC_{0-t} (ng.h/mL), Day 91	NQ	NQ	103.67	94.36	334.80	299.51	2453.44	2209.20
Noteworthy Findings:	No noteworthy findings observed in ophthalmoscopy							
Died or Sacrificed Moribund	--	--	--	--	1[a]	--	4[a,b,c]	2[b]
Body Weight Change (g)								
Days 1-92	227	106	234	100	202*	101	204*	93*
Day 92-Recovery Day 28	7	6	NA	NA	10	2	21	11
Clinical Observations	Adverse, dose-dependent, test article-related clinical signs of the skin/pelage included swelling, discolored skin (red, black, or white), firmness, and/or scabs or sores associated with dose administration sites. A lower incidence of dermal lesions noted in control groups indicated additional vehicle control article effects. Dermal lesions partially reversed during the recovery phase.							

Daily Dose (mg/kg/day)	0 (Control)		3		10		40	
Number of Animals **Main** **Recovery** **TK**	**M:10** **M:5** **M:3**	**F:10** **F:5** **F:3**	**M:10** **M:0** **M:9**	**F:10** **F:0** **F:9**	**M:10** **M:5** **M:9**	**F:10** **F:5** **F:9**	**M:10** **M:5** **M:9**	**F:10** **F:5** **F:9**
Hematology								
Red blood cell count (E6/μL)								
Day 93	9.28	8.67	9.27	8.49	9.28	8.44	8.70*	8.21*
Recovery Day 29	9.32	8.58	NA	NA	9.16	8.18	9.21	7.94*
Hemoglobin (g/dL)								
Day 93	16.0	16.1	16.1	15.7	15.9	15.5*	15.0*	14.4*
Recovery Day 29	15.9	15.5	NA	NA	15.8	15.2	16.1	14.9
Hematocrit (%)								
Day 93	51.0	50.5	50.9	49.5	51.6	49.1	49.0	46.2*
Recovery Day 29	52.1	49.8	NA	NA	51.6	48.1	53.6	46.9
Reticulocyte count (E3/μL)								
Day 93	249.2	227.3	259.5	252.1	298.4*	274.3	315.2*	320.0*
Recovery Day 29	196.0	186.2	NA	NA	211.4	179.2	245.2*	183.0
Mean cell volume (fL)								
Day 93	55.0	58.2	54.9	58.4	55.6	58.2	56.2	56.3*
Recovery Day 29	55.9	58.1	NA	NA	56.3	58.8	58.2*	59.0
White blood cell count (E3/μL)								
Day 93	8.46	5.58	9.43	6.33	8.46	6.53	10.75*	8.05*
Recovery Day 29	7.61	3.70	NA	NA	6.43	4.14	6.73	4.26
Neutrophil count (E3/μL)								
Day 93	2.22	0.91	2.11	1.27	2.03	1.06	3.72*	2.33*
Recovery Day 29	2.71	0.63	NA	NA	1.70	0.80	1.69	0.64
Eosinophil count (E3/μL)								
Day 93	0.14	0.16	0.08*	0.09	0.05*	0.05*	0.05*	0.05*
Recovery Day 29	0.11	0.08	NA	NA	0.07	0.08	0.10	0.05
Serum Chemistry								
Albumin (g/dL)								
Day 93	4.2	4.7	4.1	4.5	4.2	4.7	4.0	4.3*
Recovery Day 29	4.5	4.9	NA	NA	4.4	4.9	4.5	4.7
Albumin:globulin ratio								
Day 93	1.5	2.0	1.4	1.9	1.5	1.9	1.4*	1.6*
Recovery Day 29	1.6	2.2	NA	NA	1.6	2.1	1.7	2.1

Daily Dose (mg/kg/day)	0 (Control)		3		10		40	
Number of Animals **Main** **Recovery** **TK**	**M:10** **M:5** **M:3**	**F:10** **F:5** **F:3**	**M:10** **M:0** **M:9**	**F:10** **F:0** **F:9**	**M:10** **M:5** **M:9**	**F:10** **F:5** **F:9**	**M:10** **M:5** **M:9**	**F:10** **F:5** **F:9**
Cholesterol (mg/dL)								
Day 93	135	132	140	148	134	159*	157*	190*
Recovery Day 29	125	109	NA	NA	142	128	120	141
Anti-Keyhole Limpet Hemocyanin (KLH) Bioanalysis								
Interpolated titer anti-KLH IgM								
Day 71	278	621	494	437	114*	657	256	244
Recovery Day 21	372	762	NA	NA	513	987	933	409
Interpolated titer anti-KLH IgG								
Day 71	6918	9999	25,071*	27,221	16,437	48,951*	27,324*	46,328*
Recovery Day 28	12,994	9628	NA	NA	58,162*	83,912*	72,167*	92,491*
Organ Weights[d]								
Thymus – relative to brain weight								
Main	14.54%	13.31%	0.82X*	0.95X	0.69X*	0.77X*	0.47X*	0.53X*
Recovery	9.78%	11.30%	NA	NA	0.95X	0.86X	1.02X	0.81X
Liver – relative to brain weight								
Main	555.75%	354.60%	1.02X	1.08X	1.05X	1.12X*	1.18X*	1.38X*
Recovery	545.22%	332.40%	NA	NA	0.93X	1.10X	0.95X	1.07X
Lung – relative to brain weight								
Main	85.05%	78.05%	1.09X*	1.01X	1.13X*	1.06X	1.32X*	1.14X*
Recovery	85.90%	70.74%	NA	NA	0.99X	1.09X	1.03X	1.20X*
Heart – relative to brain weight								
Main	78.36%	59.93%	1.00X	1.02X	1.00X	1.00X	1.14X*	1.05X
Recovery	75.74%	51.83%	NA	NA	0.96X	1.10X	0.99X	1.11X
Spleen – relative to brain weight								
Main	45.86%	33.19%	1.04X	1.11X	1.03X	1.02X	1.15X	1.17X*
Recovery	41.73%	29.46%	NA	NA	0.93X	1.10X	1.00X	1.06X
Spleen – relative to body weight								
Main	0.22%	0.25%	1.05X	1.08X	1.09X	1.04X	1.18X*	1.16X*
Recovery	0.21%	0.23%	NA	NA	0.95X	1.04X	1.03X	1.00X

Daily Dose (mg/kg/day)	0 (Control)		3		10		40	
Number of Animals **Main**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**
Recovery	**M:5**	**F:5**	**M:0**	**F:0**	**M:5**	**F:5**	**M:5**	**F:5**
TK	**M:3**	**F:3**	**M:9**	**F:9**	**M:9**	**F:9**	**M:9**	**F:9**
Histopathology - Number Evaluated	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Thymus								
Depletion, lymphoid								
Minimal	--	--	--	--	3	2	4	7
Slight	--	--	--	--	--	--	4	2
Moderate	--	--	--	--	--	--	1	--
Injection sites (highest score/rat shown)								
Inflammation, chronic/chronic active								
Minimal	--	--	--	--	--	--	--	--
Moderate	--	1	1	1	2	1	--	--
Marked	10	7	7	5	8	6	5	--
Severe	--	2	2	3	--	3	5	10
Necrosis, subcutaneous tissue								
Minimal	--	1	--	1	1	1	--	--
Slight	2	--	2	2	2	1	1	--
Moderate	2	6	3	2	1	2	3	--
Marked	6	--	2	1	3	2	1	2
Severe	--	1	2	3	2	--	5	8
Degeneration/necrosis, panniculus muscle								
Minimal	--	--	--	2	1	1	1	--
Slight	2	--	1	--	--	--	--	--
Moderate	3	5	1	1	6	3	--	--
Marked	5	5	3	2	3	1	3	3
Severe	--	--	4	4	--	5	6	7
Acanthosis								
Minimal	1	--	--	--	1	--	1	--
Slight	4	8	6	7	6	7	2	4
Moderate	5	2	4	2	2	3	7	6
Erosion/ulcer								
Minimal	3	--	1	2	--	--	--	2
Slight	1	2	1	1	3	1	1	1

Daily Dose (mg/kg/day)	**0 (Control)**		**3**		**10**		**40**	
Number of Animals **Main** **Recovery** **TK**	**M:10** **M:5** **M:3**	**F:10** **F:5** **F:3**	**M:10** **M:0** **M:9**	**F:10** **F:0** **F:9**	**M:10** **M:5** **M:9**	**F:10** **F:5** **F:9**	**M:10** **M:5** **M:9**	**F:10** **F:5** **F:9**
Moderate	2	2	2	2	3	3	--	3
Marked	3	1	1	2	--	3	5	2
Severe	--	1	--	1	2	1	3	2
Exudate, epidermal surface								
Minimal	1	--	--	--	--	--	1	--
Slight	1	--	2	1	3	--	1	2
Moderate	3	7	3	5	3	3	1	2
Marked	4	1	4	3	2	6	6	2
Severe	1	1	1	--	2	1	1	4
Hemorrhage								
Minimal	1	2	2	3	2	2	3	1
Slight	5	2	3	4	5	5	6	3
Moderate	4	4	4	2	2	3	1	2
Marked	--	1	1	--	1	--	--	3
Severe	--	1	--	--	--	--	--	1
Pigment, brown								
Minimal	5	3	1	--	2	1	3	1
Moderate	--	--	--	--	--	1	--	--
Mineralization, present	--	--	1	--	--	1	5	1
Vesicle(s), intraepidermal								
Minimal	1	--	--	1	--	1	--	2
Slight	--	--	1	2	1	1	1	1
Moderate	1	--	--	--	--	--	2	--
Marked	--	--	1	--	--	--	--	
Postdose Evaluation: Number Evaluated	5	5	0	0	5	5	5	5
Thymus								
Depletion, lymphoid	--	--	--	--	--	--	--	--
Injection sites (highest score/rat shown)								
Inflammation, chronic/chronic active								
Minimal	1	2	NA	NA	--	1	1	--
Slight	4	3	NA	NA	--	--	--	5

Daily Dose (mg/kg/day)	0 (Control)		3		10		40	
Number of Animals **Main** **Recovery** **TK**	**M:10** **M:5** **M:3**	**F:10** **F:5** **F:3**	**M:10** **M:0** **M:9**	**F:10** **F:0** **F:9**	**M:10** **M:5** **M:9**	**F:10** **F:5** **F:9**	**M:10** **M:5** **M:9**	**F:10** **F:5** **F:9**
Moderate	--	--	NA	NA	--	--	4	--
Degeneration/necrosis, panniculus muscle	--	--	NA	NA	--	--	--	--
Acanthosis								
Minimal	3	2	NA	NA	--	--	2	2
Slight	--	1	NA	NA	--	1	1	2
Erosion/ulcer								
Minimal	--	--	NA	NA	--	--	--	1
Exudate, epidermal surface								
Minimal	1	1	NA	NA	--	--	--	1
Slight	--	--	NA	NA	--	1	--	2
Hemorrhage								
Minimal	--	2	NA	NA	--	--	4	--
Slight	--	--	NA	NA	--	--	1	1
Pigment, brown								
Minimal	2	2	NA	NA	--	--	1	3
Slight	--	--	NA	NA	--	--	3	1
Mineralization, present	1	--	NA	NA	--	--	3	2
Vesicle(s), intraepidermal								
Minimal	--	--	NA	NA	--	--	--	1

a. One male in this group was euthanized for reasons unrelated to the test article.
b. Two toxicity males and two toxicity females were sacrificed during the dosing phase for test article-related dermal lesions.
c. One male given 40 mg/kg/day was found dead on Day 38 of the dosing phase following clinical signs of hypoactivity and irregular respiration.
d. For controls, group means are shown for absolute and/or relative weights. For test article treated groups, change from control is shown. Statistical significance is based on actual data not change from control data.
* = Statistically significant difference from control group ($p < 0.05$); -- = no noteworthy findings; F = female; M = male; NA = not applicable; NQ = not quantifiable [samples were below the limit of quantitation (< 1 ng/mL)]

2.6.7.7.2.1.3 26-Week Subcutaneous Injection Toxicity Study in Rats Followed by a 6-Week Off Dose Period [Report 20[redacted]N254469]

Report Title:	**A Once-Daily 26-Week Subcutaneous Injection Toxicity Study in Rats Followed by a 6-Week Off-Dose Period**				
Species/ Strain:	Rat/Wistar Han	**Duration of Dosing:**	26 weeks	**Test Article (Batch No.):**	tapinarof ([redacted])
Initial Age:	7 weeks	**Duration of Postdose:**	6 weeks	**Report No.**	20[redacted]N254469
Date of First Dose:	[redacted]-[redacted]-20[redacted]	**Method of Administration:**	Subcutaneous injection, once daily	**Location in CTD:**	4.2.3.2-24
Vehicle/Formulation:	30% Captisol® /Solution			**GLP Compliance:**	Yes

Special Features: Immunophenotyping (total T lymphocytes, helper T lymphocytes, cytotoxic T lymphocytes, B lymphocytes, natural killer cells and viable T_{regs}; PBMCs: Th17 cells

No Observed Adverse Effect Level:
Based on the incidence and severity of the microscopic findings seen at the injection site of animals receiving 30 mg/kg/day (tapinarof-related necrosis, mineralization, acanthosis, and/or ulceration), as well as the occurrence of sarcomas and increases in leukocyte counts at 6 mg/kg/day, **the no observed adverse effect level (NOAEL) for local toxicity was considered to be 1 mg/kg/day.**
However, as no adverse tapinarof-related findings were observed systemically, **the systemic no observed adverse effect level (NOAEL) for this study was considered to be 30 mg/kg/day** (gender-averaged, composite, plasma tapinarof mean C_{max} of 1330 ng/mL and mean AUC_{0-t} of 3300 ng·h/mLat Week 26).

Daily Dose (mg/kg/day)		**0 (Control)**		**1**		**6**		**30**	
Number of Animals	**Main**	**M:12[a]**	**F:12**	**M:12**	**F:12**	**M:12**	**F:12**	**M:12**	**F:12**
	Recovery	**M:10**	**F:10**	**M:0**	**F:0**	**M:10**	**F:10**	**M:10[b]**	**F:10**
	TK	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**
C_{max} (ng/mL)									
	Week 13	NQ	NQ	61.2	38.9	267	297	876	1660
	Week 26	NQ	NQ	37.2	38.0	389	229	1270	1510
AUC_{0-t} (h*ng/mL)									
	Week 13	NQ	NQ	67.5	48.6	562	414	3300	2510
	Week 26	NQ	NQ	66.0	60.0	677	401	3830	2730
Noteworthy Findings:									
Died or Sacrificed Moribund		1[a]	0	0	0	0	0	1[b]	0
Clinical Observations		Skin scabbing, thin cover of the fur, swollen or reddened skin and/or fur staining (red or black) was observed at injection sites in both males and females in all groups, including controls, however there was a dose- related increase in incidence in skin scabbing and thin fur cover in rats given tapinarof.							

Daily Dose (mg/kg/day)		0 (Control)		1		6		30	
Number of Animals	Main	M:12[a]	F:12	M:12	F:12	M:12	F:12	M:12	F:12
	Recovery	M:10	F:10	M:0	F:0	M:10	F:10	M:10[b]	F:10
	TK	M:6	F:6	M:6	F:6	M:6	F:6	M:6	F:6
Hematology									
Neutrophils (10^9/L)									
	Week 4	1.15	0.74	1.05	0.79	1.27	0.91	1.45	1.17***
	Week 13	1.25	0.66	1.24	0.65	1.17	0.68	1.45	0.77
	Week 26	1.00	0.74	1.13	0.62	1.19	0.55*	1.73**	0.79
	Recovery	1.10	0.87	NA	NA	2.30	0.72	1.16	0.64
Monocytes (10^9/L)									
	Week 26	0.11	0.08	0.13	0.07	0.12	0.07	0.16**	0.08
	Recovery	0.12	0.12	NA	NA	0.28	0.13	0.14	0.10
Lymphocytes (10^9/L)									
	Week 4	7.27	4.79	7.66	5.27	7.26	5.84*	8.94*	6.24**
	Week 13	5.81	3.32	6.22	3.71	5.70	4.20	7.13*	4.14
	Week 26	4.19	2.85	4.65	2.90	4.74	2.88	5.13	3.72
	Recovery	4.04	2.80	NA	NA	3.99	2.74	4.17	2.45
WBC (10^9/L)									
	Week 4	8.83	5.72	9.12	6.28	8.92	6.99*	10.83*	7.64***
	Week 13	7.35	4.16	7.78	4.52	7.12	5.07	8.88*	5.12
	Week 26	5.42	3.77	6.06	3.67	6.18	3.57	7.14**	4.69
	Recovery	5.43	3.92	NA	NA	6.72	3.69	5.62	3.29
Hemoglobin (g/L)									
	Week 4	169	148	166	149	167	149	161***	148
	Week 13	160	147	162	147	157	147	154**	139*
	Week 26	165	157	166	156	159*	154	157***	150**
	Recovery	168	160	NA	NA	165	162	169	154
Hematocrit (%)									
	Week 4	48.0	44.3	46.9	43.9	47.7	44.6	45.7***	43.7
	Week 13	47.2	42.7	47.9	42.8	47.4	43.3	46.4	40.9
	Week 26	47.7	45.2	48.2	44.2	46.0*	44.7	45.5**	43.7
	Recovery	48.4	45.7	NA	NA	48.0	47.2	48.5	44.8
Reticulocytes (10^9/L)									
	Week 13	210.9	230.9	221.0	236.1	235.9	232.0	264.7***	236.4
	Week 26	189.6	167.5	201.4	181.9	218.2*	170.0	233.3***	186.3

Daily Dose (mg/kg/day)		0 (Control)		1		6		30	
Number of Animals	**Main**	**M:12[a]**	**F:12**	**M:12**	**F:12**	**M:12**	**F:12**	**M:12**	**F:12**
	Recovery	**M:10**	**F:10**	**M:0**	**F:0**	**M:10**	**F:10**	**M:10[b]**	**F:10**
	TK	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**
Recovery		166.0	155.7	NA	NA	200.5	132.1	162.4	155.4
Immunophenotyping		In males and females given 30 mg/kg/day, an increase in the total lymphocytes counts (1.28 to 1.37X) was observed which correlated with mild increases in the total T (1.27 to 1.43X), helper T (1.14 to 1.37X), cytotoxic T (1.54 to 1.64X) and regulatory T lymphocytes (up to 1.33X). Increases in B lymphocytes were observed in males dosed at 6 mg/kg/day (1.46 to 1.50X). Changes in total T, helper T, cytotoxic T, regulatory T and B lymphocytes returned to baseline following the off-dose period. A GSK2894512 dose dependent decrease in NK cells relative percentages (0.82- to 0.44- and 0.85- to 0.46-fold change, respectively) and absolute counts (0.83- to 0.49- and 0.71- to 0.52-fold change, respectively) was observed in males and females dosed at 1 mg/kg/day which were partially recovered following the off-dose period. The increase in Th17 cells was less pronounced following stimulation in males and females given 30 mg/kg/day than in the control group (0.68- and 0.63-fold change, respectively) and these values returned to baseline following the off-dose period.							
Organ Weights (%)[c]									
Thymus (absolute)									
Main		0.218g	0.223g	0.97X	0.91X	0.79X	0.85X	0.72X*	0.75X**
Recovery		0.204g	0.215g	NA	NA	1.01X	0.81X	0.86X	1.00X
Thymus (relative to BW)									
Main		0.052	0.093	0.96X	0.94X	0.84X	0.91X	0.77X*	0.80X*
Recovery		0.047	0.087	NA	NA	0.97X	0.84X	0.85X	1.07X
Gross Pathology (Main)									
Injection Site									
Thin haircoat		--	5	10	12	12	12	9	12
Scab		--	--	--	2	2	1	--	5
Accumulation of pale material		--	--	1	--	1	--	7	3
Thickening		--	--	--	--	--	--	1	2
Histopathology (Main)									
Injection Site									
Chronic Inflammation									
Mild		1	1	--	--	--	--	--	--
Moderate		10	11	12	12	12	12	6	10
Marked		--	--	--	--	--	--	6	2
Follicular Atrophy									
Minimal		--	--	--	--	1	--	--	--
Mild		11	11	7	5	6	6	9	4

Daily Dose (mg/kg/day)	0 (Control)		1		6		30	
Number of Animals **Main**	**M:12[a]**	**F:12**	**M:12**	**F:12**	**M:12**	**F:12**	**M:12**	**F:12**
Recovery	**M:10**	**F:10**	**M:0**	**F:0**	**M:10**	**F:10**	**M:10[b]**	**F:10**
TK	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**
Moderate	--	1	5	7	5	6	2	8
Marked	--	--	--	--	--	--	1	--
Necrosis								
Minimal	--	--	--	--	--	--	4	5
Mild	--	--	--	--	--	--	5	4
Moderate	--	--	--	--	--	--	2	2
Mineralization								
Minimal	--	--	--	--	--	--	1	1
Mild	--	--	--	--	--	--	5	3
Moderate	--	--	--	--	--	--	3	1
Marked	--	--	--	--	--	--	1	1
Acanthosis								
Minimal	--	--	--	2	1	--	--	--
Mild	--	--	--	--	--	--	--	6
Ulceration								
Minimal	--	1	--	2	1	--	--	1
Mild	--	--	--	--	--	--	--	2
Thymus								
Decreased Cellularity, Lymphoid								
Minimal	--	--	--	--	--	--	8	7
Mild	--	--	--	--	--	--	4	--
Liver								
Extramedullary Hematopoiesis								
Minimal	2	4	2	7	6	8	8	11
Spleen								
Increased Hematopoiesis								
Minimal	3	7	7	6	8	8	7	4
Mild	--	3	--	4	1	4	4	8
Postdose Evaluation: Number Evaluated	**10**	**10**	**NA**	**NA**	**10**	**10**	**10**	**10**
Gross Pathology (Recovery)								
Injection Site								

Daily Dose (mg/kg/day)	0 (Control)		1		6		30	
Number of Animals **Main**	**M:12[a]**	**F:12**	**M:12**	**F:12**	**M:12**	**F:12**	**M:12**	**F:12**
Recovery	**M:10**	**F:10**	**M:0**	**F:0**	**M:10**	**F:10**	**M:10[b]**	**F:10**
TK	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**
Accumulation of pale material	1	--	NA	NA	1	--	8	8
Mass	1[d]	--	NA	NA	--	--	--	--
Subcutis								
Mass	--	--	NA	NA	1	--	1[b]	--
Histopathology (Recovery)								
Injection Site								
Chronic Inflammation								
Mild	2	3	NA	NA	--	1	--	--
Moderate	8	7	NA	NA	10	9	8	4
Marked	--	--	NA	NA	--	--	1	6
Follicular Atrophy								
Minimal	--	1	NA	NA	3	1	4	1
Mild	--	--	NA	NA	--	1	--	2
Moderate	--	--	NA	NA	--	--	1	--
Mineralization								
Minimal	--	--	NA	NA	--	--	--	3
Mild	--	--	NA	NA	--	--	1	2
Moderate	--	--	NA	NA	--	--	2	1
Marked	--	--	NA	NA	--	--	3	1
Acanthosis								
Minimal	--	--	NA	NA	--	--	1	1
Fibrosarcoma	--	--	NA	NA	1	--	--	--
Fibrous histiocytoma, malignant	--	--	NA	NA	--	--	1[b]	--
Liver								
Extramedullary Hematopoiesis								
Minimal	--	4	NA	NA	1	--	1	2
Mild	--	--	NA	NA	--	--	1[b]	--
Spleen								
Increased Hematopoiesis								
Minimal	5	9	NA	NA	4	4	5	10
Mild	--	--	NA	NA	--	1	--	--

Daily Dose (mg/kg/day)		0 (Control)		1		6		30	
Number of Animals	**Main**	**M:12[a]**	**F:12**	**M:12**	**F:12**	**M:12**	**F:12**	**M:12**	**F:12**
	Recovery	**M:10**	**F:10**	**M:0**	**F:0**	**M:10**	**F:10**	**M:10[b]**	**F:10**
	TK	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**
	Moderate	--	--	NA	NA	1	--	1[b]	--

a. One male given vehicle control was euthanized following dosing on Day 16 due to a vertebral (cervical) fracture. The cause of death was accidental. Vehicle (Captisol®) related microscopic findings were also noted at the injection site (hemorrhage; inflammation) and in the kidney, urinary bladder and synovium (vacuolation) in this male.
b. One male given 30 mg/kg/day (recovery animal) was found dead on Day 219. The cause of death was attributed to a malignant fibrous histiocytoma noted at the injection site. This finding was considered to be secondary to the chronic subcutaneous inflammatory reaction which has been reported in rodents following prolonged repeated subcutaneous administration.
c. For controls, group means are shown for absolute and/or relative weights. For test article treated groups, change from control is shown. Statistical significance is based on actual data not change from control data.
d. A keratoacanthoma was present in the skin overlying the injection site in a control male and was considered an incidental finding
* = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$; -- = no noteworthy findings; F = female; M = male; NA = not applicable; NQ = not quantifiable [samples were below the limit of quantitation (< 0.3 ng/mL)]

2.6.7.8 Genotoxicity: *In Vitro*

2.6.7.8.1 Bacterial Reverse Mutation Test of WBI-1001 [Report 20[redacted]N163822]

Report Title:	**Bacterial Reverse Mutation Test of WBI-1001**				
Test for Induction of:	Reverse Mutation in bacterial cells	**No. of Independent Assays:**	2	**Test Article (Batch No.):**	tapinarof ([redacted])
Strains:	*S. Typhimurium* (TA98, TA100, TA1535, TA1537) and *E. coli* (WP2*uvrA)*	**No. of Replicate Plates**	3 treatment plates	**Report No.**	20[redacted]N163822
Metabolizing System:	Aroclor 1254-induced rat liver S9			**Location in CTD:**	4.2.3.3.1-1
Negative Control & Test Article Vehicle:	Dimethyl sulfoxide (DMSO)			**GLP Compliance:**	No
Positive Controls Vehicles:	Experiments without S9: aqueous sodium azide and methyl methanesulfonate; DMSO solutions of 2 nitrofluorene and 9-aminoacridine hydrochloride; Experiments with S9: benzo [α] pyrene and 2-aminoanthracene in DMSO and cyclophosphamide monohydrate in water				
Treatment:	48-72 hours in the presence and absence of S9 mix via pre-incubation and plate incorporation			**Date of Treatment:**	[redacted] 20[redacted]
Cytotoxic Effects:	**Reduction in background lawn and/or revertant colonies**				
Genotoxic Effects:	**Not Mutagenic**				

Metabolic Activation	**Test Article**	**Concentration (µg/ plate)**	**Pre-incubation & Plate Incorporation Assays Mean Number of Revertant Colonies per Plate**				
			TA100	**TA1535**	**TA1537**	**TA98**	**WP2*uvr*A (pKM101)**
Pre-incubation Without Activation	DMSO	100 µL/plate	124	20	12	32	17
	tapinarof	0.77	126	25	11	30	17
	tapinarof	2.3	119	20	15	24	18
	tapinarof	6.9	114	18	12	29	28
	tapinarof	21	125	21	10	29	20
	tapinarof	62	78	18	6	20	12
	tapinarof	190	NA	NA	NA	NA	0
	Methyl methanesulfonate	1	NA	NA	NA	NA	410
	Benzo(α)pyrene	5	NA	NA	NA	NA	NA
	2-nitrofluorene	5	NA	NA	NA	2415	NA
	Cyclophosphamide	100	NA	NA	NA	NA	NA
	Sodium azide	5	2505	2196	NA	NA	NA
	9-aminoacridine hydrochloride	100	NA	NA	4007	NA	NA

Metabolic Activation	Test Article	Concentration (µg/ plate)	Pre-incubation & Plate Incorporation Assays Mean Number of Revertant Colonies per Plate				
			TA100	TA1535	TA1537	TA98	WP2*uvr*A (pKM101)
Pre-incubation With Activation	DMSO	100 µL/plate	130	16	12	30	20
	tapinarof	0.77	127	11	17	28	NA
	tapinarof	2.3	126	13	14	33	20
	tapinarof	6.9	117	10	12	32	21
	tapinarof	21	130	13	13	34	25
	tapinarof	62	127	7	10	27	19
	tapinarof	190	NA	NA	NA	NA	12
	Benzo(α)pyrene	5	1159	NA	194	566	NA
	2-Aminoanthracene	100	NA	NA	NA	NA	180
	Cyclophosphamide	100	NA	216	NA	NA	NA
Plate Incorporation Without Activation	DMSO	100 µL/plate	157	24	8	33	23
	tapinarof	0.77	157	21	11	33	20
	tapinarof	2.3	155	22	7	39	20
	tapinarof	6.9	133	21	11	36	22
	tapinarof	21	128	24	10	40	19
	tapinarof	62	123	17	4	31	20
	tapinarof	190	NA	NA	NA	NA	15
	Methyl methanesulfonate	1	NA	NA	NA	NA	410
	Sodium azide	5	718	1895	NA	NA	NA
	9-Amino acridine	100	NA	NA	3030	NA	NA
	2-Nitrofluorene	5	NA	NA	NA	1920	NA
Plate Incorporation With Activation	DMSO	100 µL/plate	148	20	15	50	27
	tapinarof	0.77	134	16	15	44	NA
	tapinarof	2.3	133	11	17	42	22
	tapinarof	6.9	139	18	14	46	30
	tapinarof	21	153	14	14	37	21
	tapinarof	62	134	15	11	44	22
	tapinarof	190	NA	NA	NA	NA	19
	Benzo(α)pyrene	5	939	NA	122	442	NA
	2-Aminoanthracene	100	NA	NA	NA	NA	180
	Cyclophosphamide	100	NA	406	NA	NA	NA

DMS0 = dimethyl sulfoxide; NA = not applicable

2.6.7.8.2 Bacterial Reverse Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* [Report 20[redacted]N170816]

Report Title:	**Bacterial Reverse Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli***				
Test for Induction of:	Reverse Mutation in bacterial cells	**No. of Independent Assays:**	1	**Test Article (Batch No.):**	tapinarof ([redacted])
Strains:	*S. Typhimurium* and *E. coli*	**No. of Replicate Plates**	3 treatment plates (6 vehicle control plates, 3 positive control plates)	**Report No.**	20[redacted]N170816
Metabolizing System:	Phenobarbital/5,6-Benzoflavone induced rat liver S9-mix (final volume 500 µL S9-mix/plate)			**Location in CTD:**	4.2.3.3.1-2
Negative Control & Test Article Vehicle:	DMSO			**GLP Compliance:**	Yes
Positive Controls Vehicles:	DMSO				
Treatment:	Plate incorporation for 3 days in the presence and absence of S9-mix			**Date of Treatment:**	[redacted] 20[redacted]
Cytotoxic Effects:	**Reduction in background lawn and revertant colonies**				
Genotoxic Effects:	**Not Mutagenic**				

Metabolic Activation	**Test Article**	**Concentration (µg/ plate)**	**Plate Incorporation Test Mean Number of Revertant Colonies per Plate**				
			TA98	**TA100**	**TA1535**	**TA1537**	**WP2 *uvrA* (pKM101)**
Without Activation	DMSO	100 µL/plate	39.0	133.7	22.3	10.7	118.2
	tapinarof	5	37.0	132.3	22.0	9.7	119.3
	tapinarof	15	38.7	146.3	24.3	11.0	120.7
	tapinarof	50	34.7	132.7	26.3	9.7	126.3
	tapinarof	150	31.7	126.0	24.0	7.7	116.7
	tapinarof	500	6.7[a]	14.3[a]	4.0[a]	2.3[a]	41.0[a]
	tapinarof	1500	0.0[a]	0.0[a]	0.0[a]	0.0[a]	0.0[a]
	tapinarof	2500	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0[b]
	tapinarof	5000	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0[b]
	2-Nitrofluorene	2	481.3[c]	NA	NA	NA	NA
	Sodium azide	2	NA	1757.7[c]	1401.7[c]	NA	NA
	9-Aminoacridine	50	NA	NA	NA	1321.0[c]	NA
	4-Nitroquinoline-1-oxide	2	NA	NA	NA	NA	2610.0[c]
With Activation	DMSO	100 µL/plate	51.2	155.3	25.0	29.0	131.0
	tapinarof	5	47.0	166.0	23.7	27.3	159.7
	tapinarof	15	53.3	146.3	26.3	23.3	126.3

Metabolic Activation	Test Article	Concentration (µg/ plate)	Plate Incorporation Test Mean Number of Revertant Colonies per Plate				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* (pKM101)
	tapinarof	50	50.7	148.7	22.7	23.0	139.0
	tapinarof	150	40.0	134.7	20.0	22.3	113.3
	tapinarof	500	11.3[a]	26.0[a]	9.0[a]	5.7[a]	61.3[a]
	tapinarof	1500	0.0[a]	0.0[a]	0.0[a]	0.0[a]	0.0[a]
	tapinarof	2500	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0[b]
	tapinarof	5000	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0[b]
	Benzo(a)pyrene	5	361.0[c]	NA	NA	183.0[c]	NA
	Benzo(a)pyrene	10	496.0[c]	NA	NA	NA	NA
	2-Aminoanthracene	5	NA	2125.3[c]	389.3[c]	NA	NA
	2-Aminoanthracene	10	NA	NA	NA	NA	1022.0[c]
	2-Aminoanthracene	20	NA	NA	NA	NA	1383.7[c]

a. Toxicity.
b. Precipitation observed by eye on the test plates at the end of incubation.
c. Positive control induced an unequivocal increase in revertant numbers.
NA = not applicable

2.6.7.8.3 Chromosome Aberration Test of WBI-1001 in Cultured Chinese Hamster Ovary Cells [Report 20[redacted]N163824]

Report Title:	**Chromosome Aberration Test of WBI-1001 in Cultured Chinese Hamster Ovary Cells**		
Test for Induction of:	Chromosomal aberration	**Test Article (Batch No.):**	tapinarof ([redacted])
Strains:	WB_L	**Report No.**	20[redacted]N163824
Metabolizing System:	Phenobarbital, 5-6 Benzoflavone-induced rat liver S9-mix	**Location in CTD:**	4.2.3.3.1-3
Negative Control & Test Article Vehicle:	DMSO	**GLP Compliance:**	No
Positive Control:	Mitomycin C (-S9); Cyclophosphamide (+S9)		
Treatment:	Incorporation in the presence and absence of S9 mix Experiment 1: 0, 1.25, 2.5, 5, 10, 20 and 40 µg/mL with and without S9 for 3 hours Experiment 2a: 0, 0.625, 1.25, 2.5, 5, 10 and 20 µg/mL with S9 for 3 hours Experiment 2b: 0, 10, 12, 14, 16, 18 and 20 µg/mL with S9 for 3 hours Experiment 3: 0, 1.25, 2.5, 5, 10, 20 and 40 µg/mL without S9 for 18 hours	**Date of Treatment:**	[redacted]-20[redacted]
Cytotoxic Effects:	**Reduction in background lawn and revertant colonies**		
Genotoxic Effects:	**Tapinarof did not induce chromosome aberrations in cultured WB_L Chinese hamster ovary cells**		

Test Article	Concentration (µg/mL)	3 hr Treatment - S9-Mix		3 hr Treatment + S9-Mix		18 hr Treatment -S9-mix	
		Relative Cell Growth (%)	Relative Mitotic Index (%)	Relative Cell Growth (%)	Relative Mitotic Index (%)	Relative Cell Growth (%)	Relative Mitotic Index (%)
tapinarof	0[b]	100	100	100	100	100	100
tapinarof	0.625	NA	NA	87	95	NA	NA
tapinarof	1.25	72	95	111	92	94	101
tapinarof	2.5[b]	102	97	90	91	79	79
tapinarof	5[b]	107	100	99	82	72	47[d]
tapinarof	10[b]	70	73	70[c]	78	49	5
tapinarof	12	NA	NA	43	59	NA	NA
tapinarof	14[b]	NA	NA	11	8[d]	NA	NA
tapinarof	16	NA	NA	1	NC	NA	NA
tapinarof	18	NA	NA	0	NC	NA	NA
tapinarof	20[b]	49	47[d]	0	NC	37	0
tapinarof	40	14	0	NA	NA	6	0

a. In the absence of S9 mix, 0.5 μg/mL mitomycin c induced chromosome aberrations in 58% after 3 hrs of exposures and in 85% of cells after 18 hrs exposure. In the presence of S9 mix, 12.5 μg/mL cyclophosphamide induced chromosome aberrations in 39% of cells.
b. Analyzable exposure concentrations were: Experiment 1 – 0, 5, 10, and 20 μg/mL; Experiment 2 – 0, 2.5, 5, 10 and 14 μg/mL; Experiment 3 - 1.25, 2.5, and 5 μg/mL.
c. Experiment 2a relative cell growth was 90% and Experiment 2b relative growth was 50%.
d. A very low background level of chromosome aberration was observed in one culture at each of these tapinarof concentrations.
hr = hour; NA = not applicable; NC = not calculated

2.6.7.8.4 *In Vitro* Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus [Report 20[redacted]N173392]

Report Title:	***In Vitro* Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus**				
Test for Induction of:	Forward mutation at the TK^+ locus	**No. of Independent Assays:**	3	**Test Article (Batch No.):**	tapinarof ([redacted])
Cell Type:	L5178Y Mouse Lymphoma Cells			**Report No.**	20[redacted]N173392
Metabolizing System:	Phenobarbital/5,6-benzoflavoneinduced rat liver S9-mix. Final concentration of S9-fraction in cultures = 2% v/v			**Location in CTD:**	4.2.3.3.1-4
Negative Control & Test Article Vehicle:	DMSO	**Positive Controls Vehicles:**	DMSO	**GLP Compliance:**	Yes
Treatment:	3 hr treatment in the presence and absence of S9-mix; treatment for 24 hr in the absence of S9-mix			**Date of Treatment:**	[redacted] 20[redacted]
Cytotoxic Effects: Reduction in relative total growth					
Genotoxic Effects: Not genotoxic					

Test Article	Concentration (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 ($x10^{-6}$)
DMSO	0	100	67	100	88	100	83
tapinarof	5	NA	NA	NA	NA	105	78
tapinarof	10	NA	NA	NA	NA	72	87
tapinarof	15	NA	NA	NA	NA	38	81
tapinarof	20	96	76	103	65	26	101
tapinarof	30	NA	NA	NA	NA	14	97
tapinarof	40	54	79	68	75	NA	NA
tapinarof	60	31	58	46	80	NA	NA
tapinarof	80	19	78	NP	NP	NA	NA
tapinarof	100	NA	NA	17	87	NA	NA
Methyl methanesulphonate	10	NA	NA	78	602[a]	NA	NA
Methyl methanesulphonate	5	NA	NA	NA	NA	66	1060[a]
Benzoapyrene	1	106	604[a]	NA	NA	NA	NA

a. Positive control induced a clear unequivocal response.
hr = hour; NA = not applicable; NP = not plated.

2.6.7.9 Genotoxicity: *In Vivo*

2.6.7.9.1 *In Vivo* Mouse Micronucleus Test of WBI-1001 [Report 20[redacted]N163826]

Report Title:	***In Vivo* Mouse Micronucleus Test of WBI-1001**				
Test for Induction of:	Structural chromosomal damage and/or aneuploidy	**Treatment Schedule:**	Single dose (vehicle, test article, and positive control article)	**Test Article (Batch No.):**	tapinarof ([redacted])
Species/ Strain:	Mouse/Crl:CD-1™(ICR)	**Sampling Time:**	24, 36, and 48 h after dosing	**Report No.**	20[redacted]N163826
Age:	7 weeks	**Method of Administration:**	Intraperitoneal injection	**Location in CTD:**	4.2.3.3.2-1
Cells Evaluated:	Polychromatic erythrocytes (PCE)	**Vehicle/ Formulation:**	DMSO/solution	**GLP Compliance:**	No
No. of Cells Analyzed/Animal:	2000 PCE			**Date of Dosing:**	[redacted]-20[redacted]
Special Features:	A preliminary range-finding study was conducted prior to the main study to determine the maximum tolerated dose which was determined to be 31.3 mg/kg				
Toxic/Cytotoxic Effects:	**Range-finding study:** unscheduled deaths at doses ≥62.5 mg/kg; clinical signs included piloerection, passivity, tremors, and prostration. **Main study:** slight decreases in mean body weight in all test article-treated groups; passivity was observed in vehicle and test article-treated groups.				
Genotoxic Effects:	**Not genotoxic** – no interaction with mitotic spindle or evidence of clastogenicity				

Test Article	Dose (mg/kg)	No. of Animals	Group Mean MPCE[a]		
			24 Hours	36 Hours	48 Hours
DMSO	0	7	1.6	1.4	1.4
tapinarof	7.8	7	2.3	0.9	1.1
tapinarof	15.6	7	1.4	1.1	1.3
tapinarof	31.3	7	1.6	0.7	1.4
Cyclophosphamide[b]	40	7	130.0	122.0	107.0

a. Group mean micronucleated PCE (MPCE) per 2000 PCE analyzed.
b. Positive control

2.6.7.9.2 4-Week Subcutaneous Toxicity Study and Bone Marrow Micronucleus Assay in Rats [Report 20[redacted]N166805]

Report Title:	**4-Week Subcutaneous Toxicity Study and Bone Marrow Micronucleus Assay in Rats**				
Test for Induction of:	Structural chromosomal damage and/or aneuploidy	**Treatment Schedule:**	4 weeks of daily dosing	**Test Article (Batch No.):**	tapinarof ([redacted])
Species/ Strain:	Rat/Wistar Han	**Sampling Time:**	Day 28	**Report No.**	20[redacted]N166805
Age:	8 weeks	**Method of Administration:**	Subcutaneous injection	**Location in CTD:**	4.2.3.3.2-2
Cells Evaluated:	PCE	**Vehicle/Formulation:**	30% Captisol®	**GLP Compliance:**	Yes
No. of Cells Analyzed/Animal:	2000 PCE			**Date of Dosing:**	[redacted]-20[redacted]
Special Features:	Bone marrow micronucleus assay conducted as part of a repeat-dose toxicity study				
Toxic/Cytotoxic Effects:	**See results in 2.6.7.7.2.1.1**				
Genotoxic Effects:	**Not genotoxic**				
Evidence of Exposure:	**See results in 2.6.7.7.2.1.1**				

Test Article	Dose (mg/kg/day)	No. of Animals Analyzed	MPCE/2000 PCE[a, b]	% PCE[c]
Vehicle control	0	5M	2.55	42
tapinarof	1	5M	1.19	46
tapinarof	6	5M	1.78	49
tapinarof	30	5M	1.38	41

a. Group mean micronucleated polychromatic erythrocytes (MPCE) per 2000 PCE analyzed.
b. Cyclophosphamide positive control slides (prepared in a separate study) showed a clear, unequivocal response (group mean 42.31 MPCE/2000 PCE; group mean 37% PCE).
c. Proportion of PCE in total erythrocyte (i.e. polychromatic + normochromatic erythrocyte) count.
M = male; MCPE = micronucleated polychromatic erythrocyte; PCE = Polychromatic erythrocytes

2.6.7.10 Carcinogenicity

2.6.7.10.1 Dermal Administration

2.6.7.10.1.1 Mouse

2.6.7.10.1.1.1 Dermal Carcinogenicity Study in Mice [Report DMVT-505-9001]

Report Title:	**GSK2894512A: A 2-Year Dermal Carcinogenicity Study in the Mouse**				
Species/Strain: Mouse/Crl:	CD1(ICR) (CD-1)	**Duration of Dosing:**	98 weeks for females, 102 weeks for males	**Test Article (Batch No.):**	Tapinarof ([redacted]) [Cream Formulation F]
Initial Age at First Dose:	Approximately 7 weeks	**Method of Administration:**	Dermal	**Report No.:**	DMVT-505-9001
Date of First Dose:	[redacted] 20[redacted]	**Vehicle/Formulation:**	0% placebo/Cream	**Location in CTD:**	4.2.3.4.1-1
Treatment of Controls:	Untreated Control – no treatment (sham); Vehicle control (placebo) - tapinarof cream, Placebo			**GLP Compliance:**	Yes
Basis for High-Dose Selection:	Results from a preceding 13-week dermal study in which there was no evidence of test article-related dermal irritation at any formulation tested (0%, 0.5%, 1.5%, and 3%); 3% is the maximum feasible dose concentration based on physiochemical properties and stability of the formulation.				
Special Features:	Ophthalmology Exams				

Daily Dose: % (mg/kg/day)[a]	**0 (Untreated)**		**0 (Vehicle)**		**0.5 (22.3)**	**0.5 (26.5)**	**1.5 (64.6)**	**1.5 (74.3)**	**3 (133.5)**	**3 (159.7)**
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
No. of Animals at Start										
Carcinogenicity	60	60	60	60	60	60	60	60	60	60
Toxicokinetic	6	6	6	6	30	30	30	30	30	30
Toxicokinetics										
C_{max} (ng/mL) Day 28	NC	NC	NC	NC	23.6	19.1	97.9	57.8	110	281
C_{max} (ng/mL) Day 182	NC[b]	NC	NC	NC	3.66	31.9	31.6	46.2	66.4	95.7
AUC_{0-t} (ng·h/mL) Day 28	NC	NC	NC	NC	37.7	33.8	188	146	560	715
AUC_{0-t} (ng·h/mL) Day 182	NC[b]	NC	NC	NC	14.1	117	96.5	255	259	444
No. Died/Euthanized Moribund	24	30	29	40	37	37	45*	36	39*	39
No. of Survivors at Terminal Necropsy	36	30	31	20	23	23	15	24	21	21
Survival (%) at Terminal Necropsy	60.0	50.0	51.7	33.3	38.3	38.3	25.0	40.0	35.0	35.0

Daily Dose: % (mg/kg/day)[a]	0 (Untreated)		0 (Vehicle)		0.5 (22.3)	0.5 (26.5)	1.5 (64.6)	1.5 (74.3)	3 (133.5)	3 (159.7)
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Noteworthy Findings:										
Body Weight (%)	--	--	--	--	--	--	--	--	--	--
Food Consumption (%)	--	--	--	--	--	--	--	--	--	--
Clinical Observations[c]										
Red Skin	29/172	21/144	30/193	28/112	51/583	24/155	38/571	28/324	40/689	25/252
Skin lesions	2/3	2/6	4/19	4/5	12/49	5/13	15/64	6/53	22/100	9/63
Skin scabs	50/506	48/249	54/781	44/238	53/1059	35/280	52/1112	42/450	55/1096	35/407
Skin papules	1/36	2/25	9/150	6/73	4/70	11/170	7/104	12/189	6/48	11/115
Ophthalmology	--	--	--	--	--	--	--	--	--	-
Gross Pathology										
Treated Skin										
Scab	2	1	6	0	16	4	14	13	16	6
Mass	0	2	0	0	0	2	1	1	0	4
Untreated Inguinal Skin										
Scab	2	2	8	2	12	5	12	4	10	10
Histopathology - Neoplastic Lesions[d]										
Treated Skin										
Papilloma; squamous cell; benign	0	0	0	0	0	1	2	1	2	4 (59)
Untreated Inguinal Skin										
Papilloma; squamous cell; benign	0	0	0	1	1	1	0	2	1	0
Histopathology - Non-Neoplastic Lesions[d]										
Treated Skin										
Hyperplasia, epidermal	2	1	60	60	59	59	52	55	55	58 (59)
Minimal	2	0	57	60	48	55	41	46	41	54
Mild	0	1	3	0	11	4	11	9	13	4
Moderate	0	0	0	0	0	0	0	0	1	0
Inflammation, mixed cell	0	1	2	0	8	3	14	9	17	5 (59)
Minimal	0	1	1	0	2	1	3	3	5	0
Mild	0	0	1	0	6	2	11	6	12	5

Daily Dose: % (mg/kg/day)[a]	0 (Untreated)		0 (Vehicle)		0.5 (22.3)	0.5 (26.5)	1.5 (64.6)	1.5 (74.3)	3 (133.5)	3 (159.7)
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Erosion/ulcer	1	1	2	0	10	3	13	11	17	5 (59)
Minimal	1	0	0	0	1	0	0	4	2	0
Mild	0	1	1	0	3	2	3	3	7	1
Moderate	0	0	1	0	6	1	10	4	8	4
Crust; serocellular	2	1	4	0	13	4	14	11	18	5 (59)
Minimal	1	0	2	0	5	2	1	0	2	0
Mild	1	1	2	0	8	2	13	10	12	4
Moderate	0	0	0	0	0	0	0	1	4	1
Fibrosis; dermal	1	1	2	0	8	2	13	8	14	5 (59)
Minimal	1	1	1	0	3	2	5	3	4	3
Mild	0	0	1	0	5	0	8	5	10	2
Untreated Thigh/Hip Skin										
Hyperplasia, epidermal	0	0	5	7	8	7 (59)	4	7 (58)	8	11
Minimal	0	0	5	7	8	7	4	7	8	11
Histopathology - Non-Neoplastic Lesions[d] (Continued)										
Untreated Inguinal Skin										
Hyperplasia, epidermal	3	1	4	2	7	4	7	5	8 (59)	9
Minimal	1	0	1	0	1	0	2	2	1	3
Mild	2	1	3	2	6	4	5	3	7	6
Inflammation, mixed cell	0	2	2	3	8	3	7	4	8	7
Minimal	0	1	0	0	3	0	0	2	3	1
Mild	0	1	2	2	5	3	7	2	5	6
Moderate	0	0	0	1	0	0	0	0	0	0
Erosion/ulcer	1	2	3	2	9	5	7	4	9	8
Minimal	0	0	2	0	2	1	2	1	2	1
Mild	1	1	0	1	4	1	2	1	5	2
Moderate	0	1	1	1	3	3	3	2	2	5
Crust; serocellular	2	2	6	2	10	5	7	4	8	9
Minimal	0	0	3	0	2	2	0	1	1	1
Mild	2	2	3	2	6	1	5	3	6	8
Moderate	0	0	0	0	2	2	2	0	1	0
Fibrosis; dermal	1	2	1	2	8	3	4	3	5	6

Daily Dose: % (mg/kg/day)[a]	0 (Untreated)		0 (Vehicle)		0.5 (22.3)	0.5 (26.5)	1.5 (64.6)	1.5 (74.3)	3 (133.5)	3 (159.7)
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Minimal	1	1	1	1	6	0	3	1	2	5
Mild	0	1	0	1	2	3	1	2	3	1
Histopathology - Non-Neoplastic Lesions[d] (Continued)										
Bone Marrow										
Increased myeloid to erythroid ratio	3	3	7	5	15	6	14	8	16	13
Minimal	3	3	3	5	4	2	0	1	5	2
Mild	0	0	4	0	11	4	14	7	11	11
Spleen										
Increased hematopoiesis	2	9 (59)	3	11	15	9	18	14	20	19
Minimal	1	2	2	2	2	2	2	3	3	2
Mild	1	7	1	9	13	7	16	10	17	17
Moderate	0	0	0	0	0	0	0	1	0	0
Lymph Node, Mandibular										
Plasmacytosis	0	1 (59)	1 (58)	2 (59)	5 (59)	3	5	5 (58)	6	8
Minimal	0	1	1	2	3	1	3	3	4	1
Mild	0	0	0	0	2	2	2	2	2	5
Moderate	0	0	0	0	0	0	0	0	0	2
Lymph Node, Mesenteric										
Plasmacytosis	0 (59)	1 (59)	0	1	3 (59)	1	4	3 (59)	1	4 (59)
Minimal	0	1	0	1	2	1	4	2	1	4
Mild	0	0	0	0	1	0	0	1	0	0

a. Calculated based on the average group mean body weights.
b. One sample on Day 182 had a tapinarof concentration of 1.06 ng/mL; however, there was insufficient sample volume remaining for reanalysis. The tapinarof concentration of all other untreated and control samples was not quantifiable.
c. Number of Animals Affected (incidence)/Number of Times Recorded (frequency). Clinical observations related to skin include both treated and untreated skin sites.
d. If the organ/tissue was not evaluated in all 60 animals/sex, the number in ( ) indicates the number of organs/tissues examined.
-- = no noteworthy findings; * = $p < 0.05$; GLP = Good Laboratory Practice; F = female; M = male; NC = not calculated.

2.6.7.10.2 Systemic Administration

2.6.7.10.2.1 Rat

2.6.7.10.2.1.1 Subcutaneous Injection Carcinogenicity Study in Rats [Report DMVT-505-9002]

Report Title:	**GSK2894512A: A 2-Year Carcinogenicity Study by Subcutaneous Injection in the Wistar-Han Rat**				
Species/Strain:	Rat/Wistar Han	**Duration of Dosing:**	60 weeks for males and 82/83 weeks for females	**Test Article (Batch No.):**	Tapinarof ([redacted])
Initial Age at First Dose:	Approximately 6 weeks	**Method of Administration:**	Subcutaneous Injection	**Report No.:**	DMVT-505-9002
Date of First Dose:	[redacted] 20[redacted]	**Vehicle/Formulation:**	30% (w/v) aqueous sulfobutyl ether 7-β-cyclodextrin (Captisol®) in sterile water for injection, final pH 7.2±0.5; changed to 10% (w/v) aqueous sulfobutyl ether 7-β-cyclodextrin (Captisol®) in sterile water for injection, final pH 7.2±0.5 beginning on Day 372	**Location in CTD:**	4.2.3.4.1-2
Treatment of Controls:	Saline Control; Vehicle Control [30% (w/v) Captisol®]			**GLP Compliance:**	Yes
Basis for High-Dose Selection:	Results from a preceding 26-week subcutaneous injection study at 0 (vehicle, 30% Captisol®), 1, 6, or 30 mg/kg/day in which the incidence and severity of the microscopic findings seen at the injection site of animals receiving 30 mg/kg/day (GSK2894512 related necrosis, mineralization, acanthosis, and/or ulceration), as well as the occurrence of sarcomas and increases in leukocyte counts at ≥ 6 mg/kg/day, the no observed adverse effect level (NOAEL) for local (injection site) toxicity was considered to be 1 mg/kg/day.				
Special Features:	Ophthalmology Exams				

Daily Dose: mg/kg/day	**0 (Saline)**		**0 (Vehicle)**		**0.1**		**0.3**		**1**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
No. of Animals at Start										
Carcinogenicity	60	60	60	60	60	60	60	60	60	60
Toxicokinetic	9	9	9	9	9	9/6[a]	9	9/6[a]	9	9/6[a]
Toxicokinetics										
30% Captisol®										
C_{max} (ng/mL) Day 28	NC	NC	NC	NC	2.98	2.08	10.1	8.05	31.9	30.4
C_{max} (ng/mL) Day 182	NC	NC	NC	NC	3.13	3.19	9.56	11.5	37.7	39.7
AUC_{0-t} (ng·h/mL) Day 28	NC	NC	NC	NC	3.83	2.52	14.0	9.46	49.3	39.8
AUC_{0-t} (ng·h/mL) Day 182	NC	NC	NC	NC	4.38	3.90	21.0	18.9	73.1	63.9
10% Captisol®										
C_{max} (ng/mL) Day 28	NA	NA	NA	NA	NA	2.11	NA	6.70	NA	35.6

Daily Dose: mg/kg/day	0 (Saline)		0 (Vehicle)		0.1		0.3		1	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
AUC_{0-t} (ng·h/mL) Day 28	NA	NA	NA	NA	NA	NC	NA	6.97	NA	37.4
No. Died/Euthanized Moribund	1	11	46	40	37	44	40	40	40	39
No. of Survivors at Terminal Necropsy	59	49	14	20	23	16	20	20	20	21
Survival (%) at Terminal Necropsy	98.3	81.7	23.3*	33.3*	38.3*	26.7*	33.3*	33.3*	33.3*	35.0*
Noteworthy Findings:										
Body Weight (%)	--	--	--	--	--	--	--	--	--	--
Food Consumption (%)	--	--	--	--	--	--	--	--	--	--
Clinical Observations	--	--	--	--	--	--	--	--	--	--
Ophthalmology	--	--	--	--	--	--	--	--	--	--
Gross Pathology[b]										
Injection Site 1										
Masses	0	0	15	5	13	8	14	4	10	7
Thick	0	0	2	4	1	1	5	3	9	4
Focus, dark	2	0	5	9	7	12	4	12	4	7
Injection Site 2										
Masses	0	0	19	21	15	24	21	23	24	19
Thick	0	0	0	1	2	0	2	2	6	0
Focus, dark	0	2	9	5	9	6	6	3	7	2
Injection Site 3										
Masses	0	0	11	5	13	3	8	3	11	6
Thick	0	0	2	6	1	1	5	3	8	1
Focus, dark	2	0	6	6	6	7	2	15	6	14
Injection Site 4										
Masses	0	0	7	15	9	16	11	11	16	14
Thick	0	0	4	3	1	1	3	2	9	0
Focus, dark	1	1	8	5	6	7	5	9	9	8
Kidney										
Discoloration, pale	0	0	8	4	6	3	4	4	3	1
Enlargement	0	0	19	1	18	2	18	2	20	2
Liver										
Enlargement	0	0	12	5	6	8	17	5	19	5
Spleen										
Enlargement	1	4	21	16	27	20	23	16	34	17
Histopathology - Neoplastic Lesions[b,c,d]										

Daily Dose: mg/kg/day	0 (Saline)		0 (Vehicle)		0.1		0.3		1	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Injection Site 1										
Fibrosarcoma, malignant	0	0	2	1	1	3	2	2	4	4
Pleomorphic Fibrosarcoma, malignant	0	0	14	3	14	5	11	3	8	5
Myxosarcoma, malignant	0	0	0	0	0	0	0	1	0	0
Fibroma, benign	0	0	0	0	0	1	0	0	0	0
Injection Site 2										
Fibrosarcoma, malignant	0	0	2	12	1	11	4	8	4	9
Pleomorphic Fibrosarcoma, malignant	0	0	18	6	15	13	15	14	18	9
Fibroma, benign	0	0	0	2	0	0	0	0	0	0
Injection Site 3										
Fibrosarcoma, malignant	0	0	2	3	1	3	0	1	0	3
Pleomorphic Fibrosarcoma, malignant	0	0	7	5	9	2	8	4	10	5
Myxosarcoma, malignant	0	0	0	0	1	0	0	0	0	0
Fibroma, benign	0	0	0	0	0	0	0	0	1	0
Injection Site 4										
Fibrosarcoma, malignant	0	0	3	5	1	13	1	11	3	9
Pleomorphic Fibrosarcoma, malignant	0	0	6	10	8	4	10	4	11	5
Myxosarcoma, malignant	0	0	0	0	0	2	0	0	0	0
Histopathology - Non-Neoplastic Lesions[b,c,e]										
Kidney										
Vacuolation, tubular	0	1	60	60	59	59	60	60	58	59
Minimal	0	0	2	7	2	5	3	3	1	0
Mild	0	0	13	16	17	14	16	14	11	25
Moderate	0	0	26	25	31	24	34	22	30	17
Marked	0	1	15	12	9	15	7	20	16	15
Severe	0	0	4	0	0	1	0	1	0	2
Dilation, tubular	4	0	20	54	19	26	9	29	31	51
Minimal	4	0	12	35	15	16	6	14	27	20
Mild	0	0	8	16	3	8	3	10	4	21
Moderate	0	0	0	3	1	2	0	5	0	10
Gland, parathyroid										
Vacuolation, cytoplasmic	0 (55)	0 (55)	16 (57)	56 (58)	7 (57)	56 (59)	7 (55)	49 (53)	13 (55)	56 (58)
Minimal	0	0	12	27	7	31	7	22	11	13
Mild	0	0	4	29	0	25	0	27	2	43

Daily Dose: mg/kg/day	0 (Saline)		0 (Vehicle)		0.1		0.3		1	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Gland, prostate										
Vacuolation, cytoplasmic	0	NA	4	NA	0	NA	0	NA	4	NA
Minimal	0	NA	4	NA	0	NA	0	NA	1	NA
Mild	0	NA	0	NA	0	NA	0	NA	3	NA
Injection Sites 1-4 combined										
Vacuolation, macrophages	0 (240)	0 (240)	165 (240)	185 (240)	187 (240)	177 (240)	203 (240)	187 (240)	87 (240)	185 (240)
Minimal	0	0	15	37	54	30	31	15	4	25
Mild	0	0	62	91	84	104	110	114	18	116
Moderate	0	0	72	57	49	39	56	56	50	40
Marked	0	0	15	0	0	4	6	2	14	4
Severe	0	0	1	0	0	0	0	0	1	0

a. Six additional females were added to the test article-treated groups for an additional toxicokinetic phase of animals dosed with 10% vehicle.
b. There were no effects on gross pathology or microscopic (neoplastic or non-neoplastic) changes attributed to tapinarof administration. Gross pathology and microscopic changes were considered vehicle-related.
c. If the organ/tissue was not evaluated in all 60 animals/sex, the number in ( ) indicates the number of organs/tissues examined.
d. In males, tumor incidence of fibromas, fibrosarcomas, pleomorphic fibrosarcomas, and myxosarcomas at all injection sites was 51/60 in vehicle control and 0/60 in saline control ($p < 0.0001$). In females, tumor incidence of fibromas, fibrosarcomas, pleomorphic fibrosarcomas, and myxosarcomas at all injection sites was 44/60 in vehicle control and 0/60 in saline control ($p < 0.0001$).
e. The cytoplasmic vacuolation is consistent with histologic findings reported for other cyclodextrin studies. As with injection site neoplasms, there were no meaningful differences in the incidence of non-neoplastic renal, parathyroid, or subcutaneous macrophage changes when the group administered cyclodextrin alone was compared with groups administered cyclodextrin combined with tapinarof.
-- = no noteworthy findings; * = $p < 0.0001$; F = female; GLP = Good Laboratory Practice; M = male; NA = not applicable; NC = not calculated.

2.6.7.11 Reproductive and Developmental Toxicity

2.6.7.11.1 Non-Pivotal Studies

Nonpivotal Studies					Test Article: tapinarof		
Type of Study	**Species/ Strain**	**Method of Administration (Vehicle/ Formulation)**	**Dosing Period**	**Doses (mg/kg/day)**	**No. per Group**	**Noteworthy Findings**	**Report Number/ Location in CTD**
Embryofetal Development Dose Range Finding	Rabbit (NZW)	Subcutaneous	Days 7 to 19 pc	0, 2, 4, 10, 30	2-4F	• Maternal toxicity (reduced food consumption, body weight loss, abortions) (≥4 mg/kg/day) • Embryolethality (10 mg/kg/day)	20[redacted]N178148/ 4.2.3.5.2-2
Juvenile Toxicity	Rat (WH)	Subcutaneous	PND 7 to 32	0, 0.7/1, 10/15, 20/30	16M/16F	• Body weight reduction (high dose) • Skin: dark foci at injection site (active groups) • Thymus: decreased weight (high dose, females); small (one high dose female) • Kidney: renal pelvis dilatation (0 and 10/15 mg/kg/day)	20[redacted]N182130/ 4.2.3.5.4-1
Juvenile Toxicity	Rat (WH)	Subcutaneous	PND 7 to 56	20/30	30M/30F	• Body weight: reduction (high dose) • Kidney: renal pelvis dilatation (active groups); hydronephrosis (active groups); renal tubule vacuolation (all groups) • Biomarker: increased urinary neutrophil gelatinase-associated lipocalin (PND 15-42 active groups) • Time of greatest sensitivity to kidney injury: PND 15 to 21 - the age of kidney development and renal tubule maturation/nephrogenesis in the rat	20[redacted]N278677/ 4.2.3.5.4-3

F = female; M = Male; NZW = New Zealand White [Crl:KBL(NZW)BR]; pc = post-coitum; PND = postnatal day; WH = Wistar Han [Crl:WI(Han)]

2.6.7.11.2 Reproductive and Developmental Toxicity: Fertility and Early Embryonic Development to Implantation (Pivotal)

2.6.7.11.2.1 Subcutaneous Female Fertility and Early Embryonic Development Study in Rats [Report 20[redacted]N211242]

Report Title:	**Subcutaneous Female Fertility and Early Embryonic Development Study in Rats**				
Design similar to ICH 4.1.1?	Yes	**Duration of Dosing:**	15 days before cohabitation, during cohabitation (maximum of 14 days), and continuing until Day 6 pc, inclusive	**Test Article (Batch No.):**	tapinarof ([redacted])
Species/ Strain:	Rat/Wistar Han	**Day of Mating:**	Day 0	**Report No.**	20[redacted]N211242
Initial Age:	~62 days	**Day of C-Section:**	Day 20 pc	**Location in CTD:**	4.2.3.5.1-1
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Subcutaneous injection	**GLP Compliance:**	Yes
Special Features:	None	**Vehicle/Formulation:**	30% Captisol®/ Solution		
No Observed Adverse Effect Level:		**F_0 Females: 30 mg/kg/day**			

Daily Dose (mg/kg/day)	**0 (Control)**	**1**	**6**	**30**
F0 Females:				
No. Animals/Group	22	22	22	22
No. Died or Euthanized Moribund	0	0	0	0
Clinical Observations (occasions/no. of animals)				
Precohabitation Period[a]				
Injection Site(s): Scab(s)	0/0	0/0	0/0	44/9
Sparse Hair Coat: Back	0/0	0/0	0/0	19/2
Back: Scab	0/0	0/0	0/0	7/2
Gestation Period				
Sparse Hair Coat: Back	0/0	22/2	106/7	297/19
Injection Site(s): Scab(s)	0/0	0/0	0/0	202/15
Body Weight[b]				
Premating Body Weight Gain (Day 1 to 4)	2.5 g	1.08X	0.56X	1.12X
Premating Body Weight Gain (Day 4 to 8)	1.6 g	0.88X	1.63X	1.06X
Premating Body Weight Gain (Day 8 to 15)	7.3 g	1.10X	1.22X	1.01X
Gestation Body Weight Gain (Day 0 to 3 pc)	12.7 g	0.94X	0.94X	0.88X
Gestation Body Weight Gain (Day 3 to 7 pc)	11.0 g	1.12X	1.07X	0.88X
Food Consumption[b]				
Premating Food Consumption (Day 1 to 8)	13.8 g	1.01X	1.01X	1.02X
Premating Food Consumption (Day 8 to 15)	14.2 g	1.00X	1.01X	0.99X
Gestation Food Consumption (Day 0 to 7 pc)	18.1 g	0.99X	0.99X	1.01X
Fertility Endpoints				

Daily Dose (mg/kg/day)	0 (Control)	1	6	30
Mean Frequency of Estrus/15 Days of Treatment	3.5	3.3	3.2	3.3
Mean No. Days Needed to Mate	3.4	2.6	2.7	2.4
Mating Index (%)[c]	100	100	100	100
Fertility Index (%)[d]	95.4	100	100	95.4
No. of Females Mated	22	22	22	22
No. of Pregnant Females	21	22	22	21
No. of Pregnant Females Evaluated	21	21[e]	22	21
Early Embryonic Development Endpoints				
Mean Gravid Uterine Weight[b]	59.91g	1.09X	1.10X	1.08X
Mean No. Corpora Lutea	13.2	13.8	13.5	13.7
Mean No. Implantations	10.7	12.1	12.6*[f]	12.3
Mean % Preimplantation Loss	20.4	12.3	6.7*[g]	10.6
Mean Total Postimplantation Loss - No. (%)	9.2	5.8	6.1	7.2
Mean No. Live Fetuses	10.1	11.4	11.8	11.3
% Live Males	46.0	53.6	52.4	50.0
Mean Fetal Body Weight (g) Males	3.78	3.69	3.72	3.79
Mean Fetal Body Weight (g) Females	3.56	3.59	3.50	3.56
External Fetal Malformations or Variations	--	--	--	--

a. Number of Animals Affected (incidence)/Number of Times Recorded (frequency).
b. For controls, group means are shown. For treated groups, change from controls is shown.
c. Mating index = (Number mated/Total number cohabited) x 100.
d. Fertility index = (Number pregnant/Number mated) x 100.
e. N = 21 for ovarian and uterine content parameters due to the exclusion of values for female 7952; this female had 9 conceptuses in the right uterine horn but only 8 corpora lutea apparent.
f. Not considered test article-related because it was within the range observed historically at the Test Facility and was not dose dependent.
g. Not considered test article related because it was within the range observed historically at the Test Facility, was not dose dependent, and reflected a value in the control group that was higher than the historical control range.
* = Statistical significance ($p \leq 0.05$) is based on raw data (not on the change from controls); -- = no noteworthy findings

2.6.7.11.3 Reproductive and Developmental Toxicity: Effects on Embryo-Fetal Development (Pivotal)

2.6.7.11.3.1 Rat

2.6.7.11.3.1.1 Subcutaneous Embryo Fetal Development Study in Rats [Report 20[redacted]N166695]

Report Title:	Subcutaneous Embryo-Fetal Development Study in Rats				
Design similar to ICH 4.1.3?	Yes	**Duration of Dosing:**	Days 6 through 17 pc	**Test Article (Batch No.):**	tapinarof ([redacted])
Species/ Strain:	Rat/Wistar Han	**Day of Mating:**	Day 0 pc	**Report No.**	20[redacted]N166695
Initial Age:	11 weeks	**Day of C-Section:**	Day 21 pc	**Location in CTD:**	4.2.3.5.2-1
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Subcutaneous injection	**GLP Compliance:**	Yes
Special Features:	None	**Vehicle/Formulation:**	30% Captisol®/ Solution		
No Observed Adverse Effect Level:		**F1 Litters: 6.9 mg/kg/day**			

Daily Dose (mg/kg/day)	**0 (Control)**	**1**	**6.9**	**34**
Dams:				
No. Animals per Group	**22**	**22**	**22**	**22**
No. Died or Sacrificed Moribund[a]	1	1	1	0
No. Pregnant	21	21	21	21
No. Aborted or with Total Resorption of Litter	0	0	0	0
No. Pregnant Evaluated[b]	20	20	20	21
Clinical Observations - Scabs	0	0	5	20
Necropsy Observations	--	--	--	--
Mean Body Weight Gain (Days 6 to 18 pc)[c]	70 g	1.01X	0.98X	1.01X
Mean Food Consumption (Days 6 to 18 pc)[c, d]	247 g	1.03X	0.99X	1.01X
Mean No. Corpora Lutea	12.2	11.6	11.2	11.4
Mean No. Implantations	10.9	10.6	10.3	10.8
Mean % Preimplantation Loss[e]	10.61%	7.19%	8.17%	5.79%
Mean Gravid Uterus Weight (g)	74.0[f]	70.7	69.0	71.5
Litters:				
No. Litters Evaluated	**20**	**20**	**20**	**21**
Mean No. Live Fetuses	10.0	9.7	9.5	10.2
Mean % Postimplantation Loss[g]	0.9 (8.86%)	1.0 (9.14%)	0.8 (9.22%)	0.5 (4.74%)
Mean Fetal Body Weight (g) - Males	5.58	5.54	5.58	5.35 *
Mean Fetal Body Weight (g) - Females	5.31	5.32	5.32	5.03 *
% Male Fetuses	55.08%	50.98%	56.05%	42.70%

Daily Dose (mg/kg/day)	0 (Control)	1	6.9	34
Fetal Anomalies: No. fetuses examined (No. litters examined)				
Gross External	200 (20)	193 (20)	189 (20)	215 (21)
	--	--	--	--
Visceral Anomalies	107 (20)	99 (20)	99 (20)	112 (21)
	--	--	--	--
Skeletal Anomalies	107 (20)	99 (20)	99 (20)	112 (21)
Skull, Incompletely Ossified Nasal – Variation Fetuses (Litters); Mean Litter %	0 (0); 0%	1 (1); 0.83%	0 (0); 0%	31 (7); 28.6% *

a. Includes total number of animals that naturally delivered and were subsequently euthanized.
b. Includes total number of pregnant animals that survived to scheduled cesarean section on Day 21 pc.
c. For controls, group means are shown. For treated groups, change from controls is shown.
d. Food consumption values for Days 6 18 pc were derived from the sum of the food consumption values for the Days 6-9, 9-12, 12-15 and 15-18 pc intervals.
e. Percent preimplantation loss = (Corpora Lutea - Implants)/Corpora Lutea X 100.
f. N = 19; 1 gravid uterus was inadvertently not weighed.
g. Percent total post implantation loss = (number early & late resorptions + dead fetuses) / Total number implantations X 100.
* = Statistical significance ($p \leq 0.05$) is based on raw data (not on the change from controls); -- = no noteworthy findings; pc = post-coitum

2.6.7.11.3.2 Rabbit

2.6.7.11.3.2.1 Subcutaneous Embryo Fetal Development Study in Female Rabbits [Report 20[redacted]N189059]

Report Title:	**Subcutaneous Embryo-Fetal Development Study in Female Rabbits**				
Design similar to ICH 4.1.3?	Yes	**Duration of Dosing:**	Days 7 to 19 pc	**Test Article (Batch No.):**	tapinarof ([redacted])
Species/ Strain:	New Zealand White rabbit	**Day of Mating:**	Day 0 pc	**Report No.**	20[redacted]N189059
Initial Age:	~5.5 months	**Day of C-Section:**	Day 29 pc	**Location in CTD:**	4.2.3.5.2-3
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Subcutaneous injection (2x daily ~ 6 hrs apart)	**GLP Compliance:**	Yes
Special Features:	TK	**Vehicle/Formulation:**	30% Captisol®/ Solution		
No Observed Adverse Effect Level:	**F1 Litters: 1 mg/kg/day**				

Daily Dose (mg/kg/day)	0 (Control)	0.3	1	3
Dams/Does:				
Toxicokinetics:				
C_{max} (ng/mL) – Day 11 pc	NC	5.65	122	56.8
AUC_{0-t} (h.ng/mL) – Day 11 pc	NC	16.5	128	239

Daily Dose (mg/kg/day)	0 (Control)	0.3	1	3
No. Animals/Group	**22**	**22**	**22**	**22**
No. Pregnant	**22**	**22**	**21**	**20**
No. Pregnant Evaluated	**21**	**21**	**20**	**19**
No. Died or Sacrificed Moribund	1	0	1	1
No. Aborted or Naturally Delivered	0	1	0	0
No. with Total Resorption of Litter	0	0	0	0
Clinical Observations	--	--	--	--
Necropsy Observations	--	--	--	--
Body Weight Gain (Day 7 to 10 pc)[a]	0.03 kg	0.67X	0.67X	0.00X
Body Weight Gain (Day 7 to 20 pc)[a]	0.16 kg	0.88X	1.00X	0.75X
Food Consumption (Day 7 to 20 pc)[a]	118.4 g/day	0.96X	1.00X	0.94X
Mean No. Corpora Lutea	9.8	9.2	12.4	10.0
Mean No. Implantations	9.0	8.5	9.5	9.3
Mean % Preimplantation Loss	8.1	7.5	14.8	7.0
Litters:				
No. Litters Evaluated[b]	21	21	20	19
Mean No. Live Fetuses	8.6	8.2	9.2	8.6
Mean % Postimplantation Loss	0.3 (3.8)	0.3 (3.9)	0.3 (3.2)	0.7 (8.0)
Mean Fetal Body Weight (g) - Males	41.69	42.41	40.95	40.32
Mean Fetal Body Weight (g) - Females	40.40	41.67	39.20	39.94
% Male Fetuses	47.7	43.4	49.9	41.3
Fetal Anomalies:				
Gross External	--	--	--	--
Visceral	--	--	--	--
Skeletal				
Skull – Interparietals, extra suture - Variation				
No. Fetuses (ratio, %)	0/181 (0)	1/172 (0.6)	0/183 (0)	3/163 (1.8)
No. Litters (ratio)	0/21	1/21	0/20	2/19
Skull – Parietal, contains an intraparietal -Variation				
No. Fetuses (ratio, %)	0/181 (0)	2/172 (1.2)	1/183 (0.5)	5/163 (3.1)*
No. Litters (ratio)	0/21	2/21	1/20	3/19

a. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance ($p \leq 0.05$) is based on raw data (not on the percent differences).
b. Method of fetal evaluation: external, visceral, and skeletal.
* = Statistical significance ($p \leq 0.05$) is based on raw data (not on the change from controls); -- = no noteworthy findings; NC = not calculated

2.6.7.11.3.2.2 Subcutaneous Infusion Embryo Fetal Development Study in Rabbits [Report 20[redacted]N244027]

Report Title:	**Subcutaneous Infusion Embryo-Fetal Development Study in Rabbits**				
Design similar to ICH 4.1.3?	Yes	**Duration of Dosing:**	GD 7 to 19	**Test Article (Batch No.):**	tapinarof ([redacted])
Species/ Strain:	New Zealand White rabbit	**Day of Mating:**	GD 0	**Report No.**	20[redacted]N244027
Initial Age:	5 to 6 months	**Day of C-Section:**	GD 29	**Location in CTD:**	4.2.3.5.2-4
Date of First Dose:	[redacted]-20[redacted]	**Method of Administration:**	Subcutaneous Infusion (24 h daily)	**GLP Compliance:**	Yes
Special Features:	None	**Vehicle/Formulation:**	30% Captisol®/ Solution		
No Observed Adverse Effect Level:		**F_1 Litters:**	**3 mg/kg/day**		

Daily Dose (mg/kg/day)	**0 (Control)**	**1**	**2**	**3**
Does				
Toxicokinetics:				
C_{ave} (ng/mL)	NC	1.09	2.66	6.64
AUC_{0-24} (ng.h/mL)	NC	26.2	63.8	159
No. Animals/Group	**22**	**22**	**22**	**22**
No. Pregnant	**21**	**21**	**20**	**21**
No. Pregnant Evaluated	21	20	20	19
No. Died or Sacrificed Moribund	0	0	0	0
No. Aborted	0	0	0	2
No. with Total Resorption of Litter	0	1	0	0
Clinical Observations (no. occasions/ no. of animals)				
Reduced appetite	7/1	6/3	4/2	19/5
Infusion site, soft, swollen	140/20	201/22	199/20	209/22
Skin blue	5/5	6/4	10/10	10/9
Skin red	20/10	38/10	17/8	24/8
Skin dry	11/5	24/9	20/6	22/6
Skin lesion	1/1	3/2	2/2	5/3
Skin scab	15/6	23/8	12/3	8/5
Necropsy Observations				
Infusion site, thick	5	5	6	5
Infusion site, dark cyst	3	5	6	1
Body Weight Gain (GD 7 to 20)[a]	0.32 kg	0.88X	0.91X	0.84X
Food Consumption (GD 7 to 20)[a]	1617.3 g	1.0X	1.0X	0.99X
Mean No. Corpora Lutea	10	9.9	9.3	10.1

Daily Dose (mg/kg/day)	0 (Control)	1	2	3
Mean No. Implantations	8.0	8.3	7.9	7.7[b]
Mean % Preimplantation Loss	18.2	14.5	14.6	22.3[b]
Litters				
No. Litters Evaluated[c]	**21**	**20**	**20**	**19**
Mean No. Live Fetuses	7.6	7.5	7.2	6.6[d]
Mean % Postimplantation Loss	4.3	9.7	9.2	15.8[e]
Mean Fetal Body Weight (g) - Males	43.7	43.5	44.5	45.0
Mean Fetal Body Weight (g) - Females	41.8	41.9	42.5	43.6
% Male Fetuses	42.9	46.5	51.7	56.0
Fetal Anomalies:				
Gross External	--	--	--	--
Visceral	--	--	--	--
Skeletal	--	--	--	--

a. For controls, group means are shown. For treated groups, fold differences from controls are shown. There were no statistically significant differences.
b. Not considered test item related, as within historical control values, not statistically significant, and implantation is expected to occur prior to dosing initiation
c. Method of fetal evaluation: external, visceral, skeletal.
d. Not considered test item related, as within historical control values, not statistically significant, and secondary to decreases in mean numbers of implantation sites.
e. Not considered test item related, as within historical control values, not statistically significant, and primarily due to 2 individual animals with low numbers of implantation sites which is known to produce post implantation loss and 1 animal with high post implantation loss that was considered incidental due to the isolated nature.
-- = no noteworthy findings; NC = not calculated

2.6.7.11.4 Reproductive and Developmental Toxicity: Effect on Prenatal and Postnatal Development, Including Maternal Function (Pivotal)

2.6.7.11.4.1 Subcutaneous Pre- and Postnatal Development Study in Rats [Report 20[redacted]N368233]

Report Title:	**Subcutaneous Pre- and Postnatal Development Study in Rats**				
Design similar to ICH 4.1.2?	Yes	**Duration of Dosing:**	GD 6 to LD 20	**Test Article (Batch No.):**	tapinarof ([redacted])
Species/ Strain:	Rat/Wistar Han	**Day of Mating:**	GD 0	**Report No.**	20[redacted]N368233
Initial Age:	69 to 75 days	**Method of Administration:**	Subcutaneous injection	**Location in CTD:**	4.2.3.5.3-1
Date of First Dose:	[redacted]-20[redacted]	**Vehicle/Formulation:**	30% Captisol®/ Solution	**GLP Compliance:**	Yes
Special Features:	TK on PND 10 (F_1 pups)	**Litters Culled/Not Culled:**	Not culled		
No Observed Adverse Effect Level:		**F_1 Males and Females:**	**1 mg/kg/day**		

Daily Dose (mg/kg/day)	**0 (Control)**	**1**	**6**	**30**
F_0 Females				
No. Animals per Group	**26[a]**	**24**	**24**	**26[a]**
No. Pregnant	**25**	**24**	**24**	**25**
No. Pregnant Survivors to Term	**25**	**24**	**24**	**24**
No. Died or Sacrificed Moribund	0	0	0	1[b]
Clinical Observations (Gestation) (No. Occasions/ No. of Animals)				
Injection Site Scab	1/1	3/1	7/2	85/16
Sparse Hair Coat - Back	0/0	2/1	48/7	57/10
Clinical Observations (Lactation) (No. Occasions/ No. of Animals)				
Injection Site Scab	3/1	39/5	50/9	300/21
Sparse Hair Coat - Back	0/0	108/8	244/14	274/18
Body Weight[c]				
Mean Gestation Body Weight Gain (GD 6 to 21) (%)	95.6g	0.99X	1.00X	0.94X
Mean Lactation Body Weight Gain (LD 1 to 21) (%)	28.0g	1.51X	1.26X	0.81X
Mean Lactation Body Weight Gain (LD 2 to 21) (%)	30.6g	1.31X	1.22X	0.92X
Food Consumption[c]				
Mean Gestation Food Consumption (GD 14 to 18) (%)	37.5g	1.06X	1.08X**[d]	1.08X*[d]
Mean Lactation Food Consumption (LD 1 to 4) (%)	21.4g	1.07X	0.87X	0.75X**
Mean Lactation Food Consumption (LD 4 to 8) (%)	37.0g	1.04X	0.99X	0.78X**
Mean Lactation Food Consumption (LD 8 to 12) (%)	41.4g	1.08X	1.02X	0.76X**
Mean Lactation Food Consumption (LD 12 to 14) (%)	62.0g	0.95X	0.94X	0.59X**
Mean Duration of Gestation (days)	22.6	22.4	22.7	23.0
Mean No. of Implantations	10.0	10.1	10.3	9.4

Daily Dose (mg/kg/day)	0 (Control)	1	6	30
Average Pup Delivery Time (minutes)	12.1	9.9	12.8	13.0
Necropsy Observations	--	--	--	--
F_1 Litters: (Preweaning)				
No. Viable F1 Litters at Birth (PND 1)	**25**[e]	24	24	24
No. Viable F1 Litters at Weaning (PND 21)	23	24	22	20
Mean No. Live Pups Born/Litter	9.4	9.4	9.1	7.5
Total No. Liveborn (% liveborn)	235 of 236 (99.6%)	227 of 227 (100%)	218 of 230 (94.8%)	180 of 203 (88.7%)*
Total No. Stillborn Pups Born (% Stillborn)[f]	1 of 236 (0.4%)	0 of 227 (0.0%)	10 of 230 (4.3%)	18 of 203 (8.9%)*
Tapinarof Plasma Concentrations - PND10 (ng/mL, range)	NQ	NQ	0.326 to 0.506	0.301 to 0.985
No. Females with Stillborn Pups	1	0	4	9**
Pup Sex Ratio at PND 1 (% Males)	54.5%	46.8%	46.4%	44.2%
No. Liveborn Pups that died after delivery on PND 1	0	0	4	17
No. Postnatal Deaths PND 4 (% Viability PND 1 to 4)	1/235 (99.6%)	5/227 (97.8%)	32/218 (85.3%)[g]	79/180 (56.1%)**[g]
Postnatal Survival to Weaning (% Viability PND 4 to 21)	0/234 (100.0%)	1/222 (99.5%)	4/186 (97.6%)**	0/101 (100.0%)
Body Weight (g; combined sexes)				
PND 1	6.1	5.8	5.5	5.3
PND 4	9.2	8.6	8.0	7.6*
PND 7	14.1	13.4	13.0	11.8*
PND 14	25.6	25.3	25.5	26.9*
PND 21 (weaning)	40.4	40.4	41.1	43.9*
Kidney Pathology PND 7 (n=20 pups/group)	--	NA	NA	--
F_1 Males:				
No. Evaluated (Subset 1)	**24**	**24**	**24**	**18**
No. Evaluated (Subset 2)	**24**	**24**	**24**	**12**
Postweaning				
Mean Body Weight Gain (g; PND 22 to 85)	308.4	1.01X	1.02X	0.98X
Mean Age of Balano-Preputial Separation (days)	45.6	44.9	45.7	46.7
Acoustic Startle (PND 27 to 29, or PND 60 to 62)	--	--	--	--
Motor Activity (PND 54 to 61)	--	--	--	--
Morris Water Maze (PND 65 to 85)	--	--	--	--
Mean No. Days in Cohabitation (1st Cohabitation, with Subset 1 females)	2.0	2.4	2.6	1.7
No. of Males that Mated (% Mating Index; 1st Cohabitation)	24 (100%)	24 (100%)	24 (100%)	17 (100%)
No. of Fertile Males (% Fertility Index; 1st Cohabitation)[h]	18/24 (75%)	20/24 (83.3%)	18/24 (75%)	5/17 (29.4%)

Daily Dose (mg/kg/day)	0 (Control)	1	6	30
Mean No. Days in Cohabitation (% Mating Index; 2nd Cohabitation with naïve females)	3.3	3.0	3.8	2.3
No. of Males that Mated (% Mating Index;2nd Cohabitation)	6 (100%)	4 (100%)	4 (66.7%)	12 (100%)
No. of Fertile Males (% Fertility Index; 2nd Cohabitation)	6/6 (100%)	4/4 (100%)	3/4 (75.0%)	12/12 (100%)
Clinical Observations	--	--	--	--
F_1 Females:				
No. Evaluated (Subset 1)	**24**	**24**	**25**	**18**[i]
No. Evaluated (Subset 2)	**24**	**24**	**23**	**14**
Postweaning				
Mean Body Weight Gain (g; PND 22 to 85)	173.9	0.96X	1.00X	1.00X
Mean Age of Vaginal Patency (days)	32.1	32.1	32.2	32.5
Acoustic Startle (PND 27 to 29, or PND 60 to 62)	--	--	--	--
Motor Activity (PND 54 to 61)	--	--	--	--
Morris Water Maze (PND 65 to 85)	--	--	--	--
Mean No. of Estrous Cycles Premating (PND 66 to 100; prior to 1st Cohabitation)	7.29	7.21	7.04	6.24
Mean No. of Estrous Cycles Premating (PND 150 to 160; prior to 2nd Cohabitation)	2.50	2.75	2.50	2.83
Mean No. Days in Cohabitation (1st Cohabitation with Subset 1 males)	2.0	2.4	2.9	1.7
No. Females that Mated (% Mating Index; 1st Cohabitation)	24 (100%)	24 (100%)	25 (100%)	17 (100%)
No. of Pregnant Females (% Fertility Index; 1st Cohabitation)	18/24 (75%)	20/24 (83.3%)	19/25 (76%)	5/17 (29.4%)
Mean No. Days in Cohabitation (2nd Cohabitation with Control Males)	3.2	3.0	2.2	3.1
No. of Females that Mated (% Mating Index; 2nd Cohabitation)	6 (100%)	4 (100%)	6 (100%)	11 of 12 (91.7%)[j]
No. Pregnant Females (% Fertility Index; 2nd Cohabitation)	6 (100%)	4 (100%)	4 of 6 (66.7%)[k]	9 of 11 (81.8%)[k]
Mean Body Weight Gain c				
GD 0 to 21 (1st Cohabitation)	115.6 g	1.00X	1.03X	0.97X[l]
GD 0 to 21 (2nd Cohabitation)	107.5 g	0.92X	1.03X	0.89X
LD1 to 7 (1st Cohabitation)	24.7 g	0.79X	0.81X	0.53X[l]
LD1 to 7 (2nd Cohabitation)	8.0 g	-1.3g[m]	0.90X	1.35X
Clinical Observations	--	--	--	--
Mean Duration of Gestation (days) (1st Cohabitation)	22.7	22.6	22.5	22.6
Mean Duration of Gestation (days) (2nd Cohabitation)	23.0	23.0	23.0	22.8
Average Pup Delivery Time (minutes) (1st Cohabitation)	10.5	9.8	11.9	9.6

Daily Dose (mg/kg/day)	0 (Control)	1	6	30
Average Pup Delivery Time (minutes) (2nd Cohabitation)	11.2	13.0	7.9	9.3
Mean No. of Implantations (1st Cohabitation)	13.0	12.8	12.9	10.4
Mean No. of Implantations (2nd Cohabitation)	12.0	12.0	13.0	13.3
F_2 Litters:				
No. Viable Litters at Birth (PND 1) (1st and 2nd cohabitation)	**24**	**23**	**23**	**12**[n]
No. Viable Litters on PND 7 (1st and 2nd cohabitation)	**24**	**23**	**23**	**12**
Mean No. Live Pups Born/Litter (1st Cohabitation)	12.3	12.0	12.2	9.2[l]
Mean No. Live Pups Born/Litter (2nd Cohabitation)	10.0	9.0	12.2	11.8
Mean No. Stillborn Pups/Litter (1st Cohabitation)	0.2	0.0	0.0	0.4[n]
Mean No. Stillborn Pups/Litter (2nd Cohabitation)	0.5	0.7	0.0	0.6
Postnatal Survival to Day 4 (% Survival PND 1-4; 1st Cohabitation)	99.5	99.6	99.6	95.6[o]
Postnatal Survival to Day 4 (% Survival PND 1-4; 2nd Cohabitation)	100.0	100.0	100.0	95.2
Pup Sex Ratio at PND 1 (% males; 1st Cohabitation)	49.5	46.7	50.2	62.3
Pup Sex Ratio at PND 1 (% males; 2nd Cohabitation)	58.8	40.3	42.9	45.3
Body Weight (g; combined sexes)				
PND 1 (1st Cohabitation)	5.7	5.7	5.8	6.1
PND 1 (2nd Cohabitation)	5.8	6.1	5.9	5.5
PND 7 (1st Cohabitation)	12.6	12.6	12.3*	13.6
PND 7 (2nd Cohabitation)	14.0	14.6	13.0	11.3

a. Two females (and litters) assigned for F1 kidney collection.
b. F_0 female 9300 in the 30 mg/kg/day group was euthanized on GD 19 due to adverse clinical observations which included decreased motor activity, lacrimation, ptosis, severe dehydration (based on skin turgor), hunched posture, red perivaginal substance, and 10% body weight loss from GD 18 to GD 19. At necropsy, a large spleen (1.05g) was observed and all other tissues were normal. This death was not considered test article related because it was an isolated event, and because there were no other deaths among the F_0 females.
c. For controls, group means are shown. For treated groups, change from controls is shown.
d. Not considered test article related because the magnitude of change was minimal and not dose dependent.
e. Extra animals assigned to kidney collection.
f. An additional 0, 0, 2 and 5 pups born in the 0, 1, 6, and 30 mg/kg/day groups, respectively, were found dead or partially cannibalized with unknown viability at birth.
g. Two females at 6 mg/kg/day and 4 females at 30 mg/kg/day had entire litter loss.
h. Light timer malfunction (132 hour exposure to white light) caused abnormal estrous cycles which had secondary effects on female's ability to become pregnant.
i. Female 9965 was euthanized on PND 72 due to adverse clinical observations.
j. Females which did not mate had a prolonged period of estrus (12 days) followed by 5 days of diestrus (i.e. latent effect of lighting malfunction).
k. 2 of 6 females at 6 mg/kg/day and 2 of 11 females at 30 mg/kg/day had irregular estrous cycles and mated. These females were not in an appropriate cycle to become pregnant (i.e. latent effect of lighting malfunction).
l. Based on 5 pregnant females.
m. Group mean is shown. Change from controls cannot be calculated due to negative value.
n. 14 females were pregnant (5 from the first cohabitation and 9 from the second cohabitation), but only 12 females delivered a litter. The remaining 2 females mated and were pregnant, but had irregular cycles prior to mating and litters were 100% early resorptions.
o. Based on 2 of 46 live pups that died vs. 1, 1 and 1 dead pups at 0, 1 and 6 mg/kg/day out of 222 to 240 live pups.
* = Statistically significant difference from control group ($p < 0.05$); ** = Statistically significant difference from control group ($p < 0.01$); -- = no noteworthy findings; GD = gestation day; LD = lactation day; NA = not applicable; NQ = not quantifiable [samples were below the limit of quantitation (BLQ); < 0.3 ng/mL]; PND = postnatal day

2.6.7.12 Studies on Juvenile Animals

2.6.7.12.1 Subcutaneous Juvenile Toxicity Study in Rats [Report 20[redacted]N211697]

Report Title:	**Subcutaneous Juvenile Toxicity Study in Rats**				
Design similar to ICH 4.1.2?	Yes	**Duration of Dosing:**	PND 7 to 77	**Test Article (Batch No.):**	Tapinarof ([redacted])
Species/ Strain:	Rat/Wistar Han	**Method of Administration:**	Subcutaneous injection	**Report No.**	20[redacted]N211697
Initial Age:	PND 7	**Vehicle/Formulation:**	30% Captisol®/ Solution	**Location in CTD:**	4.2.3.5.4-2
Date of First Dose:	[redacted]-20[redacted]	**Litters Culled:**	Culled to 4 males and 6 females/litter on PND 4 or to 5 males and 5 females/litter (PND 13 and 22 TK litters)	**GLP Compliance:**	Yes
Special Features:	Dose escalation on PND22, Toxicokinetic (TK) evaluation during PND 13, 21, 22, 32 and 77, learning and memory, estrous cycle in females, male fertility, immunology assessments, 4 week off-dose evaluation				
No Observed Adverse Effect Level:	**1/1.5 mg/kg/day**				

Daily Dose (mg/kg/day)[a]	**0 (Control)**		**1/1.5**		**10/15**		**20/30**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Disposition								
Juveniles Assigned to Study on PND 3-4 (M/F):								
Subset A – Main Study [necropsy PND 78, clinical pathology, histopathology, male fertility assessments]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Subset B – Recovery [necropsy PND 106, clinical pathology, histopathology, estrous cycles, behavior]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Subset C – Allocated to TK on PND 21, 32 and 77, male fertility assessments, female TDAR recovery	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Subset D1 – Behavior	**10**	**NA**	**10**	**NA**	**10**	**NA**	**10**	**NA**
Subset D2 – Behavior, estrous cycles, Recovery TDAR	**NA**	**10**	**NA**	**10**	**NA**	**10**	**NA**	**10**
Subset E – Main TDAR	**NA**	**20**	**NA**	**20**	**NA**	**20**	**NA**	**20**
Subset F – Allocated to TK on PND 13	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**
Subset F – Allocated to TK on PND 22	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Results:								
Toxicokinetics – genders combined								

Daily Dose (mg/kg/day)[a]	**0 (Control)**		**1/1.5**		**10/15**		**20/30**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
PND 13 C_{max} (ng/mL)	NC		59.5		1080		1980	
PND 22 C_{max} (ng/mL)	NC		41.9		523		858	
PND 32 C_{max} (ng/mL)	NC		46.1		510		968	
PND 77 C_{max} (ng/mL)	NC		73.1		729		1700	
PND 13 AUC_{0-t} (ng.h/mL)	NC		59.5		1320		2460	
PND 22 AUC_{0-t} (ng.h/mL)	NC		62.5		597		1380	
PND 32 AUC_{0-t} (ng.h/mL)	NC		91.6		716		1610	
PND 77 AUC_{0-t} (ng.h/mL)	NC		86.4		1320		3230	
Mortality[b]								
Main Study and Recovery	1	0	0	0	0	1	0	1
TDAR	NA	0	NA	1	NA	0	NA	0
Clinical Observations (treatment-related)								
Thin fur cover at the injection sites	+	+	+++	+++	+++	+++	+++	+++
Skin scabs at injection sites (postweaning)	--	--	+	--	+	+	++	++
Body Weight Changes[c]								
PND 7 to 21	22.3 g	22.1 g	1.03X	1.05X*	1.02X	1.01X	1.00X	0.99X
PND 21 to 77	282.3 g	164.2 g	0.99X	0.98X	1.03X	0.98X	1.00X	0.94X
PND 77 to 105	48.1 g	20.9 g	1.16X	1.03X	1.09X	1.00X	1.16X	1.10X
Body Weight[c]								
PND 7	14.30 g	14.12 g	1.04X	1.03X	1.06X	1.03X	1.07X	1.04X
PND 21	36.55 g	36.18 g	1.03X	1.04X	1.04X	1.02X	1.03X	1.01X
PND 77	318.9 g	200.0 g	1.00X	0.99X	1.03X	0.99X	1.00X	0.95X
PND 105	370.3 g	220.3 g	1.00X	1.02X	1.01X	0.99X	1.02X	0.96X
Cumulative Food Consumption[c]								
PND 28 to 70	792.5 g	666.4 g	1.02X	1.01X	1.02X	1.01X	1.03X	1.01X
PND 77 to 105	592.4 g	452.4 g	1.07X	0.95X	1.10X	0.97X	1.14X	0.95X
Physical Landmarks of Sexual Maturation								
Day of Vaginal Opening (PND)	NA	32.8	NA	33.3	NA	33.2	NA	33.8
Day of Preputial Separation (PND)	42.9	NA	42.3	NA	42.4	NA	42.8	NA
Neurobehavioral Function	--	--	--	--	--	--	--	--
No of Estrous Cycles in 14 days (treated females)	NA	3.1	NA	3.2	NA	3.1	NA	3.3
Male Reproductive Function (treated males)[d]								
Mean Days to Mating	2.8	NA	2.8	NA	2.8	NA	2.6	NA
Mating Index (%)	100.0	NA	95.0	NA	85.0	NA	85.0	NA

Daily Dose (mg/kg/day)[a]	**0 (Control)**		**1/1.5**		**10/15**		**20/30**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Fertility Index (%)	85.0	NA	70.0	NA	75.0	NA	80.0	NA
F2 Fetal Weights (offspring of treated males)[c]	3.80 g	3.61 g	1.00X	1.00X	1.03X	1.03X	1.01X	1.02X
F2 Fetal External Findings (offspring of treated males)	0	0	0	0	0	0	0	0
Urine Chemistry (Main Study - Week 11)[c]								
Total Urinary Glucose Excretion[e]	1.73 (µmol/ collection period)	2.01 (µmol/ collection period)	1.17X	1.16X	1.39X	1.28X	1.97X	0.99X
Total Urinary Protein Excretion[e]	4.04 (mg/ collection period)	1.13 (mg/ collection period)	1.20X	4.27X	1.61X	1.03X	1.83X	1.19X
Organ Weights (Main Study Necropsy PND 78)[c]								
Thymus (absolute)	0.454 g	0.453 g	0.94X	0.90X	0.89X	0.87X	0.76X*	0.80X
Thymus (% relative to body weight)	0.152	0.246	0.94X	0.92X	0.87X	0.86X	0.78X*	0.84X
Thymus (% relative to brain weight)	23.492	25.719	0.95X	0.88X	0.89X	0.88X	0.77X*	0.82X
Microscopic Observations (Main Study Necropsy PND 78) (No. of animals examined)	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Kidney								
Pelvic dilatation	0	1	0	0	5	3	5	3
minimal	0	1	0	0	2	2	2	2
mild	0	0	0	0	2	1	1	1
moderate	0	0	0	0	1	0	2	0
Tubular vacuolation[f]	10	10	10	10	10	10	10	10
minimal	0	1	0	1	0	0	1	2
mild	10	9	10	9	10	10	9	8
Thymus								
Decreased cellularity	0	0	0	0	2	2	7	1
minimal	0	0	0	0	2	1	3	1
mild	0	0	0	0	0	1	4	0
Injection Sites (interscapular subcutaneous tissue)								
Necrosis	4	0	3	1	2	1	7	3
Hemorrhage	6	5	7	8	6	6	9	7
minimal	1	3	2	1	2	1	2	3

Daily Dose (mg/kg/day)[a]	0 (Control)		1/1.5		10/15		20/30	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
mild	5	1	2	5	3	5	5	4
moderate	0	1	3	2	1	0	2	0
Infiltration, mixed cell	7	6	8	8	8	8	10	10
minimal	4	3	4	6	5	6	5	8
mild	3	3	4	2	2	2	5	2
marked	0	0	0	0	1	0	0	0
Microscopic Observations (Off-Dose Necropsy PND 106) (No. of animals examined)	**9**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Kidney								
Pelvic dilatation	1	1	0	0	4	2	6	1
minimal	0	0	0	0	1	1	1	0
mild	1	1	0	0	1	0	4	0
moderate	0	0	0	0	2	1	1	1
Tubular vacuolationf	9	10	10	10	10	10	10	10
minimal	1	0	1	3	1	1	2	1
mild	8	10	9	7	9	9	8	9
Injection Sites (interscapular subcutaneous tissue)								
Infiltration, mixed cell	5	2	5	1	4	1	7	3
minimal	5	2	5	1	4	1	7	3
Bone Measurements (Main Study and Off-Dose Necropsies)	--	--	--	--	--	--	--	--
Spermatogenic Cycle Assessments (Main Study necropsies)	--	NA	--	NA	--	NA	--	NA
Immune Function								
TDAR (Main Study and Off-Dose Necropsies)	--	--	--	--	--	--	--	--
Immunophenotyping (Main Study - PND 78) (No. of animals examined)	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Blood Immunophenotyping								
Cytotoxic T Lymphocytes – Relative Percentages (%) [Group Arithmetic Mean]	14.34	15.59	15.59	17.22	18.62*	19.50*	16.74*	19.16*
Immunophenotyping (Main Study - PND 78) (No. of animals examined)	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Blood Immunophenotyping								
Cytotoxic T Lymphocytes – absolute (cells/µL) [Group Arithmetic Mean]	989.06	763.13	929.22	812.41	1322.35*	1038.19	1091.25	1137.48*

Daily Dose (mg/kg/day)[a]	**0 (Control)**		**1/1.5**		**10/15**		**20/30**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Natural Killer (NK) Cells – Relative Percentages (%) g [Group Geometric Mean]	4.15		3.87		2.20*		1.72* g	
Natural Killer (NK) Cells – absolute (cells/µL) [Group Geometric Mean]	294.80	183.48	209.91	194.76	165.71*	103.15*	106.53*	98.85*
Thymus Immunophenotyping[g]								
Total Lymphocyte Count (cells/thymus) x 10^6 [Group Arithmetic Mean]	933.9		794.5		814.2		545.5*	
CD4 Single Positive Thymocytes – absolute (cells/thymus) x 10^6 [Group Arithmetic Mean]	84.97		70.14		76.08		57.98*	
CD4/CD8a Double Positive Thymocytes – absolute (cells/thymus) x 10^6 [Group Arithmetic Mean]	785.12		665.67		671.51		443.84*	
CD4/CD8a Double Negative Thymocytes – absolute (cells/thymus) x 10^6 [Group Arithmetic Mean]	22.81		21.60		20.83		13.95*	
Tregs– absolute (cells/thymus) x 10^6 [Group Arithmetic Mean]	5.17		4.65		4.96		3.69*	
CD4/CD8a Double Positive Thymocytes – Relative Percentages (%) [Group Arithmetic Mean]	83.92		83.64		82.63		80.95*	
Immunophenotyping (Off-Dose - PND 106) (No. of animals examined)	**9**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Blood Immunophenotyping								
Cytotoxic T Lymphocytes – Relative Percentages (%) [Group Arithmetic Mean]	14.43	16.52	16.26	18.78	17.78	20.20*	17.74	20.31*
Cytotoxic T Lymphocytes – absolute (cells/µL) [Group Geometric Mean]	814.79	792.28	1016.08	882.67	1191.41*	1034.23	1284.93*	914.26
NK Cells – Relative Percentages [Group Geometric Mean][g]	3.44		3.07		2.28*		1.91*	
NK Cells – absolute (cells/µL) [Group Geometric Mean]	223.57	150.33	169.00	166.06	145.13	124.51	144.35	85.55*

a. Dose escalation was used, such that the first dose level was given from PND 7 to 21, and the second dose level was given from PND 22 to 77.
b. No test article related deaths. Control group male died of renal nephroblastoma, 1/1.5 mg/kg/day group female died of accidental head trauma, and 10/15 or 20/30 mg/kg/day group females died following blood collection procedures.
c. For controls, group means are shown. For treated groups, the magnitude of change relative to controls is shown.
d. Mating index (%): number of males mating / number of males placed for mating x 100; Fertility index (%): number of males producing a pregnant female / number of males placed for mating x 100.
e. Minimal increases were noted in total urinary glucose excretion in 4/10 males given 10/15 mg/kg/day (1.6 to 2.7X) and 4/10 males given 20/30 mg/kg/day (2.3 to 4.5X). There were concurrent increases in total urinary protein excretion in 4/10 male rats given 10/15 mg/kg/day (1.9X to 4.0X) and 5/10 male rats at 20/30 mg/kg/day (1.8X to 3.0X). Following the recovery period, these findings were no longer observed. Any other differences in the urine chemistry parameters were judged to be due to biological variation and not related to the administration of tapinarof.
f. Not considered test item-related, as findings are consistent with the use of cyclodextrin vehicle.
g. Sexes combined.
* = Statistically significant difference from control group ($p < 0.05$); -- = no noteworthy findings; + = present at low incidence; ++ = present at moderate incidence; +++ = present at high incidence; F = female; M = male; NA = not applicable; NC = not calculated; PND = post-natal day; TDAR = T cell dependent antibody response

2.6.7.13 Local Tolerance

2.6.7.13.1 Summary of Local Tolerance Studies - tapinarof

Test Article: tapinarof						
Type of Study	**Species/ Strain**	**Method of Administration**	**Dose or Concentration**	**Gender and No. Per Group**	**Noteworthy Findings**	**Report Number/ Location in CTD**
Local Tolerance: Hemolysis	Göttingen Minipig Blood	*In vitro*	0, 1.38, 4.15 mg/mL	NA	Tapinarof and Captisol® were not hemolytic	20[redacted]N162009/ 4.2.3.6-1
Local Tolerance: Skin Irritation	EpiDerm Culture	*In vitro*	0.5%	NA	All formulations are expected to be non-irritating	20[redacted]N178086/ 4.2.3.6-2
Local Tolerance: Skin Irritation	EpiDerm Culture	*In vitro*	0.5%, 1%, 2%	NA	All formulations are expected to be non-irritating	20[redacted]N235202/ 4.2.3.6-3
Local Tolerance: Skin Sensitization Study (Beuhler Test Method)	Guinea Pigs (Crl:HA(BR))	Dermal	1%, 4%, 8%	5, 10, or 20M	Tapinarof was non-sensitizing	20[redacted]N163830/ 4.2.3.6-4
Local Tolerance: Acute Dermal Irritation	Rabbit (NZW)	Dermal	8%	3F	Irritation potential of tapinarof was negligible	20[redacted]N163832/ 4.2.3.6-5
Local Tolerance: Local Lymph Node Assay	Mouse (CBA/CaCrl)	Dermal	1%, 2%, 4%	5F	Tapinarof was not a contact sensitizer	20[redacted]N175961/ 4.2.3.6-6
Local Tolerance: Phototoxicity	Mouse (Crl:SKH1-hr hairless)	Dermal	1%, 4%, 8%	6M	• Tapinarof did not elicit skin reactions indicative of substantive primary irritation • Tapinarof followed by radiation from xenon lamp did not elicit skin reactions indicative of phototoxicity	20[redacted]N163834/ 4.2.3.6-7
Local Tolerance: Acute Eye Irritation/ Corrosion	Rabbit (NZW)	Ocular	8%	3F	• Tapinarof was classified as Practically Non-Irritating	20[redacted]N163833/ 4.2.3.6-8

F = female; M = male; NA = not applicable; NZW = New Zealand White [Crl:KBL(NZW)BR]