MODULE 2.6.6. TOXICOLOGY WRITTEN SUMMARY

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

1. BRIEF SUMMARY

Cabotegravir (also referred to as GSK1265744, or simply CAB throughout m2.6) has undergone a comprehensive toxicological evaluation during the nonclinical development program. Single dose intramuscular (IM) and subcutaneous (SC) studies were performed in the rat and monkey, and a 3 month repeat dose SC/IM study in the rat and repeat oral dose studies were also conducted for durations of up to 26 weeks in the rat and up to 39 weeks in the monkey. The potential for genetic toxicity of CAB was investigated in the Ames test, mouse lymphoma assay, and micronucleus test, and the tumorigenic potential was studied in oral carcinogenicity studies in the mouse and the rat. A range of reproductive toxicity studies were performed in the rat and rabbit following oral administration. Additionally, studies were conducted to investigate the potential for immunotoxicity and local tolerance.

A listing of all the pivotal toxicology studies performed with CAB is given in Table 1.1.

Table 1.1 Listing of Pivotal Toxicology Studies Performed with CAB

Study Type and Duration	Route of Administration	Species	Compound Administered
Repeat Dose Toxicity			
Up to 26 weeks	Oral	Rat	Sodium salt
3 months	SC / IM	Rat	Free acid
Up to 39 weeks	Oral	Monkey	Sodium salt
Genotoxicity			
Ames test	In vitro	Bacterial cells	Sodium salt
Mouse lymphoma assay	In vitro	L5178Y cells	Sodium salt and free acid
Micronucleus	Oral	Rat	Sodium salt
Carcinogenicity	Oral	Mouse and Rat	Sodium salt
Reproductive and Developmental			
Fertility & early embryonic development	Oral	Rat	Sodium salt
Embryofetal development	Oral	Rat, Rabbit	Sodium salt
Pre- and post-natal development	Oral	Rat	Sodium salt
Local Tolerance			
Dermal irritancy	In vitro	Human model	Sodium salt
Ocular irritancy	In vitro	Human model	Sodium salt
Local lymph node assay	Topical	Mouse	Sodium salt
Other			
Immunotoxicology	In vivo	Rat	Sodium salt

Key:
SC = subcutaneous; IM = intramuscular.

Most pivotal studies were performed using both the oral route of administration as this is one of the proposed therapeutic routes in humans. Select bridging studies were also conducted using subcutaneous / intramuscular injections, as the parenteral route of administration is another proposed therapeutic route for human use. The species and strain used in these investigations were selected based on similarities in the pharmacokinetic and metabolic handling of CAB between the selected species and humans. Furthermore, for the species and strains used in the toxicological evaluation of CAB, considerable data on the background pathology and the response to a wide variety of pharmaceuticals are available to assist in the evaluation of the findings and extrapolation of their relevance to humans.

Most oral dosing studies described in this section were performed using the sodium salt of CAB (unless otherwise indicated), while the subcutaneous and intramuscular injection studies used the free acid of CAB. The sodium salt of CAB is the form proposed for oral administration in humans while the free acid of CAB is the form proposed for parenteral administration. In most instances, doses and concentrations quoted in this summary are expressed in terms of the free acid (parent compound) which is referred to simply as CAB.

All definitive studies were performed in full compliance with GLP regulations and were conducted in an Organisation for Economic and Cooperation and Development (OECD) member country in accordance with the OECD Test Guidelines. Studies undertaken to establish suitable dose levels were performed in accordance with the general principles of GLP regulations. A list of studies that were undertaken with CAB but are not included in this submission is presented in Appendix 1.

The impurity profiles of the drug substance batches used in the nonclinical toxicology studies were comparable to the impurity profile of the material used in clinical investigations and that proposed for use in the marketed product. There are 6 specified impurities in the proposed CAB Drug Substances Specifications [see Section 4.6]. Drug substance batch numbers and details of the formulations used in the toxicology studies are presented. A genotoxic risk assessment of the CAB drug substance impurities is provided in Section 4.6.

A bullet point summary of the important findings from the toxicology program is provided below. Details of the study designs and important findings are presented in Sections 2 to 8, and in m2.6.7, Tables 5.1 to 17.2. A critical assessment of all the toxicology data is presented in Section 9, Discussion and Conclusions.

Single dose toxicity

- Single dose acute toxicity studies were not conducted with CAB; however, the potential for acute toxicity was assessed in repeat dose studies at the highest possible systemic exposure based on saturation of absorption (rat) or highest tolerable dose (monkey).

Repeat dose toxicity

- The effect of prolonged daily treatment with high doses of CAB has been evaluated in repeat oral dose toxicity studies in rats (26 weeks) and in monkeys (39 weeks). There were no drug-related adverse effects in rats or monkeys given CAB orally at doses up to 1000 mg/kg/day or 500 mg/kg/day, respectively. In the 14 day monkey toxicity study, a dose of 1000 mg/kg/day was not tolerated and resulted in morbidity associated with gastrointestinal (GI) effects (body weight loss, emesis, loose/watery feces, and moderate to severe dehydration).
- In the 4 week (28 day) monkey toxicity study, end of study exposure at 500 mg/kg/day was similar to that achieved in the 14 day study at 1000 mg/kg/day. This suggests that GI intolerance observed in the 14 day study was the result of local drug administration and not systemic toxicity.

Genotoxicity

- CAB was negative in the pivotal in vitro and in vivo genetic toxicology assessments and there are no impurities of mutagenic concern, indicating that CAB does not pose a genotoxic risk in humans.

Carcinogenicity

- CAB was not carcinogenic in 2 year rat or mouse carcinogenicity studies.

Reproductive and developmental toxicity

- CAB had no effects on male or female fertility in rats.
- In pre- and postnatal development studies in rats, CAB (1000 mg/kg/day) delayed the onset of parturition, and in some rats, this delay was associated with an increased number of stillbirths and neonatal mortalities immediately after birth. There were no alterations to growth and development of surviving offspring. When rat pups born to CAB-treated dams (1000 mg/kg/day) were cross-fostered at birth and nursed by control mothers, a similar incidence of stillbirths and neonatal mortalities was observed; there was no effect on neonatal survival of control pups nursed from birth by CAB-treated mothers. A lower dose of 5 mg/kg/day CAB was not associated with delayed parturition or neonatal mortality in rats. When CAB at doses of 1000 or 2000 mg/kg/day was administered orally to pregnant rats and rabbits during organogenesis, there was no effect on survival when fetuses were delivered by caesarean.
- CAB crosses the placenta and can be detected in fetal tissue.
- No adverse effects on embryofetal development were observed in rabbit fetuses up to 2000 mg/kg/day. In rats, alterations in fetal growth (decreased body weights) were observed at 1000 mg/kg/day but no test article-related fetal malformations or variations at any dose.

Local tolerance

- In vitro, CAB is considered a non-irritant in ocular and dermal studies.
- There was no indication of contact sensitization in a mouse local lymph node assay when CAB was administered topically.

Immunotoxicity

- In the first assessment of the T cell-dependent antibody response, the no observed effect level (NOEL), under the conditions of the study, was 5 mg/kg/day in males based on a statistically significant decrease in IgG response and 1000 mg/kg/day in females. In this study, CAB was not considered immunosuppressive because the effect in males at 1000 mg/kg/day was minimal, there were measurable levels of anti-KLH IgG detected in the majority of the animals indicating no adverse effect on the ability of the animals to mount and immune response, and no effects were observed on the female anti-KLH IgG response or on the anti-KLH IgM response in either sex.
- In a follow up study, CAB was not immunotoxic as assessed by T cell dependent antibody response (TDAR) in adult rats at doses ≤1000 mg/kg/day.

2. SINGLE DOSE TOXICITY

In accordance with ICH M3 (R2), acute toxicity information can be obtained from appropriately conducted dose escalation studies or short duration dose ranging studies that define an MTD in the general toxicity test species. Therefore, acute toxicity studies have not been conducted; however, a series of single dose toxicity studies were designed and conducted during the development of CAB and these studies are described in this section.

2.1. Introduction

Single dose toxicity studies were performed to assess the effects of administration of oral, subcutaneous and intramuscular doses of CAB, and to compare the toxicokinetics for the different routes of administration.

A table listing the batches of CAB together with information on method of formulation used in these investigations is presented in Table 2.2 of this summary.

A full listing of the single dose studies performed, together with the location of the reports within this submission and their GLP status, is provided in Table 2.1.

Table 2.1 List of Single Dose Toxicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Dose escalation	Mouse (CD-1)	15M	Oral	B	10, 100, 1000, 2000	Single	No	GSK	RD2009/00691 (M42451)	m4.2.3.1
Toxicokinetic	Rat (Sprague Dawley)	6M 6M	SC IM	A	10 10	Single	No	GSK	RD2009/00865 (R42469)	m4.2.3.1
Toxicokinetic	Rat (Sprague Dawley)	3M 3M	SC IM	A	10, 30, 50 5, 10, 35	Single	No	GSK	RD2009/00906 (R42473)	m4.2.3.1
Toxicokinetic	Rat (Sprague Dawley)	3M 3M	SC IM	A	10, 30, 50 5, 10, 35	Single	No	GSK	RD2009/01216 (R42506)	m4.2.3.1
Single dose	Rat (Sprague Dawley)	10M/10F 10M/10F	SC IM	A	10, 30, 100 2.5, 10, 75	Single	Yes	GSK	RD2009/01359 (R42516)	m4.2.3.1
Toxicokinetic	Monkey (cynomolgus)	4M 4M	SC IM	A	1, 5 1, 5	Single	No	GSK	CD2009/00373 (D09052)	m4.2.3.1
Toxicokinetic	Monkey (cynomolgus)	4M 4M	SC IM	A	5 5	Single	No	GSK	CD2009/00513 (D09084)	m4.2.3.1
Toxicokinetic	Monkey (cynomolgus)	4M 4M	SC IM	A	10 10	Single	No	GSK	CD2009/00656 (D09112)	m4.2.3.1

List of Single Dose Toxicity Studies Performed with CAB (Continued)

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Dose escalation	Monkey (cynomolgus)	2M	Oral (gavage)	B	150, 300, 1000	Single	No	[redacted]	RD2007/01415 (E-265744-TF-006-R)	m4.2.3.1
Toxicokinetic	Monkey (cynomolgus)	2M 2M 4M	IM	A	10 (CAB) 60 (RPV) 10 CAB) + 60 (RPV)	Single	No	GSK	2010N105579 (8234628)	m4.2.3.1

Key:
a = Crossover design.
A = GSK1265744A, the parent form.
B = GSK1265744B, the sodium salt.

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

2.2. Mouse

2.2.1. Oral administration

CAB (sodium salt) was given as a single dose to male CD-1 mice (15/group) at doses of 10, 100, 1000 or 2000 mg/kg by oral gavage [Report RD2009/00691, m4.2.3.1]. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. Parameters that were evaluated during the study were clinical observations and toxicokinetics data collected on Day 1. A tabulated summary of this study is presented in m2.6.7, Table 5.1.

The systemic exposure (C_{max} and AUC_{0-24}) in plasma increased less than proportionally with the increase in dose. There was no difference in systemic exposure following dosing at 2000 mg/kg compared to that after a 1000 mg/kg dose.

One mouse given 2000 mg/kg had clinical signs of decreased activity and irregular breathing shortly after dosing. Hepatocellular necrosis was noted microscopically in this animal and was considered of uncertain relationship to test article administration.

2.3. Rat

2.3.1. Intramuscular and subcutaneous administration

CAB (free acid) was administered as a single dose to groups of male Sprague Dawley rats via subcutaneous (SC) or intramuscular (IM) injections at dose levels of 0 (control; n=3/group) or 10 mg/kg (n=6/group) [Report RD2009/00865, m4.2.3.1]. CAB was formulated as a wet bead-milled suspension in aqueous 1.7% (w/v) polyvinylpyrrolidone (PVP)/0.2% (w/v) Tween 80/0.18% (w/v) methylparaben/ 0.02% (w/v) propylparaben/0.004 M NaH_2PO_4 H_20/0.006 M Na_2HPO_4 with NaCl (particle size of x50 at 0.72 micron and x90 at 1.26 microns) or in aqueous 2% (w/w) pluronic F127/0.2% (w/v) Tween 80/0.18% (w/v) methylparaben/0.02% (w/v) propylparaben/0.004 M NaH_2PO_4 H_20/0.006 M Na_2HPO_4 with NaCl (particle size of x50 at 0.27 micron and x90 at 1.05 microns). Both formulations were given by each route of administration. The following endpoints were evaluated: clinical observations, body weights, microscopic evaluation of the injection site(s) and heart, and toxicokinetic evaluation on whole blood samples collected on Days 1, 2, 3, 4, 6, 8, 15, 22, 29, 36, 43, 50, 57 and 64. A tabulated summary of this study is presented in m2.6.7, Table 5.1.

One male given CAB in the PVP formulation SC was found dead on Day 44, 1 day after the last blood sampling for toxicokinetic evaluation. No clinical signs were noted prior to death. This rat had a malignant neoplasm (2 x 1 cm; morphologically consistent with chondrosarcoma and noted macroscopically as white foreign material) occluding the majority of the right ventricular lumen with involvement of the pulmonary valve, local invasion into the myocardium, and multiple metastases to the lung. The right ventricle was secondarily enlarged and had moderate myocardial degeneration and necrosis almost exclusively limited to the right ventricle. The neoplasm and secondary effects were considered the cause of death. The size of this neoplasm coupled with the significant

compensatory remodelling of the heart suggests it was pre-existing and therefore, unlikely test article related.

Histological examination of the hearts from the remaining rats on this study revealed 2 rats given the 10 mg/kg PVP formulation with myocardial degeneration/necrosis more severe than in concurrent control rats. However, there were only 3 control rats given the PVP formulation alone (SC and IM) compared with 12 rats given the 10 mg/kg PVP formulation (SC or IM). While minimal (and occasionally mild) myocardial degeneration/necrosis is a common spontaneous change, as evidenced by its presence in 5 of 6 control and 10 of 23 treated rats in this study, the severity of degeneration/necrosis in these 2 rats was at the upper end or exceeded that commonly seen spontaneously in standard 1-month toxicity studies. However, these rats were terminated at an age approximately 5 weeks older than rats terminated at the end of a standard 1-month toxicity study (20 weeks of age versus 15 weeks). Similar severity of myocardial degeneration and necrosis was not observed in the 3 control rats given the pluronic F formulation alone or the 12 rats that were given the 10 mg/kg pluronic F formulation. Additionally, in previous 14 day, 4-week, and 26-week repeat dose studies in which 10 to 12 male and 10 to 12 female Sprague Dawley rats were given doses up to 1000 mg/kg/day by oral gavage and achieved systemic exposures (AUC_{0-24} and C_{max}) up to approximately 10- to 28-fold greater and a total AUC value (AUC_{0-24} x 180 days for the 26-week study) approximately 86-fold greater than AUC_{0-t} in this study, no cardiac findings were observed. Furthermore, no cardiac findings were observed in a GLP single dose SC and IM toxicity study (n=10/sex/group, described below) at doses up to 100 mg/kg and AUC_{0-t} exposures approximately 12-fold greater than the AUC_{0-t} in this study. Therefore, the increased severity of myocardial degeneration/necrosis in rats given the 10 mg/kg PVP formulation is not considered to be related to administration of CAB.

Four rats given the 10 mg/kg PVP formulation SC had minimal to moderate subcutaneous inflammation (predominately granulomatous) associated with the injection sites (most likely test article and/or vehicle within the center of the granulomatous inflammation). Additionally, minimal degeneration and/or regeneration of the muscularis layer of subcutaneous tissue in and minimal chronic inflammation of the adipose tissue was observed and may have been associated with injection of test article and vehicle (10 mg/kg pluronic F formulation IM).

One rat given the 10 mg/kg PVP formulation SC had slight swelling around the injection site immediately after dosing, and on Days 2 to 6, and red/pink area around the injection site on Days 7 to 14; this was considered related to CAB.

In a second study, CAB (free acid) was administered to groups of male Sprague Dawley rats (n=3/group) as single SC injections at 0 (control; SC and IM), 10, 30 and 50 mg/kg and IM injections at 5, 20 and 35 mg/kg and toxicokinetic and toxicity assessments were conducted up to 56 days [Report RD2009/00906, m4.2.3.1]. CAB was formulated as a suspension in 2% pluronic F127, 0.2% Tween 80, 0.18% methylparaben, 0.02% propylparaben, 0.004 M NaH_2PO_4, 0.006 M Na_2HPO_4 with 0.83% NaCl. Clinical observations (including detailed observation of injection sites) and body weights were evaluated. Toxicokinetic evaluation was performed on samples collected on Days 1, 2, 3,

4, 6, 8, 15, 22, 29, 35, 42, 49 and 56. A tabulated summary of this study is presented in m2.6.7, Table 5.1.

The apparent plasma half-life of CAB following the SC and IM doses ranged from 200 to 227 hours and from 204 to 218 hours, respectively. There was no apparent difference in plasma half-life values between the dose routes, or among the dose levels.

All doses by both routes of administration were well tolerated.

In a third study, CAB (free acid) was administered to male Sprague Dawley rats (n=3/group) as single SC injections at 0 (control; SC and IM), 10, 30 and 50 mg/kg and IM injections at 5, 20 and 35 mg/kg and toxicokinetic and toxicity assessments were conducted up to 106 days [Report RD2009/01216, m4.2.3.1]. CAB was formulated as a suspension in 2% Tween 20, 2% polyethylene glycol 3350, and 4.5% mannitol in water. Clinical observations and body weights were evaluated. Toxicokinetic evaluation was performed on samples collected on Days 1, 2, 3, 4, 6, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 85, 92, 99 and 106. A tabulated summary of this study is presented in m2.6.7, Table 5.1.

Following the SC dose, plasma concentrations of CAB remained above the $PAIC_{90}$ (protein-adjusted) of 0.16 μg/mL through the last time point (Day 106) for every animal. Following the IM dose, plasma concentrations remained above 0.16 μg/mL through the last time point of Day 106 in all 3 animals that received 20 mg/kg, and in 2 of the 3 animals that received 35 mg/kg. Following 5 mg/kg, the plasma concentrations remained above 0.16 μg/mL to Day 71.

Swelling around the SC injection site occurred in one animal given 10 mg/kg and 50 mg/kg. Discoloration around the IM injection site occurred in one animal given 35 mg/kg. Slightly decreased body weights (0.85X) were noted in rats given 50 mg/kg SC.

In a definitive study, CAB (free acid) was administered to groups of Sprague Dawley rats (n=10/sex/group) as a single SC injection at dose levels of 0 (control), 5, 30 or 100 mg/kg or as a single IM injection at 2.5, 10 or 75 mg/kg [Report RD2009/01359, m4.2.3.1]. Additional animals (n=3/sex/group) were added for toxicokinetic analysis. Dosing was followed by at least a 74 day nontreatment period. CAB was formulated as a wet bead milled suspension in 2% Tween 20, 2% polyethylene glycol 3350 and 4.5% Mannitol in Sterile Water for Injection. The following endpoints were evaluated for toxicology animals: clinical observations, skin irritation (Draize scoring of injection sites), body weights, food consumption, hematology, coagulation, clinical chemistry, urinalysis, ophthalmoscopic observations, organ weights, and macroscopic and microscopic observations (including stage-dependent evaluation of spermatogenesis). Toxicokinetic evaluation was performed on plasma samples collected on Days 1, 2, 3, 4, 6, 8, 15, 21, 31, 41, 51, 61, 75 and 85 (SC only). A tabulated summary of this study is presented in m2.6.7, Table 5.2.

One toxicokinetic male given 100 mg/kg SC was found dead on Day 39. The cause of death could not be determined but was not considered test article related because there were no other deaths in any group, the only test article related finding in rats assigned to

toxicology groups was non-adverse injection site reactions, and systemic exposure (AUC_{0-720}) for this rat was less than the other 2 toxicokinetic males in this group.

Skin irritation noted as erythema and edema was observed at the injection sites following SC and IM administration. Generally, the number of rats affected, duration, and severity of erythema and edema increased in a dose dependent manner for rats given ≥5 mg/kg SC. The erythema and edema correlated with the histopathological injection site findings which were noted in rats given ≥30 mg/kg/day SC or 75 mg/kg IM. At the injection sites, skin irritation (as assessed by Draize Scoring) was noted as very slight to well-defined erythema in up to 3 males given ≥30 mg/kg and up to 10 females given ≥5 mg/kg SC. Very slight erythema was observed in 1 female given 75 mg/kg IM. Very slight erythema for the females given ≥30 mg/kg SC remained present until termination. Very slight to moderate edema was noted in up to 10 males and up to 10 females given ≥5 mg/kg and very slight to slight edema was observed in 2 males and 2 females given 75 mg/kg IM. Very slight edema noted for males and females given 30 mg/kg and very slight to well-defined edema noted for males and females given 100 mg/kg SC remained until termination.

Lesions associated with the SC injection site were readily identified macroscopically in rats given ≥30 mg/kg and microscopically were typical of a foreign body response (granuloma) to injected material. Based on macroscopic and microscopic examination, there is less residual injected material and foreign body reaction with IM injections, and this is consistent with systemic exposure (AUC) which resulted in less systemic exposure with IM injections late in the study due to less depot effect.

Histological changes of the reproductive tract reflective of persistent estrus were observed only in females given 100 mg/kg SC. The weight of evidence indicates that these changes were spontaneous occurrences of a natural aging process, and not test article-related.

CAB-related clinical pathology changes were non-specific and of minimal magnitude. Decreased total bilirubin was observed in males given ≥5 mg/kg SC during Weeks 4 and 13; and in males given ≥2.5 mg/kg IM, in females given 100 mg/kg SC, and in females given 75 mg/kg IM during Week 4. Decreased urine specific gravity was observed in females given ≥5 mg/kg SC during Week 4, in females given ≥30 mg/kg SC during Week 13, and in females given ≥2.5 mg/kg IM during Weeks 4 and 11. Increased urine volume was observed males and females given ≥5 mg/kg SC during Week 4, in females given ≥30 mg/kg during Week 13, and in females given ≥2.5 mg/kg IM during Weeks 4 and 11. The minimally increased serum calcium in females given ≥5 mg/kg SC during Weeks 4 and 13 and in females given ≥2.5 mg/kg IM during Week 4 was of uncertain relationship to CAB-treatment. Because these clinical pathology changes were within the range of biological variation and lacked histologic correlates, they were considered non-adverse.

There were no test article-related changes in the stage-dependent evaluation of spermatogenesis.

Based on the lack of adverse findings, the NOAEL was 100 mg/kg for SC administration and 75 mg/kg for IM administration. The gender-averaged mean systemic exposure at

100 mg/kg SC was 162 μg.h/mL for $AUC_{(0-24)}$, 49508 μg.h/mL for $AUC_{(0-720)}$, 122300 μg.h/mL for $AUC_{(0-t)}$, and 101 μg/mL for mean C_{max}. The gender-averaged mean systemic exposure at 75 mg/kg IM was 286 μg.h/mL for $AUC_{(0-24)}$, 62418 μg.h/mL for $AUC_{(0-720)}$, 96487 μg.h/mL for $AUC_{(0-t)}$ and 115 μg/mL for C_{max}.

2.4. Monkey

2.4.1. Oral administration

In a single dose toxicokinetic study, CAB (sodium salt) was administered to male monkeys (n=2) at escalating dose levels of 150, 300 and 1000 mg/kg with a 13 day washout period between doses [Report RD2007/01415, m4.2.3.1]. CAB was formulated in 0.5% w/w HPMC and 0.1% w/w Tween 80. Clinical observations and measurements of body weights and food consumption were conducted periodically and hematology and clinical chemistry evaluations were conducted during the pre-test period (Days -12 and -5) and 2, 6, 7 or 13 days after each dosing. A tabulated summary of this study is presented in m2.6.7, Table 5.1.

No adverse effects on body weights, food consumption, hematology or clinical chemistry were observed at ≤1000 mg/kg.

2.4.2. Intramuscular and subcutaneous administration

CAB (free acid) was administered to groups of male cynomolgus monkeys (n=4/group) as a single SC or IM injection at dose levels of 0 (control), 1 or 5 mg/kg and toxicokinetic and toxicity assessments were conducted up to 85 days [Report CD2009/00373, m4.2.3.1]. CAB was formulated in 1.7% PVP, 0.2% Tween 80, 0.18% methylparaben, 0.02% propylparaben, 0.004 M monosodium phosphate, 0.006 M disodium phosphate, and 0.84% NaCl. Doses of 1 and 5 mg/kg were administered to monkeys via each route using dose volumes of 0.05 and 0.0618 mL/kg with dose concentrations of 20 (particle size = 5.11 micron) and 80.94 (particle size = 6.84 micron) mg/mL, respectively. The following endpoints/parameters were evaluated: clinical observations (including qualitative assessment of food consumption) and body weights. Toxicokinetic evaluation (serial profiling) was performed on samples collected up to 85 days. A tabulated summary of this study is presented in m2.6.7, Table 5.1.

Systemic exposure increased less than proportionally with increasing dose but was similar between SC and IM routes of administration at the same dose. All doses were well tolerated with no CAB-related findings and no clinical observations at the injection sites.

A second study was conducted in which CAB (free acid) was administered to groups of male cynomolgus monkeys (n=4/group) as a single SC or IM injection at dose levels of 0 (control) or 5 mg/kg and toxicokinetic and toxicity assessments were conducted up to 56 days [Report CD2009/00513, m4.2.3.1]. CAB was formulated as a suspension in 1.7% PVP, 0.2% Tween 80, 0.18% methylparaben, 0.02% propylparaben, 0.004 M monosodium phosphate, 0.006 M disodium phosphate, and 0.84% NaCl (drug particle

size 67.7 microns). The following endpoints/parameters were evaluated: clinical observations (including qualitative assessment of food consumption) and body weights. Toxicokinetic evaluation (serial profiling) was performed on samples collected up to 56 days. A tabulated summary of this study is presented in m2.6.7, Table 5.1.

Plasma concentrations were quantifiable up to 1344 hours in the SC and IM groups. Systemic exposure was generally higher via the IM route as compared to SC administration of 5 mg/kg. All doses were well tolerated with no CAB-related findings and no clinical observations at the injection sites.

In a third study, CAB (free acid) was administered to groups of male cynomolgus monkeys (n=4/group) as a single SC or IM injection at dose levels of 0 (control) or 10 mg/kg and toxicokinetic and toxicity assessments were conducted up to 49 days [Report CD2009/00656, m4.2.3.1]. CAB was formulated as a suspension in 2% Pluronic F-127, 0.2% Tween 80, 0.18% methylparaben, 0.02% propylparaben, 0.008M $NaH_2PO_4H_2O$, 0.006M Na_2HPO_4 and 0.81% NaCl. The following endpoints/parameters were evaluated: clinical observations (including qualitative assessment of food consumption) and body weights. Toxicokinetic evaluation (serial profiling) was performed on samples collected up to 49 days. A biopsy of a mass present at the SC injection site of one male was collected on Day 51, and macroscopic and microscopic observations were recorded. A tabulated summary of this study is presented in m2.6.7, Table 5.1.

Overall, mean C_{max} via the IM route was higher than via the SC route at a dose of 10 mg/kg. On approximately Day 49, plasma concentrations were approaching the protein-adjusted 90% inhibitory concentration ($PAIC_{90}$) of 166 ng/mL in the SC group and were below the $PAIC_{90}$ in the IM group.

All 4 monkeys given SC injections of 10 mg/kg were observed to have skin thickening at the injection sites (intrascapular region), beginning as early as Day 4 and continuing until Day 23 or 25 for 3 monkeys and Day 51 for 1 monkey. Skin reddening was also observed at the injection site in 1 monkey from Days 4 through 6 and Days 15 through 22. Additionally, 2 monkeys were noted to have a mass present at the injection site from Day 25 through 41 or Day 5 through 51. Subcutaneous granulomatous inflammation was observed within the skin biopsy of the persistent injection site mass in one monkey given 10 mg/kg SC.

All 4 monkeys given IM injections of 10 mg/kg were observed to have skin thickening at the injection sites (left gluteal region), beginning as early as Day 4 and continuing until Days 18, 22, or 25. A mass was noted at the injection site of 1 monkey on Day 5 only.

There were no CAB-related observations other than skin reactions and injection site observations.

A combination study was conducted in male cynomolgus monkeys to investigate the effects of a single IM injection of CAB (free acid; 10 mg/kg) and rilpivirine (RPV) (60 mg/kg) when given alone (n=2/group) or when given in combination (as separate injections; n=4 monkeys), followed by a 61 day off-treatment period [Report 2010N105579, m4.2.3.1]. CAB was prepared for dosing in a formulation of 2% Tween

20, 2% polyethylene glycol 3350 and 4.5% mannitol in sterile water for injection, and RPV was prepared using a proprietary formulation as provided by Janssen. Parameters that were determined during the study included clinical observations (including potential injection site reactions), toxicokinetics (on samples collected up through Day 61), and body weights. A tabulated summary of this study is presented in m2.6.7, Table 5.1.

The systemic exposure to CAB or RPV (mean plasma C_{max} or AUC values) when dosed in combination or alone was similar, suggesting there is no PK interaction between CAB and RPV in monkeys.

CAB was well tolerated throughout the study. RPV caused slight edema on Day 4 in 1 animal given RPV alone and in one animal given both CAB and RPV. Both CAB and RPV were well tolerated after a single dose administration and were quantifiable through 61 days after dosing when given alone.

Table 2.2 Batch Numbers of CAB and Formulations Used in Single Dose Toxicity Studies

Batch or Lot Number(s)	Study Type	Species (Strain) or Test System	Form	Duration of Dosing	Report No. (Study No.)	Concentration (mg/mL)	Formulation
[redacted]	Single oral	Mouse (CD-1)	B	Single	RD2009/00691 (M42451)	1, 10, 100, 200	1
[redacted]	Single IM / SC	Rat (Sprague Dawley)	A	Single	RD2009/00865 (R42469)	20	2, 3
[redacted]	Single IM / SC	Rat (Sprague Dawley)	A	Single	RD2009/00906 (R42473)	10, 20, 40, 60, 70, and 100	3
[redacted]	Single IM / SC	Rat (Sprague Dawley)	A	Single	RD2009/01216 (R42506)	IM: 25, 102, 178 SC: 36, 107, 178	4
[redacted]	Single IM / SC	Rat (Sprague Dawley)	A	Single	RD2009/01359 (R42516)	6.7, 10, 26.7, 60 and 200	4
[redacted]	Single oral	Monkey (cynomolgus)	B	Single	RD2007/01415 (E-265744-TF-006-R)	15, 30, 100	1
[redacted]	Single IM / SC	Monkey (cynomolgus)	A	Single	CD2009/00373 (D09052)	16.2, 20, 80.9, 100	5
[redacted]	Single IM / SC	Monkey (cynomolgus)	A	Single	CD2009/00513 (D09084)	85	5
[redacted]	Single IM / SC	Monkey (cynomolgus)	A	Single	CD2009/00656 (D09112)	200	6
CAB: [redacted] RPV: [redacted]	Single IM	Monkey (cynomolgus)	A	Single	2010N105579	CAB: 200 RPV: 300	CAB: 4 RPV: 7

Note: CAB materials from multiple routes of synthesis were used in the nonclinical studies. The impurity profile of the materials used in the nonclinical safety studies were consistent with that proposed for clinical use.

Batch Numbers of CAB and Formulations Used in Single Dose Toxicity Studies (Continued)

Batch or Lot Number(s)	Study Type	Species (Strain) or Test System	Form	Duration of Dosing	Report No. (Study No.)	Concentration (mg/mL)	Formulation

Key:
A = GSK1265744A, the parent form.
B = GSK1265744B, the sodium salt.
NA = Not applicable.

Formulation Code:
1 = Aqueous 0.5% hydroxypropylmethylcellulose (HPMC) and 0.1% Tween 80.
2 = 1.7% polyvinylpyrrolidone (PVP), 0.2% Tween 80, 0.18% methylparaben, 0.02% propylparaben, 0.004 M NaH_2PO_4 H_20, 0.006 M Na_2HPO_4.
3 = Aqueous 2% pluronic F127, 0.2% Tween 80, 0.18% methylparaben, 0.02% propylparaben, 0.004 M NaH_2PO_4 H_20, 0.006 M Na_2HPO_4 with NaCl.
4 = 2% Tween 20, 2% polyethylene glycol 3350 and 4.5% Mannitol in sterile water for injection.
5 = 1.7% polyvinylpyrrolidone (PVP), 0.2% Tween 80, 0.18% methylparaben, 0.02% propylparaben, 0.004 M NaH_2PO_4 H_20, 0.006 M Na_2HPO_4 with NaCl in sterile water for injection.
6 = Aqueous 2% pluronic F127, 0.2% Tween 80, 0.18% methylparaben, 0.02% propylparaben, 0.008 M NaH_2PO_4 H_20, 0.006 M Na_2HPO_4 with NaCl.
7 = Formulation is proprietary to Janssen.

3. REPEAT DOSE TOXICITY

3.1. Introduction

Repeat dose toxicity studies investigating the effects of repeated administration of CAB have been performed in Sprague Dawley rats and cynomolgus monkeys. These were preceded, where appropriate, by preliminary studies to establish the maximum repeatable daily doses for use in the definitive studies. Repeat dose toxicity studies up to 13 weeks in duration have also been conducted in CD-1 mice to establish suitable dose levels for use in oral carcinogenicity studies. To support the long-term therapeutic use of CAB tablets, studies were performed by the oral route of administration for periods up to 26 weeks in the rat and 39 weeks in the monkey. To support the long-term therapeutic use of long-acting parenteral (LAP) CAB, a repeat dose injection study was conducted in rats for up to 3 months, to bridge the toxicity assessment of LAP CAB to the oral toxicity assessment. Sufficient animals were used in each study to allow meaningful evaluation of the data. Studies undertaken to establish suitable dose levels for use in repeat dose toxicity studies were performed in accordance with the general principles of Good Laboratory Practice (GLP) regulations. All definitive studies were performed in full compliance with GLP regulations.

A table listing the batches of CAB together with information on the method of formulation used in these investigations is presented in Table 3.2 of this summary.

A full listing of the repeat dose toxicity studies performed, together with the GLP status and the location of the reports within this submission, is provided in Table 3.1. An inter-species comparison of CAB plasma concentrations following repeated administration in the definitive toxicity studies is presented in Section 9, Table 9.1. A tabular summary of the repeat dose toxicokinetic data derived from the toxicity studies is presented in m2.6.7, Table 3.

Table 3.1 List of Repeat Dose Toxicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
14 day	Mouse (CD-1)	10M/10F	Oral (gavage)	B	10, 75, **1000**	14 days	Yes	GSK	RD2009/00692 (M42452)	m4.2.3.2
13 week	Mouse (CD-1)	12M/12F	Oral (gavage)	B	10, **75**, 1000	13 weeks	Yes	[redacted]	2012N142081 (M42936)	m4.2.3.2
13 week	Rat (Sprague Dawley)	12M/12F	SC (monthly) IM (monthly) SC (weekly)	A	5, 30, **100** 2.5, 10, **75** **100**	13 weeks	Yes	[redacted]	2010N104820 (R42698)	m4.2.3.2
14 day	Rat (Sprague Dawley)	10M/10F[a]	Oral (gavage)	A	30, 100, **300**	14 days	Yes	GSK	RD2006/01741 (R41937)	m4.2.3.2
4 week	Rat (Sprague Dawley)	10M/10F[b]	Oral (gavage)	B	1, 75, **1000**	4 weeks	Yes	GSK	RD2008/00448 (R42288)	m4.2.3.2
26 week	Rat (Sprague Dawley)	12M/12F[b]	Oral (gavage)	B	0.5, 5, **1000**	26 weeks	Yes	GSK	RD2009/00031 (R42404)	m4.2.3.2
7 day	Monkey (cynomolgus)	1M/1F	Oral (gavage)	B	50, 150, 1000	7 days	No	GSK	CD2007/00577 (D07170)	m4.2.3.2
14 day	Monkey (cynomolgus)	3M/3F	Oral (gavage)	B	8, **25**, 1000	14 days	Yes	GSK	CD2007/00680 (G07171)	m4.2.3.2

List of Repeat Dose Toxicity Studies Performed with CAB (Continued)

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
4 week	Monkey (cynomolgus)	3M/3F[c]	Oral (gavage)	B	5, 50, **500**	4 weeks	Yes	GSK	CD2008/00632 (G08079)	m4.2.3.2
39 week	Monkey (cynomolgus)	4M/4F[d]	Oral (gavage)	B	5, 50, **500**	39 weeks	Yes	[redacted]	RD2009/00027 (P42405)	m4.2.3.2

Key:
a = An additional 3/sex/group were added for toxicokinetic evaluation.
b = An additional 6/sex/group were added at 1000 mg/kg/day as 2 week recovery animals.
c = An additional 2/sex/group were added at 500 mg/kg/day as 6 week recovery animals.
d = An additional 2/sex/group were added at 500 mg/kg/day as 6 week recovery animals.
A = GSK1265744A, the free acid. B = GSK1265744B, the sodium salt.
Note: No observed adverse effect levels (NOAELs) values are in **bold** type.

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

3.2. Mouse

3.2.1. Oral administration

3.2.1.1. 14 day study

In a 14 day repeat dose oral toxicity study, CAB (sodium salt) was administered to CD-1 mice (10/sex/group) at doses of 0 (control), 10, 75 and 1000 mg/kg/day [Report RD2009/00692, m4.2.3.2]. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. Parameters that were evaluated during the study were clinical observations, toxicokinetics, body weights, food consumption, hematology and clinical chemistry, ophthalmoscopic observations, organ weights, macroscopic observations and microscopic pathology (including stage dependent evaluation of spermatogenesis). A tabulated summary of this study is presented in m2.6.7, Table 6.2.

The systemic exposure (plasma C_{max} and AUC_{0-24} values) of CAB increased less than proportionally with the increase in dose in each sex on both Days 1 and 14. Although the systemic exposure was slightly higher (about 10% to 70%) on Day 14 compared to Day 1, there were no marked differences in exposure. There were no gender differences in systemic exposure.

Minimal to moderate increases in serum enzymes alanine aminotransferase (ALT), glutamate dehydrogenase (GLDH), and aspartate aminotransferase (AST) were noted in one male and female mouse each given 1000 mg/kg/day. No hepatic histological correlates were observed in the male, and it could not be determined if the minimal hepatocellular necrosis in the female was responsible for the minimal to mild elevated serum enzymes, as a control male had comparable hepatocellular necrosis, but with no enzyme elevations. Although likely test article-related, a definitive relationship could not be established because there were no histologic correlates or similar changes in other mice. These findings were considered non-adverse.

Other clinical or anatomic pathology changes were within the range of biological variation and were not considered related to treatment with CAB. There were no changes considered related to CAB administration in the stage-dependent evaluation of spermatogenesis.

The NOAEL was 1000 mg/kg/day [mean AUC_{0-24} 2587 μg.h/mL; mean C_{max} 142 μg/mL (gender-averaged based on Day 14 values)].

3.2.1.2. 13 week study

CAB (sodium salt) was given by oral gavage to groups of CD-1 mice (12/sex/group) at dose levels of 0 (control), 10, 75 and 1000 mg/kg/day once daily for 13 weeks [Report 2012N142081, m4.2.3.2]. Nine animals/sex (vehicle control) and 54 animals/sex (10, 75, and 1000 mg/kg/day) were added for toxicokinetic evaluation (TK). CAB was formulated with 0.5% HPMC and 0.1% Tween 80. Parameters that were evaluated during the study included clinical observations, toxicokinetics, body weights, food

consumption measurements, haematology and clinical chemistry, ophthalmoscopic observations, organ weights, and macroscopic and microscopic observations. A tabulated summary of this study is presented in m2.6.7, Table 7.1.

The composite C_{max} and AUC_{0-t} values (systemic exposure) for CAB in females were similar (difference within 35%) to those in males at each dose level and on each sampling day (Day 1, Weeks 4 and 13). The systemic exposure values for CAB increased less than proportionally to the increase in dose in males and females on each sampling day. A 7.5- or 100-fold increase in dose from 10 mg/kg/day resulted in a 2- to 3-fold or a 3- to 5-fold increase, respectively, in systemic exposure. The systemic exposure values for CAB at Week 13 were generally slightly greater (generally 19 to 96% higher) than those values on Day 1. The systemic exposure values for CAB at Week 13 were similar (difference within 26%) to those values on Week 4.

Four animals died or were euthanized in poor condition (3 toxicokinetic [TK] animals given either 10, 75, or 1000 mg/kg/day, and one toxicology group animal given 1000 mg/kg/day) and findings were considered related to dosing method complications or unrelated to systemic exposure of the test item.

On Day 68, one toxicology group male given 1000 mg/kg/day was euthanized at approximately 6 hours post-dose due to observations of labored breathing, distended abdomen, purple skin (abdominal/lumbar), partly closed eyes, cold to touch and suspected dehydration. Prior to euthanasia, dosing reflux was noted. Macroscopic findings included dilatation of the stomach and small intestine with no microscopic correlate. Marked degeneration/regeneration of the epithelium of the nasal cavity with pronounced inflammation and exudate were noted microscopically. Bronze-colored material consistent with foreign matter was present within the exudate. The findings were consistent with gastric reflux as the cause of death and, therefore, not related to systemic exposure to CAB.

Three (2 males and 1 female) TK animals, one at each dose, were euthanized or found dead on Days 18, 37 and 47. One TK male given 10 mg/kg/day was euthanized due to a gavage accident. One TK male given 75 mg/kg/day had the following clinical signs noted prior to euthanasia on Day 37 (approximately 5 hours post-dose): breathing abnormalities/panting, blue skin on the abdomen and suspected dehydration. Macroscopic and microscopic examination revealed no lesions that could have contributed to the moribundity of this animal. The lack of potentially test item-related lesions in this animal and all toxicology animals given 75 mg/kg/day suggest this was likely related to gavage dosing and not a direct test item effect. There were no clinical signs noted for the female animal given 1000 mg/kg/day prior to death, however, this animal was found dead less than an hour after dosing on Day 47. The lack of potentially CAB-related lesions in this animal, and the mortality close to dosing, suggest that the death was likely related to gavage dosing and not a direct CAB effect.

CAB-related microscopic changes were noted in the nasal cavity/sinuses of some males and females given 1000 mg/kg/day and consisted of degeneration/regeneration of both olfactory and respiratory epithelium with inflammation and exudate. In two animals, the exudates contained bronze-colored material consistent with foreign matter. The findings

are consistent with gastric reflux of the gavage material into the nasal cavity rather than a systemic effect of CAB. CAB-related increases in mean neutrophil counts were observed in males given 1000 mg/kg/day (1.71X controls) and were possibly related to inflammatory degeneration/regeneration of olfactory and respiratory epithelium described histologically in some affected animals.

Mean absolute and relative (to body weight) heart (up to 1.15X control) and kidney (up to 1.17X control) weights were increased in male animals given 1000 mg/kg/day. These changes occurred in the absence of any microscopic correlates and were considered non-adverse.

Non-adverse, dose-related minimal decreases in glucose concentrations were noted in males given ≥75 mg/kg/day (down to 0.77X controls) and in females given ≥10 mg/kg/day (down to 0.80X controls).

Slightly lower mean body weights were noted in males given 1000 mg/kg/day and females given ≥75 mg/kg/day. These were not associated with any changes in food consumption or clinical observations and were considered non-adverse. These body weight differences resulted in CAB-related lower mean body weight gains at the end of the study for both males and females.

Two females given 1000 mg/kg/day had minimal to slight myeloid hypercellularity in the bone marrow. One of the two animals also had degeneration/regeneration of the epithelium with inflammation in nasal cavity. Because of these concurrent changes in this animal and evidence of gastric reflux in other animals, the bone marrow change was considered likely secondary to the nasal cavity inflammation and not a direct CAB-related effect.

The NOAEL was 75 mg/kg/day. The gender-averaged CAB AUC_{0-t} exposure at 75 mg/kg/day for Week 13 was 1345 μg.h/mL (1330 to 1360 μg.h/mL); C_{max} 72.8 μg/mL (69.1 to 76.4 μg/mL).

3.3. Rat

3.3.1. Oral administration

3.3.1.1. 14 day study

Groups of Sprague Dawley rats (10/sex/group) were given CAB (free acid) at doses of 0 (control), 30, 100, or 300 mg/kg/day once daily for 14 or 15 days by oral gavage [Report RD2006/01741, m4.2.3.2]. An additional 3 animals/sex were included at each dose level for toxicokinetic evaluation. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. The following parameters were evaluated for toxicology animals: clinical observations, neurobehavioral assessment, body weights, food consumption measurements, hematology, coagulation, clinical chemistry, urinalysis, ophthalmoscopic observations, organ weights, and macroscopic and microscopic observations (including stage-dependent evaluation of spermatogenesis). Toxicokinetic evaluation was

performed on samples collected on Days 1 and 14, and P450 isoform evaluation was performed on samples collected on Day 15 (results reported separately). A tabulated summary of this study is presented in m2.6.7, Table 7.3.

The mean systemic exposure to CAB (as measured by AUC_{0-24} and C_{max}) increased in a less than dose-proportional manner in male and female rats on Days 1 and 14. No notable (greater than 2-fold) sex differences in mean AUC_{0-24} and C_{max} values were observed. Exposures were approximately 3- to 6-fold higher on Day 14 compared with Day 1 at all doses.

CAB-related microscopic findings occurred in the kidney (300 mg/kg/day) and adrenal glands (30, 100, and 300 mg/kg/day) in males. Similar findings were observed in both tissues in control males, but the extent of each change was increased in treated males. In the adrenal glands of males given ≥30 mg/kg/day, cytoplasmic vacuolation in cortical cells in the zona fasciculata was mildly increased above that observed spontaneously in the control males. The extent of the cortical vacuolation did not appear to change significantly in relation to dose. In the kidneys of males given 300 mg/kg/day, a mild to moderate increase in eosinophilic droplets in the cytoplasm of proximal renal tubule epithelium correlated with a mild proteinuria. Immunohistochemistry confirmed that in rats given 300 mg/kg/day, the majority of eosinophilic droplets stained positive for α2μ globulin and a minority stained positive for albumin. Overall, the increase in renal eosinophilic droplets in the treated male rats was due to a combination of increased α2μ globulin and albumin.

Mildly increased absolute and relative heart weights (≤1.15X control for absolute) in males given ≥100 mg/kg/day and increased thymus weights in males given ≥30 mg/kg/day did not correlate with any other findings in this study. These tissues were generally normal microscopically, or in the case of the heart in some animals, only minimal changes were noted, and these were consistent with findings in concurrent controls.

The CAB-related changes in the kidneys, adrenal glands, heart, and thymus were considered non-adverse. The changes in the kidneys and adrenals represented alterations in the extent of a normally occurring observation and did not significantly impact clinical health in the context of this study based on evaluation of body weight, food consumption, clinical signs, and clinical pathology parameters. The organ weight changes in the heart and thymus did not correlate with any other study findings, did not impact clinical health, and were not associated with any microscopic changes.

Additional test article-related changes in clinical pathology parameters included mild to moderate decreases in total bilirubin in males and females at all doses and a minimal increase in phosphorus in females given 300 mg/kg/day. These findings were non-adverse based on the magnitude of the changes and lack of histopathologic correlation.

Due to the absence of adverse findings, the no observed adverse effect level (NOAEL) was 300 mg/kg/day.

3.3.1.2. 4 week study

CAB (sodium salt) was administered by oral gavage to groups of Sprague Dawley rats at doses of 0 (control), 1, 75 or 1000 mg/kg/day once daily for 28 or 29 days [Report RD2008/00448, m4.2.3.2]. Sixteen rats/sex each were given 0 or 1000 mg/kg/day, and 10 rats/sex each were given 1 or 75 mg/kg/day. The first 6 animals/sex given 0 or 1000 mg/kg/day were assigned to a 2-week recovery period. An additional 3 animals/sex were included at each dose level for toxicokinetic evaluation. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. The following parameters were evaluated for toxicology animals: clinical observations, toxicokinetics, body weights, food consumption measurements, hematology, coagulation, clinical chemistry, urinalysis, ophthalmoscopic observations, organ weights, and macroscopic and microscopic observations (including stage-dependent evaluation of spermatogenesis). A tabulated summary of this study is presented in m2.6.7, Table 7.4.

Mean systemic exposure to CAB in male and female rats increased in a less than dose-proportional manner as the dose was increased from 1 to 1000 mg/kg/day on Days 1 and 28. Notable (≥2-fold) differences in mean plasma systemic exposure (AUC_{0-24} and C_{max}) to CAB on Day 28 compared to Day 1 were observed in the 1 mg/kg/day dose group (8.1- to 11-fold) and in the 75 mg/kg/day dose group (2.2- to 2.6-fold). No notable differences in mean systemic exposure were noted in the 1000 mg/kg/day dose group. No notable differences in systemic exposure between males and females were observed.

Administration of CAB resulted in a variety of non-adverse changes in clinical pathology parameters including minimal to mild increases in alanine aminotransferase (ALT), glutamate dehydrogenase (GLDH), and aspartate aminotransferase (AST) in females given 1000 mg/kg/day and males given ≥75 mg/kg/day. In addition, there were decreases in total bilirubin in males and females at all doses, a decrease in absolute reticulocyte counts in males given 1000 mg/kg/day, and minimal increases in urine glucose:volume in females given ≥1 mg/kg/day. By the end of the 2-week recovery period, changes included decreases in total bilirubin, total protein, globulin, and urine creatinine:volume in males and minimal increases in urine glucose:volume in females. There were no macroscopic or microscopic pathology changes attributed to CAB administration. Test article-related changes in body weight consisted of a decrease in group mean body weight (0.91-0.95X mean control) and body weight gain (compared to concurrent controls) in males given ≥1 mg/kg/day at the end of the dosing and recovery periods. No changes attributable to CAB were noted at stage-dependent evaluation of spermatogenesis and/or at microscopic examination of the testes at any dose level.

Based on the absence of adverse effects, the no observable adverse effect level (NOAEL) is 1000 mg/kg/day [mean AUC_{0-24} 3735 μg.h/mL, range 3214 to 4629 μg.h/mL; mean C_{max} 171.5 μg/mL, range 149 to 214 μg/mL (gender-averaged based on Day 28 values)].

3.3.1.3. 26 week study

In a 26 week study, CAB (sodium salt) was given by oral gavage to groups of Sprague Dawley rats [12/sex/main study group; 6/sex/recovery group (0 and 1000 mg/kg/day only)] at doses of 0 (control), 0.5, 5, or 1000 mg/kg/day. Three animals/sex were added

at each dose level for toxicokinetic evaluation [Report RD2009/00031, m4.2.3.2]. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. The following parameters were evaluated for toxicology animals: clinical observations, toxicokinetics, body weights, food consumption measurements, hematology, coagulation, clinical chemistry, urinalysis, ophthalmoscopic observations, organ weights, and macroscopic and microscopic observations. A tabulated summary of this study is presented in m2.6.7, Table 7.5.

The systemic exposure to CAB (as defined by AUC_{0-24} and C_{max} values) increased less than proportionately with the increase in dose on each sampling occasion (Weeks 4, 13, and 26) in both sexes. For a 2000-fold increase in dose from 0.5 to 1000 mg/kg/day, the mean AUC_{0-24} and C_{max} values increased 6- to 11-fold. Systemic exposure to CAB was not notably different (>2-fold) among sampling occasions at any dose level.

Two animals were found dead/euthanized during this study. One female given 5 mg/kg/day (found dead on Day 61) and 1 male given 1000 mg/kg/day (euthanized on Day 126) were each observed to have lymphoma. The lymphomas were considered spontaneous in origin because the incidence did not increase with dose or duration of treatment, the clinical and macroscopic presentations of the lymphomas were different in both animals, and the lymphomas were of different cell lineages. Also, there were no test article related potential precursor lymphoid effects.

In the limiting ridge of the non-glandular stomach of animals given 5 mg/kg/day (males only) and animals given 1000 mg/kg/day, there was non-adverse minimal to slight increased cell death (apoptosis) in the squamous mucosa with vacuolar degeneration and regenerative hyperplasia and associated submucosal infiltration of mixed inflammatory cells. Following a 6-week recovery period, these findings were still observed in both genders, although with decreased incidence and severity, indicating that the lesions were reversible. The changes in the non-glandular stomach were not considered adverse as there were no functional changes (e.g. no fecal changes, and no negative effects on food consumption or body weight) and the changes were only present in the limiting ridge, with the vast majority of the non-glandular stomach unaffected.

In the nasal cavity, minimal to slight turbinate fusion, minimal epithelial degeneration/regeneration and minimal to moderate inflammation at different stages of chronicity were observed in some males and/or females given 1000 mg/kg/day. These findings were not observed in animals from the recovery phase and were considered secondary to reflux of gavage material. The primary ventral distribution of these lesions and the fact that some were acute and others chronic with evidence of repair suggests they were secondary to occasional reflux of gavage material rather than a direct effect of CAB.

Transient increases in aspartate aminotransferase (1.12x) were seen in females at 1000 mg/kg/day during Week 26. However, no histopathology correlate was noted in the striated muscle, and increases were not observed following recovery.

The no observed adverse effect level (NOAEL) was 1000 mg/kg/day [mean AUC_{0-24} 3992 μg.h/mL and mean C_{max} 186 μg/mL (gender averaged based on Week 26 values)].

3.3.2. Subcutaneous and intramuscular administration

3.3.2.1. 13 week study

Groups of male and female Sprague Dawley rats (n=12/sex/group) were given CAB (free acid) by subcutaneous (SC) injection in the inter-scapula region at 0 (control), 5, 30, or 100 mg/kg/dose once monthly for 3 months followed by a 75 day off dose (non-treatment) period and at 0 (vehicle) or 100 mg/kg/dose once weekly for 13 weeks, followed by a 14-day off-dose period. Additionally, CAB was also given to male and female rats (12/sex/group) at 0 (control), 2.5, 10 or 75 mg/kg/dose once monthly for 3 months by intramuscular (IM) injection in the thigh, followed by a 51-day off dose period [Report 2010N104820, m4.2.3.2]. Three animals/sex were added at each dose level/route of administration for toxicokinetic evaluation. CAB was formulated with 2% Tween 20, 2% polyethylene glycol 3350, and 4.5% mannitol in sterile water for injection. Data that were collected included toxicokinetics, clinical observations and local irritation assessment, body weights, food consumption, hematology, coagulation, clinical chemistry, urinalysis, ophthalmology, organ weights, and macroscopic and microscopic observations. A tabulated summary of this study is presented in m2.6.7, Table 7.2.

The systemic exposure (mean C_{max} and AUC values) of CAB tended to be higher (as much as 95%) in female rats than in male rats, particularly at the highest dose levels (SC and IM), however, these differences did not exceed 2-fold. The systemic exposure during the first and third monthly SC dose intervals increased less than proportionally to the increase in dose. The systemic exposure during the first and third monthly IM dose intervals increased less than proportionally to the increase in dose, or in proportion to the increase in dose. The mean AUC value during the third monthly SC dose intervals ranged from 2- to 3-fold higher than those during the first monthly dose intervals, whereas the increase in AUC values over this timeframe following monthly IM injections was minimal (1.1-to 1.4-fold).

Sporadic non-treatment related mortality occurred in animals receiving 75 mg/kg/month IM or 100 mg/kg/month SC; one main study male (75 mg/kg/dose IM) was euthanized on Day 39, while two animals (male at 75 mg/kg/dose IM, and male at 100 mg/kg/dose monthly SC) were found dead on Days 61 and 122, respectively. One female (100 mg/kg/dose monthly SC) was euthanized on Day 108 for humane reasons due to the presence of a large mass (100 x 100 x 70 mm) on the right hindlimb which impeded the animal's normal function and resulted in a rapidly deteriorating condition. The etiology of the mass was considered unrelated to dosing with CAB. The clinical signs noted prior to death were comparable to that of animals euthanized at study termination, except for one animal which had the following clinical observations: decrease in activity, partly closed eyes, generalized weakness, prominent backbone, decreased muscle tone, hunched posture, shallow breathing/irregular respiratory rate, suspected dehydration, absence of feces in the animal's tray, lack of pinching reflex and generalized incoordination (most of the aforementioned clinical signs were exclusively noted for this single animal). The cause of moribundity or death in these animals was not linked to any underlying pathology findings (macro or microscopic), as none of these animals had explanatory pathology findings distinct from survivors. There were no adverse clinical signs seen in surviving animals administered test article at the above dose levels and route or once

weekly SC, no organ weight changes, no adverse histological correlates, and no increase in incidence of mortalities with prolonged/repeated exposure. The systemic exposure through Day 96 in animals that received 100 mg/kg/dose weekly SC (combined mean $AUC_{0\text{-}2280h}$ of 337152 μg.h/mL, a combined mean C_{max} of 194 μg/mL) was higher than that compared to a similar interval during once a month dosing [$AUC_{0\text{-}2280h}$ of 232982 μg.h/mL for once monthly SC (100 mg/kg/dose) or $AUC_{0\text{-}2280h}$ 264641 μg.h/mL for once monthly IM (75 mg/kg/dose)]. Taken together, these mortalities were not considered treatment related.

CAB-related clinical signs were limited to swelling and redness noted at the injection site (SC and IM injections). These clinical signs were noted as early as Day 7 and persisted throughout the treatment and non-treatment periods. The incidence of these clinical signs was dose-proportional and considerably higher in those animals administered CAB via SC injections compared to those in animals receiving IM injections. Additionally, a number of animals administered CAB IM or SC, monthly or weekly, had erythema and/or edema at the sites of injection following the dosing occasions and persisting during non-treatment periods. These clinical signs were present in groups administered 75 mg/kg/dose (monthly IM injections), 30 mg/kg/dose (monthly SC injections) and, at a higher incidence, at 100 mg/kg/dose (monthly and weekly SC injections) and in females at 5 mg/kg/dose (monthly SC injections). The severity of the erythema and/or edema ranged from very slight to moderate/severe. The above-mentioned erythema and/or edema observations were consistent with the clinical signs noted throughout the study (i.e. swelling and redness noted at the injection site) as well as gross and microscopic findings at the sites of injection. These clinical signs of local reactions at the injection site were rarely scored as a severe response. There were no adverse clinical signs indicative of systemic toxicity.

Test article-related changes in body weights were observed in males given ≥5 mg/kg/dose, females given 5 mg/kg/dose monthly SC and females given ≥2.5 mg/kg/dose monthly IM. However, as these changes did not correspond with clinical signs, they were determined to not be adverse.

Increased neutrophil counts (1.82X and 1.65X compared to control, respectively) were noted in males and females given 100 mg/kg/dose weekly SC and persisted into the non-treatment period in females (1.54X compared to control). This finding is consistent with the inflammation present at the injection sites.

Clinical chemistry changes were seen in animals administered ≥30 mg/kg/dose. CAB-related decreases in total bilirubin were observed in males and females given CAB monthly SC injection at 30 and 100 mg/kg/dose (down to 0.62X of controls), in males and females given IM injection at 75 mg/kg/dose (down to 0.57X of controls) and in males and females given CAB weekly via SC injection at 100 mg/kg/dose (down to 0.31X of controls), all of which persisted following the non-treatment periods. CAB-related increases in triglyceride concentrations were observed in males given CAB at 30 and 100 mg/kg/dose via SC monthly injections (up to 1.41X of controls) recovering after the non-treatment period. Increases in urea, creatinine and phosphorus concentrations were observed in females given CAB weekly via SC injections at 100 mg/kg/dose, with increases in phosphorus in males given 100 mg/kg/dose. Minimal increases in urea and

phosphorus persisted in females given 100 mg/kg/dose following the non-treatment period. CAB-related decreases in albumin and total protein concentrations were observed in males and females given CAB weekly via SC injections at 100 mg/kg/dose, recovering after the non-treatment period.

Administration of CAB resulted in granulomatous inflammation and mixed inflammatory cell infiltration at the injection sites. These changes correlated with macroscopic changes (pale areas and foci, raised areas, nodules, masses) and were generally dose-dependent. All other changes affected low numbers of animals, were evenly distributed in all groups or were considered as common background changes in rats of this strain and age and, therefore, were not considered to be test article related.

Although doses were slightly different, subcutaneous injections were generally associated with changes of higher incidence and severity than intramuscular injections. Of the two subcutaneous treatment regimens, injection site changes were most severe in animals receiving weekly subcutaneous injections having the shortest recovery period.

The NOAEL for monthly administration were 100 mg/kg/dose SC and 75 mg/kg/dose IM. At the NOAEL, the mean $AUC_{1440-2160h}$ at 100 mg/kg/dose (subcutaneous injection) during the 3rd dosing interval was 70494 and 116602 µg.h/mL, and the mean third dose C_{max} was 118 and 195 µg/mL, for males and females, respectively. At 75 mg/kg/dose (intramuscular injection), the mean $AUC_{1440-2160h}$ during the third dosing interval was 78051 and 107080 µg.h/mL and the mean third dose C_{max} was 120 and 170 µg/mL for males and females, respectively. The NOAEL for weekly SC administration was 100 mg/kg/dose. At the NOAEL, the $AUC_{2016-2184h}$ at 100 mg/kg/week was 22291 and 34315 µg.h/mL, and C_{max} was 143 and 223 µg/mL for males and females, respectively.

3.4. Monkey

3.4.1. Oral administration

3.4.1.1. 7 day study

In a 7 day study, CAB (sodium salt) was given orally by gavage to cynomolgus monkeys (n=1/sex/group) at doses of 0 (control), 50, 150 or 1000 mg/kg/day [Report CD2007/00577, m4.2.3.2]. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. The following parameters were evaluated: clinical observations, toxicokinetics, body weights, hematology and clinical chemistry. A tabulated summary of this study is presented in m2.6.7, Table 6.1.

Except for an approximately proportional increase in females between 50 and 150 mg/kg/day on Day 1, the systemic exposure to CAB (as measured by AUC_{0-24} and C_{max}) generally increased in a less than dose-proportional manner in monkeys on Days 1 and 7. No notable (greater than 2-fold) sex differences in AUC_{0-24} and C_{max} values were observed. No notable difference in exposure was observed on Day 7 compared to Day 1, except for an approximately 70% decrease in both AUC_{0-24} and C_{max} values in the female given 150 mg/kg/day.

Excessive salivation was noted on Days 6 and 7, and emesis was noted on Days 5 through 7 in the male given 1000 mg/kg/day. Decreased food consumption was observed in this animal on Days 6 through 8. Abnormal feces was noted at all doses with a dose-dependent increase in incidence and severity. Sporadic episodes of emesis were also seen in males given 0 (vehicle), 50 and 150 mg/kg/day.

3.4.1.2. 14 day study

CAB (sodium salt) was administered to groups of cynomolgus monkeys (n=3/sex/group) at doses of 0 (control), 8, 25 or 1000 mg/kg/day by oral gavage for approximately 14 days [Report CD2007/00680, m4.2.3.2]. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. Parameters that were evaluated during the study included toxicokinetics, clinical observations (including qualitative evaluation of food consumption), body weight, ophthalmoscopy, electrocardiography, hematology, coagulation, clinical chemistry, urinalysis, organ weights, macroscopic and microscopic pathology (excluding qualitative evaluation of spermatogenesis). A tabulated summary of this study is presented in m2.6.7, Table 7.6.

Systemic exposure to CAB (as defined by $AUC_{0\text{-}t}$ and C_{max}) increased in an approximately dose-proportional manner (1.4- to 2.2-fold) as the dose was increased from 8 to 25 mg/kg/day, and in a less than dose-proportional manner as the dose was increased from 25 to 1000 mg/kg/day. Systemic exposure to CAB was generally similar on Days 1 and 14 of the study, and there were generally no notable sex-related differences.

Males given 1000 mg/kg/day were euthanized on Day 14 as a result of test article-related body weight loss, emesis, loose/watery/discolored feces, inappetence, salivation, reluctance to move and dehydration. There were macroscopic findings of generalized distension of the gastrointestinal tract and red mucosal discoloration in stomach, cecum and small intestine that correlated with microscopic findings of degeneration/regeneration in the stomach characterized by glandular dilation and mucous depletion, degeneration/regeneration in the lamina propria of the cecum and colon characterized by glandular dilation, goblet cell hypertrophy and increased thickness of the lamina propria, and villous atrophy in the small intestine. Minimal changes in the glandular region of the stomach were noted for a single female given 1000 mg/kg/day and were characterized primarily by regeneration (basophilia) of mucosa, focal edema and fibrin deposition in the lamina propria and by minimal loss of glands. This finding in this individual female occurred in the absence of associated clinical observations or body weight loss and without any other accompanying effects in the gastrointestinal tract. Based on the minimal severity of the change and limited distribution, it was not considered adverse.

Bone marrow depletion, with corresponding decreases in peripheral leukocyte, reticulocyte and platelet counts, was seen in males given 1000 mg/kg/day.

Microvesicular vacuolation with margination of cytoplasm in the liver of one male given 1000 mg/kg/day was not considered adverse due to the minimal severity, limited distribution, and lack of a corresponding hepatic clinicopathologic alteration.

Parotid and mandibular salivary gland atrophy noted in males given 1000 mg/kg/day were likely secondary changes related to weight loss and debilitation and were not considered direct effects of CAB.

Dilation of the distal convoluted tubules was noted in one male given 1000 mg/kg/day and was associated with a minimal increase in serum urea. Increased serum urea was also evident in one other male given 1000 mg/kg/day in the absence of microscopic renal findings. Given the severity of clinical dehydration noted in male monkeys in this group, increased urea values were attributed to prerenal azotemia/dehydration rather than renal functional impairment, and the tubular dilation noted in the one monkey may have been associated with morbidity rather than a direct test article effect.

Minimal to moderate thymic lymphoid atrophy was noted in all males given 25 or 1000 mg/kg/day but was also noted in one control male and in one male given 8 mg/kg/day. Minimal to mild, diffuse hypertrophy of cells in the adrenal cortex was present in males given ≥25 mg/kg/day and females given ≥8 mg/kg/day. These thymic and adrenal changes were considered non-adverse and were likely exacerbated by a stress response.

Clinical observations in surviving monkeys that could be attributed to CAB included tan discolored feces for females given 1000 mg/kg/day and slight to moderate salivation for females given ≥8 mg/kg/day. One female given 1000 mg/kg/day had emesis on two occasions during the first week of treatment that was considered test article-related. In the absence of associated body weight loss, decreased food consumption and adverse microscopic findings and due to the infrequency of the emesis, these clinical observations were not considered adverse.

Due to the minimal nature of the microscopic findings, 25 mg/kg/day was considered the male NOAEL [mean AUC_{0-24} 233252 ng.h/mL, mean C_{max} 22699 ng/mL (based on Day 14 values)]. Based on the lack of adverse clinical or microscopic findings, 1000 mg/kg/day was considered the female NOAEL [mean AUC_{0-24} 945723 ng.h/mL, mean C_{max} 65870 ng/mL (based on Day 14 values)].

3.4.1.3. 4 week study

Groups of cynomolgus monkeys (n=3 or 5/sex/group) were given CAB (sodium salt) by oral gavage at doses of 0 (control), 5, 50 or 500 mg/kg/day once daily for approximately 28 days [Report CD2008/00632, m4.2.3.2]. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. Parameters that were evaluated during the study included toxicokinetics, clinical observations (including qualitative assessment of food consumption), body weights, hematology, coagulation, clinical chemistry, urinalysis, ophthalmoscopy, electrocardiography, organ weights, stage-dependent spermatogenesis, and macroscopic and microscopic observations. A tabulated summary of this study is presented in m2.6.7, Table 7.7.

No notable (≥2-fold) differences in mean plasma systemic exposure (AUC_{0-24} and C_{max}) to CAB on Day 28 were observed compared to Day 1, and there were no notable differences between males and females on Days 1 or 28, for any dose group. Mean

systemic exposure increased in a less than dose-proportional manner as the dose increased.

All doses were well-tolerated. Intermittent episodes of excessive salivation and discolored feces (tan) were observed in animals given 500 mg/kg/day during the treatment period. Based on the lack of CAB-related adverse clinical or microscopic findings in both males and females, 500 mg/kg/day was considered the NOAEL [mean AUC_{0-24} 902.5 μg.h/mL, mean C_{max} 61.6 μg/mL (based on Day 28 values)].

3.4.1.4. 39 week study

In a 39 week study, CAB (sodium salt) was administered to groups of cynomolgus monkeys (n=4/sex/group) at doses of 0 (control), 5, 50 or 500 mg/kg/day once daily by oral gavage [Report RD2009/00027, m4.2.3.2]. An additional 2 animals/sex were added to the control and high dose group to assess reversibility of test article-related effects following a 6 week off drug period. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. Parameters that were evaluated during the study included toxicokinetics, clinical observations, body weights, food evaluation, hematology, coagulation, clinical chemistry, urinalysis, ophthalmoscopy, electrocardiography, organ weights, and macroscopic and microscopic observations. A tabulated summary of this study is presented in m2.6.7, Table 7.8.

The increase in mean systemic exposure to CAB was less than proportional to the increase in dose. No consistent notable (>2-fold or <0.5-fold) difference in the mean systemic exposure to CAB was observed between males and females at any CAB dose or among sampling occasions.

There were no mortalities during the study and no test article related changes were noted in any parameter. Therefore, the NOAEL was 500 mg/kg/day [C_{max} of 34.6 μg/mL and AUC_{0-24} of 547 μg.h/mL for males and females combined at Week 39] in this study.

Table 3.2 Batch Numbers of CAB and Formulations Used in Repeat Dose Toxicity Studies

Batch or Lot Number(s)	Study Type	Species (Strain) or Test System	Form	Duration of Dosing	Report No. (Study No.)	Concentration (mg/mL)	Formulation
[redacted]	Repeat dose	Rat (Sprague Dawley)	A	14 or 15 days	RD2006/01741 (R41937)	3, 10, 30	1
[redacted]	Repeat dose	Monkey (cynomolgus)	B	7 days	CD2007/00577 (D07170)	6.25, 18.75, 125	1
[redacted]	Repeat dose	Monkey (cynomolgus)	B	14 days	CD2007/00680 (G07171)	1, 3.125, 125	1
[redacted]	Repeat dose	Rat (Sprague Dawley)	B	4 weeks	RD2008/00448 (R42288)	1, 7.5, 100	1
[redacted]	Repeat dose	Monkey (cynomolgus)	B	4 weeks	CD2008/00632 (G08079)	1.25, 12.5, 125	1
[redacted]	Repeat dose	Mouse (CD-1)	B	14 days	RD2009/00692 (M42452)	1, 7.5, 100	1
[redacted]	Repeat dose	Mouse (CD-1)	B	13 weeks	2012N142081 (M42936)	1, 7.5, 100	1
[redacted]	Repeat dose	Rat (Sprague Dawley)	B	26 weeks	RD2009/00031 (R42404)	0.05, 0.5, 100	1
[redacted]	Repeat dose	Monkey (cynomolgus)	B	39 weeks	RD2009/00027 (P42405)	1.25, 12.5, 125	1
[redacted]	Repeat dose	Rat (Sprague Dawley)	A	13 weeks	2010N104820 (R42698)	6.7, 10. 26.7, 60 and 200	2

Note: CAB materials from multiple routes of synthesis were used in the nonclinical studies. The impurity profile of the materials used in the nonclinical safety studies was consistent with that proposed for the marketed product.

Key:
NA = Not applicable.
A = CAB free acid.
B = CAB sodium salt.

Formulation Code:
1 = Aqueous 0.5% w/w hydroxypropylmethylcellulose (HPMC) and 0.1% w/w Tween 80.
2 = 2% Polysorbate 20 (Tween 20), 2% polyethylene glycol 3350 and 4.5% Mannitol in Sterile Water for Injection (w/v).

4. GENOTOXICITY

4.1. Introduction

CAB has been evaluated for genotoxicity potential both in vitro and in vivo. Potential mutagenic activity has been assessed in bacteria cells in vitro by the standard Ames test. The genotoxic potential of CAB has been assessed in mammalian cells in vitro in the L5178Y mouse lymphoma assay. In vitro experiments were carried out both in the presence and absence of a rat liver post-mitochondrial metabolising system (S9-mix), together with appropriate vehicle and positive controls. The potential for clastogenic effects has also been assessed in vivo using the oral micronucleus test in the rat. In addition, an assessment of the route of synthesis for CAB has been conducted to determine whether any impurities might be present which are known or suspected DNA-reactive mutagens, and to assess the likelihood of any such impurities being present in final drug product.

The impurity profile of the batches of test material used in these investigations was consistent with that used in the clinical evaluation of CAB and proposed for use in the marketed product.

A table listing the batches of CAB, together with information on method of formulation used in these investigations, is presented in Table 4.3 of this summary.

All studies were conducted in full compliance with GLP regulations. All assays used internationally recognised and validated techniques in full accordance with the ICH Harmonised Tripartite Guidelines [ICH S2(R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use].

A full listing of studies performed and the GLP status, together with the location of the reports within this submission, is provided in Table 4.1.

Table 4.1 List of Genotoxicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
CAB										
Ames test	NA	NA	In vitro	B	1.5 to 238 μg/plate[a]	NA	Yes	[redacted]	WD2007/00787 (V27580)	m4.2.3.3.1
Screening mouse lymphoma assay	NA	NA	In vitro	A	2 to 140 μg/mL[b]	NA	No	GSK	WD2007/01740 (MLA-600)	m4.2.3.3.1
Mouse lymphoma assay	NA	NA	In vitro	B	4 to 23.8 μg/mL[a]	NA	Yes	[redacted]	WD2007/00788 (V27561)	m4.2.3.3.1
Micronucleus	Rat (Sprague Dawley)	6M[c]	Oral (gavage)	B	1000, 2000	2 days	Yes	[redacted]	WD2007/00789 (R27562)	m4.2.3.3.2
Impurities[d]										
Ames test with gsk004*	NA	NA	In vitro	NA	Up to 5000 μg/plate	NA	No	GSK	2014N213336 (Ames-2047)	m4.2.3.3.1

Key:
a = Dose limited by solubility.
b = Dose limited by cytotoxicity.
c = Doses of 500, 1000 and 2000 mg/kg/dose and 3 rats/sex/group were used in the dose range finding test.
d = Listing of potential impurities that were negative for genotoxicity is provided in Table 4.2 below.
A = GSK1265744A, the parent form.
B = GSK1265744B, the sodium salt.
NA = Not applicable.

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

*新薬承認情報提供時に置き換え

4.2. In Vitro Studies (CAB)

4.2.1. Non-mammalian cell systems

4.2.1.1. Ames assay

CAB (sodium salt) was tested in *Salmonella typhimurium* (strains TA98, TA100, TA1535 and TA1537) or *Escherichia coli* strain WP2 *uvrA* (pKM101) at concentrations ranging from 1.5 to 238 μg per plate in the presence or absence of an in vitro metabolic activation system (S9-mix) [Report WD2007/00787, m4.2.3.3.1]. The maximum concentration tested was limited by solubility in dimethyl sulphoxide (DMSO). The negative and positive controls all produced acceptable responses. A tabulated summary of this study, with noteworthy findings, is presented in m2.6.7, Table 8.1.

CAB was not mutagenic in the bacterial mutation assay in either the presence or absence of S9-mix.

4.2.2. Mammalian cell systems

The mutagenic potential of CAB has been assessed in mammalian cells in vitro in two mouse lymphoma assays. Appropriate vehicle and positive controls were included in all assays which were conducted in both the presence and absence of a rat liver post-mitochondrial metabolizing system (S9-mix). In both studies, the positive controls produced biologically significant increases in mutation frequency.

4.2.2.1. Mouse lymphoma assay

In a preliminary mouse lymphoma L5178Y $TK^{+/-}$ screen, CAB (free acid) was tested for 3 hours in the presence of S9-mix and was tested for 24 hours in the absence of S9-mix [Report WD2007/01740, m4.2.3.3.1]. The maximum test concentration examined for the 3 hour treatment period in the presence of S9-mix was limited by toxicity to 140 μg/mL. The maximum concentration examined for the 24 hour treatment period in the absence of S9-mix was limited by toxicity to 20 μg/mL. A tabulated summary of this study, with noteworthy findings, is presented in m2.6.7, Table 8.3.

The results for the vehicle control (DMSO) were within acceptable ranges, determined from laboratory historical data, and the positive controls induced clear unequivocal increases in the numbers of mutant colonies.

In this screening assay, CAB was negative when tested for 3 hours in the presence of S9-mix (the relative total growth was reduced to 26%). CAB was genotoxic when tested for 24 hours in the absence of S9-mix (the relative total growth was reduced to 14%).

In a definitive GLP mouse lymphoma L5178Y $TK^{+/-}$ assay, CAB (sodium salt) was tested up to the maximum solubility limit of 23.8 μg/mL (solubility limit in the vehicle DMSO) for 3 hours in the presence and absence of rat liver S9-mix, and for 24 hours in the

absence of S9-mix [Report WD2007/00788, m4.2.3.3.1]. A tabulated summary of this study in presented in m2.6.7, Table 8.2.

The vehicle control data were within acceptable ranges and positive controls all produced acceptable responses, therefore, the performance of the vehicle and positive controls was consistence with a valid assay.

CAB was not genotoxic in the mouse lymphoma L5178Y $TK^{+/-}$ assay either in the presence or absence of S9-mix. At the maximum concentration tested, the relative total growth was 109% and 57% in the presence and absence of S9-mix, respectively, for the 3 hour incubation period and 33% in the absence of S9-mix for the 24 hour incubation period.

4.3. In Vivo Studies (CAB)

Any clastogenic or spindle formation effect of CAB on eukaryotic cells in vivo has been assessed using the micronucleus test performed by the oral route in the rat.

4.3.1. Oral micronucleus test in the rat

CAB (sodium salt) was tested in vivo in the rat bone marrow micronucleus assay following doses of 0 (control), 1000 or 2000 mg/kg/day administered orally on two consecutive days to groups of 6 male Sprague Dawley rats [Report WD2007/00789, m4.2.3.3.2]. CAB was formulated in a vehicle of 0.5% HPMC and 0.1% Tween 80. Cyclophosphamide was used as the positive control. A tabulated summary of this study, with noteworthy findings, is presented in m2.6.7, Table 9.1.

The results for the vehicle control were within the ranges determined from laboratory historical data and the positive control induced clear unequivocal increases in micronuclei, therefore, the performance of the controls was consistent with a valid assay.

No notable increases in group mean MPCE/2000 PCE was observed at any of the doses tested, therefore, CAB was not genotoxic in the oral rat micronucleus assay.

4.4. Potential Impurities (Positive)

A bacterial mutagenesis assay (Ames test) was conducted to assess the potential of gsk004*, an intermediate in the synthesis of CAB, to induce gene mutations in vitro in *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537) and *Escherichia coli* WP2*uvrA* (pKM101) [Report 2014N213336, m4.2.3.3.1]. One standard plate incorporation test was conducted for strain TA100 both in the presence and absence of rat liver S9-mix, together with appropriate vehicle and positive controls. The maximum concentration tested was 5000 μg/plate in accordance with current guidelines. Acetonitrile was used as the solvent for formulation.

gsk004* was mutagenic in the bacterial mutation assay, when tested in either the presence or absence of S9-mix.

*新薬承認情報提供時に置き換え

4.5. Potential Impurities (Negative)

4.5.1. In vitro tests

Additional Ames tests were conducted on potential impurities / degradants and synthetic intermediates and these studies are listed in Table 4.2. Each of the studies listed in this table tested negative for genotoxicity in the Ames test.

Table 4.2 List of Genotoxicity Studies Performed with Potential Impurities in CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Impurities									
Ames Test with gsk008*	In vitro	NA	In vitro	Up to 5000 μg/plate	In vitro	No	GSK	2012N150640 (Ames-1452)	m4.2.3.3.1
Ames Test with gsk009*	In vitro	NA	In vitro	Up to 5000 μg/plate	In vitro	No	GSK	2012N150637 (Ames-1451)	m4.2.3.3.1
Ames Test with gsk010*	In vitro	NA	In vitro	Up to 5000 μg/plate	In vitro	No	GSK	2012N149508 (Ames-1449)	m4.2.3.3.1
Ames Test with gsk011*	In vitro	NA	In vitro	Up to 5000 μg/plate	In vitro	No	GSK	2014N212365 (Ames-2038)	m4.2.3.3.1
Ames Test with gsk012*	In vitro	NA	In vitro	Up to 5000 μg/plate	In vitro	No	GSK	2014N212376 (Ames-2039)	m4.2.3.3.1
Ames Test with gsk013*	In vitro	NA	In vitro	Up to 5000 μg/plate	In vitro	No	GSK	2014N213208 (Ames-2040)	m4.2.3.3.1
Ames Test with gsk014*	In vitro	NA	In vitro	Up to 5000 μg/plate	In vitro	No	GSK	2014N213980 (Ames-2048)	m4.2.3.3.1
Ames Test with gsk015*	In vitro	NA	In vitro	Up to 5000 μg/plate	In vitro	No	GSK	2014N215867 (Ames-2071)	m4.2.3.3.1

Note: All studies listed in the table tested negative in the Ames or Mouse Lymphoma Assay.

Testing Facility:
GSK = GlaxoSmithKline.

*新薬承認情報提供時に置き換え

4.6. Route Assessment for Genotoxic Impurities

The proposed drug substance specifications [see m3.2.S.4.1, free acid and m3.2.S.4.1 sodium salt)] for CAB indicate that the specified impurities, gsk006*, gsk007*, gsk005*, gsk002*, gsk001* and gsk003* (each impurity also occurs in the drug substance of CAB sodium salt, and is designated with the suffix "B") do not exceed the 0.15% w/w ICH qualification threshold [ICH Q3A (R2)]. All 6 impurities were considered not genotoxic based on in silico assessments (DEREK software program).

An assessment of the commercial route of synthesis for CAB was also conducted to assess the likelihood that any known or potential mutagens might be present in the final drug substance as impurities. This assessment included an evaluation for genotoxicity structural alerts using the software programs DEREK and Leadscope. Synthetic intermediate gsk004* (see Section 4.4 above) and hypothetical impurity methyl methanesulfonate [NTP] were identified as known mutagens.

The structures of these impurities are provided in m3.2.S.2.6, Table 15 (CAB free acid) and Table 16 (CAB sodium salt). Based on the treatment regimen, a Less-Than-Lifetime (LTL) Threshold of Toxicological Concern (TTC) of 10 μg/dose is applied due to the intermittent nature of the cabotegravir treatment: as the injection is administered monthly, the total number of dosing days over a lifetime would be below 3650, which equates to the duration category of 1 to 10 years. For cabotegravir sodium drug substance, this corresponds to a LTL TTC-based acceptable limit of 15 μg/g for any individual mutagenic impurity. This figure is considered the acceptable limit in the ICH M7 risk assessment. These impurities are controlled by the manufacturing process. Therefore, there are no mutagenic impurities of concern in the final drug substances [m3.2.S.2.6, Section 2.1.6.3 (CAB sodium salt) and m3.2.S.2.6, Section 2.1.6.5 (CAB free acid)].

In summary, there are no impurities of mutagenic concern at a level that would exceed the threshold of toxicological concern (TTC) as defined by the CHMP guidelines on the limits of genotoxic impurities (i.e., >10 μg/dose).

*新薬承認情報提供時に置き換え

Table 4.3 Batch Numbers of CAB and Formulations Used in Genotoxicity Studies

Batch or Lot Number(s)	Study Type	Species (Strain) or Test System	Form	Duration of Dosing	Report No. (Study No.)	Concentration (mg/mL)	Formulation
[redacted]	Mouse lymphoma assay	NA	A	NA	WD2007/01740 (MLA-600)	0.01 to 25	2
[redacted]	Ames test	NA	B	NA	WD2007/00787 (V27580)	0.015 to 2.38	2
[redacted]	Mouse lymphoma assay	NA	B	NA	WD2007/00788 (V27561)	0.009297 to 2.38	2
[redacted]	Rat micronucleus	Rat (Sprague Dawley)	B	2 days	WD2007/00789 (R27562)	100, 200	1

Note: CAB materials from multiple routes of synthesis were used in the nonclinical studies. The impurity profile of the materials used in the nonclinical safety studies was consistent with that proposed for the marketed product.

Key:
NA = Not applicable.
A = CAB free acid.
B = CAB sodium salt.

Formulation Code:
1 = Aqueous 0.5% w/w hydroxypropylmethylcellulose (HPMC) and 0.1% w/w Tween 80.
2 = Dimethylsulfoxide.

5. CARCINOGENICITY

5.1. Introduction

Carcinogenicity studies of lifetime duration (104 weeks) were performed using the oral route of administration to determine the tumorigenic potential of CAB in the CD-1 mouse and Sprague Dawley rat. These studies were preceded by preliminary studies to determine suitable high doses for use in the main studies. Both main studies were conducted in accordance with GLP regulations. The mouse and the rat are the species of choice for this type of investigation and the strains used were selected because of the considerable amount of knowledge available to the investigators regarding both their background pathology and their reactions to a wide variety of drugs. Furthermore, information on the pharmacokinetics and metabolism of CAB in these species and strains confirms their suitability for selection (see m2.6.4, Pharmacokinetics Written Summary). Sufficient animals were used in each study to allow meaningful evaluation of the data.

The studies described in this section were performed using the sodium salt of CAB. All doses and concentrations quoted in this summary are expressed in terms of the free acid or parent compound (referred to simply as CAB). The impurity profile of the batches of test material used in these investigations was consistent with that used in the clinical evaluation of CAB and that proposed for use in the marketed product.

A table listing the batches of CAB together with information on the method of formulation used in these investigations is presented in Table 5.2 of this summary.

A complete listing of studies performed and the GLP status of the studies together with the location of the reports within this submission is provided in Table 5.1. Additional tabulations of List of Tissues Studied, Tumour Incidence, Chronological Listing of Tumour Occurrence, and Survival and Fate of Animals are presented in Appendix 1.

Table 5.1 List of Carcinogenicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Carcinogenicity	Mouse (CD-1)	60 9[TKa] 42[TKb]	Oral	B	M: 2.5, 10 or 75 F: 2.5, 5 or 35	104 weeks	Yes	[redacted]	2017N310750 (M30877G)	m4.2.3.4.1
Carcinogenicity	Rat (Sprague Dawley)	70 3 (TK all groups)	Oral	B	0.25, 2.5 or 75	104 weeks	Yes	[redacted]	2017N310751 (R30876G)	m4.2.3.4.1

Key:
B = CAB sodium salt.
TKa = Satellite groups for toxicokinetics analysis in vehicle control.
TKb = Satellite groups for toxicokinetics analysis in CAB dose groups.
M = Male.
F = Female.

Testing Facility:
[redacted] = [redacted]

5.2. Mouse

Preliminary studies were conducted to determine appropriate dose levels of CAB to use in an oral carcinogenicity study in CD-1 mice (see Section 3.2.1, Repeat Dose Toxicity, for further information pertaining to these studies).

5.2.1. Oral administration

5.2.1.1. Carcinogenicity study

Groups of CD-1 mice (n=60/sex/group) were administered CAB, sodium salt, at 0 (control), 2.5, 10 or 75 mg/kg/day (males) and at 0 (control), 2.5, 5 or 35 mg/kg/day (females) once daily for 104 weeks [Report 2017N310750, m4.2.3.4.1]. Satellite groups of toxicokinetics animals (9/sex/control group and 42/sex/CAB-treated groups) were added for toxicokinetic evaluation during the first 26 weeks of the study. Other parameters evaluated during the study included clinical observations (including mass palpation), body weights, food consumption, ophthalmoscopic observations, and macroscopic and microscopic observations. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. A tabulated summary of this study, with noteworthy findings, is presented in m2.6.7, Table 10.1.

Systemic exposure (composite C_{max} and AUC_{0-t}) increased with increasing dose. The systemic exposure during Week 26 was similar to that during Week 4 at each dose level for both males and females. At the dose level of 2.5 mg/kg/day administered to both males and females, there was no marked (>2-fold) gender difference in the systemic exposure during both Weeks 4 and 26.

There were no statistically-significant increases in mortality due to CAB. The slight decrease in survivability in males given 75 mg/kg/day (50% survival at Week 104) compared to controls (58% at Week 104) was attributed to a slightly higher background incidence of obstructive uropathy.

There were dose-dependent, slight decreases in mean body weight gains in females at 5 or 35 mg/kg/day (0.91X or 0.86X controls).

There was no CAB-related effect on the distribution of neoplastic or non-neoplastic lesions contributing to death or preterminal euthanasia of animals, and there were no neoplastic or non-neoplastic CAB-related macroscopic and microscopic pathology findings.

5.3. Rat

5.3.1. Oral administration

5.3.1.1. Carcinogenicity study

Groups of Sprague Dawley rats (n=70/sex/group) were administered CAB, sodium salt, by oral gavage once daily at dose levels of 0 (control), 0.25, 2.5 or 75 mg/kg/day as part of a 104 week carcinogenicity study [Report 2017N310751, m4.2.3.4.1]. In addition, 3 animals/sex were used at each dose level for toxicokinetic evaluation during the first 26 weeks of the study. Other parameters that were evaluated during the study included clinical observations (including mass palpation), body weights, food consumption, ophthalmoscopic observations, and macroscopic and microscopic observations. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. A tabulated summary of this study, with noteworthy findings, is presented in m2.6.7, Table 10.2.

Systemic exposure (gender-averaged C_{max} and AUC_{0-t}) increased with increasing dose. The systemic exposure was similar in Week 26 as compared to Week 4. There were no marked differences (> 2-fold) in exposure between male and female animals.

Clinical signs attributed to CAB were limited to skin dryness in males given 2.5 and 75 mg/kg/day and in females given 0.25, 2.5 and 75 mg/kg/day. Mean body weight loss over the last 20 weeks of the study was observed in males given 75 mg/kg/day. Females given 75 mg/kg/day had increased overall body weight gains compared to controls from Weeks 52 to 80. Slight, generally lower food consumption was seen in males given 75 mg/kg/day.

Mortality was higher in males given 75 mg/kg/day than other male groups, which resulted in termination of the males after 101 weeks of dosing when survival reached 15. There were no histopathological findings related to CAB to account for the higher mortality.

There was no CAB-related effect on the distribution of neoplastic or non-neoplastic findings.

Table 5.2 Batch Numbers of CAB and Formulations Used in Carcinogenicity Studies

Batch or Lot Number(s)	Study Type	Species (Strain) or Test System	Form	Duration of Dosing	Report No. (Study No.)	Concentration (mg/mL)	Formulation
[redacted]	Carcinogenicity	Mouse (CD-1)	B	104 weeks	2017N310750 (M30877G)	0.25, 0.50, 1.0, 3.5 and 7.5 mg/mL	1
[redacted]	Carcinogenicity	Rat (Sprague Dawley)	B	104 weeks	2017N310751 (R30876G)	0.025, 0.25 and 7.5	1

Note: CAB materials from multiple routes of synthesis were used in the nonclinical studies. The impurity profile of the materials used in the nonclinical safety studies was consistent with that proposed for the marketed product.

Key:
B = CAB sodium salt.

Formulation Code:
1 = Aqueous 0.5% w/w HPMC and 0.1% w/w Tween 80.

6. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

6.1. Introduction

A range of reproductive toxicity studies have been performed to investigate the consequences of repeated administration of large doses of CAB on the mammalian reproductive processes. The effects of CAB on fertility and general reproductive performance and peri- and post-natal development have been investigated in Sprague Dawley rats, while the effects on embryofetal development have been investigated in Sprague Dawley rats and Dutch belted rabbits. Studies were conducted to support the use of CAB in women of child-bearing age.

Studies undertaken to establish suitable dose levels for use in repeat dose toxicity studies were performed in accordance with the general principles of the Good Laboratory Practice (GLP) regulations. All definitive studies were performed in full compliance with GLP regulations.

All studies described in this section were performed using the sodium salt of CAB. All doses and concentrations quoted in this summary are expressed in terms of the free acid or parent compound (referred to simply as CAB). The impurity profile of the batches of test material used in these investigations was consistent with that used in the clinical evaluation of CAB and proposed for use in the marketed product.

A table listing the batches of CAB together with information on the method of formulation used in these investigations is presented in Table 6.2 of this summary.

A full listing of studies performed and the GLP status, together with the location of the reports within this submission, is provided in Table 6.1.

Table 6.1 List of Reproductive and Developmental Toxicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Male fertility	Rat (Sprague Dawley)	25M	Oral (gavage)	B	0.5, 5, **1000**	64 to 66 days[a]	Yes	[redacted]	2014N207479 (R70481G)	m4.2.3.5.1
Female fertility & Embryofetal development	Rat (Sprague Dawley)	25F	Oral (gavage)	B	0.5, **5** 1000	2 weeks prior to mating, during mating and up to Day 17 pc, inclusive	Yes	GSK	CD2009/00105 (G08284)	m4.2.3.5.1
Dose range study	Rabbit (Dutch Belted, pregnant)	4F	Oral (gavage)	B	30, 250, 500, 1000, 2000[b]	13 days (Days 7 to 19 pc)	No	GSK	CD2008/01276 (D08251)	m4.2.3.5.2
Embryofetal development	Rabbit (Dutch Belted, pregnant)	22F	Oral (gavage)	B	30, 500, and **2000**	13 days (Days 7 to 19 pc)	Yes	GSK	CD2009/00842 (G08307)	m4.2.3.5.2
Pre- & post-natal development	Rat (Sprague Dawley)	24F	Oral (gavage)	B	0.5, **5**, 1000[c]	Day 6 pc to Day 20 pp	Yes	[redacted]	2015N236973 (R70586G)	m4.2.3.5.3
Investigative pre- & post-natal development	Rat (Sprague Dawley)	48F	Oral (gavage)	B	1000	Gestation Day 6 to Lactation Day 7	No	[redacted]	2016N281797 (R70909N)	m4.2.3.5.3

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

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Investigative Toxicokinetic Study	Rat (Sprague Dawley)	8F	Oral (gavage)	B	5, 1000	Gestation Day 6 and Gestation Day 6 to 20	No	[redacted]	2017N311115 (R71069N)	m4.2.3.5.3

Key:
a = Rats were dosed 15 days prior to co-habitation, through two co-habitation periods to Days 64 to 66.
b = The 2000 mg/kg/day dose was administered as a single dose and as a twice daily (BID) dose of 1000 mg/kg/dose.
c = The NOAEL for maternal reproductive function was 1000 mg/kg/day.
B = GSK1265744B, the sodium salt. pc = Post coitum.
Note: No observed adverse effect levels (NOAELs) values are in **bold** type.

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

6.2. Fertility and Early Embryonic Development

6.2.1. Rat

Groups of female Sprague Dawley rats (n=25/group) were administered CAB (sodium salt) by oral gavage at dose levels of 0 (control), 0.5, 5 or 1000 mg/kg/day for 15 days before cohabitation, through mating and from Day 0 to 17 postcoitum (pc) [Report CD2009/00105, m.4.2.3.5.1]. Mated females and their litters were euthanized on Day 21 pc. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. The following parameters were evaluated during the study for F_0 females: mortality, clinical observations, body weights, food consumption, estrous cycle, mating, fertility, necropsy, corpora lutea and uterine weights; and for F_1 litters: implantations, resorptions, live and dead fetuses, fetal weight, sex, and placental and fetal morphology (external, visceral and skeletal). A tabulated summary of this study is presented in m2.6.7, Table 12.1.

No deaths occurred on the study. There were no test-article related clinical observations. There were no test article-related effects on female body weights, food consumption, estrous cycle, mating, numbers of corpora lutea, implantations, resorptions, live or dead fetuses per litter, sex ratio, gravid uterine weight or placental morphology. CAB-related decreases (6%) in mean male and female fetal body weights were observed in the 1000 mg/kg/day dose group. There were no CAB-related fetal malformations or variations at any dose. There were no test article-related effects on female fertility at any dose. Therefore, the no observed adverse effect level (NOAEL) for female fertility was 1000 mg/kg/day, however, as male and female fetal weights were decreased at 1000 mg/kg/day, the NOAEL for rat embryofetal development was 5 mg/kg/day.

In another study to assess male fertility, groups of male Sprague Dawley rats (n=25/group) were given CAB (sodium salt) at dose levels of 0 (control), 0.5, 5 or 1000 mg/kg/day beginning on Day 1 of the study and continuing until termination (64 to 66 doses) [Report 2014N207479, m4.2.3.5.1]. After 14 days of treatment, treated males were cohabited 1:1 with untreated females (first cohabitation period). Due to equivocal fertility results from the first cohabitation, the study was extended to mate treated males with a new set of untreated females (second cohabitation period). Following this period, mated females and their litters were euthanized on Day 20 pc. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. The following parameters were evaluated during the study for treated F_0 males: viability, clinical observations, body weights, food consumption, mating, fertility, necropsy and male reproductive organ weights, sperm concentration and sperm motility; untreated F_0 females: viability, clinical observations, body weights, macroscopic observation of uterus and cervix, corpora lutea and uterine weights; and for F_1 litters: implantations, resorptions, live and dead fetuses, fetal weight, sex, and placental and fetal external morphology. A tabulated summary of this study is presented in m2.6.7, Table 12.2.

CAB-related clinical observations of excess salivation (slight; 24 occasions in 11 males) and urine-stained abdominal fur (3 occasions in 3 males) occurred in male rats at 1000 mg/kg/day. Transient CAB-related decreases in male mean body weight gain occurred at 1000 mg/kg/day on Days 1 to 15 and 1 to 22 of study (0.90X and 0.91X controls,

respectively). There were also transient test article-related decreases in male mean food consumption at 1000 mg/kg/day on Days 1 to 8 (0.94X controls) and 8 to 15 of study (0.95X controls).

There was no CAB-related effect on days needed for mating, mating index, fertility index, necropsy observations, male reproductive organ weights, or sperm motility or density for males at any dose.

The difference in the fertility index between the control and 1000 mg/kg/day groups (100% in controls versus 84% at 1000 mg/kg/day) after the first cohabitation period was not repeated after the second cohabitation period (92.0 % in controls versus 91.7% at 1000 mg/kg/day). In fact, all the males that did not sire a litter during the first cohabitation successfully sired a litter during the second cohabitation, except for one male at 1000 mg/kg/day. In addition, all the fertility indices were within the historical control range of 78.3% to 100%. Thus, the initial difference was not considered test article related.

Treatment of the males also did not affect numbers of corpora lutea, implantations, resorptions, live and dead fetuses per litter, sex ratio, fetal body weight, gravid uterine weight, placental morphology, or fetal morphology seen in the untreated females or F_1 fetuses.

The NOAEL for reproductive effects in the male rat was 1000 mg/kg/day, the highest dose tested.

6.3. Embryofetal Development Studies

6.3.1. Rat

6.3.1.1. Oral administration

The potential of CAB to affect embryofetal development in rats was determined as part of a study to assess effects on female fertility (refer to Section 6.2.1, discussion of Report CD2009/00105).

6.3.2. Rabbit

6.3.2.1. Oral administration

An oral dose range finding study was conducted in Dutch belted rabbits to assess the tolerance and toxicokinetics of CAB sodium salt [Report CD2008/01276, m4.2.3.5.2]. CAB was administered to groups of pregnant rabbits (n=4/group, except control n=2) during gestation on Days 7 to 19 postcoitum (pc) at dose levels of 0 (control), 30, 250, 500, 1000 or 2000 mg/kg/day (once daily) or 2000 mg/kg/day (at 1000 mg/kg twice daily). CAB was formulated with 0.5% HPMC and 0.1% Tween 80. The following parameters were evaluated during the study: in-life animal observations, body weights, food consumption, uterine weights, corpora lutea, implantations, resorptions, live and

dead fetuses, fetal weights, and fetal external morphology. Blood samples were also collected at various timepoints for toxicokinetic analysis. A tabulated summary of this study is presented in m2.6.7, Table 11.1.

The systemic exposure to CAB (expressed as mean AUC_{0-24} and C_{max} values) increased less than proportionately with the increase in dose. No notable difference in mean systemic exposure was observed between Day 11 and Day 19 pc or between the 2000 mg/kg/day dosing regimens.

There were no effects on maternal body weight or food consumption at any dose level. The clinical observation of pale feces at 2000 mg/kg/day was presumed to be test article in the feces. There were no apparent effects on developmental parameters. Based on a limited number of litters (n=4), there was no test article-related effect on numbers of corpora lutea, implantations, resorptions or live and dead fetuses per litter, gravid uterine weight or placental morphology. There were no apparent effects on fetal body weight or external morphology.

In a definitive embryofetal development study, CAB (sodium salt) was given orally at dose levels of 0 (control), 30, 500 or 2000 mg/kg/day to groups of pregnant Dutch belted rabbits (n=22/group) on Days 7 to 19 pc [Report CD2009/00842, m4.2.3.5.2]. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. The following examinations and endpoints were evaluated for F_0 females: mortality, clinical observations, body weight, food consumption, plasma concentrations of CAB on Day 11 and 12 pc, necropsy, uterine weight, and corpora lutea; and for F_1 litters: implantations, resorptions, live and dead fetuses, fetal weight, sex, and placental and fetal morphology (external, visceral, and skeletal) and photographs. A tabulated summary of this study is presented in m2.6.7, Table 13.1.

The systemic exposure (plasma C_{max} and AUC_{0-24}) of CAB increased less than proportionally with the increase in dose.

Pale feces (consistent with test article present in feces) was noted at 2000 mg/kg/day. There were statistically significant, yet transient, CAB-related decreases in body weight gain and food consumption at 2000 mg/kg/day at the onset of dosing. Mean maternal body weight gain was decreased (0.85X control mean gain) between Days 7 to 20 pc and food consumption was decreased (0.84X control mean) for one day after the first dose on Day 7 pc.

There were no CAB-related effects on mean numbers of corpora lutea or implantations, resorptions, preimplantation loss, post-implantation loss, total live fetuses, percent live males, placental morphology or on uterus weight at any dose tested. There were no CAB-related effects on fetal body weight, fetal malformations or variations at any dose level. The NOAEL for rabbit embryofetal development was 2000 mg/kg/day, the highest dose tested.

6.4. Pre-Natal and Post-Natal Development, Including Maternal Function

6.4.1. Rat

In a pre- and postnatal development study, CAB (sodium salt) was administered orally to female rats (n=24/group) at dose levels of 0 (control), 0.5, 5 or 1000 mg/kg/day [Report 2015N236973, m4.2.3.5.3]. Groups of time-mated Sprague Dawley rats were dosed once daily from Day 6 postcoitum (pc) to Day 20 postpartum (pp). CAB was formulated with 0.5% HPMC and 0.1% Tween 80. The following examinations and endpoints were evaluated for F_0 females: mortality, clinical observations, body weight, food consumption, parturition, lactation, maternal behavior, and necropsy; for F_1 offspring: viability, gender, external morphology, clinical observations, body weight, food consumption starting on postnatal day (PND) 29, CAB exposure in plasma of pups via mother's milk on PND 10, attainment of physical landmarks of sexual maturation (including vaginal opening in females and balano-preputial skin fold separation in males), neurobehavioral function (acoustic startle habituation, locomotor activity, and learning and memory using the Morris water maze), estrous cycling, reproductive performance, parturition, maternal behavior, and necropsy; and for F_2 litters: viability, gender, external morphology, clinical observations, and body weight. A tabulated summary of this study is presented in m2.6.7, Table 14.1.

There were no CAB-related clinical signs, necropsy observations, or effects on F_0 female body weight gain or food consumption during the postcoitum or postpartum periods at any dose. Likewise, natural delivery parameters for F_0 females, including, mean gestation length (22.2 to 22.7 days), parturition (average pup delivery times: 9.8 to 11.6 minutes per pup), sex ratio (47.7% to 50.6% male pups/litter), implantation sites per litter (12.4 to 12.9 sites), and F_1 pup weights at birth (6.8 to 7.0 g/litter mean on PND 1) were unaffected by CAB treatment. Conversely, there was a statistically significant, CAB-related decrease in F_1 pup survival at 1000 mg/kg/day as evidenced by an increase in the number of pups that were dead at birth (2.9% stillborn pups vs. 0.7% in control) and that died during the early postnatal period (10.2% dead or missing [presumed cannibalized] on PND 2 to 4 vs. 0.7% in control). The latter resulted in a statistically significant, test article-related decrease in pup viability during PND 1 to 4 (87.4% vs. 98.9% in control) and a corresponding decrease in live litter size on PND 4 (10.0 pups/litter vs. 11.5 in control, PND 4). Similar results were not evident for litters in the 0.5 or 5 mg/kg/day groups. After PND 4, there was no further test article-related effect on F_1 pup survival or litter size at 1000 mg/kg/day. There were no maternal observations indicating abnormalities in the caretaking and nursing of pups that would explain the increased number of pup deaths at 1000 mg/kg/day.

Maternal F_0 exposure to CAB during gestation and lactation did not cause any immediate or latent effects on F_1 growth and development, including body weight, food consumption, sexual maturation, neurobehavioral development, and reproductive performance at any dose. In fact, group mean values for age at vaginal opening (32.8 to 33.4 days) and balano-preputial separation (44.0 to 44.5 days), as well as, mean frequency of estrus (1.8 to 2.2 times in estrus during 10 day period), days needed for mating (2.3 to 2.9 days) and mating index (no. mated/no. cohabited: 95.8% to 100%)

were comparable across all dose groups. Similarly, 21 or 22 mated F_1 females per group were fertile (87.5% to 91.7%) and each delivered a litter (gestation length: 22.3 to 22.6 days) with comparable pup delivery times [average pup delivery time: 10.3 to 14.2 minutes per pup), implantation sites per litter (15.4 to 17.3 sites), and sex ratios (47.9% to 50.8% male pups/litter). There was no test article-related effect on F_2 survival, growth and development, as there was no discernible difference from control in mean values for pup body weights (PND 1: 6.5 to 6.7 g; PND 7: 12.9 to 14.0 g) and viability (PND 1 to 4: 97.2% to 98.8%; PND 4 to 7: 98.6% to 99.7%). Lastly, there was no test article effect on any F_1 neurobehavioral endpoint as group mean values for startle response, locomotor activity, and learning and memory (Morris water maze) were comparable across all dose groups.

The NOAEL for maternal (F_0) reproductive function was 1000 mg/kg/day and for the pre- and postnatal development of the offspring in rats (F1) was 5 mg/kg/day. At 5 mg/kg/day, the C_{max} in F_1 pups on PND 10 was 58400 ng/mL in males and 52600 ng/mL in females, indicating the presence of CAB in maternal milk.

A follow up study was conducted to investigate if the cause of increased F_1 offspring postnatal deaths that were seen during the first 4 days of life in the preceding pre- and postnatal (PPN) development study was due to in utero toxicity associated with CAB exposure during gestation or test article exposure through mothers' milk during lactation [Report 2016N281797, m4.2.3.5.3]. Groups of time-mated female Sprague Dawley rats were given CAB (sodium salt) by oral gavage at dose levels of 0 (control; n=36 rats) or 1000 mg/kg/day (n=48 rats) from gestation day (GD) 6 until natural delivery then continued through lactation day (LD) 7 to ensure continued treatment of F_1 pups during lactation. Following completion of natural delivery (LD 1), a group of litters from test article-treated dams remained with their natural mother to investigate recapitulation of F_1 postnatal deaths that were seen in the original PPN study. Separate groups of natural born litters from control and treated dams were cross-fostered to determine if postnatal pup deaths were likely caused by test article-related gestational or lactational exposure. In addition, a group of litters from control dams remained with their natural mother for comparison. CAB was formulated with 0.5% HPMC and 0.1% Tween 80. The following examinations and endpoints were evaluated for F_0 females: viability, clinical observations, body weight, food consumption, natural delivery, maternal behavior, necropsy, and pregnancy status; and for F_1 pups: viability, external morphology, clinical observations (including examinations for presence/absence of milk in stomach), necropsy, and body weight. A tabulated summary of this study is presented in m2.6.7, Table 14.2.

There were no remarkable clinical observations for any of the females on study. One female (and her litter) in the 1000 mg/kg/day group was euthanized on GD 22 due to a prolapsed uterus during delivery. This female delivered a total of 13 pups, including the last 2 pups that were stillborn. There were no test article-related clinical observations recorded for this female during the study including the hours leading up to natural delivery. While this finding occurred in isolation, a relationship to CAB treatment cannot be determined based on the delayed onset of parturition in this group.

There were no CAB-related effects on mean maternal body weight or body weight gains during the gestation periods in the 1000 mg/kg/day group compared to vehicle-treated dams; however, a decrease in body weight gain (0.32X of vehicle control) was evident between LD 1 and 4. Thereafter, as the number of postnatal deaths declined and the remaining pups in each test article litter developed, the females at 1000 mg/kg/day gained body weight such that mean values exceeded vehicle values during LD4 to 8 (1.69X of vehicle control). There were no CAB-related effects on mean maternal food consumption during the gestation period in the 1000 mg/kg/day group compared to the vehicle control group. Due to the reduced postnatal period, F_0 food consumption was not measured during the lactation period.

All 84 time-mated female rats naturally delivered a litter. While the mean duration of gestation in the 1000 mg/kg/day group was comparable to the vehicle group value (22.8 days compared to 22.3 days, respectively), the majority of females in the 1000 mg/kg/day group initiated and completed natural delivery on GD 23 (41 of 48 females; 85.4%) compared to the vehicle group which initiated and completed deliveries primarily on GD 22 (26 of 36 females; 72.2%); only a small number of deliveries in the vehicle group occurred on GD 23 (10 of 36; 27.8%). Delivery results indicate an increase in mean number of stillbirths for the GSK1265744-treated group (24 stillbirths out of 577 pups born versus 2 stillbirths out of 457 pups born in the vehicle control). While there were only 2 stillbirths evident among 88 pups exposed in utero to GSK1265744 that were delivered on GD 22 (8.3% of stillbirths), there was a much higher incidence of stillbirths among treated litters that were delivered on GD 23 (91.7% of still births) with the majority of stillbirths occurring primarily in 6 of 41 litters. In comparison, there were only 2 stillbirths in total for dams exposed to the vehicle during gestation and the stillbirths that occurred were found in litters that were delivered on GD23. In addition to stillbirths, there was a higher incidence of F1 postnatal deaths among pups exposed in utero to GSK1265744 that were born alive on GD 23 but died within hours after delivery completion (18 pup deaths of 489 pups born versus 0 pup deaths of 129 pups born in vehicle control group on GD 23). There were no GSK1265744-related effects on the total number of pups delivered and no effects on average pup delivery time despite the delay in onset of parturition. However, the slight reduction in mean number of live born pups at 1000 mg/kg/day (11.5 pups/litter versus 12.6 pups, vehicle control) was attributable to the increase in number of stillbirths that were evident for this group.

There was reproducibility of early F_1 postnatal deaths that were seen previously at 1000 mg/kg/day in the original PPN study as evidenced by increased number of pup deaths among litters exposed to test article in utero and lactationally (Subset D) as well as a similar increase in pup deaths among CAB-treated litters that were only exposed to the test article in utero (Subset A).

In Subset A, where pups exposed to CAB in utero were fostered to vehicle-treated dams, one female lost an entire litter of CAB-exposed pups within approximately 24 hours of fostering and another 6 foster dams had an increase in number of dead pups (found dead or cannibalized) during the first few days of life. Of the 297 total pups from 24 litters that were fostered to this group, 56 pups primarily from 8 litters died during PND 1 to 3 (18.8%). Except for 11 pups that were born alive in the afternoon or late evening hours on GD 22, all other pups that died were born to treated females that delivered a litter on

GD 23. In comparison, when pups exposed to the vehicle in utero were fostered to CAB-treated dams (Subset C) there were minimal early F_1 postnatal deaths (7 of 308 total pups fostered). The increase in early postnatal pup deaths among pups exposed to CAB in utero (Subset A) resulted in a decrease in pup viability during PND 1 to 8 (80.8%) and a corresponding reduction in mean live litter size on PND 4 (10.0 pups/litter on PND 4 versus 12.4 pups/litter on PND 1) and beyond.

A similar increase in F_1 postnatal deaths occurred among non-fostered pups that were exposed to CAB both in utero and lactationally (Subset D). Of the 244 total pups fostered from 23 litters, 57 pups died, and these deaths occurred primarily in 9 litters. Except for a single pup that died towards the end of the study, all other postnatal deaths involving pups exposed to CAB in utero and lactationally occurred during the first few days of life, primarily on PND 2. Of the 23 CAB-treated dams evaluated in Subset D, one female delivered 11 stillborn pups and her only liveborn pup died within hours of delivery completion; 3 other dams lost entire litters due to a combination of stillbirths and/or early postnatal deaths by PND 3. Another 6 CAB-treated dams had an increase in number of early postnatal deaths (2 to 8 pups per litter) with the majority of pups dying after delivery completion on PND 1 or the following day. Collectively, the findings in Subset D resulted in a low viability index during PND 1 to 8 (77%) and a corresponding decrease in live litter size starting on PND 4 (8.2 pups/litter on PND 4 versus 10.6 pups/litter on PND 1). For comparison, there were minimal F_1 postnatal deaths evident for pups born to vehicle-treated dams who were then exposed to CAB via milk from CAB-treated foster dams (Subset C; 6 pups of 308 total pups fostered) as evidenced by a high viability index of 98% during PND 1 to 8. Likewise, there was no effect on pup survival during the first week of life (97.2%) for vehicle control litters that were not fostered (Subset B).

Clinical observations indicate the pups that died had no treatment-related external abnormalities and that F_1 postnatal deaths in this group are not likely to be related to poor maternal care by foster dams as most of the pups that died had milk in their stomach when given enough time to nurse. Likewise, there were no treatment-related visceral abnormalities noted for any of the pups that were found dead or euthanized during the study.

There was essentially no difference in survival rates or timing of death for pups that were exposed to CAB in utero only (Subset A) or in utero and lactationally (Subset D); very few deaths occurred among pups that were exposed in utero to the vehicle but were exposed lactationally to CAB (Subset C). Thus, the weight of evidence suggests the increase in F_1 postnatal deaths among treated pups at 1000 mg/kg/day is likely related to gestational exposure to CAB.

An additional study was conducted to assess the toxicokinetics in pregnant rats during late gestation and determine if there is accumulation in the fetal compartment with repeated dosing [Report 2017N311115, m4.2.3.5.3]. Groups of pregnant Sprague Dawley rats (n=8/group) were given CAB (sodium salt) orally at either 5 or 1000 mg/kg/day within two separate study cohorts. The first cohort of rats was given a single dose of either 5 or 1000 mg/kg/day on gestation day (GD) 20, and the second cohort of rats was given either dose level daily from GD 6 through 20 (day of mating was

designated as GD 0). CAB was formulated with 0.5% HPMC and 0.1% Tween 80. Blood samples were collected on GD 20 at multiple timepoints between 1 and 8 hours post-dosing from all pregnant rats in each group. Samples were then analyzed to determine whether repeat dosing would lead to change in systemic exposure. Within one hour of completion of 8 hour post-dose maternal blood collections, a cesarean section was performed. Fetuses were analyzed to determine CAB tissue concentrations. The pregnant females assigned to study groups were evaluated daily for viability, clinical observations, body weight (for calculation of dose volume), and food consumption. In addition, uterine data (numbers of implantations, resorptions, and live and dead status of fetuses) and fetal viability, birth weight and placental weights, and sex for F1 litters were determined. A tabulated summary of this study is presented in m2.6.7, Table 14.3.

Mean C_{max} and AUC_{0-8} values for maternal plasma were approximately 5.0-fold higher at 1000 mg/kg/day after a single dose on GD 20 when compared to values for female rats given a single dose of 5 mg/kg/day. However, following repeat dosing throughout pregnancy, the same toxicokinetic parameters remained relatively unchanged for females given 1000 mg/kg/day from GD 6 to 20, while at 5 mg/kg/day, maternal exposures increased approximately 3.0-fold during the same period resulting in mean C_{max} and AUC_{0-8} values on GD 20 that were similar to values reported for the 1000 mg/kg/day group (<2.0-fold difference between groups). Fetal tissue to corresponding maternal plasma ratios for single and repeat dose cohorts were comparable across the groups. Similar to maternal plasma levels, mean fetal tissue concentrations at 1000 mg/kg/day, on GD 20 after repeated gestational exposure, were relatively the same as values reported for the single exposure cohort whereas mean fetal tissue concentrations at 5 mg/kg/day increased after repeat exposure (mean litter concentrations were up to 6.0-fold higher than single dose data) with very little intra- or inter-litter variability. The increase in fetal tissue concentrations at 5 mg/kg/day after repeated gestational exposure resulted in mean values that were within 2.0-fold of values reported for fetuses at 1000 mg/kg/day on GD 20. The data indicate that fetal concentrations increased proportionally with an increase in maternal plasma levels and that there was no evidence of preferential accumulation of CAB within individual fetal compartments at either dose.

Table 6.2 Batch Numbers of CAB and Formulations Used in Reproductive and Developmental Toxicity Studies

Batch or Lot Number(s)	Study Type	Species (Strain) or Test System	Form	Duration of Dosing	Report No. (Study No.)	Concentration (mg/mL)	Formulation
[redacted]	Female fertility, early embryonic and embryofetal development	Rat (Sprague Dawley)	B	Up to 46 days	CD2009/00105 (G08284)	0.05, 0.5, 100	1
[redacted]	Embryofetal development	Rabbit (Dutch Belted)	B	13 days	CD2009/00842 (G08307)	6, 100, 143	1
[redacted]	Male fertility	Rat (Sprague Dawley)	B	64 to 66 days	2014N207479 (R70481G)	0.05, 0.5, 100	1
[redacted]	Pre- and post-natal development	Rat (Sprague Dawley)	B	Day 6 pc to Day 20 pp	2015N236973 (R70586G)	0.05, 0.5, 100	1
[redacted]	Investigative pre- and post-natal development	Rat (Sprague Dawley)	B	Gestation Day 6 to Lactation Day 7	2016N281797 (R70909N)	100	1

Note: CAB materials from multiple routes of synthesis were used in the nonclinical studies. The impurity profile of the materials used in the nonclinical safety studies was consistent with that proposed for the marketed product.

Key:
B = CAB sodium salt.

Formulation Code:
1 = Aqueous 0.5% w/w hydroxypropylmethylcellulose (HPMC) and 0.1% w/w Tween 80.

7. LOCAL TOLERANCE

7.1. Introduction

Local tolerance studies with CAB were performed to assess worker health and safety hazards associated with manufacture of the drug product, or to assess irritancy potential. These studies included ocular and skin irritancy studies, as well as studies of the potential to cause allergic contact dermatitis (skin sensitization), performed in various models. All studies were performed in full compliance with GLP regulations.

All studies described in this section were performed using the sodium salt of CAB. All doses and concentrations quoted in this summary are expressed in terms of the parent compound or free acid (referred to simply as CAB). The impurity profile of the batches of test material used in these investigations was consistent with that used in the clinical evaluation of CAB and that proposed for use in the marketed product.

A table listing the batches of CAB together with information on the method of formulation used in these investigations is presented in Table 7.2 of this summary.

A full listing of studies performed and the GLP status, along with the location of the reports within this submission, is provided in Table 7.1.

Table 7.1 List of Local Tolerance Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Skin irritancy study	Reconstituted human skin (SkinEthic™)	NA	In vitro	16 mg/site	Up to 42 minutes	Yes	[redacted]	2019N396399 (41501616)	m4.2.3.6
Ocular irritancy study	Reconstituted human corneal model (SkinEthic™)	NA	In vitro	30 mg/site	10 or 60 minutes	Yes	[redacted]	2019N396400 (41501617)	m4.2.3.6
Local lymph node assay	Mouse (CBA/Ca)	5F	Topical	25% (25 μL/ear)	3 days	Yes	[redacted]	2019N396237 (41501619)	m4.2.3.6

Key:
All local tolerance studies were performed using the sodium salt of CAB.

Testing Facility:
[redacted] = [redacted]

7.2. Dermal Irritancy

7.2.1. In vitro

An in vitro study was performed to determine the skin irritation potential of CAB using the SkinEthic™ reconstructed human epidermis model [Report 2019N396399, m4.2.3.6]. Tissue samples (n=3) were treated with 16 mg of CAB (sodium salt) at room temperature for a treatment period of 42 minutes, then tissues were rinsed and incubated at 37°C for a period of 42 hours. Viability of the CAB-treated tissue was assessed. A summary of this study is presented in m2.6.7, Table 16.1.

The relative mean viability of CAB-treated tissues was 77.6% after the 42 minute exposure period and 42 hour post-exposure incubation period. It was considered unnecessary to proceed with tissue histology or analysis of inflammatory mediators. CAB was classified as non-irritant.

7.3. Ocular Irritancy

7.3.1. In vitro

An ocular irritancy study was performed in vitro using the SkinEthic™ reconstructed human corneal epithelial model and the irritancy potential for CAB was assessed [Report 2019N396400, m4.2.3.6]. Tissue samples (n=2/group) were treated with 30 mg of CAB (sodium salt) and incubated at 37°C for periods of 10 and 60 minutes and then rinsed and incubated at 37°C for 3 hours. Viability of the CAB-treated tissue was assessed. A summary of this study is presented in m2.6.7, Table 16.1.

The relative mean viability of the CAB-treated tissues was 104.5% after a 10 minute exposure period and 105.5% after a 60 minute exposure period, which provided an unequivocal negative result. CAB was considered not to be a significant irritant. It was considered unnecessary to proceed with tissue histology.

7.4. Skin Sensitization Potential

7.4.1. Mouse

7.4.1.1. Local Lymph Node Assay

The skin sensitization potential of CAB (sodium salt) was determined in the CBA/Ca mouse following topical application to the dorsal surface of the ear [Report 2019N396237, m4.2.3.6]. CAB (25% w/w, maximum attainable concentration) or vehicle (propylene glycol) was topically administered to the ear (25 µL/ear) of female mice (n=5/group) once a day for 3 consecutive days. On Day 6, the mice were given a single intravenous injection of [^{3}H]-methyl thymidine (20 µCi/mouse) and 5 hours later the auricular lymph nodes were removed, single cell suspensions prepared and the

lymphocyte stimulation index (SI) determined. A summary of the study design and the results from this study are presented in m2.6.7, Table 16.1.

No signs of systemic toxicity or changes in body weights were noted. CAB was a non-sensitizer under the conditions of this test with a SI of 1.27.

Table 7.2 Batch Numbers of CAB and Formulations Used in Local Tolerance Studies

Batch or Lot Number(s)	Study Type	Species (Strain) or Test System	Duration of Dosing	Report No. (Study No.)	Concentration (mg/mL)	Formulation
[redacted]	Skin irritation	In vitro	Up to 42 minutes	2019N396399 (41501616)	16 mg	NA
[redacted]	Eye irritation	In vitro	10 or 60 minutes	2019N396400 (41501617)	30 mg	NA
[redacted]	Skin sensitization potential	Mouse (CBA/Ca)	Single	2019N396237 (41501619)	25% w/w	Propylene glycol

Note: CAB materials from multiple routes of synthesis were used in the nonclinical studies. The impurity profile of the materials used in the nonclinical safety studies was consistent with that proposed for the marketed product. Local tolerance studies were performed with CAB sodium salt form, unless otherwise noted.

Key:
NA = not applicable

8. OTHER TOXICITY STUDIES

8.1. Introduction

To more fully characterize the toxicological profile of CAB, two further toxicity studies were conducted and are detailed in this section. These two studies were conducted in rats to assess the effects of oral administration of CAB on T-cell dependent antibody response. The first study was performed in full compliance with GLP and the second study was non-GLP.

The studies described in this section were performed using the sodium salt of CAB. All concentrations and doses quoted in this summary are expressed in terms of the parent compound (referred to simply as CAB). The impurity profile of the batches of test material used in these investigations was consistent with that used in the clinical evaluation of CAB and that proposed for use in the marketed product.

A table listing the batches of CAB together with information on the method of formulation used in these investigations is presented in Table 8.2.

A full listing of studies performed and the GLP status, along with the location of the reports within this submission, is provided in Table 8.1.

Table 8.1 List of Other Toxicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Immunotoxicity	Rat (Sprague Dawley)	40	Oral	B	0.5, 5 or 1000	28 days	Yes	[redacted]	2013N179070	m4.2.3.7.2
Immunotoxicity	Rat (Sprague Dawley)	10	Oral	B	5 or 1000	39 days	No	[redacted]	2018N367799	m4.2.3.7.2

Key:
B = Sodium salt.

Testing Facility:
[redacted] = [redacted]

8.2. Immunotoxicity

8.2.1. T-cell dependent antibody response (TDAR)

The effect of CAB (sodium salt) on T-cell dependent antibody response was evaluated in Sprague Dawley rats (n=40/sex/group) after oral administration at dose levels of 0 (control), 0.5, 5 or 1000 mg/kg/day for 28 days [Report 2013N179070, m4.2.3.7.2]. CAB was formulated in 0.5% HPMC with 0.1% Tween 80. The following endpoints were evaluated: clinical observations, body weights, macroscopic observations, and TDAR (i.e. antibody response to keyhole limpet hemocyanin [KLH]). A tabulated summary of the study design and the results from this study are presented in m2.6.7, Table 17.1.

Daily administration of CAB up to 1000 mg/kg/day was well tolerated, with no unscheduled deaths, no CAB-related clinical signs or macroscopic observations, and no CAB-related effects on body weight.

A CAB-related, statistically significant decrease ($p \leq 0.05$) in anti-KLH IgG antibody response was noted on Day 26 (0.30X of control) and Day 29 (0.14X of control) in males given 1000 mg/kg/day. This decrease was attributable to an increased incidence of males in the 1000 mg/kg/day group with anti-KLH IgG responses in the lowest statistical rank. However, measurable levels of anti-KLH IgG were detected in the majority of males given 1000 mg/kg/day (8/10 and 10/10 on Days 26 and 29, respectively), indicating that these animals were able to mount an immune response. The anti-KLH IgG response in males given 1000 mg/kg/day was comparable to that observed historically in control animals. Furthermore, the decrease in male anti-KLH IgG response observed was minimal relative to that previously demonstrated (in a different study) with the immunosuppressant, cyclophosphamide, where animals were unable to mount a measurable anti-KLH IgG antibody response. There were no CAB-related effects on the anti-KLH IgG response in females or on the anti-KLH IgM antibody response in either sex. Taken together, the data are not suggestive of an immunosuppressive effect with CAB administration.

Since the effect in males at 1000 mg/kg/day was minimal, and no effects were observed on the female anti-KLH IgG response or on the anti-KLH IgM response in either sex, CAB is not considered immunosuppressive under the conditions of this study. Based on the T cell-dependent antibody response assessment, the no observed effect level (NOEL), under the conditions of this study, is 5 mg/kg/day in males and 1000 mg/kg/day in females.

A further study was designed to investigate the potential effect of CAB (sodium salt) on primary and secondary TDAR with up to 39 days dosing, and the potential recovery from any effects during an 8 week off-dose period [Report 2018N367799, m4.2.3.7.2]. CAB was given by oral gavage to Sprague Dawley rats (10/sex/group) at doses of 0 (control), 5 or 1000 mg/kg/day for 39 days. Additional animals (10/sex/group) were added to the 0 and 1000 mg/kg/day groups as recovery animals. Two additional groups of rats (10/sex/group) received cyclosporine orally at 0 or 5 mg/kg/day from Days 8 to 39. CAB was formulated in a vehicle of 0.5% HPMC and 0.1% Tween 80. The following

endpoints/parameters were evaluated: dose formulation analysis (Weeks 1 and 5), clinical observations during dosing and off-dose periods (twice daily mortality/moribundity checks, once daily cage side observations, once weekly detailed clinical observations), once weekly body weights, TDAR evaluation, and macroscopic examinations (gross pathology) at necropsy. A tabulated summary of the study design and the results from this study are presented in m2.6.7, Table 17.2.

On Day 1 (prior to KLH injection), there were no detectable levels of anti-KLH IgM or IgG antibodies in any animal. At the end of the dosing period, individual animals given 0, 5, or 1000 mg/kg/day CAB mounted measurable anti-KLH IgM (3.88 to 537 μg/mL on Day 33) and IgG (1.40 to 366 μg/mL on Day 40) responses. During the dosing period there were no statistically-significant, CAB-related changes observed in the anti-KLH IgM or IgG response. Two of 10 males given CAB at 5 mg/kg/day and 1/10 males given 1000 mg/kg/day presented a lower anti-KLH IgM response compared to 0 mg/kg/day animals, especially on Days 31 and 33 (5 and 7 days post second KLH immunization, respectively); however, this observation represented a low animal incidence. Furthermore, the anti-KLH IgG response for these animals was generally within the range of concurrent controls, indicating that they were immunologically competent. Taken together, the changes in anti-KLH IgM for these three animals are not considered to be CAB-related. Since no CAB-related effects on anti-KLH IgM or IgG antibody response were observed during the dosing period, TDAR samples collected during the off-dose period were not evaluated. In males given cyclosporine, statistically-significant decreases were observed in anti-KLH IgG, but not IgM, response. In females given cyclosporine, statistically-significant decreases were observed in both anti-KLH IgM and IgG responses. Based on the TDAR assessment, the no observed effect level (NOEL) under the conditions of this study is 1000 mg/kg/day CAB.

Table 8.2 Batch Numbers of CAB and Formulations Used in Other Toxicity Studies

Batch or Lot Number(s)	Study Type	Species (Strain) or Test System	Form	Duration of Dosing	Report No. (Study No.)	Concentration (mg/mL)	Formulation
[redacted]	Immunotoxicity	Rat (Sprague Dawley)	B	4 weeks	2013N179070 (R70426G)	0.05, 0.5, 100	1
[redacted]	Immunotoxicity	Rat (Sprague Dawley)	B	39 days	2018N367799 (R71343N)	0.5, 100	1

Note: CAB materials from multiple routes of synthesis were used in the nonclinical studies. The impurity profile of the materials used in the nonclinical safety studies was consistent with that proposed for the marketed product.

Key:
B = Sodium salt.

Formulation Code:
1 = 0.5% HPMC with 0.1% Tween 80

9. DISCUSSION AND CONCLUSIONS

The toxicology profile of CAB was established following oral administration in safety pharmacology studies in Sprague Dawley rats and cynomolgus monkeys and repeat dose oral toxicity studies up to 26 weeks duration in rats, and 39 weeks in monkeys. Two toxicity studies were conducted in rats to characterize the toxicity and toxicokinetics of a CAB injectable suspension: a single dose study by SC and IM administration followed by a 74 to 86 day non-treatment period and a 3 month (weekly and monthly administration) SC and IM study followed by a 14 day (SC, weekly administration), 75 day (SC, monthly administration) or 51 day (IM, monthly administration) non-treatment period. In vitro and in vivo genetic toxicology studies were also conducted. Reproductive and developmental toxicity studies were conducted following oral administration to Sprague Dawley rats and Dutch Belted rabbits. Carcinogenicity studies in mice and rats were conducted to assess the tumorigenic potential of CAB and immunotoxicology studies in rats were performed to assess the effects of CAB on the antibody response to the T cell-dependent antigen.

9.1. Moribundity

In the 14-day monkey toxicity study, all male monkeys given 1000 mg/kg/day were euthanized in moribund condition on Day 14. Body weight loss, repeated emesis mostly during Week 2, repeated loose/watery feces, inappetence, salivation and discolored feces preceded morbidity which was generally characterized by moderate to severe dehydration, decreased activity, hunched posture and/or reluctance to move and was believed to be secondary to the GI effects discussed below. Bone marrow depletion with corresponding decreases in peripheral leukocyte, reticulocyte and platelet counts occurred in male monkeys given 1000 mg/kg/day and was characterized by a generalized decrease in cellularity of all precursor populations. No effects on bone marrow were observed in monkeys given 8 or 25 mg/kg/day or in females given 1000 mg/kg/day. No adverse effects on bone marrow were observed in monkeys given ≤500 mg/kg/day in the 4-week or 39-week toxicity studies. Additional findings considered secondary to the debilitated condition of the male monkeys given 1000 mg/kg/day in the 14 day study included dilation of the distal convoluted tubules in one male with associated minimal increase in serum urea and increased serum urea in one other male given 1000 mg/kg/day in the absence of microscopic renal findings. Given the severity of dehydration noted in male monkeys in this group, increased urea values were attributed to prerenal azotemia/dehydration rather than renal functional impairment, and the tubular dilation noted in the one monkey may have been associated with morbidity rather than a direct test article effect. In addition, parotid and mandibular salivary gland atrophy noted in males given 1000 mg/kg/day were also likely secondary to weight loss and debilitation and were not considered direct effects of the test article.

Because the 1000 mg/kg/day males were euthanized on Day 14 following the 4 hour toxicokinetic time point, systemic exposure (C_{max} and AUC_{0-24}) are given for Day 1 in males (67.0 µg/mL and 1051 µg.h/mL, respectively). For comparison, in male monkeys given 1000 mg/kg/day, the AUC_{0-4} was 132 µg.h/mL on Day 1 and 224 µg.h/mL on Day 14. There were no adverse effects at doses up to 500 mg/kg/day (highest dose

tested) in the 4 week toxicity study and the 39 week toxicity study. Day 28 exposure in the 4 week study at 500 mg/kg/day was similar to that achieved in the 14 day study at 1000 mg/kg/day (gender mean AUC_{0-24} of 902.5 µg.h/mL at 500 mg/kg/day compared to 1051 µg.h/mL in males on Day 1, 961 µg.h/mL in females on Day 1, and 946 µg.h/mL in females on Day 14).

9.2. Findings considered associated with stress

In the 14-day monkey toxicity study, minimal to moderate thymic lymphoid atrophy was noted in all male monkeys given 25 or 1000 mg/kg/day but was also noted in one control male and in one male given 8 mg/kg/day. Minimal to mild, diffuse hypertrophy of cells in the adrenal cortex were present in males given ≥25 mg/kg/day and females given ≥8 mg/kg/day. These thymic and adrenal changes were not associated with a change in organ weights and were considered non-adverse and likely a stress response.

9.3. Gastrointestinal effects

In the 14 day monkey toxicity study, the morbidity in males given 1000 mg/kg/day, euthanized on Day 14, was considered a consequence of test article-related effects on the GI tract. Treatment-related effects included microscopic findings of degeneration/regeneration, glandular dilation and mucous depletion in the glandular and fundic regions of the stomach; degeneration/regeneration, glandular dilation, goblet cell hypertrophy and increased thickness of the lamina propria of the cecum and colon; and villous atrophy in the small intestine. GI findings were associated with body weight loss, emesis, loose/watery feces, salivation, lethargy and dehydration. No adverse effects on the GI system were observed in monkeys given 8 or 25 mg/kg/day or in females given 1000 mg/kg/day. Regenerative gastric changes were noted in a single female given 1000 mg/kg/day but were not considered adverse due to their minimal severity, limited distribution within the GI tract and lack of accompanying clinical signs or weight loss. No adverse effects on the GI system were observed in monkeys given ≤500 mg/kg/day in the 4 week or 39 week toxicity studies.

9.4. Cardiovascular effects

In a cardiovascular study in conscious, non-restrained male monkeys, a single oral dose of CAB at 1000 mg/kg (C_{max} 67.0 µg/mL, AUC_{0-24} 1051 µg.h/mL Day 1 systemic exposure data in males from the monkey 14 day oral toxicity study) produced a mild, transient increase in mean arterial pressure (3.7 to 8.6%) and a transient increase in heart rate (16 to 23%) during the first 2 h after dosing. No blood pressure or heart rate changes were observed in monkeys given single oral doses of 8 or 25 mg/kg (C_{max} 20.8 µg/mL, AUC_{0-24} 233 µg.h/mL, Day 1 systemic exposure data in males from the monkey 14 day oral toxicity study). There were no adverse effects on the heart (organ weight or histopathology) and no ECG waveform or interval changes occurred after single or 14 consecutive oral doses of CAB of up to 1000 mg/kg/day, after approximately 3 weeks at ≤500 mg/kg/day (C_{max} 61.6 µg/mL, AUC_{0-24} 902.5 µg.h/mL, Day 28 systemic exposure data in males from the monkey 4-week oral toxicity study), or after approximately 38 weeks of dosing at ≤500 mg/kg/day.

9.5. Studies to support LA administration

CAB was administered by monthly SC injection (5, 30 and 100 mg/kg/dose); monthly IM injection (2.5, 10 and 75 mg/kg/dose) or by weekly SC injection (100 mg/kg/dose) to rats for up to 3 months, followed by non-dose periods of up to 75 days to characterize toxicity and toxicokinetics of a LA formulation of CAB in order to support clinical studies of CAB injectable suspension. There were no adverse effects noted and no new target organ toxicities identified via these routes of administration. Dose-proportional signs of redness and swelling were present following SC or IM injections at all dose levels. These were accompanied with local inflammatory reactions (erythema and edema graded very slight to severe) in animals given 75 mg/kg/dose (monthly IM injections), at all doses in female animals given monthly SC injections (≥5 mg/kg/month) and in males given ≥30 mg/kg/month, and at a higher incidence in animals given 100 mg/kg/dose monthly and weekly SC injections. Treatment-related histology findings were limited to granulomatous inflammation and mixed inflammatory cell infiltration at the corresponding injection sites, with correlating macroscopic changes. These changes were dose-dependent and were most severe in animals receiving 100 mg/kg/dose SC once weekly and having the shortest non-dose period. Therefore, the NOAELs for monthly administration were 100 mg/kg/dose SC and 75 mg/kg/dose IM. Exposure at both NOAELs ($AUC_{1440\text{-}2160h}$ = $AUC_{60\text{-}90days}$) corresponds to ~38X the human $AUC_{(0\text{-}t)}$ for a 400 mg IM dose (2461 μg.h/mL).

9.5.1. Reproductive toxicity

CAB had no effects on male or female fertility in rats. In PPN studies in rats, CAB (1000 mg/kg/day) delayed the onset of parturition, and in some rats, this delay was associated with an increased number of stillbirths and neonatal mortalities immediately after birth. There were no alterations to growth and development of surviving offspring. When rat pups born to CAB-treated dams (1000 mg/kg/day) were cross-fostered at birth and nursed by control mothers, a similar incidence of stillbirths and neonatal mortalities was observed. There was no effect on neonatal survival of control pups nursed from birth by CAB-treated mothers, suggesting effects were related to in utero exposure not lactational exposure. A lower dose of 5 mg/kg/day CAB was not associated with delayed parturition or neonatal mortality in rats. When CAB (1000 or 2000 mg/kg/day) was administered orally to pregnant rats and rabbits during organogenesis, there was no effect on survival when fetuses were delivered by caesarean. CAB crosses the placenta and can be detected in fetal tissue. No adverse effects on embryofetal development were observed in rabbit fetuses up to 2000 mg/kg/day. In rats, alterations in fetal growth (decreased body weights) were observed at 1000 mg/kg/day but no test article-related fetal malformations or variations at any dose.

9.5.2. Carcinogenicity

CAB was not carcinogenic in oral 2 year rat or mouse carcinogenicity studies.

9.5.3. Conclusion

There were no drug-related adverse effects in rats given CAB orally at doses up to 1000 mg/kg/day for 26 weeks. In the 14 day monkey toxicity study, a dose of 1000 mg/kg/day was not tolerated by male monkeys and resulted in morbidity associated with clinical signs suggestive of GI effects including body weight loss, emesis, loose/watery feces, inappetence and moderate to severe dehydration. There were no adverse effects in monkeys given CAB up to 500 mg/kg/day in the 4 week or 39 week toxicity studies. Day 28 exposure at 500 mg/kg/day (gender averaged AUC_{0-24} of 902.5 μg.h/mL at 500 mg/kg/day) was similar to that achieved in the 14 day study at 1000 mg/kg/day (1051 μg.h/mL in males on Day 1 and 961 μg.h/mL in females on Day 1 and 946 μg.h/mL in females on Day 14). This suggests that GI intolerance observed in the 14 day study was the result of local drug administration and not systemic toxicity.

Data suggest that CAB does not present a genotoxic hazard to humans. Overall, the data indicate there was no immunotoxicity in rats treated with CAB. CAB was not carcinogenic in oral 2 year rat or mouse carcinogenicity studies.

Where CAB was administered by monthly SC injection (5, 30 and 100 mg/kg/dose); monthly IM injection (2.5, 10 and 75 mg/kg/dose) or by weekly SC injection (100 mg/kg/dose) to rats for up to 3 months, followed by non-dose periods of up to 75 days, there were no adverse effects noted and no new target organ toxicities identified versus what was seen in the oral toxicity studies. Therefore, the NOAELs for monthly administration were 100 mg/kg/dose SC and 75 mg/kg/dose IM. Exposure at both NOAELs ($AUC_{1440-2160h} = AUC_{60-90days}$) corresponds to ~38X the human $AUC_{(0-t)}$ for a 400 mg IM dose (2461 μg.h/mL).

Table 9.1 A Table of the Exposure Ratio of CAB in Toxicology Test Species and Humans Following Oral Administration

Species (Duration)	Dose (mg/kg/day)	Sex	C_{max} (μg/mL)		AUC_{0-24} (μg.h/mL)		Animal to human ratio for AUC[a]
			Day 1	End of Study	Day 1	End of Study	
Mouse[h] (102 weeks)	2.5	M	13.5	12.3	250	230	1.58
	2.5	F	18.8	17.1	306	296	2.03
	10	M	33.3	32.6	583	574	3.93
	5	F	31.8	28.8	538	532	3.64
	75	M	67.5	65.4	1290	1140	7.81
	35	F	70.9	70.2	1370	1060	7.26
Rat[b] (14 days)	30	M	14.4	82.1	294	1849	12.66
		F	14.4	73.8	308	1605	10.99
	100	M	22.9	98.4	490	2223	15.23
		F	24.0	111	472	2435	16.68
	300 (NOAEL)	**M**	**35.8 [33.9 to 37.9]**	**114 [112 to 115]**	**708 [668 to 761]**	**2510 [2422 to 2640]**	**17.19**
		F	**41.0 [39.6 to 43.6]**	**147 [131 to 171]**	**799 [760 to 842]**	**3277 [2952 to 3828]**	**22.45**
Rat[b] (4 weeks)	1	M	4.23	34.3	70.7	739	5.06
		F	4.48	38.8	78.3	852	5.84
	75	M	66.1	143	1309	3000	20.55
		F	72.8	176	1484	3832	26.25
	1000 (NOAEL)	**M**	**161 [150 to 180]**	**150 [149 to 151]**	**3368 [3266 to 2519]**	**3345 [3214 to 3432]**	**22.91**
		F	**181 [161 to 200]**	**193 [172 to 214]**	**3732 [3451 to 3993]**	**4125 [3659 to 4229]**	**28.25**
Rat[b] (26 weeks)	0.5	M	16.2	23.1	329	451	3.09
		F	19.4	31.6	404	675	4.62
	5	M	93.2	91.4	1961	1861	12.75
		F	85.1	102	1672	2083	14.27
	1000 (NOAEL)	**M**	**174 [167 to 179]**	**148 [146 to 150]**	**3753 [3656 to 3896]**	**3203 [3005 to 3313]**	**21.94**
		F	**210 [200 to 220]**	**224 [215 to 233]**	**4403 [4101 to 4627]**	**4781 [4711 to 4907]**	**32.75**
Rat[h] (102 weeks)	0.25	M	9.97	13.1	206	277	1.90
		F	14.2	19.7	295	428	2.93
	2.5	M	59.6	73.1	1260	1470	10.07
		F	76.3	92.0	1620	1980	13.56
	75	M	160	137	3360	2840	19.45
		F	181	230	4010	4810	32.95
Monkey[b] (14 days)	8	M	12.2	14.6	128	144[d]	0.99
		F	11.8	15.5	104	124	0.85
	25 (NOAEL)	**M**	**20.8 [20.4 to 21.5]**	**22.7 [20.1 to 24.6]**	**233 [190 to 287]**	**233 [198 to 257]**	**1.60**
		F	**23.6 [19.2 to 30.9]**	**22.2 [15.0 to 29.9]**	**234[d] [159 to 321]**	**231 [192 to 286]**	**1.58**
	1000	M	67.0	61.9	1051	224[cd]	1.53
		F	59.2	65.9	961[d]	946	6.48

A Table of the Exposure Ratio of CAB in Toxicology Test Species and Humans Following Oral Administration (Continued)

Species (Duration)	Dose (mg/kg/day)	Sex	C_{max} (μg/mL)		AUC_{0-24} (μg.h/mL)		Animal to human ratio for AUC[a]
			Day 1	End of Study	Day 1	End of Study	
Monkey[b] (4 weeks)	5	M	12.6	10.0	115	100	0.68
		F	10.4	9.07	85.3	80.9	0.55
	50	M	20.8	17.4	311	276	1.89
		F	23.9	20.0	311	279	1.91
	500 (NOAEL)	**M**	**38.2 [33.1 to 43.3]**	**58.1 [50.3 to 63.3]**	**697 [616 to 773]**	**901 [860 to 945]**	**6.17**
		F	**39.1 [33.3 to 43.1]**	**65.0 [53.7 to 79.1]**	**664 [577 to 732]**	**904 [792 to 1114]**	**6.19**
Monkey (39 weeks)	5	M	7.15	3.37	62.1	37.7	0.26
		F	8.77	6.33	69.6	67.8	0.46
	50	M	22.1	21.1	251	229	1.57
		F	27.3	17.4	303	254	1.74
	500 (NOAEL)	**M**	**45.3 [37.4 to 61.7]**	**36.8 [23.9 to 57.2]**	**644 [505 to 826]**	**542 [359 to 781]**	**3.71**
		F	**56.4 [43.5 to 66.7]**	**32.4 [29.8 to 35.1]**	**807 [557 to 1008]**	**552 [447to 623]**	**3.78**
Rabbit (Embryofetal development)[ef]	30	F	NA	0.95	NA	10.5	0.072
	500	F	NA	3.4	NA	47.4	0.32
	2000 (NOAEL)	**F**	**NA**	**1.0**	**NA**	**96.1**	**0.66**
Human[g]	30 mg	M/F	-	8.1	-	146	NA

Note: NOAELs are in **bold text**. Values in brackets represent the range.

a. Calculated for AUC based on end of treatment values.
b. Values are the mean of n=3 to 5.
c. AUC_{0-4}. All males given 1000 mg/kg/day were euthanized in moribund condition on Day 14 following the 4 hour toxicokinetic time point. Therefore, the AUC_{0-24} could not be calculated for males on Day 14.
d. Emesis was observed in one animal in this dose group.
e. Composite TK results from n=3/group.
f. Values in end of study column were from Day 11 postcoitum or dosing Day 5.
g. Mean exposure (C_{max} and AUC_{0-24}) following CAB 30 mg PO once daily (POPPK analysis), report 2018N384611.
h. AUC and C_{max} values given for Week 4 and Week 26.

Table 9.2 Estimated Margins of CAB Relative to Clinical Exposure Following Administration of CAB injectable suspension

Species	Dose (mg/kg)	Sex	Route of administration	Cmax (μg/mL)[a,b]	AUC (μg.h/mL)[a,c]	Animal to human ratio for AUC
Rat (Single dose)	5	M	SC	8.36	4346	1.77
		F	SC	9,04	5367	2.18
	30	M	SC	38.7	19978	8.12
		F	SC	36.9	19218	7.81
	100[d] (NOAEL)	**M**	**SC**	**98.3 [78.4 to 117]**	**47912 [38207 to 56466]**	**19.47**
		F	**SC**	**104 [80.9 to 133]**	**51104 [40209 to 64474]**	**20.77**
	2.5	M	IM	12.6	4321	1.76
		F	IM	14.2	4525	1.84
	10	M	IM	32.4	15926	6.47
		F	IM	40.6	16464	6.69
	75 (NOAEL)	M	IM	**105 [95.3 to 119]**	**60071 [53582 to 64941]**	**24.41**
		F	IM	**124 [107 to 141]**	**64765 [60919 to 70666]**	**26.32**
Rat (3-month)	5	M	SC monthly	19.2	11204	4.55
		F	SC monthly	26.8	15238	6.19
	30	M	SC monthly	84.8	48082	19.54
		F	SC monthly	96.8	55956	22.74
	100 (NOAEL)	**M**	**SC monthly**	**137 [107 to 166]**	**70494 [59895 to 85122]**	**28.64**
		F	**SC monthly**	**195 [172 to 208]**	**116602 [105082 to 124604]**	**47.38**
	2.5	M	IM monthly	16.9	7031	2.86
		F	IM monthly	15.9	5500	2.23
	10	M	IM monthly	49.6	26001	10.57
		F	IM monthly	55.2	24934	10.13
	75 (NOAEL)	**M**	**IM monthly**	**135 [129 to 142]**	**78051 [74734 to 80570]**	**31.72**
		F	**IM monthly**	**181 [179 to 183]**	**107080 [92466 to 115252]**	**43.51**
	100 (NOAEL)	**M**	**SC weekly**	**166 [154 to 184]**	**22291 [21631 to 22907]**	**NA**
		F	**SC weekly**	**226 [221 to 235]**	**34315 [32842 to 35565]**	**NA**
Human[e]	400 mg monthly	M/F	IM	4.2	2461	NA

Note: n=3 animals/sex/dose, except where noted. NOAELs are in **bold text**

a. Results are reported as mean and [range].
b. For rat 3-month, C_{max} reported as overall study C_{max}
c. For rat single dose, AUC reported as $AUC_{0\text{-}720}$, AUC through 30 days (morning of Day 31). For rat 3-month, AUC for SC or IM monthly groups reported for the 3rd monthly interval, $AUC_{1440\text{-}2160h}$. For rat 3-month, AUC for SC weekly groups is reported as AUC during Week 13 (from predose on Day 85 to Day 92), $AUC_{2016\text{-}2184}$.
d. n = 2 males for AUC0-t in the 100 mg/kg dose group due to unscheduled death on Day 39.
e. Mean exposure (C_{max} and $AUC_{0\text{-}t}$) month 3 onward following a 400 mg IM monthly dose (POPPK analysis), report 2018N384611.

10. REFERENCES

NTP (National Toxicology Program) – Testing Status of Methyl Methanesulfonate, https://ntp.niehs.nih.gov/testing/status/agents/ts-11115-d.html

Guidelines (not provided)

ICH M3 (R2) (CPMP/ICH/286/95): Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. June 2009.

ICH Q3A(R2) (CPMP/ICH/2737/99): Impurities in New Drug Substances. October 2006.

ICH S2(R1) (CHMP/ICH/126642/08): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (2008).

EMEA/CHMP/QWP/251344/2006 (CHMP/SWP/5199/02): Guideline on the Limits of Genotoxic Impurities. London:EMEA (European Medicines Agency), 2006.

APPENDIX 1 CARCINOGENICITY TABLES

Table 10.1 List of Tissues Studied in Carcinogenicity Studies

Tissue examined	Mouse (Report No. 2017N310750)	Rat (Report No. 2017n310751)
Abnormalities	✓	✓
Adrenals	✓	✓
Aorta (thoracic)	✓	✓
Brain (cerebrum, cerebellum, midbrain and medulla oblongata)	✓	✓
Cecum	✓	✓
Cervix (collected with uterus)	x	✓
Colon	✓	✓
Rectum	✓	✓
Duodenum	✓	✓
Epididymides	✓	✓
Esophagus	✓	✓
Eyes/Optic nerves	✓	✓
Femur (femoro-tibial joint)	✓	✓
Gallbladder	✓	x
Harderian glands	✓	✓
Heart including section of aorta	✓	✓
Ileum	✓	✓
Jejunum	✓	✓
Kidneys (included renal papilla)	✓	✓
Larynx	✓	✓
Liver (Left Lateral lobe and Right Medial Lobe.)	✓	✓
Lung (all lobes)[a]	✓	✓
Lymph node -	✓	✓
mandibular[b]	✓	✓
mesenteric	✓	✓
Mammary gland (inguinal)[c]	✓	✓
Nasal cavities with skull and nasopharynx[d]	✓	✓
Ovaries	✓	✓
Pancreas	✓	✓
Parathyroids[e]	✓	✓

List of Tissues Studied in Carcinogenicity Studies (Continued)

Tissue examined	Mouse (Report No. 2017N310750)	Rat (Report No. 2017n310751)
Pituitary	✓	✓
Preputial/clitoral gland	✓	✓
Prostate[f]	✓	✓
Salivary gland		
mandibular	✓	✓
sublingual	✓	✓
parotid	✓	✓
Sciatic nerve	✓	✓
Seminal vesicles	✓	✓
Skeletal muscle (gastrocnemius transverse section as minimum)	✓	✓
Skin (inguinal, collected with mammary gland)	✓	✓
Spinal cord		
lumbar	✓	✓
Spleen	✓	✓
Sternum with bone marrow	✓	✓
Stomach (glandular and nonglandular regions)	✓	✓
Testes	✓	✓
Thymus	✓	✓
Thyroids	✓	✓
Tongue	✓	✓
Trachea	✓	✓
Urinary bladder	✓	✓
Uterus (horns and body)	✓	✓
Vagina	✓	✓

Additional Information:

a. 2 lobes examined to include both proximal and distal regions.
b. Only one required for examination.
c. Examined for all female animals. Examined in males when present in submitted section (no recuts were required).
d. Level 3 (second palatine ridge level) examined for nasal cavities; nasopharynx not examined.
e. Collected with thyroid; at least one thyroid was examined, on recut and/or recheck in wet tissues was performed to try to find the missing tissues.
f. At a minimum, ventral lobe was examined.

Table 10.2 Carcinogenicity Study in Mice - Tumour Incidence

		Group No. (Dose mg/kg/day)			
		1 (0)	2 (2.5)	3 (10)	4 (75)
ORGAN/TISSUE	**TUMOR**	**60 Males**	**60 Males**	**60 Males**	**60 Males**
epididymis	interstitial (leydig) cell adenoma	0	0	1	0
gland, adrenal	cortical adenoma	0	1	1	1
	paraganglioma	0	0	0	1
gland, harderian	adenoma	10	5	10	6
gland, mammary	adenocarcinoma	0	0	1	1
gland, pituitary	adenoma	0	1	0	0
	carcinoma	0	0	0	1
gland, seminal vesicle	adenocarcinoma	1	0	0	0
	adenoma	0	0	1	0
	carcinoma	0	1	0	0
gland, thyroid	adenoma	0	1	1	0
	follicular cell adenoma	1	0	0	1
hemolymphoreticular tissue	histiocytic sarcoma	0	1	2	0
	leukemia, granulocytic	2	0	0	0
	lymphoma, malignant	4	7	2	4
	mast cell tumor, malignant	0	1	0	0
kidney	adenoma	1	1	0	1
	carcinoma	1	0	0	0
large intestine, colon	hemangioma	1	0	0	0
liver	hemangiosarcoma	1	2	1	1
	hepatocellular adenoma	19	11	15	10
	hepatocellular carcinoma	1	2	1	2
	hepatocholangiocellular carcinoma	0	0	0	1
lung	bronchioloalveolar adenoma	22	12	21	19
	bronchioloalveolar carcinoma	19	11	11	15
	fibrosarcoma	0	1	0	0
muscle, skeletal	hemangiosarcoma	0	1	0	1
	osteosarcoma	0	1	0	0
	sarcoma	0	1	0	0
nerve, sciatic	fibrosarcoma	0	1	0	0
pancreas	carcinoma	0	0	1	0
	islet cell adenoma	0	0	2	0
	islet cell carcinoma	1	0	0	0
skin	basal cell tumor, benign	0	1	0	0

Carcinogenicity Study in Mice - Tumour Incidence (Continued)

		Group No. (Dose mg/kg/day)			
		1 (0)	2 (2.5)	3 (10)	4 (75)
ORGAN/TISSUE	**TUMOR**	**60 Males**	**60 Males**	**60 Males**	**60 Males**
	fibroma	0	0	1	0
	papilloma	0	1	0	0
small intestine, jejunum	adenocarcinoma	1	0	0	0
spleen	hemangiosarcoma	1	0	1	0
stomach	adenocarcinoma	0	0	1	0
	leiomyoma	1	0	0	0
subcutis	basal cell tumor, malignant	0	0	0	1
	cystadenoma	0	0	0	1
	fibrosarcoma	0	1	1	0
	hair follicle tumor, benign	0	1	0	0
	hemangioma	0	0	3	0
	sarcoma	1	2	0	0
testis	interstitial (leydig) cell adenoma	2	0	0	3
	interstitial (leydig) cell carcinoma	0	1	0	0
thymus	thymoma, malignant	0	0	1	0
urinary bladder	transitional cell carcinoma	0	1	0	0
whole body	hemangiosarcoma	1	2	1	2

Carcinogenicity Study in Mice - Tumour Incidence (Continued)

		Group No. (Dose mg/kg/day)			
		1 (0)	2 (25)	3 (50)	4 (350)
ORGAN/TISSUE	**TUMOR**	**60 Females**	**60 Females**	**60 Females**	**60 Females**
cervix	endometrial stromal poly	1	0	0	0
	leiomyoma	0	0	0	1
	leiomyosarcoma	0	2	1	0
	polyp	0	1	0	0
eye	schwannoma, malignant	0	1	0	0
gland, adrenal	carcinoma	0	1	1	0
	cortical adenoma	0	0	0	2
	pheochromocytoma, benign	0	0	1	0
gland, harderian	adenocarcinoma	0	0	1	0
	adenoma	3	7	2	3
gland, mammary	adenoma	0	0	1	0
	adenocarcinoma	4	0	1	0
gland, pituitary	adenoma	2	2	1	0
	carcinoma	1	1	0	0
hemolymphoreticular tissue	histiocytic sarcoma	2	1	2	4
	leukemia, granulocytic	3	0	1	3
	lymphoma, malignant	10	11	7	12
large intestine, cecum	leiomyoma	0	0	1	0
liver	hemangiosarcoma	0	0	1	2
	hepatocellular adenoma	1	1	2	0
	hepatocellular carcinoma	0	0	0	1
lung	bronchioloalveolar adenoma	8	11	15	5
	bronchioloalveolar carcinoma	5	3	7	5
muscle, skeletal	hemangiosarcoma	1	0	0	0
ovary	adenoma	1	0	0	0
	cystadenocarcinoma	1	0	0	0
	cystadenoma	2	1	1	0
	granulosa cell tumor, benign	0	0	1	0
	leiomyosarcoma	1	0	0	0
	luteoma	0	1	0	0

Carcinogenicity Study in Mice - Tumour Incidence (Continued)

		Group No. (Dose mg/kg/day)			
		1 (0)	2 (25)	3 (50)	4 (350)
ORGAN/TISSUE	TUMOR	60 Females	60 Females	60 Females	60 Females
	sertoli cell tumor, benign	0	2	0	1
	thecoma, benign	0	0	0	1
skin	papilloma	0	1	0	0
spinal cord, lumbar	hemangioma	1	0	0	0
spleen	hemangiosarcoma	1	0	0	0
stomach	papilloma	0	0	1	0
	squamous cell carcinoma	0	0	1	0
subcutis	basal cell tumor, malignant	0	0	1	0
	fibrosarcoma	1	0	0	1
	hair follicle tumor, benign	0	1	0	0
	hemangiosarcoma	0	0	1	0
	myxosarcoma	0	0	1	0
	sarcoma	0	3	1	0
thymus	carcinoma	0	0	0	1
	hemangiosarcoma	0	0	0	1
	thymoma, malignant	1	1	1	0
urinary bladder	transitional cell carcinoma	1	0	0	0
uterus	adenocarcinoma	1	0	1	1
	adenoma	0	1	0	0
	cystadenoma	0	0	1	0
	endometrial stromal polyp	2	1	0	0
	endometrial stromal sarcoma	1	1	0	0
	hemangiosarcoma	0	0	1	0
	leiomyoma	1	1	2	0
	leiomyosarcoma	0	3	1	1
	polyp	0	2	1	0
	sarcoma	0	0	1	0
whole body	hemangiosarcoma	3	0	3	3

Table 10.3 Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1M	375	375	1007	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	420	420	1049	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	482	482	1001	U	lung	bronchioloalveolar carcinoma	Yes
	482	482	1020	U	lung	bronchioloalveolar carcinoma	Yes
	534	534	1051	U	lung	bronchioloalveolar adenoma	No
	560	560	1052	U	lung	bronchioloalveolar carcinoma	Yes
	569	569	1033	U	lung	bronchioloalveolar carcinoma	Yes
	580	648	1036	U	subcutis	sarcoma	Yes
	590	590	1040	U	lung	bronchioloalveolar adenoma	No
	590	590	1040	U	lung	bronchioloalveolar carcinoma	Yes
	605	605	1006	U	gland, harderian	adenoma	No
	621	621	1011	U	gland, seminal vesicle	adenocarcinoma	Yes
	621	621	1011	U	liver	hepatocellular adenoma	No
	624	624	1004	U	liver	hemangiosarcoma	Yes
	624	624	1004	U	lung	bronchioloalveolar adenoma	No
	624	624	1004	U	spleen	hemangiosarcoma	Yes
	628	628	1008	U	lung	bronchioloalveolar adenoma	No
	648	648	1036	U	lung	bronchioloalveolar carcinoma	Yes
	657	657	1038	U	lung	bronchioloalveolar adenoma	No
	660	660	1043	U	liver	hepatocellular adenoma	No
	660	660	1043	U	lung	bronchioloalveolar carcinoma	Yes
	669	669	1060	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	669	669	1060	U	lung	bronchioloalveolar adenoma	No
	672	672	1019	U	gland, harderian	adenoma	No
	672	672	1019	U	liver	hepatocellular adenoma	No
	672	672	1054	U	lung	bronchioloalveolar carcinoma	Yes
	672	672	1059	U	lung	bronchioloalveolar adenoma	No
	672	672	1059	U	lung	bronchioloalveolar carcinoma	Yes
	691	691	1029	U	lung	bronchioloalveolar carcinoma	Yes
	700	700	1002	U	liver	hepatocellular adenoma	No
	700	700	1002	U	lung	bronchioloalveolar carcinoma	Yes
	700	700	1003	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	700	700	1003	U	lung	bronchioloalveolar adenoma	No
	712	712	1039	U	lung	bronchioloalveolar carcinoma	Yes

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1M	713	713	1016	U	liver	hepatocellular adenoma	No
	713	713	1016	U	lung	bronchioloalveolar adenoma	No
	713	713	1016	U	lung	bronchioloalveolar carcinoma	Yes
	729	729	1030	T	lung	bronchioloalveolar carcinoma	Yes
	730	730	1025	T	liver	hepatocellular adenoma	No
	730	730	1025	T	lung	bronchioloalveolar adenoma	No
	730	730	1031	T	kidney	adenoma	No
	730	730	1031	T	lung	bronchioloalveolar carcinoma	Yes
	730	730	1035	T	kidney	carcinoma	Yes
	730	730	1035	T	liver	hepatocellular adenoma	No
	730	730	1035	T	lung	bronchioloalveolar adenoma	No
	730	730	1046	T	gland, harderian	adenoma	No
	730	730	1048	T	liver	hepatocellular adenoma	No
	730	730	1056	T	lung	bronchioloalveolar carcinoma	Yes
	730	730	1056	T	small intestine, jejunum	adenocarcinoma	Yes
	730	730	1058	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	730	730	1058	T	liver	hepatocellular adenoma	No
	733	733	1005	T	liver	hepatocellular adenoma	No
	733	733	1005	T	lung	bronchioloalveolar carcinoma	Yes
	733	733	1009	T	lung	bronchioloalveolar adenoma	No
	733	733	1010	T	gland, harderian	adenoma	No
	734	734	1012	T	liver	hepatocellular adenoma	No
	734	734	1012	T	lung	bronchioloalveolar adenoma	No
	735	735	1013	T	liver	hepatocellular carcinoma	Yes
	735	735	1013	T	pancreas	islet cell carcinoma	Yes
	735	735	1014	T	gland, harderian	adenoma	No
	735	735	1014	T	lung	bronchioloalveolar adenoma	No
	735	735	1014	T	testis	interstitial (leydig) cell ade	No
	736	736	1017	T	gland, harderian	adenoma	No
	736	736	1018	T	liver	hepatocellular adenoma	No
	736	736	1018	T	lung	bronchioloalveolar adenoma	No
	737	737	1022	T	gland, harderian	adenoma	No
	737	737	1022	T	liver	hepatocellular adenoma	No
	737	737	1022	T	lung	bronchioloalveolar adenoma	No
	737	737	1024	T	gland, harderian	adenoma	No

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
	737	737	1026	T	liver	hepatocellular adenoma	No
1M	737	737	1026	T	lung	bronchioloalveolar adenoma	No
	737	737	1026	T	testis	interstitial (leydig) cell ade	No
	737	737	1027	T	liver	hepatocellular adenoma	No
	737	740	1032	T	gland, harderian	adenoma	No
	740	740	1028	T	gland, thyroid	follicular cell adenoma	No
	740	740	1028	T	liver	hepatocellular adenoma	No
	740	740	1028	T	lung	bronchioloalveolar adenoma	No
	740	740	1032	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	741	741	1034	T	lung	bronchioloalveolar adenoma	No
	741	741	1042	T	large intestine, colon	hemangioma	No
	741	741	1042	T	stomach	leiomyoma	No
	742	742	1047	T	liver	hepatocellular adenoma	No
	742	742	1047	T	lung	bronchioloalveolar adenoma	No
	742	742	1050	T	liver	hepatocellular adenoma	No
	742	742	1053	T	lung	bronchioloalveolar carcinoma	Yes
	742	742	1055	T	lung	bronchioloalveolar adenoma	No
	742	742	1055	T	lung	bronchioloalveolar carcinoma	Yes
	742	742	1057	T	gland, harderian	adenoma	No
	742	742	1057	T	liver	hepatocellular adenoma	No
	742	742	1057	T	lung	bronchioloalveolar adenoma	No
1F	346	346	1511	U	ovary	leiomyosarcoma	Yes
	352	398	1548	U	gland, mammary	adenocarcinoma	Yes
	388	499	1516	U	gland, mammary	adenocarcinoma	Yes
	422	422	1519	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	436	442	1524	U	gland, mammary	adenocarcinoma	Yes
	442	442	1522	U	lung	bronchioloalveolar adenoma	No
	455	455	1505	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	468	468	1508	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	471	492	1549	U	gland, mammary	adenocarcinoma	Yes
	492	492	1549	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	492	492	1549	U	ovary	adenoma	No
	499	499	1516	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	520	520	1507	U	lung	bronchioloalveolar carcinoma	Yes
	536	536	1559	U	hemolymphoreticular tissue	lymphoma, malignant	Yes

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1F	547	547	1709	U	cervix	endometrial stromal polyp	No
	547	547	1709	U	uterus	endometrial stromal polyp	No
	551	551	1534	U	gland, thyroid	follicular cell carcinoma	Yes
	562	562	1506	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	570	570	1535	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	585	585	1538	U	thymus	thymoma, malignant	Yes
	591	591	1513	U	lung	bronchioloalveolar adenoma	No
	591	591	1513	U	muscle, skeletal	hemangiosarcoma	Yes
	591	591	1513	U	spleen	hemangiosarcoma	Yes
	591	591	1513	U	uterus	endometrial stromal polyp	No
	598	598	1504	U	gland, harderian	adenoma	No
	598	598	1504	U	gland, pituitary	adenoma	No
	639	639	1517	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	644	644	1536	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	644	644	1536	U	lung	bronchioloalveolar adenoma	No
	664	664	1545	U	lung	bronchioloalveolar carcinoma	Yes
	664	664	1545	U	ovary	cystadenocarcinoma	Yes
	664	664	1545	U	urinary bladder	transitional cell carcinoma	Yes
	669	669	1502	U	lung	bronchioloalveolar carcinoma	Yes
	669	669	1531	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	669	669	1540	U	lung	bronchioloalveolar adenoma	No
	671	671	1526	U	gland, harderian	adenoma	No
	671	671	1526	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	671	671	1526	U	uterus	leiomyoma	No
	683	683	1552	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	705	705	1553	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	705	705	1553	U	lung	bronchioloalveolar adenoma	No
	706	706	1525	U	gland, harderian	adenoma	No
	706	706	1525	U	lung	bronchioloalveolar adenoma	No
	706	706	1525	U	lung	bronchioloalveolar carcinoma	Yes
	706	706	1525	U	tail	hemangiosarcoma	Yes
	707	707	1510	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	716	736	1529	T	subcutis	fibrosarcoma	Yes
	718	718	1557	U	adipose tissue	hemangioma	No
	718	718	1557	U	ovary	cystadenoma	No

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1F	718	718	1557	U	uterus	adenocarcinoma	Yes
	729	729	1544	T	lung	bronchioloalveolar carcinoma	Yes
	729	729	1547	T	spinal cord, lumbar	hemangioma	No
	730	730	1515	T	uterus	endometrial stromal sarcoma	Yes
	733	733	1514	T	liver	hepatocellular adenoma	No
	733	733	1514	T	lung	bronchioloalveolar adenoma	No
	737	737	1537	T	gland, pituitary	carcinoma	Yes
	737	737	1542	T	lung	bronchioloalveolar adenoma	No
	740	740	1550	T	adipose tissue	hemangiosarcoma	Yes
	740	740	1550	T	gland, pituitary	adenoma	No
	740	740	1550	T	ovary	cystadenoma	No
2M	272	272	2003	U	muscle, skeletal	osteosarcoma	Yes
	359	629	2007	U	bone	squamous cell carcinoma	Yes
	380	741	2054	T	subcutis	hair follicle tumor, benign	No
	447	447	2031	U	lung	bronchioloalveolar adenoma	No
	464	510	2023	U	subcutis	fibrosarcoma	Yes
	473	473	2009	U	gland, adrenal	cortical adenoma	No
	473	473	2009	U	gland, harderian	adenoma	No
	473	473	2009	U	gland, thyroid	adenoma	No
	486	486	2034	U	liver	hepatocellular carcinoma	Yes
	486	486	2034	U	lung	bronchioloalveolar carcinoma	Yes
	503	503	2040	U	liver	hepatocellular adenoma	No
	503	503	2040	U	lung	bronchioloalveolar carcinoma	Yes
	503	503	2040	U	skin	papilloma	No
	564	564	2037	U	lymph node	hemangioma	No
	592	592	2001	U	lung	bronchioloalveolar carcinoma	Yes
	593	593	2042	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	611	737	2035	T	subcutis	sarcoma	Yes
	621	621	2008	U	gland, seminal vesicle	carcinoma	Yes
	621	621	2008	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	621	621	2008	U	lung	bronchioloalveolar carcinoma	Yes
	623	623	2016	U	liver	hepatocellular adenoma	No
	623	623	2016	U	lung	bronchioloalveolar adenoma	No
	623	623	2016	U	lung	bronchioloalveolar carcinoma	Yes
	630	643	2041	U	subcutis	sarcoma	Yes

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2M	643	643	2020	U	lung	bronchioloalveolar carcinoma	Yes
	643	643	2041	U	lung	bronchioloalveolar carcinoma	Yes
	643	643	2041	U	lung	fibrosarcoma	Yes
	643	643	2041	U	nerve, sciatic	fibrosarcoma	Yes
	651	651	2045	U	urinary bladder	transitional cell carcinoma	Yes
	655	655	2033	U	gland, harderian	adenoma	No
	655	655	2033	U	lung	bronchioloalveolar adenoma	No
	655	655	2033	U	lung	bronchioloalveolar carcinoma	Yes
	655	655	2033	U	muscle, skeletal	sarcoma	Yes
	662	662	2011	U	lung	bronchioloalveolar adenoma	No
	680	680	2038	U	gland, harderian	adenoma	No
	684	684	2021	U	skin	basal cell tumor, benign	No
	698	698	2049	U	liver	hepatocellular adenoma	No
	706	706	2053	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	706	706	2053	U	lung	bronchioloalveolar adenoma	No
	706	706	2053	U	lung	bronchioloalveolar carcinoma	Yes
	723	723	2004	U	lung	bronchioloalveolar adenoma	No
	725	725	2051	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	725	725	2051	U	lung	bronchioloalveolar adenoma	No
	727	727	2024	U	liver	hemangiosarcoma	Yes
	727	727	2024	U	lung	bronchioloalveolar adenoma	No
	727	727	2024	U	lung	bronchioloalveolar carcinoma	Yes
	727	727	2024	U	muscle, skeletal	hemangiosarcoma	Yes
	730	730	2012	T	lung	bronchioloalveolar carcinoma	Yes
	730	730	2036	T	liver	hepatocellular adenoma	No
	730	730	2039	T	liver	hepatocellular adenoma	No
	730	730	2039	T	lung	bronchioloalveolar adenoma	No
	730	730	2055	T	gland, harderian	adenoma	No
	730	730	2057	T	testis	interstitial (leydig) cell car	Yes
	734	734	2015	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	735	735	2017	T	liver	hepatocellular adenoma	No
	736	736	2019	T	lung	bronchioloalveolar adenoma	No
	736	736	2022	T	liver	hemangiosarcoma	Yes
	736	736	2026	T	liver	hepatocellular adenoma	No
	737	737	2028	T	lung	bronchioloalveolar adenoma	No

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2M	737	737	2032	T	kidney	adenoma	No
	737	737	2043	T	gland, pituitary	adenoma	No
	737	737	2043	T	lung	bronchioloalveolar adenoma	No
	737	737	2044	T	liver	hepatocellular adenoma	No
	740	740	2046	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	740	740	2046	T	liver	hepatocellular adenoma	No
	740	740	2046	T	liver	hepatocellular carcinoma	Yes
	741	741	2048	T	hemolymphoreticular tissue	mast cell tumor, malignant	Yes
	741	741	2052	T	gland, harderian	adenoma	No
	741	741	2054	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	741	741	2054	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	741	741	2054	T	liver	hepatocellular adenoma	No
	742	742	2058	T	liver	hepatocellular adenoma	No
2F	368	368	2515	U	lung	bronchioloalveolar adenoma	No
	395	413	2535	U	subcutis	sarcoma	Yes
	413	495	2517	U	skin	papilloma	No
	495	495	2517	U	gland, harderian	adenoma	No
	495	495	2530	U	gland, harderian	adenoma	No
	495	495	2530	U	lung	bronchioloalveolar adenoma	No
	509	509	2536	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	511	511	2554	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	523	523	2534	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	528	568	2513	U	subcutis	sarcoma	Yes
	604	604	2553	U	gland, pituitary	carcinoma	Yes
	611	611	2559	U	cervix	leiomyosarcoma	Yes
	611	611	2559	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	611	611	2559	U	uterus	leiomyosarcoma	Yes
	625	625	2506	U	uterus	endometrial stromal polyp	No
	625	625	2547	U	lung	bronchioloalveolar carcinoma	Yes
	628	628	2508	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	659	659	2511	U	ear	hair follicle tumor, benign	No
	659	659	2511	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	659	659	2511	U	lung	bronchioloalveolar adenoma	No
	676	676	2538	U	bone	sarcoma	Yes
	676	676	2538	U	gland, adrenal	carcinoma	Yes

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2F	676	676	2538	U	uterus	leiomyosarcoma	Yes
	695	695	2552	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	695	695	2552	U	lung	bronchioloalveolar adenoma	No
	701	701	2531	U	eye	schwannoma, malignant	Yes
	701	701	2531	U	lung	bronchioloalveolar adenoma	No
	701	701	2531	U	lung	bronchioloalveolar carcinoma	Yes
	706	706	2544	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	706	706	2544	U	lung	bronchioloalveolar adenoma	No
	706	706	2544	U	lung	bronchioloalveolar carcinoma	Yes
	730	730	2522	T	gland, harderian	adenoma	No
	730	730	2541	T	gland, pituitary	adenoma	No
	730	730	2541	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	730	730	2546	T	lung	bronchioloalveolar adenoma	No
	731	742	2543	T	subcutis	sarcoma	Yes
	733	733	2523	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	733	733	2555	T	gland, harderian	adenoma	No
	734	734	2501	T	ovary	luteoma	No
	735	735	2502	T	ovary	cystadenoma	No
	736	736	2503	T	gland, harderian	adenoma	No
	736	736	2503	T	uterus	polyp	No
	736	736	2504	T	cervix	polyp	No
	736	736	2504	T	uterus	polyp	No
	737	737	2520	T	liver	hepatocellular adenoma	No
	737	737	2521	T	lung	bronchioloalveolar adenoma	No
	737	737	2521	T	uterus	leiomyoma	No
	741	741	2526	T	lung	bronchioloalveolar adenoma	No
	741	741	2529	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	741	741	2529	T	subcutis	hair follicle tumor, benign	No
	741	741	2529	T	uterus	leiomyosarcoma	Yes
	742	742	2532	T	gland, harderian	adenoma	No
	742	742	2533	T	gland, pituitary	adenoma	No
	742	742	2533	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	742	742	2537	T	gland, harderian	adenoma	No
	742	742	2537	T	lung	bronchioloalveolar adenoma	No
	742	742	2537	T	thymus	thymoma, malignant	Yes

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2F	742	742	2539	T	ovary	sertoli cell tumor, benign	No
	742	742	2539	T	uterus	endometrial stromal sarcoma	Yes
	742	742	2543	T	cervix	leiomyosarcoma	Yes
	742	742	2548	T	gland, thyroid	adenoma	No
	742	742	2556	T	ovary	sertoli cell tumor, benign	No
	742	742	2560	T	lung	bronchioloalveolar adenoma	No
	742	742	2560	T	uterus	adenoma	No
3F	203	203	3502	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	286	286	3550	U	gland, pituitary	adenoma	No
	423	460	3547	U	subcutis	sarcoma	Yes
	460	460	3547	U	lung	bronchioloalveolar adenoma	No
	460	460	3547	U	uterus	leiomyosarcoma	Yes
	486	544	3543	U	gland, mammary	adenocarcinoma	Yes
	501	501	3553	U	lung	bronchioloalveolar carcinoma	Yes
	501	501	3553	U	uterus	adenocarcinoma	Yes
	519	519	3538	U	cervix	leiomyosarcoma	Yes
	534	534	3540	U	lung	bronchioloalveolar carcinoma	Yes
	544	544	3543	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	545	545	3525	U	body cavity, abdominal	sarcoma	Yes
	589	589	3503	U	lung	bronchioloalveolar adenoma	No
	637	637	3523	U	liver	hepatocellular adenoma	No
	637	637	3523	U	lung	bronchioloalveolar carcinoma	Yes
	644	644	3559	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	644	644	3559	U	lung	bronchioloalveolar adenoma	No
	658	658	3526	U	lung	bronchioloalveolar adenoma	No
	660	660	3541	U	uterus	polyp	No
	663	663	3524	U	liver	hepatocellular adenoma	No
	698	698	3505	U	uterus	hemangiosarcoma	Yes
	699	699	3555	U	uterus	sarcoma	Yes
	701	701	3507	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	703	742	3539	T	subcutis	basal cell tumor, malignant	Yes
	709	722	3519	U	subcutis	hemangiosarcoma	Yes
	722	722	3519	U	lung	bronchioloalveolar adenoma	No
	722	722	3519	U	lung	bronchioloalveolar carcinoma	Yes
	726	726	3556	U	large intestine, cecum	leiomyoma	No

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
3F	729	729	3529	T	ovary	cystadenoma	No
	730	730	3504	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	730	730	3504	T	stomach	squamous cell carcinoma	Yes
	730	730	3533	T	lung	bronchioloalveolar carcinoma	Yes
	730	730	3533	T	ovary	granulosa cell tumor, benign	No
	730	730	3545	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	730	730	3545	T	lung	bronchioloalveolar adenoma	No
	730	730	3558	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	730	730	3558	T	lung	bronchioloalveolar adenoma	No
	733	733	3508	T	gland, harderian	adenoma	No
	734	734	3509	T	lung	bronchioloalveolar adenoma	No
	734	734	3509	T	subcutis	myxosarcoma	Yes
	735	735	3510	T	lung	bronchioloalveolar adenoma	No
	735	735	3514	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	735	735	3514	T	liver	hemangiosarcoma	Yes
	735	735	3514	T	lung	bronchioloalveolar carcinoma	Yes
	735	735	3514	T	uterus	leiomyoma	No
	737	737	3518	T	lung	bronchioloalveolar adenoma	No
	737	737	3518	T	lung	bronchioloalveolar carcinoma	Yes
	737	737	3522	T	gland, harderian	adenoma	No
	737	737	3527	T	lung	bronchioloalveolar adenoma	No
	737	742	3546	T	gland, harderian	adenocarcinoma	Yes
	741	741	3531	T	uterus	cystadenoma	No
	741	741	3535	T	gland, adrenal	pheochromocytoma, benign	No
	741	741	3535	T	thymus	thymoma, malignant	Yes
	741	741	3535	T	uterus	leiomyoma	No
	742	742	3536	T	stomach	papilloma	No
	742	742	3539	T	lung	bronchioloalveolar adenoma	No
	742	742	3546	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	742	742	3548	T	gland, adrenal	carcinoma	Yes
	742	742	3549	T	body cavity, oral	papilloma	No
	742	742	3551	T	lung	bronchioloalveolar adenoma	No
	742	742	3554	T	gland, mammary	adenoma	No
	742	742	3557	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	742	742	3557	T	lung	bronchioloalveolar adenoma	No

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
3F	742	742	3560	T	lung	bronchioloalveolar adenoma	No
4M	369	369	4060	U	gland, harderian	adenoma	No
	471	471	4022	U	liver	hepatocellular adenoma	No
	538	538	4018	U	gland, mammary	adenocarcinoma	Yes
	538	538	4018	U	liver	hepatocellular adenoma	No
	538	538	4018	U	lung	bronchioloalveolar adenoma	No
	548	558	4027	U	subcutis	fibrosarcoma	Yes
	558	558	4027	U	lung	bronchioloalveolar carcinoma	Yes
	561	561	4017	U	body cavity, thoracic	sarcoma	Yes
	561	561	4017	U	lung	bronchioloalveolar carcinoma	Yes
	571	571	4012	U	lung	bronchioloalveolar carcinoma	Yes
	579	579	4045	U	gland, thyroid	adenoma	No
	587	587	4031	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	590	590	4032	U	lung	bronchioloalveolar adenoma	No
	604	642	4037	U	skin	fibroma	No
	607	607	4019	U	lung	bronchioloalveolar adenoma	No
	607	607	4019	U	lung	bronchioloalveolar carcinoma	Yes
	611	611	4055	U	lung	bronchioloalveolar adenoma	No
	611	611	4055	U	thymus	thymoma, malignant	Yes
	621	621	4020	U	liver	hemangiosarcoma	Yes
	621	621	4020	U	lung	bronchioloalveolar adenoma	No
	621	621	4020	U	spleen	hemangiosarcoma	Yes
	624	624	4049	U	lung	bronchioloalveolar carcinoma	Yes
	642	642	4037	U	lung	bronchioloalveolar adenoma	No
	642	642	4037	U	lung	bronchioloalveolar carcinoma	Yes
	664	664	4059	U	lung	bronchioloalveolar carcinoma	Yes
	692	692	4038	U	lung	bronchioloalveolar adenoma	No
	692	692	4047	U	lung	bronchioloalveolar carcinoma	Yes
	712	712	4007	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	712	712	4007	U	lung	bronchioloalveolar adenoma	No
	713	713	4016	U	bone	osteosarcoma	Yes
	713	713	4016	U	lung	bronchioloalveolar carcinoma	Yes
	713	713	4016	U	pancreas	carcinoma	Yes
	713	713	4016	U	subcutis	hemangioma	No
	716	716	4057	U	lung	bronchioloalveolar adenoma	No

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
4M	716	716	4057	U	lung	bronchioloalveolar carcinoma	Yes
	727	727	4011	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	729	729	4050	T	body cavity, thoracic	mesothelioma, malignant	Yes
	729	729	4050	T	gland, harderian	adenoma	No
	730	730	4001	T	gland, harderian	adenoma	No
	730	730	4001	T	liver	hepatocellular carcinoma	Yes
	730	730	4001	T	lung	bronchioloalveolar adenoma	No
	730	730	4014	T	lung	bronchioloalveolar adenoma	No
	730	730	4014	T	lung	bronchioloalveolar carcinoma	Yes
	730	730	4034	T	gland, harderian	adenoma	No
	730	730	4034	T	liver	hepatocellular adenoma	No
	730	730	4035	T	lung	bronchioloalveolar adenoma	No
	730	730	4043	T	lung	bronchioloalveolar adenoma	No
	730	730	4046	T	lung	bronchioloalveolar adenoma	No
	730	730	4051	T	gland, seminal vesicle	adenoma	No
	733	733	4002	T	gland, harderian	adenoma	No
	733	733	4002	T	liver	hepatocellular adenoma	No
	733	733	4002	T	lung	bronchioloalveolar adenoma	No
	733	733	4003	T	liver	hepatocellular adenoma	No
	733	733	4005	T	gland, harderian	adenoma	No
	733	733	4005	T	liver	hepatocellular adenoma	No
	735	735	4008	T	liver	hepatocellular adenoma	No
	735	735	4008	T	lung	bronchioloalveolar adenoma	No
	735	735	4010	T	gland, harderian	adenoma	No
	735	735	4010	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	735	735	4010	T	liver	hepatocellular adenoma	No
	735	735	4010	T	pancreas	islet cell adenoma	No
	737	737	4024	T	epididymis	interstitial (leydig) cell adenoma	No
	737	737	4024	T	liver	hepatocellular adenoma	No
	737	737	4024	T	lung	bronchioloalveolar adenoma	No
	737	737	4024	T	subcutis	hemangioma	No
	737	737	4025	T	lung	bronchioloalveolar adenoma	No
	737	737	4028	T	liver	hepatocellular adenoma	No
	737	737	4029	T	liver	hepatocellular adenoma	No
	737	737	4029	T	lung	bronchioloalveolar adenoma	No

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
4M	737	737	4030	T	liver	hepatocellular adenoma	No
	737	737	4036	T	gland, harderian	adenoma	No
	740	740	4039	T	liver	hepatocellular adenoma	No
	740	740	4039	T	lung	bronchioloalveolar adenoma	No
	741	741	4040	T	liver	hepatocellular adenoma	No
	741	741	4040	T	stomach	adenocarcinoma	Yes
	741	741	4042	T	gland, harderian	adenoma	No
	741	741	4042	T	lung	bronchioloalveolar adenoma	No
	741	741	4052	T	gland, harderian	adenoma	No
	741	741	4052	T	liver	hepatocellular adenoma	No
	741	741	4052	T	subcutis	hemangioma	No
	741	741	4054	T	gland, adrenal	cortical adenoma	No
	741	741	4054	T	pancreas	islet cell adenoma	No
5F	423	423	5526	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	474	474	5521	U	liver	hepatocellular carcinoma	Yes
	489	489	5545	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	522	522	5542	U	lung	bronchioloalveolar carcinoma	Yes
	527	527	5506	U	gland, harderian	adenoma	No
	544	544	5537	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	553	553	5525	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	557	557	5551	U	gland, harderian	adenoma	No
	560	560	5508	U	liver	hemangiosarcoma	Yes
	581	581	5547	U	lung	bronchioloalveolar adenoma	No
	594	594	5543	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	610	610	5548	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	624	624	5533	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	624	624	5533	U	uterus	leiomyosarcoma	Yes
	638	638	5558	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	639	639	5552	U	lung	bronchioloalveolar carcinoma	Yes
	639	639	5552	U	thymus	carcinoma	Yes
	642	642	5512	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	654	686	5540	U	subcutis	fibrosarcoma	Yes
	656	656	5549	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	660	660	5505	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	677	677	5523	U	lung	bronchioloalveolar carcinoma	Yes

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
5F	677	677	5523	U	site, uncertain primary	sarcoma	Yes
	678	678	5560	U	thymus	hemangiosarcoma	Yes
	680	680	5553	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	680	680	5553	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	688	688	5520	U	gland, harderian	adenoma	No
	688	688	5520	U	lung	bronchioloalveolar adenoma	No
	690	690	5528	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	690	690	5528	U	lung	bronchioloalveolar adenoma	No
	691	691	5516	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	694	694	5510	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	717	717	5541	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	720	720	5511	U	ovary	thecoma, benign	No
	730	730	5559	T	lung	bronchioloalveolar adenoma	No
	730	730	5559	T	ovary	sertoli cell tumor, benign	No
	735	735	5504	T	cervix	leiomyoma	No
	736	736	5519	T	gland, adrenal	cortical adenoma	No
	736	736	5519	T	lung	bronchioloalveolar carcinoma	Yes
	737	737	5534	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	737	737	5544	T	liver	hemangiosarcoma	Yes
	737	737	5544	T	uterus	adenocarcinoma	Yes
	740	740	5546	T	gland, adrenal	cortical adenoma	No
	740	740	5546	T	lung	bronchioloalveolar adenoma	No
	741	741	5557	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	741	741	5557	T	lung	bronchioloalveolar carcinoma	Yes
6M	334	334	6016	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	426	426	6012	U	lung	bronchioloalveolar carcinoma	Yes
	450	450	6011	U	gland, harderian	adenoma	No
	469	469	6028	U	lung	bronchioloalveolar adenoma	No
	483	483	6035	U	lung	bronchioloalveolar adenoma	No
	483	483	6035	U	lung	bronchioloalveolar carcinoma	Yes
	486	486	6055	U	lung	bronchioloalveolar adenoma	No
	494	494	6018	U	gland, mammary	adenocarcinoma	Yes
	520	520	6015	U	gland, pituitary	carcinoma	Yes
	523	523	6042	U	liver	hepatocellular carcinoma	Yes
	525	525	6060	U	bone	hemangiosarcoma	Yes

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
6M	525	525	6060	U	liver	hepatocellular adenoma	No
	525	525	6060	U	muscle, skeletal	hemangiosarcoma	Yes
	532	532	6003	U	body cavity, abdominal	neuroendocrine cell tumor, ben	No
	532	532	6003	U	lung	bronchioloalveolar carcinoma	Yes
	573	573	6022	U	lung	bronchioloalveolar carcinoma	Yes
	573	573	6033	U	lung	bronchioloalveolar adenoma	No
	573	573	6033	U	lung	bronchioloalveolar carcinoma	Yes
	579	579	6021	U	gland, adrenal	cortical adenoma	No
	579	579	6021	U	lung	bronchioloalveolar carcinoma	Yes
	584	584	6056	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	584	584	6056	U	liver	hepatocellular carcinoma	Yes
	590	590	6006	U	lung	bronchioloalveolar carcinoma	Yes
	594	594	6020	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	594	594	6020	U	kidney	adenoma	No
	637	637	6014	U	lung	bronchioloalveolar adenoma	No
	687	687	6017	U	lung	bronchioloalveolar carcinoma	Yes
	688	737	6037	T	subcutis	basal cell tumor, malignant	Yes
	697	697	6009	U	liver	hepatocellular adenoma	No
	697	697	6009	U	lung	bronchioloalveolar adenoma	No
	716	716	6038	U	gland, harderian	adenoma	No
	716	716	6038	U	liver	hemangiosarcoma	Yes
	716	716	6038	U	lung	bronchioloalveolar adenoma	No
	721	721	6025	U	liver	hepatocellular adenoma	No
	721	721	6025	U	liver	hepatocholangiocellular carcin	Yes
	721	721	6025	U	lung	bronchioloalveolar carcinoma	Yes
	729	729	6058	T	liver	hepatocellular adenoma	No
	729	729	6058	T	lung	bronchioloalveolar adenoma	No
	730	730	6031	T	lung	bronchioloalveolar adenoma	No
	730	730	6032	T	liver	hepatocellular adenoma	No
	730	730	6039	T	liver	hepatocellular adenoma	No
	730	730	6039	T	lung	bronchioloalveolar adenoma	No
	730	730	6039	T	lung	bronchioloalveolar carcinoma	Yes
	730	730	6052	T	gland, adrenal	paraganglioma	Yes
	733	733	6002	T	gland, harderian	adenoma	No
	733	733	6002	T	lung	bronchioloalveolar carcinoma	Yes

Carcinogenicity Study in Mice - Chronological Listing of Tumour Occurrence (Continued)

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
6M	733	733	6002	T	subcutis	cystadenoma	No
	733	733	6004	T	lung	bronchioloalveolar adenoma	No
	733	733	6005	T	lung	bronchioloalveolar carcinoma	Yes
	735	735	6008	T	gland, harderian	adenoma	No
	735	735	6008	T	lung	bronchioloalveolar adenoma	No
	735	735	6010	T	testis	interstitial (leydig) cell ade	No
	736	736	6013	T	lung	bronchioloalveolar carcinoma	Yes
	736	736	6013	T	testis	interstitial (leydig) cell ade	No
	737	737	6030	T	lung	bronchioloalveolar carcinoma	Yes
	737	737	6034	T	gland, harderian	adenoma	No
	737	737	6034	T	lung	bronchioloalveolar adenoma	No
	737	737	6036	T	gland, thyroid	follicular cell adenoma	No
	737	737	6036	T	liver	hepatocellular adenoma	No
	737	737	6037	T	body cavity, abdominal	mesothelioma, malignant	Yes
	737	737	6037	T	liver	hepatocellular adenoma	No
	737	737	6037	T	lung	bronchioloalveolar adenoma	No
	740	740	6043	T	gland, harderian	adenoma	No
	740	740	6044	T	lung	bronchioloalveolar adenoma	No
	741	741	6045	T	liver	hepatocellular adenoma	No
	741	741	6048	T	lung	bronchioloalveolar adenoma	No
	741	741	6050	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	741	741	6050	T	lung	bronchioloalveolar adenoma	No
	741	741	6051	T	lung	bronchioloalveolar carcinoma	Yes
	741	741	6051	T	testis	interstitial (leydig) cell ade	No
	741	741	6057	T	liver	hepatocellular adenoma	No
	741	741	6057	T	lung	bronchioloalveolar adenoma	No
	741	741	6059	T	lung	bronchioloalveolar adenoma	No

Key:
A = Accidental death.
T = Terminal kill.
U = Unscheduled death.

Group 1 dose level = 0 mg/kg/day
Group 2 dose level = 2.5 mg/kg/day
Group 3 dose level = 5 mg/kg/day
Group 4 dose level = 10 mg/kg/day
Group 5 dose level = 35 mg/kg/day
Group 6 dose level = 75 mg/kg/day

Table 10.4 Carcinogenicity Study in Mice - Summary of Survival and Fate of Animals

Sex: Male																						
Dose	0 mg/kg/day						2.5 mg/kg/day						10 mg/kg/day						75 mg/kg/day				
Week	E	D	A	K	N		E	D	A	K	N		E	D	A	K	N		E	D	A	K	N
4	60	.	.	.	0		60	.	.	.	0		60	.	.	.	0		60	.	.	.	0
11	60	.	.	.	0		60	1	.	.	1		60	.	.	1	1		60	.	.	.	0
13	60	.	.	.	0		59	.	.	.	0		59	.	.	.	0		60	.	.	.	0
17	60	.	.	.	0		59	.	.	.	0		59	.	.	1	1		60	.	.	.	0
18	60	.	.	.	0		59	.	.	.	0		58	.	.	.	0		60	.	.	.	0
22	60	.	.	.	0		59	.	.	.	0		58	1	.	.	1		60	.	.	.	0
27	60	.	.	.	0		59	.	.	.	0		57	.	1	.	1		60	.	.	.	0
29	60	.	.	.	0		59	.	.	.	0		56	.	.	.	0		60	.	.	.	0
33	60	.	.	.	0		59	1	.	.	1		56	.	.	.	0		60	.	.	.	0
36	60	.	.	.	0		58	.	.	.	0		56	.	.	.	0		60	.	.	.	0
38	60	.	.	.	0		58	.	.	.	0		56	.	.	.	0		60	.	.	.	0
39	60	.	.	.	0		58	.	.	1	1		56	.	.	.	0		60	.	.	.	0
41	60	.	.	.	0		57	.	.	.	0		56	.	.	.	0		60	.	.	.	0
42	60	.	.	.	0		57	.	.	.	0		56	.	.	.	0		60	.	.	.	0
48	60	.	.	.	0		57	1	.	1	2		56	.	.	.	0		60	.	.	1	1
50	60	.	.	.	0		55	.	.	.	0		56	.	.	.	0		59	.	.	.	0
51	60	.	.	.	0		55	.	.	.	0		56	1	.	.	1		59	.	.	.	0
53	60	.	.	.	0		55	.	.	.	0		55	1	.	1	2		59	.	.	.	0
54	60	.	.	1	1		55	.	1	1	2		53	.	.	.	0		59	.	.	.	0
55	59	.	.	.	0		53	1	.	.	1		53	.	.	.	0		59	.	.	.	0
57	59	.	.	.	0		52	.	.	.	0		53	.	.	.	0		59	.	.	.	0
59	59	.	.	.	0		52	.	.	.	0		53	.	.	.	0		59	.	.	.	0
59	59	.	.	.	0		52	.	.	.	0		53	.	.	.	0		59	.	.	.	0
60	59	1	.	.	1		52	.	.	.	0		53	.	.	.	0		59	.	.	.	0
61	58	.	.	.	0		52	.	.	.	0		53	1	.	.	1		59	1	.	.	1
63	58	.	.	.	0		52	.	.	.	0		52	.	.	.	0		58	.	.	.	0
64	58	.	.	.	0		52	.	.	1	1		52	.	.	.	0		58	.	.	.	0
65	58	.	.	.	0		51	.	.	.	0		52	.	.	.	0		58	.	.	1	1
66	58	.	.	.	0		51	.	.	.	0		52	.	.	.	0		57	.	.	.	0
67	58	.	.	.	0		51	.	.	.	0		52	.	.	.	0		57	1	.	.	1
68	58	.	.	.	0		51	1	.	.	1		52	.	.	1	1		56	.	.	.	0
69	58	1	.	1	2		50	.	.	.	0		51	.	.	.	0		56	.	.	1	1
70	56	.	.	.	0		50	1	.	.	1		51	.	.	1	1		55	1	.	.	1
71	56	.	.	.	0		49	.	.	.	0		50	.	.	.	0		54	2	.	.	2
72	56	.	.	.	0		49	.	.	1	1		50	.	.	.	0		52	.	.	.	0
73	56	.	.	.	0		48	.	.	1	1		50	.	.	.	0		52	.	.	1	1
75	56	.	.	.	0		47	.	.	.	0		50	.	.	.	0		51	2	.	2	4

Carcinogenicity Study in Mice - Summary of Survival and Fate of Animals (Continued)

Sex: Male																						
Dose	**0 mg/kg/day**						**2.5 mg/kg/day**						**10 mg/kg/day**						**75 mg/kg/day**				
Week	E	D	A	K	N		E	D	A	K	N		E	D	A	K	N		E	D	A	K	N
76	56	.	.	.	0		47	.	.	.	0		50	.	.	.	0		47	1	.	.	1
77	56	1	.	.	1		47	.	.	.	0		50	1	.	.	1		46	.	.	.	0
78	55	.	.	.	0		47	.	.	.	0		49	.	.	.	0		46	.	.	.	0
79	55	.	.	.	0		47	.	.	.	0		49	.	.	.	0		46	.	.	1	1
80	55	.	.	1	1		47	.	.	1	1		49	.	.	1	1		45	.	.	.	0
81	54	.	.	.	0		46	1	.	.	1		48	.	.	1	1		45	.	.	.	0
82	54	.	.	1	1		45	.	.	.	0		47	1	.	.	1		45	.	.	2	2
83	53	1	.	.	1		45	.	.	.	0		46	.	.	1	1		43	.	.	1	1
84	52	.	.	.	0		45	.	.	.	0		45	.	.	1	1		42	2	.	.	2
85	52	.	.	1	1		45	1	.	1	2		44	.	.	1	1		40	.	.	2	2
86	51	.	.	.	0		43	.	.	.	0		43	.	.	.	0		38	.	.	.	0
87	51	1	.	.	1		43	.	.	.	0		43	.	.	1	1		38	1	.	.	1
88	50	.	.	.	0		43	.	.	.	0		42	.	.	1	1		37	.	.	.	0
89	50	1	.	.	1		43	.	.	2	2		41	1	.	1	2		37	.	.	1	1
90	49	1	.	1	2		41	.	.	1	1		39	.	.	1	1		36	.	.	.	0
91	47	.	.	.	0		40	.	.	.	0		38	.	.	.	0		36	.	.	1	1
92	47	.	.	.	0		40	.	.	2	2		38	.	.	1	1		35	.	.	.	0
93	47	.	.	1	1		38	1	.	.	1		37	.	.	.	0		35	.	.	.	0
94	46	1	.	.	1		37	1	.	.	1		37	.	.	.	0		35	.	.	.	0
95	45	.	.	1	1		36	1	.	.	1		37	.	.	1	1		35	.	.	.	0
96	44	1	.	3	4		35	.	.	.	0		36	.	.	.	0		35	.	.	.	0
97	40	.	.	.	0		35	.	.	.	0		36	.	.	.	0		35	.	.	.	0
98	40	.	.	.	0		35	1	.	1	2		36	1	.	.	1		35	.	.	1	1
99	40	.	.	1	1		33	.	.	.	0		35	1	.	1	2		34	.	.	1	1
100	39	.	.	2	2		33	.	.	1	1		33	.	.	.	0		33	1	.	.	1
101	37	.	.	.	0		32	.	.	1	1		33	.	.	.	0		32	.	.	.	0
102	37	.	.	2	2		31	.	.	.	0		33	.	.	2	2		32	.	.	.	0
103	35	.	.	.	0		31	.	.	.	0		31	.	.	1	1		32	.	.	2	2
104	35	.	.	.	0		31	1	.	3	4		30	.	.	1	1		30	.	.	.	0
105 #	35	.	.	.	14		27	.	.	.	12		29	.	.	.	15		30	.	.	.	13
106 #	21	.	.	.	21		15	.	.	.	15		14	.	.	.	14		17	.	.	.	17

Carcinogenicity Study in Mice - Summary of Survival and Fate of Animals (Continued)

Sex: Female																						
Dose	**0 mg/kg/day**						**2.5 mg/kg/day**						**5 mg/kg/day**						**35 mg/kg/day**				
Week	E	D	A	K	N		E	D	A	K	N		E	D	A	K	N		E	D	A	K	N
4	60	.	.	.	0		60	.	.	.	0		60	1	.	.	1		60	.	.	.	0
11	60	.	.	.	0		60	.	.	.	0		59	.	.	.	0		60	.	.	.	0
13	60	.	.	.	0		60	.	.	.	0		59	.	.	.	0		60	1	.	.	1
17	60	.	.	.	0		60	.	.	.	0		59	.	.	.	0		59	.	.	.	0
18	60	.	.	.	0		60	.	.	.	0		59	.	.	.	0		59	.	.	1	1
22	60	.	1	.	1		60	.	.	.	0		59	.	.	.	0		58	.	.	.	0
27	59	.	.	.	0		60	.	.	.	0		59	.	.	.	0		58	.	.	1	1
29	59	.	.	1	1		60	.	.	.	0		59	1	.	.	1		57	.	.	.	0
33	58	.	.	.	0		60	.	.	.	0		58	.	.	.	0		57	.	.	.	0
36	58	.	.	.	0		60	.	.	.	0		58	1	.	1	2		57	.	.	.	0
38	58	.	.	.	0		60	.	.	.	0		56	.	.	.	0		57	.	.	1	1
39	58	.	.	.	0		60	.	.	.	0		56	.	.	.	0		56	.	.	.	0
41	58	.	.	.	0		60	.	.	.	0		56	.	.	1	1		56	.	.	.	0
42	58	.	.	.	0		60	.	.	.	0		55	.	.	.	0		56	.	.	1	1
48	58	.	.	.	0		60	.	.	.	0		55	.	.	.	0		55	.	.	.	0
50	58	.	.	1	1		60	.	.	.	0		55	.	.	.	0		55	.	.	.	0
51	57	.	.	.	0		60	.	.	1	1		55	.	.	.	0		55	.	.	.	0
53	57	.	.	.	0		59	1	.	.	1		55	.	.	.	0		55	.	.	.	0
54	57	.	.	.	0		58	.	.	.	0		55	.	.	.	0		55	.	.	.	0
55	57	.	.	.	0		58	.	.	.	0		55	.	.	.	0		55	.	.	.	0
57	57	.	.	1	1		58	.	.	.	0		55	.	.	.	0		55	.	.	.	0
59	56	.	.	.	0		58	.	.	1	1		55	.	.	1	1		55	.	.	.	0
60	56	.	.	.	0		57	.	.	.	0		54	.	.	.	0		55	.	.	.	0
61	56	.	.	1	1		57	.	.	.	0		54	.	.	.	0		55	.	.	1	1
63	55	.	.	1	1		57	.	.	.	0		54	.	.	.	0		54	1	.	.	1
64	54	.	.	2	2		57	.	.	.	0		54	.	.	.	0		53	.	.	1	1
65	52	.	.	1	1		57	.	.	.	0		54	.	.	.	0		52	.	.	1	1
66	51	.	.	.	0		57	.	.	.	0		54	.	.	1	1		51	.	.	1	1
67	51	.	.	1	1		57	.	.	.	0		53	.	.	.	0		50	.	.	.	0
68	50	.	.	1	1		57	.	.	.	0		53	.	.	.	0		50	.	.	1	1
69	49	.	.	.	0		57	.	.	.	0		53	.	.	.	0		49	.	.	.	0
70	49	1	.	.	1		57	.	.	.	0		53	.	.	.	0		49	.	.	1	1
71	48	.	.	1	1		57	.	.	2	2		53	.	.	.	0		48	1	.	.	1
72	47	.	.	1	1		55	.	.	1	1		53	1	.	.	1		47	.	.	.	0
73	46	.	.	.	0		54	2	.	.	2		52	.	.	.	0		47	.	.	.	0
75	46	.	.	1	1		52	.	.	1	1		52	1	.	.	1		47	1	.	.	1
76	45	.	.	.	0		51	.	.	.	0		51	.	.	.	0		46	.	.	1	1

Carcinogenicity Study in Mice - Summary of Survival and Fate of Animals (Continued)

Sex: Female																					
Dose	**0 mg/kg/day**						**2.5 mg/kg/day**						**5 mg/kg/day**						**35 mg/kg/day**				
Week	E	D	A	K	N		E	D	A	K	N		E	D	A	K	N		E	D	A	K	N
77	45	1	.	.	1		51	.	.	.	0		51	.	.	1	1		45	.	.	.	0
78	44	.	.	1	1		51	.	.	.	0		50	1	.	1	2		45	.	.	1	1
79	43	2	.	.	2		51	.	.	1	1		48	.	.	.	0		44	.	.	1	1
80	41	.	.	.	0		50	.	.	1	1		48	.	.	.	0		43	.	.	2	2
81	41	.	.	1	1		49	.	.	.	0		48	.	.	.	0		41	.	.	.	0
82	40	.	.	1	1		49	.	.	2	2		48	.	.	.	0		41	.	.	.	0
83	39	.	.	.	0		47	.	.	.	0		48	.	.	.	0		41	.	.	1	1
84	39	.	.	1	1		47	.	.	.	0		48	1	.	.	1		40	.	.	.	0
85	38	1	.	.	1		47	.	.	.	0		47	.	.	2	2		40	1	.	.	1
86	37	.	.	1	1		47	.	.	.	0		45	.	.	.	0		39	.	.	.	0
87	36	.	.	.	0		47	.	.	1	1		45	.	.	1	1		39	.	.	.	0
88	36	.	.	.	0		46	.	.	1	1		44	.	.	.	0		39	1	.	.	1
89	36	.	.	.	0		45	.	.	.	0		44	.	.	.	0		38	.	.	.	0
90	36	.	.	.	0		45	.	.	3	3		44	1	.	.	1		38	1	.	.	1
91	36	.	.	.	0		42	.	.	.	0		43	.	.	1	1		37	.	.	.	0
92	36	.	.	2	2		42	.	.	.	0		42	.	.	1	1		37	1	.	3	4
93	34	.	.	.	0		42	.	.	1	1		41	.	.	.	0		33	.	.	.	0
94	34	.	.	1	1		41	.	.	.	0		41	1	.	.	1		33	1	.	.	1
95	33	.	.	1	1		41	.	.	1	1		40	1	.	1	2		32	1	.	.	1
96	32	2	.	2	4		40	.	.	.	0		38	.	.	1	1		31	.	.	.	0
97	28	.	.	.	0		40	.	.	1	1		37	.	.	.	0		31	1	.	1	2
98	28	1	.	.	1		39	.	.	.	0		37	.	.	.	0		29	1	.	1	2
99	27	.	.	.	0		39	.	.	.	0		37	.	.	.	0		27	1	.	2	3
100	27	.	.	.	0		39	.	.	1	1		37	.	.	2	2		24	.	.	1	1
101	27	2	.	1	3		38	.	.	2	2		35	.	.	2	2		23	.	.	.	0
102	24	.	.	.	0		36	.	.	.	0		33	.	.	.	0		23	.	.	.	0
103	24	.	.	1	1		36	.	.	.	0		33	.	.	.	0		23	1	.	2	3
104	23	.	.	.	0		36	.	.	1	1		33	1	.	1	2		20	.	.	.	0
105 #	23	.	.	.	11		35	.	.	.	11		31	.	.	.	10		20	.	.	.	10
106 #	12	.	.	.	12		24	.	.	.	24		21	.	.	.	21		10	.	.	.	10

Key:
E = Number of animals entering period.
D = Animals found dead.
A = Animals with accidental death.
K = Animals killed moribund.
N = Animals necropsied.
# = Terminal kill.

Table 10.5 Carcinogenicity Study in Rats - Tumor Incidence

		Group No. (Dose mg/kg/day)			
		1 (0)	2 (0.25)	3 (2.5)	4 (75)
ORGAN/TISSUE	TUMOR	70 Males	70 Males	70 Males	70 Males
body cavity, nasal	adenoma	0	1	1	0
	squamous cell carcinoma	1	0	0	0
brain	astrocytoma, malignant	2	1	0	1
	granular cell tumor, malignant	0	1	0	0
	hemangioma	0	0	1	0
	meningioma, malignant	0	0	1	0
gland, adrenal	cortical adenoma	0	0	1	0
	pheochromocytoma, benign	11	11	5	1
	pheochromocytoma, malignant	2	1	2	1
gland, mammary	adenocarcinoma	0	2	1	1
	adenoma	1	0	0	0
	fibroadenoma	2	5	2	4
gland, parathyroid	adenoma	0	1	0	0
gland, pituitary	adenoma	22	23	25	24
	carcinoma, pars distalis	2	0	0	1
gland, thyroid	c-cell adenoma	8	7	6	12
	c-cell carcinoma	1	3	0	0
	follicular cell adenoma	4	1	0	2
	follicular cell carcinoma	0	1	1	0
hemolymphoreticular tissue	histiocytic sarcoma	2	2	4	3
	leukemia, granulocytic	1	3	4	5
	lymphoma, malignant	0	1	1	2
kidney	liposarcoma	1	0	0	0
	tubular cell adenoma	0	1	1	0
	tubular cell carcinoma	4	4	5	5
large intestine, cecum	hemangiosarcoma	1	0	0	0
liver	hemangiosarcoma	0	0	1	0
	hepatocellular adenoma	2	3	1	0
	hepatocellular carcinoma	0	1	0	0
lung	adenoma	0	0	1	0
	hemangiosarcoma	0	1	0	0
lymph node, mesenteric	hemangiosarcoma	2	2	4	0
muscle, skeletal	fibroma	0	0	1	0
	fibrosarcoma	0	0	1	0
pancreas	adenocarcinoma	2	0	0	1
	adenoma	4	9	7	8
	adenoma, acinar	0	2	0	1
	carcinoma	0	1	0	0

Carcinogenicity Study in Rats - Tumor Incidence (Continued)

ORGAN/TISSUE	TUMOR	Group No. (Dose mg/kg/day)			
		1 (0)	2 (0.25)	3 (2.5)	4 (75)
		70 Males	70 Males	70 Males	70 Males
skin	carcinoma	0	1	0	0
	basal cell tumor, malignant	0	0	1	0
	hair follicle tumor, benign	0	1	2	0
	keratoacanthoma	4	4	8	4
	papilloma	0	3	1	2
	polyp	0	0	0	2
	sebaceous cell adenoma	0	1	0	0
	squamous cell carcinoma	1	1	0	0
small intestine, jejunum	adenocarcinoma	0	1	0	0
spleen	sarcoma	0	0	1	0
stomach	leiomyosarcoma	0	0	0	1
subcutis	fibrolipoma	0	0	1	0
	fibroma	7	4	11	5
	fibroma/fibrosarcoma	9 @	9	13	16 #
	fibrosarcoma	5 @	6	4	12 #
	hemangioma	0	0	0	1
	hemangiosarcoma	1	0	0	0
	lipoma	3	1	2	4
	liposarcoma	0	0	1	0
	myxoma	0	0	0	1
	myxosarcoma	1	2	1	0
	sarcoma	1	0	0	2
testis	hemangioma	0	0	1	0
	interstitial (leydig) cell adenoma	3	1	2	2
urinary bladder	papilloma	0	1	0	0
	polyp	0	1	0	0
whole body	hemangiosarcoma	3	3	5	0

Carcinogenicity Study in Rats - Tumor Incidence (Continued)

		Group No. (Dose mg/kg/day)			
		1 (0)	2 (0.25)	3 (2.5)	4 (75)
ORGAN/TISSUE	TUMOR	70 Females	70 Females	70 Females	70 Females
brain	astrocytoma, malignant	3	0	0	0
cervix	leiomyosarcoma	1	0	0	0
	polyp	0	1	0	0
gland, adrenal	cortical adenoma	1	1	0	1
	pheochromocytoma, benign	1	1	1	1
	pheochromocytoma, malignant	0	1	0	0
	adenocarcinoma	18	29 #	23	19
gland, mammary	adenoma	7	7	6	6
	fibroadenoma	46 +	42	46	49
gland, parathyroid	adenoma	0	1	0	0
gland, pituitary	adenoma	41	45	44	45
	carcinoma, pars distalis	0	2	1	0
gland, thyroid	c-cell adenoma	5	6	7	9
	c-cell carcinoma	0	2	1	0
	follicular cell adenoma	1	2	0	1
hemolymphoreticular tissue	histiocytic sarcoma	2	2	1	1
	leukemia, granulocytic	0	1	0	0
	lymphoma, malignant	0	1	0	0
kidney	lipoma	0	1	0	0
	liposarcoma	1	0	0	0
	tubular cell adenoma	0	1	1	1
	tubular cell carcinoma	2	4	2	3
large intestine, cecum	leiomyoma	0	1	0	0
large intestine, rectum	hemangioma	0	0	1	0
	hemangiosarcoma	0	0	0	1
	polyp	1	0	0	0
larynx	polyp	1	0	0	0
liver	cholangioma	0	1	1	0
lung	hemangiosarcoma	0	0	0	1
	sarcoma	0	1	0	0
lymph node, mesenteric	hemangiosarcoma	1	0	1	0
muscle, skeletal	liposarcoma	0	0	0	1
ovary	granulosa cell tumor, malignant	0	1	0	0
pancreas	adenocarcinoma	2	1	0	0
	adenoma	3 +	4	3	7

Carcinogenicity Study in Rats - Tumor Incidence (Continued)

ORGAN/TISSUE	TUMOR	Group No. (Dose mg/kg/day)			
		1 (0)	2 (0.25)	3 (2.5)	4 (75)
		70 Females	70 Females	70 Females	70 Females
skin	carcinoma	0	1	1	0
	hair follicle tumor, benign	2	0	0	0
	keratoacanthoma	1	0	0	0
	papilloma	1	0	0	0
	polyp	1	0	0	0
	squamous cell carcinoma	3	0	0	1
small intestine, jejunum	liposarcoma	0	1	0	0
subcutis	fibroma	2	3	3	4
	fibroma/fibrosarcoma	6	7	5	8
	fibrosarcoma	4	5	2	4
	hemangiosarcoma	0	0	0	1
	lipoma	2	0	6	2
	myxosarcoma	0	0	1	0
	sarcoma	1	0	0	0
urinary bladder	papilloma	0	0	0	1
uterus	adenocarcinoma	0	0	1	0
	endometrial stromal sarcoma	1	1	2	0
	fibroma	0	0	0	1
	hemangioma	1	0	0	1
	leiomyoma	1	0	0	0
	leiomyosarcoma	1	0	0	0
	polyp	3	3	3	4
vagina	polyp	0	1	0	0
whole body	hemangiosarcoma	1	0	1	2

Key:
+: $P \leq 0.05$ (Trend Test)
@: $P \leq 0.025$ (Trend Test)
#: $P \leq 0.05$ (Pairwise Comparison)

Table 10.6 Carcinogenicity Study in Rats - Chronological Listing of Tumour Occurrence

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1M	257	257	1055	U	gland, pituitary	adenoma	No
	257	257	1055	U	kidney	tubular cell carcinoma	Yes
	275	275	1063	U	gland, pituitary	adenoma	No
	315	315	1035	U	body cavity, nasal	squamous cell carcinoma	Yes
	315	315	1035	U	gland, thyroid	c-cell adenoma	No
	315	315	1035	U	kidney	tubular cell carcinoma	Yes
	318	318	1001	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	320	593	1024	U	subcutis	fibroma	No
	373	373	1062	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	399	399	1028	U	gland, pituitary	adenoma	No
	418	418	1037	U	gland, pituitary	adenoma	No
	418	418	1037	U	kidney	tubular cell carcinoma	Yes
	435	435	1047	U	gland, pituitary	adenoma	No
	482	482	1054	U	bone	osteoma	No
	482	482	1054	U	gland, adrenal	pheochromocytoma, benign	No
	502	712	1006	T	subcutis	fibrosarcoma	Yes
	502	716	1034	T	skin	keratoacanthoma	No
	502	503	1050	U	skin	keratoacanthoma	No
	503	503	1050	U	gland, pituitary	adenoma	No
	520	520	1025	U	liver	hepatocellular adenoma	No
	522	522	1009	U	subcutis	hemangiosarcoma	Yes
	537	653	1022	U	subcutis	fibrosarcoma	Yes
	537	540	1049	U	subcutis	fibroma	No
	544	544	1021	U	gland, pituitary	adenoma	No
	551	713	1011	T	subcutis	lipoma	No
	551	653	1022	U	subcutis	lipoma	No
	570	570	1012	U	gland, pituitary	adenoma	No
	572	716	1034	T	subcutis	fibroma	No
	589	589	1052	U	gland, thyroid	c-cell adenoma	No
	593	593	1024	U	gland, pituitary	adenoma	No
	596	596	1017	A	gland, pituitary	adenoma	No
	604	604	1043	U	gland, pituitary	adenoma	No
	604	604	1043	U	pancreas	adenoma	No
	614	614	1059	U	brain	astrocytoma, malignant	Yes

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1M	614	614	1059	U	gland, pituitary	adenoma	No
	614	614	1059	U	gland, thyroid	c-cell carcinoma	Yes
	614	614	1059	U	pancreas	adenoma	No
	614	643	1065	U	skin	squamous cell carcinoma	Yes
	629	629	1023	U	body cavity, abdominal	fibrosarcoma	Yes
	634	634	1031	U	gland, thyroid	c-cell adenoma	No
	635	719	1039	T	subcutis	fibroma	No
	642	677	1003	U	subcutis	fibroma	No
	643	643	1065	U	gland, thyroid	follicular cell adenoma	No
	646	653	1022	U	subcutis	fibroma	No
	653	653	1022	U	gland, pituitary	adenoma	No
	656	712	1005	T	skin	keratoacanthoma	No
	665	665	1016	U	gland, pituitary	adenoma	No
	671	713	1013	T	skin	keratoacanthoma	No
	671	720	1051	T	subcutis	myxosarcoma	Yes
	671	708	1066	U	subcutis	fibrosarcoma	Yes
	677	677	1003	U	gland, pituitary	adenoma	No
	677	677	1003	U	kidney	tubular cell carcinoma	Yes
	677	677	1003	U	large intestine, cecum	hemangiosarcoma	Yes
	677	677	1003	U	lymph node, mesenteric	hemangiosarcoma	Yes
	677	677	1003	U	pancreas	adenocarcinoma	Yes
	677	677	1003	U	subcutis	fibrosarcoma	Yes
	686	686	1046	U	gland, thyroid	c-cell adenoma	No
	691	712	1005	T	gland, mammary	adenoma	No
	691	716	1026	T	gland, mammary	fibroadenoma	No
	691	719	1040	T	subcutis	lipoma	No
	691	721	1068	T	subcutis	sarcoma	Yes
	706	713	1015	T	subcutis	fibrosarcoma	Yes
	706	708	1066	U	gland, mammary	fibroadenoma	No
	707	707	1041	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	708	708	1056	U	gland, adrenal	pheochromocytoma, benign	No
	708	708	1056	U	gland, pituitary	adenoma	No
	708	708	1066	U	brain	astrocytoma, malignant	Yes
	708	708	1066	U	gland, adrenal	pheochromocytoma, benign	No
	708	708	1066	U	gland, adrenal	pheochromocytoma, malignant	Yes

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1M	708	708	1066	U	gland, pituitary	carcinoma, pars distalis	Yes
	708	708	1066	U	subcutis	fibroma	No
	709	709	1036	T	testis	interstitial (leydig) cell ade	No
	712	712	1004	T	gland, adrenal	pheochromocytoma, benign	No
	712	712	1004	T	gland, thyroid	follicular cell adenoma	No
	712	712	1006	T	gland, adrenal	pheochromocytoma, benign	No
	712	712	1006	T	gland, pituitary	adenoma	No
	712	712	1006	T	gland, thyroid	c-cell adenoma	No
	712	712	1008	T	bone	osteoma	No
	712	712	1008	T	gland, adrenal	pheochromocytoma, malignant	Yes
	713	713	1011	T	gland, adrenal	pheochromocytoma, benign	No
	713	713	1013	T	gland, pituitary	adenoma	No
	713	713	1015	T	gland, thyroid	c-cell adenoma	No
	713	713	1015	T	pancreas	adenocarcinoma	Yes
	715	715	1019	T	gland, thyroid	c-cell adenoma	No
	715	715	1019	T	testis	interstitial (leydig) cell ade	No
	715	715	1038	T	gland, adrenal	pheochromocytoma, benign	No
	715	715	1038	T	liver	hepatocellular adenoma	No
	716	716	1020	T	gland, adrenal	pheochromocytoma, benign	No
	716	716	1020	T	gland, pituitary	adenoma	No
	716	716	1020	T	pancreas	adenoma	No
	716	716	1020	T	testis	interstitial (leydig) cell ade	No
	716	716	1026	T	ear	carcinoma	Yes
	716	716	1026	T	ear	sarcoma	Yes
	716	716	1034	T	gland, adrenal	pheochromocytoma, benign	No
	716	716	1034	T	gland, thyroid	follicular cell adenoma	No
	719	719	1039	T	gland, pituitary	adenoma	No
	719	719	1040	T	gland, adrenal	pheochromocytoma, benign	No
	719	719	1040	T	gland, thyroid	c-cell adenoma	No
	719	719	1042	T	gland, pituitary	adenoma	No
	719	719	1042	T	kidney	liposarcoma	Yes
	719	719	1048	T	gland, thyroid	follicular cell adenoma	No
	720	720	1051	T	gland, pituitary	adenoma	No
	720	720	1051	T	pancreas	adenoma	No
	720	720	1057	T	gland, pituitary	carcinoma, pars distalis	Yes

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1M	720	720	1058	T	lymph node, mesenteric	hemangiosarcoma	Yes
	721	721	1070	T	body cavity, abdominal	fibrosarcoma	Yes
	721	721	1070	T	gland, adrenal	pheochromocytoma, benign	No
1F	76	590	1519	U	gland, mammary	adenocarcinoma	Yes
	209	562	1513	U	gland, mammary	fibroadenoma	No
	216	514	1514	U	gland, mammary	fibroadenoma	No
	216	523	1523	U	gland, mammary	fibroadenoma	No
	272	442	1520	U	gland, mammary	adenocarcinoma	Yes
	272	526	1536	U	gland, mammary	fibroadenoma	No
	279	456	1516	U	gland, mammary	fibroadenoma	No
	307	472	1540	U	gland, mammary	adenocarcinoma	Yes
	307	456	1559	U	gland, mammary	fibroadenoma	No
	322	666	1517	U	gland, mammary	fibroadenoma	No
	330	330	1539	U	gland, pituitary	adenoma	No
	339	339	1530	U	gland, pituitary	adenoma	No
	339	339	1530	U	kidney	tubular cell carcinoma	Yes
	339	339	1530	U	lymph node, mesenteric	hemangiosarcoma	Yes
	341	341	1554	U	gland, pituitary	adenoma	No
	342	590	1519	U	gland, mammary	fibroadenoma	No
	356	588	1529	U	gland, mammary	fibroadenoma	No
	363	679	1557	U	gland, mammary	adenoma	No
	370	370	1549	U	gland, pituitary	adenoma	No
	384	589	1506	U	gland, mammary	fibroadenoma	No
	384	607	1515	U	gland, mammary	fibroadenoma	No
	384	631	1522	U	gland, mammary	fibroadenoma	No
	384	706	1568	T	gland, mammary	fibroadenoma	No
	405	702	1505	U	gland, mammary	fibroadenoma	No
	412	569	1503	U	gland, mammary	fibroadenoma	No
	412	442	1520	U	gland, mammary	fibroadenoma	No
	412	412	1521	U	gland, pituitary	adenoma	No
	412	412	1521	U	gland, thyroid	c-cell adenoma	No
	412	532	1544	U	gland, mammary	adenocarcinoma	Yes
	419	706	1518	T	gland, mammary	fibroadenoma	No
	419	636	1556	U	gland, mammary	adenocarcinoma	Yes
	422	422	1570	U	gland, pituitary	adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1F	426	530	1510	U	gland, mammary	fibroadenoma	No
	426	636	1556	U	gland, mammary	fibroadenoma	No
	429	429	1553	U	gland, pituitary	adenoma	No
	437	437	1525	U	gland, pituitary	adenoma	No
	440	667	1502	U	gland, mammary	fibroadenoma	No
	440	440	1531	U	uterus	leiomyosarcoma	Yes
	442	442	1520	U	gland, pituitary	adenoma	No
	447	569	1503	U	gland, mammary	adenocarcinoma	Yes
	454	706	1528	T	gland, mammary	fibroadenoma	No
	454	636	1547	U	gland, mammary	fibroadenoma	No
	481	481	1512	U	brain	astrocytoma, malignant	Yes
	482	706	1532	T	gland, mammary	fibroadenoma	No
	489	667	1534	U	gland, mammary	fibroadenoma	No
	489	679	1558	U	gland, mammary	fibroadenoma	No
	489	625	1567	U	gland, mammary	adenocarcinoma	Yes
	496	708	1562	T	gland, mammary	fibroadenoma	No
	500	500	1504	U	gland, pituitary	adenoma	No
	500	500	1504	U	kidney	liposarcoma	Yes
	503	706	1524	T	gland, mammary	fibroadenoma	No
	506	511	1501	U	gland, mammary	fibroadenoma	No
	510	707	1535	T	gland, mammary	fibroadenoma	No
	511	511	1501	U	gland, mammary	adenocarcinoma	Yes
	511	511	1501	U	gland, pituitary	adenoma	No
	511	511	1501	U	pancreas	adenocarcinoma	Yes
	524	524	1538	U	cervix	leiomyosarcoma	Yes
	524	524	1538	U	gland, mammary	adenocarcinoma	Yes
	525	544	1543	U	gland, mammary	adenocarcinoma	Yes
	525	671	1545	U	subcutis	lipoma	No
	525	679	1557	U	gland, mammary	adenocarcinoma	Yes
	525	679	1557	U	gland, mammary	fibroadenoma	No
	525	709	1565	T	gland, mammary	fibroadenoma	No
	526	526	1526	U	gland, pituitary	adenoma	No
	526	526	1536	U	uterus	leiomyoma	No
	530	530	1510	U	gland, pituitary	adenoma	No
	531	706	1527	T	gland, mammary	fibroadenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1F	532	532	1544	U	gland, mammary	fibroadenoma	No
	532	532	1544	U	gland, pituitary	adenoma	No
	537	537	1507	U	brain	astrocytoma, malignant	Yes
	537	537	1507	U	gland, thyroid	c-cell adenoma	No
	538	707	1548	T	gland, mammary	fibroadenoma	No
	544	544	1543	U	gland, pituitary	adenoma	No
	559	627	1508	U	gland, mammary	fibroadenoma	No
	559	627	1508	U	skin	squamous cell carcinoma	Yes
	559	706	1511	T	gland, mammary	fibroadenoma	No
	559	709	1565	T	gland, mammary	adenocarcinoma	Yes
	559	625	1567	U	gland, mammary	fibroadenoma	No
	569	569	1503	U	gland, pituitary	adenoma	No
	569	569	1503	U	gland, thyroid	follicular cell adenoma	No
	569	569	1503	U	uterus	endometrial stromal sarcoma	Yes
	572	572	1563	U	gland, pituitary	adenoma	No
	573	702	1505	U	subcutis	fibrosarcoma	Yes
	580	588	1529	U	subcutis	sarcoma	Yes
	580	667	1534	U	subcutis	fibrosarcoma	Yes
	588	588	1529	U	gland, mammary	adenoma	No
	589	589	1506	U	gland, pituitary	adenoma	No
	594	703	1537	U	gland, mammary	fibroadenoma	No
	602	707	1542	T	gland, mammary	adenocarcinoma	Yes
	615	707	1542	T	skin	polyp	No
	622	707	1560	T	gland, mammary	fibroadenoma	No
	625	625	1567	U	body cavity, oral	squamous cell carcinoma	Yes
	625	625	1567	U	gland, pituitary	adenoma	No
	625	625	1567	U	gland, thyroid	c-cell adenoma	No
	627	627	1508	U	gland, pituitary	adenoma	No
	631	631	1522	U	gland, pituitary	adenoma	No
	636	636	1547	U	larynx	polyp	No
	636	636	1547	U	pancreas	adenoma	No
	636	636	1556	U	gland, pituitary	adenoma	No
	636	636	1556	U	uterus	hemangioma	No
	636	708	1564	T	skin	squamous cell carcinoma	Yes
	636	709	1565	T	subcutis	fibrosarcoma	Yes

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1F	643	707	1535	T	skin	keratoacanthoma	No
	643	707	1542	T	gland, mammary	fibroadenoma	No
	643	677	1550	U	gland, mammary	adenocarcinoma	Yes
	647	647	1566	U	gland, pituitary	adenoma	No
	663	671	1545	U	gland, mammary	fibroadenoma	No
	663	707	1560	T	gland, mammary	adenocarcinoma	Yes
	663	709	1569	T	subcutis	fibrosarcoma	Yes
	666	666	1517	U	gland, mammary	adenoma	No
	666	666	1517	U	gland, pituitary	adenoma	No
	666	666	1517	U	uterus	polyp	No
	667	667	1502	U	gland, adrenal	pheochromocytoma, benign	No
	667	667	1502	U	gland, pituitary	adenoma	No
	667	667	1502	U	skin	hair follicle tumor, benign	No
	667	667	1534	U	gland, thyroid	c-cell adenoma	No
	671	706	1533	T	gland, mammary	fibroadenoma	No
	671	671	1545	U	gland, pituitary	adenoma	No
	671	671	1545	U	skin	hair follicle tumor, benign	No
	671	671	1545	U	skin	papilloma	No
	671	707	1552	T	gland, mammary	fibroadenoma	No
	671	708	1564	T	gland, mammary	fibroadenoma	No
	677	677	1550	U	gland, mammary	fibroadenoma	No
	677	677	1550	U	gland, pituitary	adenoma	No
	678	679	1558	U	gland, mammary	adenocarcinoma	Yes
	679	679	1557	U	gland, pituitary	adenoma	No
	679	679	1557	U	gland, thyroid	c-cell adenoma	No
	679	679	1557	U	uterus	polyp	No
	679	679	1558	U	gland, mammary	adenoma	No
	679	679	1558	U	pancreas	adenocarcinoma	Yes
	679	679	1558	U	subcutis	lipoma	No
	685	707	1542	T	gland, mammary	adenoma	No
	700	709	1569	T	gland, mammary	fibroadenoma	No
	700	709	1569	T	skin	squamous cell carcinoma	Yes
	702	702	1505	U	gland, pituitary	adenoma	No
	703	703	1537	U	gland, pituitary	adenoma	No
	703	703	1537	U	pancreas	adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
1F	703	703	1537	U	uterus	polyp	No
	706	706	1511	T	gland, mammary	adenocarcinoma	Yes
	706	706	1524	T	gland, pituitary	adenoma	No
	706	706	1527	T	large intestine, rectum	polyp	No
	706	706	1528	T	gland, mammary	adenoma	No
	706	706	1528	T	gland, pituitary	adenoma	No
	706	706	1528	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	706	706	1528	T	subcutis	fibroma	No
	706	706	1532	T	gland, pituitary	adenoma	No
	706	706	1533	T	gland, pituitary	adenoma	No
	706	707	1552	T	gland, mammary	adenocarcinoma	Yes
	706	706	1568	T	gland, pituitary	adenoma	No
	707	707	1542	T	gland, pituitary	adenoma	No
	707	707	1542	T	pancreas	adenoma	No
	707	707	1546	T	gland, pituitary	adenoma	No
	707	707	1546	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	707	707	1546	T	kidney	tubular cell carcinoma	Yes
	707	707	1548	T	brain	astrocytoma, malignant	Yes
	707	707	1552	T	gland, pituitary	adenoma	No
	707	707	1560	T	gland, pituitary	adenoma	No
	708	708	1562	T	subcutis	fibroma	No
	708	708	1564	T	gland, adrenal	cortical adenoma	No
	708	708	1564	T	gland, pituitary	adenoma	No
	709	709	1565	T	gland, pituitary	adenoma	No
	709	709	1569	T	gland, mammary	adenoma	No
2M	159	196	2049	U	skin	carcinoma	Yes
	180	419	2067	U	gland, mammary	fibroadenoma	No
	196	196	2049	U	kidney	tubular cell adenoma	No
	348	541	2003	U	subcutis	myxosarcoma	Yes
	355	712	2062	T	subcutis	fibrosarcoma	Yes
	371	371	2043	U	gland, pituitary	adenoma	No
	371	371	2043	U	kidney	tubular cell carcinoma	Yes
	375	375	2033	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	383	383	2050	U	brain	astrocytoma, malignant	Yes
	404	404	2019	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2M	404	404	2019	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	439	475	2040	U	gland, mammary	fibroadenoma	No
	446	446	2016	U	gland, pituitary	adenoma	No
	446	446	2016	U	gland, thyroid	c-cell carcinoma	Yes
	446	446	2016	U	kidney	tubular cell carcinoma	Yes
	448	448	2037	A	subcutis	fibroma	No
	449	449	2029	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	453	713	2015	T	subcutis	fibroma	No
	475	475	2040	U	gland, pituitary	adenoma	No
	491	491	2069	U	gland, pituitary	adenoma	No
	496	496	2001	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	502	517	2061	U	bone	osteosarcoma	Yes
	504	504	2042	A	gland, pituitary	adenoma	No
	510	510	2002	U	gland, pituitary	adenoma	No
	517	517	2061	U	pancreas	adenoma	No
	530	604	2038	U	subcutis	fibrosarcoma	Yes
	537	555	2044	U	skin	keratoacanthoma	No
	541	541	2003	U	gland, mammary	fibroadenoma	No
	541	541	2003	U	gland, pituitary	adenoma	No
	541	541	2003	U	gland, thyroid	c-cell adenoma	No
	541	541	2003	U	kidney	tubular cell carcinoma	Yes
	551	637	2041	U	subcutis	myxosarcoma	Yes
	571	608	2057	U	skin	squamous cell carcinoma	Yes
	575	575	2063	U	body cavity, nasal	adenoma	No
	575	575	2063	U	gland, adrenal	pheochromocytoma, benign	No
	575	575	2063	U	gland, thyroid	c-cell carcinoma	Yes
	575	575	2063	U	skin	papilloma	No
	586	617	2012	U	subcutis	fibrosarcoma	Yes
	593	713	2015	T	subcutis	fibrosarcoma	Yes
	600	608	2057	U	skin	keratoacanthoma	No
	600	600	2068	U	body cavity, thoracic	sarcoma	Yes
	600	600	2068	U	gland, adrenal	pheochromocytoma, benign	No
	600	600	2068	U	gland, pituitary	adenoma	No
	604	604	2038	U	gland, adrenal	pheochromocytoma, benign	No
	607	607	2006	U	pancreas	adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2M	607	607	2023	U	brain	granular cell tumor, malignant	Yes
	607	607	2023	U	small intestine, jejunum	adenocarcinoma	Yes
	608	608	2057	U	gland, pituitary	adenoma	No
	614	719	2059	T	subcutis	lipoma	No
	617	617	2012	U	gland, pituitary	adenoma	No
	617	617	2012	U	skin	keratoacanthoma	No
	621	698	2066	U	gland, mammary	fibroadenoma	No
	629	629	2051	U	gland, pituitary	adenoma	No
	637	637	2041	U	gland, adrenal	pheochromocytoma, benign	No
	637	637	2041	U	pancreas	adenoma, acinar	No
	637	637	2041	U	pancreas	adenoma	No
	641	671	2014	U	subcutis	fibrosarcoma	Yes
	649	716	2027	T	subcutis	fibrosarcoma	Yes
	653	653	2009	U	gland, pituitary	adenoma	No
	653	653	2009	U	gland, thyroid	c-cell adenoma	No
	653	653	2009	U	kidney	tubular cell carcinoma	Yes
	653	653	2009	U	pancreas	adenoma	No
	653	653	2058	U	gland, pituitary	adenoma	No
	656	656	2013	U	gland, pituitary	adenoma	No
	656	713	2015	T	gland, mammary	adenocarcinoma	Yes
	656	656	2025	U	gland, pituitary	adenoma	No
	665	665	2054	U	liver	hepatocellular carcinoma	Yes
	665	665	2054	U	lung	hemangiosarcoma	Yes
	667	667	2022	U	body cavity, abdominal	fibrosarcoma	Yes
	667	667	2022	U	gland, thyroid	c-cell adenoma	No
	667	667	2022	U	gland, thyroid	follicular cell adenoma	No
	669	713	2015	T	skin	sebaceous cell adenoma	No
	669	714	2020	T	skin	hair follicle tumor, benign	No
	671	671	2014	U	bone	fibrosarcoma	Yes
	676	714	2020	T	skin	papilloma	No
	676	721	2070	T	subcutis	fibroma	No
	684	684	2060	U	gland, pituitary	adenoma	No
	684	684	2060	U	pancreas	carcinoma	Yes
	698	698	2066	U	gland, pituitary	adenoma	No
	698	698	2066	U	pancreas	adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2M	700	700	2008	A	gland, pituitary	adenoma	No
	700	700	2008	A	gland, thyroid	c-cell adenoma	No
	700	700	2008	A	liver	hepatocellular adenoma	No
	700	700	2056	U	gland, pituitary	adenoma	No
	712	712	2011	T	gland, adrenal	pheochromocytoma, benign	No
	712	716	2032	T	skin	keratoacanthoma	No
	712	712	2035	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	712	712	2062	T	skin	papilloma	No
	713	713	2015	T	gland, adrenal	pheochromocytoma, benign	No
	713	713	2015	T	gland, thyroid	c-cell adenoma	No
	713	713	2015	T	pancreas	adenoma	No
	713	713	2018	T	lymph node, mesenteric	hemangiosarcoma	Yes
	714	714	2020	T	lymph node, mesenteric	hemangiosarcoma	Yes
	715	715	2021	T	gland, adrenal	pheochromocytoma, benign	No
	715	715	2021	T	gland, pituitary	adenoma	No
	715	715	2021	T	gland, thyroid	follicular cell carcinoma	Yes
	716	716	2027	T	gland, parathyroid	adenoma	No
	716	716	2027	T	gland, pituitary	adenoma	No
	716	716	2027	T	gland, thyroid	c-cell carcinoma	Yes
	716	716	2027	T	liver	hepatocellular adenoma	No
	716	716	2027	T	pancreas	adenoma	No
	716	716	2032	T	gland, adrenal	pheochromocytoma, benign	No
	716	716	2032	T	pancreas	adenoma	No
	716	716	2046	T	gland, mammary	fibroadenoma	No
	716	716	2046	T	gland, thyroid	c-cell adenoma	No
	719	719	2047	T	gland, pituitary	adenoma	No
	719	719	2047	T	gland, thyroid	c-cell adenoma	No
	719	719	2047	T	pancreas	adenoma, acinar	No
	719	719	2047	T	pancreas	adenoma	No
	719	719	2047	T	urinary bladder	polyp	No
	719	719	2059	T	gland, adrenal	pheochromocytoma, benign	No
	719	719	2059	T	gland, adrenal	pheochromocytoma, malignant	Yes
	719	719	2059	T	gland, mammary	adenocarcinoma	Yes
	719	719	2059	T	liver	hepatocellular adenoma	No
	720	720	2064	T	gland, adrenal	pheochromocytoma, benign	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2M	720	720	2064	T	gland, pituitary	adenoma	No
	720	720	2065	T	ear	carcinoma	Yes
	720	720	2065	T	subcutis	fibroma	No
	720	720	2065	T	testis	interstitial (leydig) cell ade	No
	720	720	2065	T	urinary bladder	papilloma	No
	721	721	2070	T	gland, adrenal	pheochromocytoma, benign	No
2F	188	366	2523	U	gland, mammary	fibroadenoma	No
	209	410	2506	U	gland, mammary	fibroadenoma	No
	209	371	2543	U	gland, mammary	adenocarcinoma	Yes
	223	406	2552	U	gland, mammary	adenocarcinoma	Yes
	244	359	2503	U	gland, mammary	fibroadenoma	No
	244	706	2519	T	gland, mammary	fibroadenoma	No
	258	380	2562	U	gland, mammary	adenocarcinoma	Yes
	272	491	2501	U	gland, mammary	fibroadenoma	No
	307	531	2505	U	gland, mammary	fibroadenoma	No
	321	321	2509	U	gland, pituitary	adenoma	No
	321	321	2509	U	kidney	tubular cell carcinoma	Yes
	335	570	2524	U	gland, mammary	adenocarcinoma	Yes
	335	561	2569	U	gland, mammary	fibroadenoma	No
	354	354	2554	U	gland, pituitary	adenoma	No
	354	354	2554	U	gland, thyroid	c-cell adenoma	No
	354	354	2554	U	kidney	tubular cell adenoma	No
	359	359	2503	U	gland, pituitary	adenoma	No
	368	368	2525	U	gland, mammary	fibroadenoma	No
	368	368	2525	U	gland, pituitary	adenoma	No
	370	419	2541	U	gland, mammary	adenocarcinoma	Yes
	380	380	2562	U	liver	cholangioma	No
	384	570	2524	U	gland, mammary	fibroadenoma	No
	384	481	2565	U	gland, mammary	adenocarcinoma	Yes
	384	673	2568	U	gland, mammary	adenocarcinoma	Yes
	391	441	2556	U	gland, mammary	fibroadenoma	No
	399	589	2513	U	gland, mammary	fibroadenoma	No
	405	620	2526	U	gland, mammary	fibroadenoma	No
	405	529	2546	U	gland, mammary	fibroadenoma	No
	406	406	2552	U	gland, pituitary	adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2F	413	573	2537	U	gland, mammary	adenocarcinoma	Yes
	429	429	2550	U	gland, pituitary	adenoma	No
	434	706	2529	T	gland, mammary	fibroadenoma	No
	435	435	2514	U	gland, pituitary	adenoma	No
	435	435	2514	U	gland, thyroid	c-cell adenoma	No
	435	435	2514	U	kidney	tubular cell carcinoma	Yes
	440	573	2537	U	gland, mammary	fibroadenoma	No
	441	441	2556	U	gland, pituitary	adenoma	No
	447	707	2527	T	gland, mammary	fibroadenoma	No
	447	709	2553	T	subcutis	fibrosarcoma	Yes
	447	473	2557	U	gland, mammary	fibroadenoma	No
	447	447	2567	U	gland, pituitary	adenoma	No
	451	451	2570	U	gland, pituitary	adenoma	No
	451	451	2570	U	kidney	tubular cell carcinoma	Yes
	452	518	2533	U	gland, mammary	fibroadenoma	No
	461	590	2511	U	gland, mammary	fibroadenoma	No
	461	709	2547	T	gland, mammary	adenocarcinoma	Yes
	469	497	2566	U	subcutis	fibrosarcoma	Yes
	473	473	2557	U	gland, adrenal	pheochromocytoma, malignant	Yes
	473	473	2557	U	gland, pituitary	adenoma	No
	475	648	2534	U	gland, mammary	fibroadenoma	No
	481	481	2565	U	gland, pituitary	adenoma	No
	481	481	2565	U	kidney	tubular cell carcinoma	Yes
	482	706	2521	T	gland, mammary	fibroadenoma	No
	482	482	2530	U	gland, pituitary	adenoma	No
	483	483	2532	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	485	485	2518	U	gland, pituitary	adenoma	No
	496	507	2540	U	gland, mammary	adenocarcinoma	Yes
	503	706	2508	T	gland, mammary	fibroadenoma	No
	503	513	2551	U	gland, mammary	adenoma	No
	507	507	2540	U	gland, mammary	adenoma	No
	507	507	2540	U	gland, pituitary	adenoma	No
	507	507	2540	U	large intestine, cecum	leiomyoma	No
	508	508	2520	U	gland, mammary	adenocarcinoma	Yes
	508	508	2520	U	gland, pituitary	adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2F	513	513	2551	U	gland, pituitary	adenoma	No
	515	620	2526	U	gland, mammary	adenocarcinoma	Yes
	517	646	2560	U	gland, mammary	adenocarcinoma	Yes
	525	709	2547	T	gland, mammary	fibroadenoma	No
	525	606	2548	U	gland, mammary	adenocarcinoma	Yes
	525	579	2558	U	gland, mammary	adenocarcinoma	Yes
	525	579	2558	U	gland, mammary	fibroadenoma	No
	529	529	2546	U	gland, pituitary	adenoma	No
	531	531	2505	U	gland, pituitary	adenoma	No
	531	709	2553	T	gland, mammary	fibroadenoma	No
	531	557	2563	U	gland, mammary	adenocarcinoma	Yes
	538	590	2511	U	gland, mammary	adenocarcinoma	Yes
	542	542	2515	U	gland, pituitary	adenoma	No
	542	542	2515	U	uterus	polyp	No
	552	552	2555	U	gland, pituitary	adenoma	No
	557	557	2563	U	gland, pituitary	adenoma	No
	557	557	2563	U	pancreas	adenoma	No
	558	707	2542	T	gland, mammary	fibroadenoma	No
	558	701	2561	U	gland, mammary	fibroadenoma	No
	561	561	2569	U	gland, pituitary	adenoma	No
	566	566	2531	U	gland, pituitary	adenoma	No
	566	566	2531	U	uterus	polyp	No
	570	570	2524	U	gland, adrenal	cortical adenoma	No
	570	570	2524	U	gland, parathyroid	adenoma	No
	570	570	2524	U	gland, pituitary	adenoma	No
	572	653	2512	U	gland, mammary	fibroadenoma	No
	572	707	2535	T	gland, mammary	fibroadenoma	No
	573	573	2537	U	gland, pituitary	adenoma	No
	579	579	2558	U	body cavity, oral	squamous cell carcinoma	Yes
	579	579	2558	U	uterus	endometrial stromal sarcoma	Yes
	587	701	2502	U	gland, mammary	fibroadenoma	No
	587	631	2528	U	gland, mammary	fibroadenoma	No
	587	707	2539	T	gland, mammary	fibroadenoma	No
	587	709	2547	T	subcutis	fibrosarcoma	Yes
	587	646	2560	U	gland, mammary	fibroadenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2F	589	589	2513	U	gland, pituitary	adenoma	No
	590	590	2511	U	gland, pituitary	adenoma	No
	594	706	2504	T	gland, mammary	fibroadenoma	No
	594	706	2507	T	gland, mammary	fibroadenoma	No
	594	706	2508	T	gland, mammary	adenocarcinoma	Yes
	601	707	2516	T	gland, mammary	fibroadenoma	No
	601	707	2542	T	subcutis	fibrosarcoma	Yes
	606	606	2548	U	gland, pituitary	adenoma	No
	608	701	2502	U	gland, mammary	adenocarcinoma	Yes
	608	707	2510	T	subcutis	fibrosarcoma	Yes
	608	707	2536	T	gland, mammary	adenocarcinoma	Yes
	615	706	2538	T	gland, mammary	adenoma	No
	620	620	2526	U	gland, pituitary	adenoma	No
	620	620	2526	U	uterus	polyp	No
	629	657	2544	U	skin	carcinoma	Yes
	631	631	2528	U	gland, pituitary	adenoma	No
	636	653	2512	U	gland, mammary	adenoma	No
	643	701	2561	U	gland, mammary	adenocarcinoma	Yes
	646	646	2560	U	gland, pituitary	adenoma	No
	646	646	2560	U	gland, thyroid	c-cell carcinoma	Yes
	648	648	2534	U	gland, pituitary	adenoma	No
	649	649	2517	U	gland, pituitary	adenoma	No
	653	653	2512	U	gland, pituitary	adenoma	No
	656	656	2549	U	gland, mammary	adenoma	No
	656	656	2549	U	gland, pituitary	adenoma	No
	657	706	2538	T	gland, mammary	adenocarcinoma	Yes
	657	657	2544	U	gland, pituitary	adenoma	No
	671	706	2538	T	gland, mammary	fibroadenoma	No
	671	708	2545	T	subcutis	fibroma	No
	673	673	2568	U	gland, mammary	adenoma	No
	673	673	2568	U	gland, mammary	fibroadenoma	No
	673	673	2568	U	gland, pituitary	carcinoma, pars distalis	Yes
	673	673	2568	U	kidney	lipoma	No
	673	673	2568	U	lung	sarcoma	Yes
	685	707	2536	T	gland, mammary	fibroadenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2F	692	707	2510	T	gland, mammary	fibroadenoma	No
	692	707	2527	T	gland, mammary	adenocarcinoma	Yes
	692	706	2529	T	gland, mammary	adenocarcinoma	Yes
	694	694	2522	U	gland, mammary	fibroadenoma	No
	694	694	2522	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	694	694	2522	U	pancreas	adenoma	No
	701	701	2561	U	gland, pituitary	adenoma	No
	706	706	2504	T	gland, adrenal	pheochromocytoma, benign	No
	706	706	2504	T	gland, mammary	adenocarcinoma	Yes
	706	706	2504	T	gland, thyroid	follicular cell adenoma	No
	706	706	2507	T	gland, thyroid	c-cell carcinoma	Yes
	706	706	2508	T	gland, pituitary	adenoma	No
	706	706	2508	T	ovary	granulosa cell tumor, malignan	Yes
	706	706	2519	T	gland, pituitary	adenoma	No
	706	706	2519	T	gland, thyroid	c-cell adenoma	No
	706	706	2519	T	small intestine, jejunum	liposarcoma	Yes
	706	706	2529	T	gland, pituitary	adenoma	No
	706	706	2529	T	hemolymphoreticular tissue	lymphoma, malignant	Yes
	706	706	2529	T	subcutis	fibroma	No
	706	706	2538	T	gland, pituitary	adenoma	No
	706	709	2559	T	gland, mammary	adenocarcinoma	Yes
	707	707	2510	T	subcutis	fibroma	No
	707	707	2516	T	gland, mammary	adenocarcinoma	Yes
	707	707	2527	T	gland, thyroid	c-cell adenoma	No
	707	707	2527	T	pancreas	adenoma	No
	707	707	2539	T	gland, mammary	adenocarcinoma	Yes
	707	707	2539	T	gland, mammary	adenoma	No
	707	707	2539	T	gland, pituitary	adenoma	No
	707	707	2539	T	gland, thyroid	c-cell adenoma	No
	707	707	2539	T	pancreas	adenocarcinoma	Yes
	707	707	2542	T	gland, mammary	adenocarcinoma	Yes
	707	707	2542	T	gland, pituitary	adenoma	No
	707	707	2542	T	gland, thyroid	follicular cell adenoma	No
	708	708	2545	T	gland, mammary	fibroadenoma	No
	708	708	2545	T	gland, pituitary	adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
2F	709	709	2547	T	body cavity, abdominal	mesothelioma, malignant	Yes
	709	709	2547	T	gland, thyroid	c-cell adenoma	No
	709	709	2547	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	709	709	2553	T	gland, pituitary	carcinoma, pars distalis	Yes
	709	709	2553	T	pancreas	adenoma	No
	709	709	2559	T	cervix	polyp	No
	709	709	2559	T	vagina	polyp	No
3M	243	243	3042	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	271	271	3064	U	body cavity, abdominal	sarcoma	Yes
	397	397	3039	U	kidney	tubular cell carcinoma	Yes
	421	421	3018	U	gland, pituitary	adenoma	No
	435	435	3049	U	gland, pituitary	adenoma	No
	435	435	3062	U	brain	hemangioma	No
	435	435	3062	U	gland, pituitary	adenoma	No
	435	435	3062	U	kidney	tubular cell carcinoma	Yes
	439	483	3037	U	subcutis	myxosarcoma	Yes
	439	571	3068	U	subcutis	fibrolipoma	No
	441	441	3059	U	gland, pituitary	adenoma	No
	452	452	3051	U	gland, pituitary	adenoma	No
	452	452	3051	U	gland, thyroid	c-cell adenoma	No
	452	452	3051	U	kidney	tubular cell carcinoma	Yes
	453	587	3023	U	bone	osteosarcoma	Yes
	459	518	3024	U	subcutis	fibroma	No
	459	667	3035	U	subcutis	fibroma	No
	469	469	3045	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	470	470	3036	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	474	474	3014	A	gland, thyroid	c-cell adenoma	No
	474	716	3033	T	subcutis	fibroma	No
	478	478	3027	U	gland, pituitary	adenoma	No
	483	483	3012	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	509	509	3001	U	gland, pituitary	adenoma	No
	509	511	3047	U	gland, mammary	adenocarcinoma	Yes
	510	510	3070	U	gland, pituitary	adenoma	No
	511	511	3047	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	516	588	3009	U	subcutis	lipoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
3M	523	587	3023	U	skin	keratoacanthoma	No
	528	528	3046	U	liver	hepatocellular adenoma	No
	534	534	3006	U	bone	osteosarcoma	Yes
	534	534	3006	U	lymph node, mesenteric	hemangiosarcoma	Yes
	538	538	3032	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	542	542	3020	A	gland, adrenal	pheochromocytoma, benign	No
	542	542	3020	A	skin	keratoacanthoma	No
	545	545	3015	U	gland, pituitary	adenoma	No
	561	561	3021	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	571	588	3009	U	ear	carcinoma	Yes
	571	571	3068	U	skin	basal cell tumor, malignant	Yes
	571	571	3068	U	testis	interstitial (leydig) cell ade	No
	573	573	3019	U	gland, pituitary	adenoma	No
	586	667	3041	U	subcutis	fibrosarcoma	Yes
	588	588	3009	U	body cavity, nasal	adenoma	No
	588	588	3009	U	spleen	sarcoma	Yes
	593	720	3055	T	subcutis	fibrosarcoma	Yes
	599	599	3008	U	gland, thyroid	c-cell adenoma	No
	599	599	3008	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	599	599	3008	U	kidney	tubular cell carcinoma	Yes
	599	599	3008	U	testis	hemangioma	No
	600	719	3043	T	skin	keratoacanthoma	No
	600	721	3058	T	skin	keratoacanthoma	No
	600	702	3061	U	skin	keratoacanthoma	No
	602	602	3011	U	body cavity, thoracic	sarcoma	Yes
	602	602	3011	U	gland, pituitary	adenoma	No
	602	602	3011	U	gland, thyroid	c-cell adenoma	No
	607	714	3028	T	subcutis	fibroma	No
	607	721	3050	T	subcutis	fibroma	No
	612	612	3060	U	gland, thyroid	c-cell adenoma	No
	621	635	3040	U	brain	meningioma, malignant	Yes
	622	622	3010	U	kidney	tubular cell adenoma	No
	628	712	3007	T	subcutis	fibroma	No
	628	713	3026	T	gland, mammary	fibroadenoma	No
	628	628	3048	U	gland, adrenal	pheochromocytoma, malignant	Yes

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
3M	633	633	3017	U	gland, pituitary	adenoma	No
	633	633	3017	U	lung	adenoma	No
	635	635	3066	U	pancreas	adenoma	No
	639	639	3052	U	pancreas	adenoma	No
	642	667	3041	U	subcutis	fibroma	No
	643	643	3067	U	gland, pituitary	adenoma	No
	649	713	3016	T	gland, mammary	fibroadenoma	No
	656	667	3035	U	skin	hair follicle tumor, benign	No
	656	709	3057	T	subcutis	fibrosarcoma	Yes
	667	667	3041	U	gland, pituitary	adenoma	No
	670	720	3055	T	subcutis	fibroma	No
	677	719	3044	T	subcutis	lipoma	No
	677	721	3050	T	skin	keratoacanthoma	No
	684	714	3028	T	skin	keratoacanthoma	No
	690	690	3030	U	gland, pituitary	adenoma	No
	691	719	3063	T	subcutis	fibroma	No
	698	720	3056	T	subcutis	fibrosarcoma	Yes
	709	709	3057	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	709	709	3057	T	pancreas	adenoma	No
	709	709	3057	T	skin	keratoacanthoma	No
	712	712	3003	T	gland, pituitary	adenoma	No
	712	712	3005	T	gland, pituitary	adenoma	No
	712	712	3007	T	lymph node, mesenteric	hemangiosarcoma	Yes
	712	712	3013	T	gland, pituitary	adenoma	No
	712	712	3013	T	liver	hemangiosarcoma	Yes
	712	719	3044	T	subcutis	fibroma	No
	713	713	3016	T	gland, adrenal	pheochromocytoma, benign	No
	713	713	3016	T	gland, pituitary	adenoma	No
	713	713	3025	T	lymph node, mesenteric	hemangiosarcoma	Yes
	713	713	3026	T	gland, thyroid	c-cell adenoma	No
	713	713	3026	T	pancreas	adenoma	No
	715	715	3029	T	gland, adrenal	pheochromocytoma, benign	No
	715	715	3029	T	lymph node, mesenteric	hemangiosarcoma	Yes
	716	716	3033	T	gland, pituitary	adenoma	No
	716	716	3034	T	gland, adrenal	cortical adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
3M	716	716	3034	T	gland, pituitary	adenoma	No
	716	716	3034	T	pancreas	adenoma	No
	716	716	3038	T	gland, pituitary	adenoma	No
	716	716	3038	T	kidney	tubular cell carcinoma	Yes
	716	716	3038	T	pancreas	adenoma	No
	716	716	3038	T	skin	papilloma	No
	719	719	3043	T	gland, pituitary	adenoma	No
	719	719	3043	T	gland, thyroid	follicular cell carcinoma	Yes
	719	719	3043	T	muscle, skeletal	fibroma	No
	719	719	3043	T	subcutis	fibroma	No
	719	719	3044	T	gland, adrenal	pheochromocytoma, malignant	Yes
	719	719	3044	T	testis	interstitial (leydig) cell ade	No
	719	721	3050	T	subcutis	liposarcoma	Yes
	719	719	3063	T	gland, pituitary	adenoma	No
	720	720	3055	T	gland, adrenal	pheochromocytoma, benign	No
	720	720	3056	T	gland, pituitary	adenoma	No
	720	720	3056	T	pancreas	adenoma	No
	721	721	3050	T	skin	hair follicle tumor, benign	No
	721	721	3058	T	muscle, skeletal	fibrosarcoma	Yes
	721	721	3069	T	gland, adrenal	pheochromocytoma, benign	No
3F	188	576	3507	U	gland, mammary	fibroadenoma	No
	223	485	3523	U	gland, mammary	adenocarcinoma	Yes
	258	359	3536	U	gland, mammary	adenocarcinoma	Yes
	272	539	3566	U	gland, mammary	fibroadenoma	No
	307	572	3509	U	gland, mammary	fibroadenoma	No
	318	318	3541	U	gland, pituitary	adenoma	No
	318	318	3541	U	kidney	tubular cell adenoma	No
	328	543	3506	U	gland, mammary	fibroadenoma	No
	329	329	3546	U	gland, pituitary	adenoma	No
	334	334	3508	U	gland, pituitary	adenoma	No
	335	471	3519	U	gland, mammary	adenocarcinoma	Yes
	348	396	3553	U	subcutis	lipoma	No
	356	486	3524	U	gland, mammary	fibroadenoma	No
	359	359	3536	U	gland, pituitary	adenoma	No
	370	543	3506	U	gland, mammary	adenocarcinoma	Yes

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
3F	370	543	3517	U	gland, mammary	fibroadenoma	No
	377	485	3523	U	gland, mammary	fibroadenoma	No
	387	387	3554	U	gland, pituitary	adenoma	No
	387	387	3554	U	liver	cholangioma	No
	391	486	3524	U	gland, mammary	adenocarcinoma	Yes
	396	396	3553	U	gland, thyroid	c-cell adenoma	No
	399	526	3501	U	gland, mammary	fibroadenoma	No
	399	527	3526	U	gland, mammary	fibroadenoma	No
	399	692	3552	U	gland, mammary	fibroadenoma	No
	409	409	3529	U	gland, mammary	adenocarcinoma	Yes
	409	409	3529	U	gland, pituitary	adenoma	No
	409	409	3529	U	kidney	tubular cell carcinoma	Yes
	409	409	3529	U	large intestine, rectum	hemangioma	No
	409	409	3529	U	lymph node	hemangioma	No
	413	590	3511	U	gland, mammary	fibroadenoma	No
	413	562	3530	U	gland, mammary	adenocarcinoma	Yes
	413	576	3534	U	gland, mammary	fibroadenoma	No
	413	709	3570	T	subcutis	fibroma	No
	426	677	3502	U	gland, mammary	fibroadenoma	No
	426	566	3520	U	subcutis	lipoma	No
	426	637	3563	U	gland, mammary	fibroadenoma	No
	434	706	3510	T	subcutis	lipoma	No
	434	706	3538	T	gland, mammary	fibroadenoma	No
	434	451	3548	U	gland, mammary	fibroadenoma	No
	434	607	3549	U	gland, mammary	adenocarcinoma	Yes
	447	607	3531	U	gland, mammary	fibroadenoma	No
	447	707	3544	T	gland, mammary	fibroadenoma	No
	447	707	3544	T	subcutis	fibrosarcoma	Yes
	451	451	3548	U	gland, pituitary	adenoma	No
	451	451	3548	U	gland, thyroid	c-cell adenoma	No
	451	451	3548	U	pancreas	adenoma	No
	454	508	3551	U	gland, mammary	adenocarcinoma	Yes
	454	454	3565	U	gland, pituitary	adenoma	No
	461	643	3516	U	gland, mammary	fibroadenoma	No
	461	706	3533	T	gland, mammary	fibroadenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
3F	468	572	3509	U	subcutis	fibroma	No
	468	566	3520	U	gland, mammary	fibroadenoma	No
	468	657	3556	U	gland, mammary	adenocarcinoma	Yes
	468	486	3564	U	subcutis	fibrosarcoma	Yes
	468	709	3567	T	gland, mammary	fibroadenoma	No
	470	470	3514	U	gland, pituitary	adenoma	No
	471	471	3519	U	gland, pituitary	adenoma	No
	482	580	3532	U	gland, mammary	fibroadenoma	No
	482	666	3558	U	subcutis	lipoma	No
	485	485	3523	U	gland, pituitary	adenoma	No
	486	486	3524	U	gland, pituitary	adenoma	No
	486	486	3564	U	gland, pituitary	adenoma	No
	486	486	3564	U	lymph node, mesenteric	hemangiosarcoma	Yes
	489	580	3532	U	gland, mammary	adenocarcinoma	Yes
	489	707	3537	T	gland, mammary	fibroadenoma	No
	503	527	3526	U	gland, mammary	adenocarcinoma	Yes
	503	509	3561	U	gland, mammary	adenocarcinoma	Yes
	506	506	3513	U	gland, pituitary	adenoma	No
	508	508	3551	U	gland, pituitary	adenoma	No
	509	509	3561	U	gland, pituitary	adenoma	No
	525	549	3503	U	gland, mammary	adenoma	No
	525	657	3522	U	gland, mammary	fibroadenoma	No
	525	562	3527	U	gland, mammary	fibroadenoma	No
	525	534	3540	U	gland, mammary	adenocarcinoma	Yes
	525	534	3540	U	gland, mammary	fibroadenoma	No
	526	526	3501	U	gland, pituitary	adenoma	No
	534	534	3540	U	gland, pituitary	adenoma	No
	538	706	3512	T	gland, mammary	fibroadenoma	No
	538	692	3521	U	gland, mammary	fibroadenoma	No
	539	539	3566	U	uterus	adenocarcinoma	Yes
	543	543	3517	U	gland, mammary	adenocarcinoma	Yes
	543	543	3517	U	gland, pituitary	adenoma	No
	549	549	3503	U	gland, pituitary	adenoma	No
	554	554	3560	U	gland, pituitary	adenoma	No
	559	706	3533	T	gland, mammary	adenocarcinoma	Yes

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
3F	559	706	3538	T	gland, mammary	adenoma	No
	559	666	3558	U	gland, mammary	fibroadenoma	No
	562	562	3527	U	gland, pituitary	adenoma	No
	566	566	3520	U	gland, pituitary	adenoma	No
	566	707	3535	T	gland, mammary	fibroadenoma	No
	566	566	3628	U	gland, pituitary	adenoma	No
	572	572	3509	U	pancreas	adenoma	No
	573	605	3542	U	gland, mammary	adenocarcinoma	Yes
	573	607	3549	U	gland, mammary	fibroadenoma	No
	576	576	3507	U	gland, mammary	adenocarcinoma	Yes
	576	576	3507	U	pancreas	adenoma	No
	576	576	3534	U	gland, mammary	adenocarcinoma	Yes
	576	576	3534	U	gland, pituitary	adenoma	No
	580	580	3532	U	gland, pituitary	adenoma	No
	580	707	3537	T	gland, mammary	adenoma	No
	580	706	3538	T	gland, mammary	adenocarcinoma	Yes
	580	666	3558	U	subcutis	myxosarcoma	Yes
	586	586	3562	U	gland, pituitary	adenoma	No
	586	586	3562	U	gland, thyroid	c-cell adenoma	No
	586	586	3562	U	kidney	tubular cell carcinoma	Yes
	586	586	3562	U	uterus	endometrial stromal sarcoma	Yes
	587	632	3505	U	gland, mammary	adenoma	No
	587	673	3515	U	gland, mammary	fibroadenoma	No
	590	590	3511	U	body cavity, abdominal	lipoma	No
	590	590	3511	U	gland, mammary	adenocarcinoma	Yes
	590	590	3511	U	gland, pituitary	adenoma	No
	594	707	3543	T	gland, mammary	fibroadenoma	No
	594	657	3556	U	gland, mammary	fibroadenoma	No
	605	605	3542	U	gland, pituitary	carcinoma, pars distalis	Yes
	607	607	3549	U	gland, pituitary	adenoma	No
	607	607	3549	U	gland, thyroid	c-cell carcinoma	Yes
	609	609	3559	U	gland, pituitary	adenoma	No
	615	706	3518	T	gland, mammary	adenocarcinoma	Yes
	621	707	3545	T	gland, mammary	fibroadenoma	No
	632	632	3505	U	gland, mammary	fibroadenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
3F	632	632	3505	U	gland, pituitary	adenoma	No
	636	706	3510	T	gland, mammary	fibroadenoma	No
	657	706	3518	T	gland, mammary	fibroadenoma	No
	657	657	3522	U	bone	osteosarcoma	Yes
	657	657	3522	U	gland, adrenal	pheochromocytoma, benign	No
	657	707	3539	T	gland, mammary	fibroadenoma	No
	657	657	3556	U	uterus	polyp	No
	657	708	3557	T	gland, mammary	fibroadenoma	No
	671	707	3545	T	skin	carcinoma	Yes
	673	673	3515	U	bone	fibrosarcoma	Yes
	673	673	3515	U	gland, mammary	adenocarcinoma	Yes
	673	673	3515	U	gland, pituitary	adenoma	No
	677	677	3502	U	gland, mammary	adenoma	No
	677	677	3502	U	gland, pituitary	adenoma	No
	706	706	3504	T	gland, mammary	fibroadenoma	No
	706	706	3510	T	gland, pituitary	adenoma	No
	706	706	3510	T	gland, thyroid	c-cell adenoma	No
	706	706	3512	T	subcutis	fibroma	No
	706	706	3512	T	uterus	polyp	No
	706	706	3518	T	gland, pituitary	adenoma	No
	706	706	3518	T	gland, thyroid	c-cell adenoma	No
	706	706	3518	T	subcutis	lipoma	No
	706	706	3525	T	gland, mammary	fibroadenoma	No
	706	706	3525	T	gland, pituitary	adenoma	No
	706	706	3538	T	gland, pituitary	adenoma	No
	706	707	3547	T	gland, mammary	fibroadenoma	No
	707	707	3535	T	gland, pituitary	adenoma	No
	707	707	3539	T	gland, pituitary	adenoma	No
	707	707	3543	T	gland, pituitary	adenoma	No
	707	707	3543	T	gland, thyroid	c-cell adenoma	No
	707	707	3544	T	gland, mammary	adenoma	No
	707	707	3544	T	gland, pituitary	adenoma	No
	707	707	3545	T	gland, pituitary	adenoma	No
	707	707	3545	T	gland, thyroid	c-cell adenoma	No
	707	707	3545	T	subcutis	lipoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
3F	708	708	3555	T	gland, mammary	fibroadenoma	No
	708	708	3555	T	uterus	endometrial stromal sarcoma	Yes
	708	708	3555	T	uterus	polyp	No
	709	709	3567	T	gland, pituitary	adenoma	No
	709	709	3567	T	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	709	709	3568	T	gland, pituitary	adenoma	No
	709	709	3570	T	gland, mammary	fibroadenoma	No
4M	180	576	4039	U	subcutis	fibrosarcoma	Yes
	267	267	4011	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	313	437	4015	U	subcutis	fibroma	No
	320	539	4036	U	subcutis	fibrosarcoma	Yes
	328	328	4014	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	341	601	4010	U	subcutis	lipoma	No
	352	352	4003	U	gland, thyroid	c-cell adenoma	No
	352	352	4003	U	kidney	tubular cell carcinoma	Yes
	362	712	4042	T	subcutis	lipoma	No
	377	377	4020	U	kidney	tubular cell carcinoma	Yes
	383	629	4048	U	gland, mammary	fibroadenoma	No
	390	437	4015	U	subcutis	sarcoma	Yes
	412	412	4045	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	413	413	4067	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	432	496	4070	U	gland, mammary	fibroadenoma	No
	437	437	4015	U	gland, thyroid	c-cell adenoma	No
	437	437	4015	U	kidney	tubular cell carcinoma	Yes
	453	453	4041	U	gland, pituitary	adenoma	No
	453	453	4041	U	gland, thyroid	c-cell adenoma	No
	453	453	4041	U	kidney	tubular cell carcinoma	Yes
	460	590	4068	U	subcutis	fibrosarcoma	Yes
	466	466	4059	U	subcutis	sarcoma	Yes
	488	633	4007	U	skin	keratoacanthoma	No
	493	493	4058	U	skin	papilloma	No
	502	631	4033	U	skin	papilloma	No
	512	512	4028	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	518	518	4001	U	gland, pituitary	adenoma	No
	518	518	4001	U	testis	interstitial (leydig) cell ade	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
4M	522	712	4042	T	subcutis	fibroma	No
	530	596	4062	U	ear	carcinoma	Yes
	530	596	4062	U	head	fibrosarcoma	Yes
	534	534	4056	U	gland, pituitary	adenoma	No
	534	534	4056	U	skin	polyp	No
	537	679	4035	U	subcutis	fibrosarcoma	Yes
	542	542	4065	U	body cavity, abdominal	fibrosarcoma	Yes
	544	640	4060	U	skin	keratoacanthoma	No
	559	559	4018	U	gland, pituitary	adenoma	No
	559	559	4034	U	body cavity, oral	squamous cell carcinoma	Yes
	559	559	4034	U	body cavity, thoracic	mesothelioma, malignant	Yes
	559	559	4034	U	gland, pituitary	adenoma	No
	559	559	4034	U	kidney	tubular cell carcinoma	Yes
	572	572	4063	U	gland, pituitary	adenoma	No
	579	666	4019	U	gland, mammary	fibroadenoma	No
	579	713	4023	T	subcutis	lipoma	No
	579	649	4054	U	subcutis	fibroma	No
	586	707	4030	U	subcutis	fibrosarcoma	Yes
	586	647	4044	U	subcutis	lipoma	No
	590	590	4068	U	gland, thyroid	c-cell adenoma	No
	596	596	4062	U	gland, pituitary	adenoma	No
	596	596	4062	U	gland, thyroid	follicular cell adenoma	No
	601	601	4010	U	gland, pituitary	adenoma	No
	601	601	4010	U	hemolymphoreticular tissue	lymphoma, malignant	Yes
	615	615	4017	U	gland, pituitary	adenoma	No
	615	615	4017	U	gland, thyroid	c-cell adenoma	No
	615	615	4017	U	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	616	616	4005	U	pancreas	adenoma	No
	616	616	4005	U	skin	polyp	No
	617	617	4027	U	gland, pituitary	adenoma	No
	622	622	4047	U	gland, pituitary	carcinoma, pars distalis	Yes
	627	627	4057	U	gland, pituitary	adenoma	No
	628	712	4043	T	skin	keratoacanthoma	No
	629	629	4048	U	gland, pituitary	adenoma	No
	635	709	4009	T	subcutis	fibrosarcoma	Yes

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
4M	635	712	4013	T	subcutis	fibrosarcoma	Yes
	635	713	4023	T	subcutis	fibrosarcoma	Yes
	635	711	4050	T	subcutis	fibrosarcoma	Yes
	638	638	4021	U	gland, pituitary	adenoma	No
	638	638	4021	U	gland, thyroid	c-cell adenoma	No
	640	640	4040	U	gland, pituitary	adenoma	No
	640	640	4040	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	640	640	4040	U	subcutis	hemangioma	No
	640	640	4060	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	640	640	4060	U	pancreas	adenoma, acinar	No
	642	642	4064	U	pancreas	adenoma	No
	642	642	4064	U	stomach	leiomyosarcoma	Yes
	647	647	4044	U	body cavity, oral	squamous cell carcinoma	Yes
	649	716	4037	T	subcutis	fibrosarcoma	Yes
	649	649	4054	U	pancreas	adenocarcinoma	Yes
	655	712	4043	T	subcutis	myxoma	No
	666	666	4019	U	gland, pituitary	adenoma	No
	670	713	4024	T	subcutis	fibrosarcoma	Yes
	678	678	4053	U	gland, pituitary	adenoma	No
	678	678	4053	U	gland, thyroid	c-cell adenoma	No
	686	686	4002	U	pancreas	adenoma	No
	691	712	4043	T	subcutis	fibroma	No
	692	692	4031	U	gland, pituitary	adenoma	No
	692	692	4031	U	pancreas	adenoma	No
	696	696	4038	U	gland, pituitary	adenoma	No
	705	713	4024	T	gland, mammary	fibroadenoma	No
	705	712	4042	T	skin	keratoacanthoma	No
	706	706	4049	U	gland, adrenal	pheochromocytoma, benign	No
	706	706	4049	U	gland, pituitary	adenoma	No
	707	707	4030	U	gland, pituitary	adenoma	No
	708	708	4066	U	brain	astrocytoma, malignant	Yes
	708	708	4066	U	gland, pituitary	adenoma	No
	709	709	4009	T	gland, pituitary	adenoma	No
	712	712	4013	T	gland, thyroid	c-cell adenoma	No
	712	712	4013	T	subcutis	fibroma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
4M	712	712	4016	T	gland, thyroid	c-cell adenoma	No
	712	712	4016	T	subcutis	fibrosarcoma	Yes
	712	712	4042	T	pancreas	adenoma	No
	713	713	4024	T	gland, mammary	adenocarcinoma	Yes
	713	713	4024	T	pancreas	adenoma	No
	713	713	4025	T	gland, pituitary	adenoma	No
	713	713	4025	T	gland, thyroid	c-cell adenoma	No
	713	713	4025	T	hemolymphoreticular tissue	leukemia, granulocytic	Yes
	715	715	4032	T	gland, thyroid	c-cell adenoma	No
	716	716	4037	T	gland, adrenal	pheochromocytoma, malignant	Yes
	716	716	4037	T	gland, thyroid	follicular cell adenoma	No
	716	716	4037	T	pancreas	adenoma	No
	716	716	4037	T	testis	interstitial (leydig) cell ade	No
	716	716	4051	T	pancreas	adenoma	No
	716	716	4069	T	gland, pituitary	adenoma	No
	716	716	4069	T	gland, thyroid	c-cell adenoma	No
4F	69	385	4563	U	gland, mammary	adenocarcinoma	Yes
	160	217	4549	U	gland, mammary	adenocarcinoma	Yes
	216	471	4566	U	gland, mammary	fibroadenoma	No
	223	335	4504	U	gland, mammary	adenocarcinoma	Yes
	223	476	4511	U	gland, mammary	fibroadenoma	No
	223	471	4519	U	gland, mammary	fibroadenoma	No
	223	629	4557	U	gland, mammary	adenocarcinoma	Yes
	244	570	4551	U	gland, mammary	fibroadenoma	No
	269	269	4516	U	gland, pituitary	adenoma	No
	272	328	4545	U	gland, mammary	adenocarcinoma	Yes
	286	335	4504	U	gland, mammary	fibroadenoma	No
	307	481	4510	U	gland, mammary	fibroadenoma	No
	314	621	4553	U	gland, mammary	fibroadenoma	No
	321	321	4501	U	gland, mammary	fibroadenoma	No
	321	321	4501	U	gland, pituitary	adenoma	No
	328	524	4520	U	gland, mammary	fibroadenoma	No
	330	330	4539	U	gland, pituitary	adenoma	No
	330	330	4539	U	kidney	tubular cell adenoma	No
	330	330	4539	U	uterus	fibroma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
4F	330	330	4539	U	uterus	hemangioma	No
	335	335	4504	U	gland, thyroid	c-cell adenoma	No
	342	701	4527	U	gland, mammary	fibroadenoma	No
	348	619	4515	U	gland, mammary	fibroadenoma	No
	348	629	4557	U	gland, mammary	fibroadenoma	No
	376	376	4513	U	gland, pituitary	adenoma	No
	377	609	4565	U	gland, mammary	fibroadenoma	No
	391	592	4508	U	gland, mammary	fibroadenoma	No
	391	580	4512	U	gland, mammary	fibroadenoma	No
	399	562	4509	U	subcutis	fibroma	No
	399	482	4524	U	gland, mammary	fibroadenoma	No
	399	399	4548	U	gland, pituitary	adenoma	No
	405	460	4523	U	gland, mammary	fibroadenoma	No
	408	408	4518	U	gland, pituitary	adenoma	No
	408	408	4518	U	kidney	tubular cell carcinoma	Yes
	413	709	4562	T	gland, mammary	fibroadenoma	No
	434	451	4522	U	gland, mammary	fibroadenoma	No
	434	706	4560	T	gland, mammary	adenoma	No
	440	512	4529	U	gland, mammary	fibroadenoma	No
	440	524	4568	U	gland, mammary	fibroadenoma	No
	447	460	4523	U	subcutis	fibrosarcoma	Yes
	451	451	4522	U	gland, pituitary	adenoma	No
	451	451	4522	U	kidney	tubular cell carcinoma	Yes
	454	521	4517	U	gland, mammary	adenocarcinoma	Yes
	454	521	4517	U	gland, mammary	fibroadenoma	No
	454	706	4541	T	subcutis	fibrosarcoma	Yes
	454	707	4554	T	gland, mammary	adenoma	No
	454	590	4555	U	gland, mammary	fibroadenoma	No
	461	637	4532	U	gland, mammary	fibroadenoma	No
	461	708	4559	T	gland, mammary	fibroadenoma	No
	469	580	4512	U	gland, mammary	adenocarcinoma	Yes
	470	470	4507	U	gland, mammary	fibroadenoma	No
	470	470	4507	U	gland, pituitary	adenoma	No
	475	524	4520	U	gland, mammary	adenoma	No
	482	482	4524	U	gland, pituitary	adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
4F	482	482	4524	U	gland, thyroid	c-cell adenoma	No
	482	706	4541	T	gland, mammary	fibroadenoma	No
	482	615	4547	U	gland, mammary	adenocarcinoma	Yes
	492	492	4528	U	gland, pituitary	adenoma	No
	492	492	4535	U	gland, pituitary	adenoma	No
	492	492	4535	U	kidney	tubular cell carcinoma	Yes
	496	706	4560	T	gland, mammary	fibroadenoma	No
	503	572	4526	U	subcutis	lipoma	No
	503	590	4555	U	gland, mammary	adenocarcinoma	Yes
	511	572	4526	U	skin	squamous cell carcinoma	Yes
	511	706	4531	T	gland, mammary	fibroadenoma	No
	511	633	4533	U	gland, mammary	fibroadenoma	No
	511	511	4567	A	gland, pituitary	adenoma	No
	511	524	4568	U	gland, mammary	adenocarcinoma	Yes
	512	512	4529	U	bone	osteosarcoma	Yes
	517	653	4536	U	gland, mammary	fibroadenoma	No
	517	706	4552	T	gland, mammary	fibroadenoma	No
	517	568	4561	U	gland, mammary	fibroadenoma	No
	521	521	4517	U	gland, adrenal	cortical adenoma	No
	521	521	4517	U	gland, pituitary	adenoma	No
	521	521	4517	U	gland, thyroid	c-cell adenoma	No
	524	524	4520	U	gland, pituitary	adenoma	No
	524	524	4542	U	gland, pituitary	adenoma	No
	524	524	4542	U	gland, thyroid	c-cell adenoma	No
	524	524	4542	U	uterus	polyp	No
	524	524	4568	U	gland, pituitary	adenoma	No
	525	707	4537	T	gland, mammary	fibroadenoma	No
	525	707	4540	T	gland, mammary	fibroadenoma	No
	530	530	4521	U	gland, pituitary	adenoma	No
	538	708	4558	T	gland, mammary	fibroadenoma	No
	544	562	4509	U	gland, mammary	adenoma	No
	553	635	4569	U	gland, mammary	fibroadenoma	No
	558	707	4554	T	gland, mammary	fibroadenoma	No
	562	562	4509	U	gland, mammary	adenocarcinoma	Yes
	562	562	4509	U	gland, thyroid	c-cell adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
4F	568	568	4561	U	gland, pituitary	adenoma	No
	572	572	4526	U	gland, mammary	fibroadenoma	No
	572	572	4526	U	gland, pituitary	adenoma	No
	573	706	4534	T	gland, mammary	fibroadenoma	No
	573	707	4546	T	subcutis	lipoma	No
	587	707	4550	T	subcutis	fibrosarcoma	Yes
	590	590	4555	U	gland, pituitary	adenoma	No
	592	592	4508	U	gland, mammary	adenocarcinoma	Yes
	592	592	4508	U	gland, pituitary	adenoma	No
	592	592	4508	U	pancreas	adenoma	No
	594	707	4546	T	gland, mammary	fibroadenoma	No
	594	707	4556	T	gland, mammary	fibroadenoma	No
	594	709	4570	T	gland, mammary	fibroadenoma	No
	601	701	4527	U	gland, mammary	adenocarcinoma	Yes
	601	707	4540	T	subcutis	fibroma	No
	603	603	4544	U	gland, pituitary	adenoma	No
	603	603	4544	U	gland, thyroid	c-cell adenoma	No
	608	708	4559	T	subcutis	fibrosarcoma	Yes
	609	609	4565	U	gland, pituitary	adenoma	No
	615	706	4502	T	gland, mammary	fibroadenoma	No
	615	615	4547	U	gland, pituitary	adenoma	No
	615	615	4547	U	gland, thyroid	follicular cell adenoma	No
	615	615	4547	U	pancreas	adenoma	No
	619	619	4515	U	gland, pituitary	adenoma	No
	619	619	4515	U	large intestine, rectum	hemangiosarcoma	Yes
	619	619	4515	U	lung	hemangiosarcoma	Yes
	619	619	4515	U	pancreas	adenoma	No
	621	653	4536	U	gland, mammary	adenocarcinoma	Yes
	621	621	4553	U	gland, pituitary	adenoma	No
	622	622	4525	U	gland, mammary	adenoma	No
	622	622	4525	U	gland, mammary	fibroadenoma	No
	622	622	4525	U	gland, pituitary	adenoma	No
	622	622	4525	U	gland, thyroid	c-cell adenoma	No
	628	628	4503	U	gland, pituitary	adenoma	No
	629	629	4557	U	gland, pituitary	adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
4F	633	633	4533	U	gland, pituitary	adenoma	No
	635	635	4569	U	hemolymphoreticular tissue	histiocytic sarcoma	Yes
	637	637	4532	U	gland, thyroid	c-cell adenoma	No
	648	648	4564	U	gland, pituitary	adenoma	No
	653	653	4536	U	gland, pituitary	adenoma	No
	657	706	4505	T	gland, mammary	fibroadenoma	No
	664	693	4538	U	gland, mammary	fibroadenoma	No
	664	708	4558	T	gland, mammary	adenocarcinoma	Yes
	692	707	4537	T	gland, mammary	adenocarcinoma	Yes
	692	707	4550	T	gland, mammary	fibroadenoma	No
	693	693	4538	U	gland, pituitary	adenoma	No
	706	706	4505	T	gland, mammary	adenocarcinoma	Yes
	706	706	4505	T	subcutis	fibroma	No
	706	706	4530	T	gland, pituitary	adenoma	No
	706	706	4531	T	gland, mammary	adenoma	No
	706	706	4531	T	gland, pituitary	adenoma	No
	706	706	4531	T	subcutis	fibroma	No
	706	707	4540	T	gland, mammary	adenocarcinoma	Yes
	706	706	4541	T	gland, pituitary	adenoma	No
	706	706	4541	T	uterus	polyp	No
	706	707	4543	T	gland, mammary	fibroadenoma	No
	706	707	4550	T	gland, mammary	adenocarcinoma	Yes
	706	706	4552	T	gland, pituitary	adenoma	No
	706	706	4552	T	gland, thyroid	c-cell adenoma	No
	706	706	4552	T	pancreas	adenoma	No
	706	706	4552	T	urinary bladder	papilloma	No
	707	707	4537	T	gland, pituitary	adenoma	No
	707	707	4543	T	gland, pituitary	adenoma	No
	707	707	4546	T	pancreas	adenoma	No
	707	707	4550	T	gland, pituitary	adenoma	No
	707	707	4550	T	subcutis	hemangiosarcoma	Yes
	707	707	4554	T	gland, pituitary	adenoma	No
	707	707	4554	T	uterus	polyp	No
	707	707	4556	T	gland, pituitary	adenoma	No
	708	708	4558	T	gland, pituitary	adenoma	No

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

Group/ Sex	Day first seen	Day of necropsy	Animal No.	Death code	Tissue	Tumor	Malignant
4F	708	708	4558	T	pancreas	adenoma	No
	708	708	4559	T	gland, pituitary	adenoma	No
	709	709	4562	T	gland, adrenal	pheochromocytoma, benign	No
	709	709	4562	T	gland, pituitary	adenoma	No
	709	709	4562	T	pancreas	adenoma	No
	709	709	4570	T	muscle, skeletal	liposarcoma	Yes
	709	709	4570	T	uterus	polyp	No

Key:
A = Accidental death.
T = Terminal kill.
U = Unscheduled death.

Group 1 dose level = 0 mg/kg/day;
Group 2 dose level = 0.25 mg/kg/day;
Group 3 dose level = 2.5 mg/kg/day
Group 4 dose level = 75 mg/kg/day

Table 10.7 Carcinogenicity Study in Rats - Summary of Survival and Fate of Animals

Sex: Male																					
Dose	0 mg/kg/day						0.25 mg/kg/day						2.5 mg/kg/day					75 mg/kg/day				
Week	E	D	A	K	N		E	D	A	K	N		E	D	A	K	N	E	D	A	K	N
6	70	.	.	.	0		70	.	.	.	0		70	.	.	.	0	70	.	.	.	0
8	70	.	.	.	0		70	.	1	.	1		70	.	.	.	0	70	.	1	.	1
12	70	.	.	.	0		69	1	.	.	1		70	.	.	.	0	69	.	.	.	0
16	70	.	.	.	0		68	.	.	.	0		70	.	.	.	0	69	.	1	.	1
17	70	.	.	.	0		68	.	.	.	0		70	.	.	.	0	68	1	.	.	1
21	70	.	.	.	0		68	.	1	.	1		70	.	.	.	0	67	.	.	.	0
22	70	1	.	.	1		67	.	.	.	0		70	.	.	.	0	67	.	.	.	0
28	69	.	.	.	0		67	.	.	1	1		70	.	.	.	0	67	.	.	.	0
30	69	.	.	.	0		66	.	.	.	0		70	.	.	.	0	67	.	.	.	0
31	69	1	.	.	1		66	.	.	.	0		70	.	.	.	0	67	.	.	.	0
32	68	.	.	.	0		66	1	.	.	1		70	.	.	.	0	67	.	.	.	0
34	68	.	.	.	0		65	.	.	.	0		70	.	.	.	0	67	.	.	.	0
35	68	.	.	.	0		65	.	.	.	0		70	.	.	1	1	67	.	.	.	0
36	68	.	.	.	0		65	.	.	1	1		69	.	.	.	0	67	.	.	.	0
37	68	.	.	1	1		64	.	.	.	0		69	.	.	.	0	67	.	.	.	0
38	67	.	.	.	0		64	1	.	.	1		69	.	.	.	0	67	.	.	.	0
39	67	.	.	.	0		63	.	.	.	0		69	1	.	.	1	67	1	.	.	1
40	67	.	.	1	1		63	.	.	.	0		68	.	.	.	0	66	.	.	.	0
41	66	1	.	.	1		63	.	.	.	0		68	.	.	.	0	66	.	.	.	0
45	65	.	.	1	1		63	.	.	.	0		68	.	.	.	0	66	.	.	.	0
46	64	1	.	.	1		63	.	.	.	0		68	.	.	.	0	66	.	.	.	0
47	63	1	1	.	2		63	.	.	.	0		68	.	.	.	0	66	.	.	1	1
48	61	.	.	1	1		63	.	.	.	0		68	.	.	.	0	65	.	.	.	0
49	60	.	.	.	0		63	.	.	.	0		68	.	.	.	0	65	.	.	.	0
50	60	.	.	.	0		63	.	.	.	0		68	.	.	1	1	65	.	.	.	0
51	60	.	.	.	0		63	.	.	.	0		67	.	.	.	0	65	1	.	.	1
52	60	.	.	.	0		63	.	.	.	0		67	.	.	.	0	64	.	.	.	0
53	60	1	.	.	1		63	.	.	1	1		67	.	.	.	0	64	.	.	.	0
54	59	.	.	1	1		62	1	.	.	1		67	.	.	.	0	64	.	.	1	1
55	58	.	.	.	0		61	1	.	1	2		67	.	.	.	0	63	.	.	.	0
56	58	2	.	.	2		59	.	.	.	0		67	.	.	.	0	63	.	.	.	0
57	56	.	.	1	1		59	1	.	.	1		67	.	.	1	1	63	.	.	.	0
58	55	.	.	.	0		58	1	.	.	1		66	.	.	.	0	63	.	.	.	0
59	55	.	.	.	0		57	.	.	.	0		66	.	.	.	0	63	1	.	1	2
60	55	.	.	1	1		57	1	.	1	2		66	.	.	.	0	61	.	.	.	0
61	54	.	.	.	0		55	.	.	.	0		66	.	.	1	1	61	.	.	.	0
62	54	.	.	.	0		55	.	.	.	0		65	.	.	.	0	61	.	.	.	0

Carcinogenicity Study in Rats - Summary of Survival and Fate of Animals (Continued)

Sex: Male																					
Dose	0 mg/kg/day						0.25 mg/kg/day						2.5 mg/kg/day					75 mg/kg/day				
Week	E	D	A	K	N		E	D	A	K	N		E	D	A	K	N	E	D	A	K	N
63	54	.	.	1	1		55	.	.	.	0		65	2	.	1	3	61	1	.	.	1
64	53	.	.	.	0		55	1	1	1	3		62	.	.	.	0	60	.	.	.	0
65	53	.	.	.	0		52	.	.	1	1		62	.	.	1	1	60	.	.	1	1
66	53	1	.	.	1		51	.	.	.	0		61	.	.	.	0	59	.	.	.	0
67	52	.	.	.	0		51	.	.	.	0		61	.	.	1	1	59	.	.	1	1
68	52	.	.	.	0		51	.	.	1	1		60	.	1	1	2	58	2	.	.	2
69	52	1	.	.	1		50	.	.	.	0		58	.	.	3	3	56	.	.	.	0
70	51	.	.	.	0		50	.	.	.	0		55	1	.	.	1	56	.	.	.	0
71	51	.	.	.	0		50	1	.	2	3		54	.	.	.	0	56	1	.	1	2
72	51	.	.	1	1		47	.	2	.	2		54	.	.	.	0	54	.	.	.	0
73	50	1	.	.	1		45	1	.	.	1		54	1	.	2	3	54	.	.	.	0
74	49	.	.	.	0		44	.	.	1	1		51	.	.	1	1	54	.	.	2	2
75	49	1	.	1	2		43	.	.	.	0		50	.	.	.	0	52	.	.	.	0
76	47	.	.	.	0		43	.	.	.	0		50	1	.	.	1	52	.	.	.	0
77	47	.	.	.	0		43	.	.	.	0		49	1	.	1	2	52	.	.	2	2
78	47	2	.	1	3		43	.	.	1	1		47	.	1	1	2	50	.	.	1	1
79	44	.	.	1	1		42	.	.	.	0		45	.	.	.	0	49	.	.	.	0
80	43	.	.	.	0		42	1	.	.	1		45	.	.	.	0	49	.	.	2	2
81	43	.	.	.	0		41	.	.	.	0		45	.	.	1	1	47	.	.	.	0
82	43	1	.	.	1		41	.	.	.	0		44	1	.	1	2	47	2	.	.	2
83	42	.	.	.	0		41	1	.	.	1		42	.	.	.	0	45	.	.	1	1
84	42	.	.	.	0		40	.	.	.	0		42	.	.	2	2	44	.	.	.	0
85	42	1	.	1	2		40	.	.	.	0		40	.	.	.	0	44	.	.	1	1
86	40	.	1	.	1		40	1	.	.	1		40	2	.	.	2	43	1	.	1	2
87	39	1	.	1	2		39	2	.	3	5		38	.	.	.	0	41	.	.	.	0
88	37	.	.	1	1		34	.	.	.	0		38	1	.	.	1	41	1	.	1	2
89	36	.	.	.	0		34	1	.	.	1		37	1	.	.	1	39	1	.	1	2
90	36	.	.	1	1		33	1	.	.	1		36	1	.	.	1	37	.	.	2	2
91	35	1	.	.	1		32	1	.	1	2		35	1	.	2	3	35	3	.	.	3
92	34	.	1	1	2		30	.	.	.	0		32	1	.	1	2	32	1	.	3	4
93	32	.	.	.	0		30	.	.	.	0		30	.	.	.	0	28	1	.	2	3
94	32	1	.	.	1		30	.	.	4	4		30	.	.	.	0	25	1	.	.	1
95	31	1	.	.	1		26	.	.	1	1		30	.	.	.	0	24	.	.	.	0
96	30	.	.	.	0		25	2	.	.	2		30	.	.	2	2	24	.	.	1	1
97	30	.	.	1	1		23	.	.	.	0		28	.	.	.	0	23	1	.	1	2
98	29	1	.	.	1		23	.	.	1	1		28	1	.	.	1	21	1	.	.	1
99	28	.	.	.	0		22	.	.	.	0		27	1	.	.	1	20	1	.	.	1

Carcinogenicity Study in Rats - Summary of Survival and Fate of Animals (Continued)

Sex: Male																					
Dose	0 mg/kg/day						0.25 mg/kg/day						2.5 mg/kg/day						75 mg/kg/day				
Week	E	D	A	K	N		E	D	A	K	N		E	D	A	K	N		E	D	A	K	N
100	28	.	.	.	0		22	.	1	2	3		26	.	.	.	0		19	1	.	.	1
101	28	.	.	1	1		19	.	.	.	0		26	1	.	.	1		18	.	.	2	2
102 #	27	.	.	2	13		19	.	.	.	10		25	.	.	.	11		16	.	.	1	12
103 #	14	.	.	.	14		9	.	.	.	9		14	.	.	.	14		4	.	.	.	4

Carcinogenicity Study in Rats - Summary of Survival and Fate of Animals (Continued)

Sex: Female																					
Dose	0 mg/kg/day						0.25 mg/kg/day						2.5 mg/kg/day						75 mg/kg/day				
Week	E	D	A	K	N		E	D	A	K	N		E	D	A	K	N		E	D	A	K	N
6	70	.	.	.	0		70	.	.	.	0		70	.	1	.	1		70	.	.	.	0
8	70	.	.	.	0		70	.	.	.	0		69	.	.	.	0		70	.	2	.	2
12	70	.	.	.	0		70	.	.	.	0		69	.	.	.	0		68	.	.	.	0
16	70	.	.	.	0		70	.	.	.	0		69	.	.	.	0		68	.	.	.	0
17	70	.	.	.	0		70	.	.	.	0		69	.	.	.	0		68	.	.	.	0
21	70	.	.	.	0		70	.	.	.	0		69	.	.	.	0		68	.	.	.	0
22	70	.	.	.	0		70	.	.	.	0		69	.	.	.	0		68	.	.	.	0
28	70	.	.	.	0		70	.	.	.	0		69	.	.	.	0		68	.	.	.	0
30	70	.	1	.	1		70	.	.	.	0		69	.	.	.	0		68	.	.	.	0
31	69	.	.	.	0		70	.	.	.	0		69	.	.	.	0		68	.	.	1	1
32	69	.	.	.	0		70	.	.	.	0		69	.	.	.	0		67	.	.	.	0
34	69	.	1	.	1		70	.	.	.	0		69	.	.	.	0		67	.	.	.	0
35	68	.	.	.	0		70	.	.	.	0		69	.	.	.	0		67	.	.	.	0
36	68	.	.	.	0		70	.	.	.	0		69	.	.	.	0		67	.	.	.	0
37	68	.	.	.	0		70	.	.	.	0		69	.	.	.	0		67	.	.	.	0
38	68	.	.	.	0		70	.	.	.	0		69	.	.	.	0		67	.	.	.	0
39	68	.	.	.	0		70	.	.	.	0		69	.	.	.	0		67	.	.	1	1
40	68	.	.	.	0		70	.	.	.	0		69	.	.	.	0		66	.	.	.	0
41	68	.	.	.	0		70	.	.	.	0		69	.	.	.	0		66	.	.	.	0
45	68	.	.	1	1		70	.	.	.	0		69	.	.	.	0		66	.	.	.	0
46	67	.	.	.	0		70	.	.	1	1		69	.	.	1	1		66	.	.	1	1
47	67	.	.	.	0		69	.	.	.	0		68	.	.	1	1		65	1	.	.	1
48	67	.	.	1	1		69	.	.	.	0		67	.	.	1	1		64	.	.	2	2
49	66	1	.	1	2		69	.	.	.	0		66	.	.	.	0		62	.	.	.	0
50	64	.	.	.	0		69	.	.	.	0		66	.	.	.	0		62	.	.	.	0
51	64	.	.	.	0		69	1	.	.	1		66	.	.	.	0		62	.	.	.	0

Carcinogenicity Study in Rats - Summary of Survival and Fate of Animals (Continued)

Sex: Female																						
Dose	0 mg/kg/day						0.25 mg/kg/day						2.5 mg/kg/day					75 mg/kg/day				
Week	E	D	A	K	N		E	D	A	K	N		E	D	A	K	N	E	D	A	K	N
52	64	.	.	.	0		68	.	.	1	1		66	.	.	1	1	62	.	.	.	0
53	64	.	.	1	1		67	.	.	3	3		65	.	.	.	0	62	.	.	.	0
54	63	.	.	.	0		64	.	.	.	0		65	.	.	.	0	62	.	.	1	1
55	63	.	.	.	0		64	.	.	1	1		65	.	.	.	0	61	.	.	1	1
56	63	.	.	.	0		63	.	.	.	0		65	1	.	.	1	60	.	.	.	0
57	63	.	.	.	0		63	.	.	.	0		64	1	.	.	1	60	1	.	.	1
58	63	.	.	.	0		63	.	.	1	1		63	.	.	.	0	59	.	.	.	0
59	63	.	.	1	1		62	.	.	1	1		63	.	.	1	1	59	.	.	1	1
60	62	.	.	.	0		61	.	.	1	1		62	.	.	.	0	58	.	.	.	0
61	62	1	.	.	1		60	.	.	.	0		62	.	.	.	0	58	.	.	.	0
62	61	.	.	1	1		60	.	.	1	1		62	.	.	.	0	58	.	.	.	0
63	60	.	.	2	2		59	.	.	2	2		62	.	.	.	0	58	.	.	.	0
64	58	.	.	1	1		57	.	.	1	1		62	.	.	.	0	58	.	.	.	0
65	57	.	.	.	0		56	1	.	1	2		62	1	.	1	2	58	.	.	1	1
66	57	.	.	2	2		54	.	.	.	0		60	.	.	.	0	57	.	.	1	1
67	55	.	.	.	0		54	.	.	.	0		60	.	.	.	0	56	.	.	.	0
68	55	.	.	1	1		54	1	.	.	1		60	.	.	2	2	56	.	.	4	4
69	54	.	.	1	1		53	.	.	3	3		58	.	.	.	0	52	.	.	2	2
70	53	.	.	.	0		50	.	.	1	1		58	1	.	2	3	50	.	.	.	0
71	53	.	.	.	0		49	.	.	2	2		55	.	.	.	0	50	.	.	2	2
72	53	.	.	1	1		47	.	.	.	0		55	.	.	.	0	48	.	.	.	0
73	52	.	.	1	1		47	1	.	1	2		55	.	.	3	3	48	.	1	.	1
74	51	.	.	1	1		45	.	.	2	2		52	.	.	.	0	47	.	.	1	1
75	50	.	.	2	2		43	.	.	.	0		52	.	.	.	0	46	1	.	3	4
76	48	.	.	4	4		43	.	.	2	2		52	.	.	2	2	42	1	.	.	1
77	44	.	.	1	1		41	.	.	.	0		50	.	.	2	2	41	.	.	.	0
78	43	.	.	1	1		41	.	.	1	1		48	.	.	2	2	41	.	.	.	0
79	42	.	.	.	0		40	.	.	1	1		46	.	.	1	1	41	.	.	.	0
80	42	.	.	.	0		39	.	.	1	1		45	.	.	1	1	41	.	.	.	0
81	42	.	.	1	1		38	.	.	2	2		44	.	.	4	4	41	.	.	1	1
82	41	1	.	1	2		36	.	.	2	2		40	.	.	1	1	40	.	.	3	3
83	39	.	.	.	0		34	.	.	1	1		39	.	.	3	3	37	1	.	.	1
84	39	.	.	1	1		33	.	.	.	0		36	.	.	1	1	36	.	.	.	0
85	38	.	.	2	2		33	.	.	2	2		35	.	.	1	1	36	.	.	2	2
86	36	.	.	.	0		31	.	.	.	0		34	.	.	.	0	34	.	.	.	0
87	36	.	.	1	1		31	.	.	1	1		34	.	.	4	4	34	.	.	2	2
88	35	.	.	.	0		30	.	.	.	0		30	.	.	.	0	32	.	.	1	1

Carcinogenicity Study in Rats - Summary of Survival and Fate of Animals (Continued)

Sex: Female																						
Dose	0 mg/kg/day						0.25 mg/kg/day						2.5 mg/kg/day					75 mg/kg/day				
Week	E	D	A	K	N		E	D	A	K	N		E	D	A	K	N	E	D	A	K	N
89	35	.	.	.	0		30	.	.	1	1		30	.	.	.	0	31	.	.	3	3
90	35	1	.	1	2		29	.	.	.	0		30	.	.	.	0	28	.	.	2	2
91	33	.	.	3	3		29	.	.	1	1		30	.	.	2	2	26	1	.	2	3
92	30	.	.	.	0		28	.	.	.	0		28	.	.	1	1	23	.	.	.	0
93	30	1	.	.	1		28	.	.	3	3		27	.	.	.	0	23	.	.	1	1
94	29	.	.	.	0		25	1	.	2	3		27	.	.	2	2	22	.	.	1	1
95	29	.	.	.	0		22	.	.	.	0		25	.	.	.	0	21	.	.	.	0
96	29	.	.	4	4		22	.	.	.	0		25	.	.	1	1	21	.	.	.	0
97	25	.	.	3	3		22	.	.	1	1		24	.	.	2	2	21	.	.	.	0
98	22	.	.	.	0		21	.	.	.	0		22	.	.	.	0	21	.	.	.	0
99	22	.	.	.	0		21	.	.	.	0		22	1	.	1	2	21	1	.	.	1
100	22	.	.	.	0		21	.	.	1	1		20	.	.	.	0	20	.	.	.	0
101 #	22	.	.	2	18		20	.	.	2	16		20	.	.	.	15	20	.	.	1	16
102 #	4	.	.	.	4		4	.	.	.	4		5	.	.	.	5	4	.	.	.	4

Key:
E = Number of animals entering period.
D = Animals found dead.
A = Animals with accidental death.
K = Animals killed moribund.
N = Animals necropsied.
# = Terminal kill.

APPENDIX 2 ADDITIONAL INFORMATION

The following reports have been reviewed within GlaxoSmithKline (GSK) and the information is considered to have no bearing on safety (however, the reports will be available upon request). These reports are not included in the study listing tables for the following reasons:

Report No. (Study No.)	Title	Reason for Exclusion from Study Listing Tables
FD2007/00175	Assessment of stability of GSK1265744 in dimethylsulfoxide.	Stability reports for formulations used in nonclinical studies.
RD2006/01784 (S41966)	GSK1265744A: Assessment of stability and homogeneity of GSK1265744A in 0.5% hydroxypropyl methylcellulose / 0.1% polyoxyethylenesorbitan monooleate Tween™ 80 in reverse osmosis treated water.	
RD2007/00581 (S42118)	GSK1265744B: Assessment of stability and homogeneity of GSK1265744B in 0.5% hydroxypropyl methylcellulose / 0.1% polyoxyethylenesorbitan monooleate Tween™ 80 in reverse osmosis treated water.	
RD2007/00711 (S42133)	GSK1265744B: Assessment of stability and homogeneity of suspensions of GSK1265744B in 0.5% hydroxypropyl methylcellulose / 0.1% polyoxyethylenesorbitan monooleate Tween™ 80 in reverse osmosis treated water.	
RD2009/00042 (S42406)	GSK1265744B: Assessment of stability of a solution of 0.04 mg GSK1265744/mL in 0.5% hydroxypropyl methylcellulose / 0.1% polyoxyethylenesorbitan monooleate Tween 80 in reverse osmosis treated water.	
RD2009/00788 (S42461)	GSK1265744B: Assessment of stability and homogeneity of micronized GSK1265744B in 0.5% hydroxypropylmethylcellulose / 0.1% polyoxyethylenesorbitan monooleate Tween™ 80 in reverse osmosis treated water.	
RD2010/00043 (S42601)	GSK1265744A: Assessment of stability and homogeneity of GSK1265744A in 2% w/v Polysorbate 20 (Tween™ 20), 2% w/v polyethylene glycol 3350 and 4.5% w/v Mannitol in Sterile Water for Injection.	

Report No. (Study No.)	Title	Reason for Exclusion from Study Listing Tables
2014N216504 (S43256G)	GSK1265744B (micronized): Assessment of stability of a solution of 0.02 mg/mL in 0.5% hydroxypropyl methylcellulose (w/v) / 0.1% polyoxyethylenesorbitan monooleate Tween™ 80 (w/v) in reverse osmosis treated water.	Stability reports for formulations used in nonclinical studies.
2018N379378	GSK1265744: 3-Week Tolerability and Pharmacokinetic Study in Male Rats Using Delivery Via Subdermal Implants.	The formulation used is not relevant to the current marketing application, and no new or unexpected toxicities were noted.
2020N432961	Evaluation of the Systemic Exposure of Potentially Long Acting Parenteral Formulations of GSK1265744A (Cabotegravir) Following Either Intramuscular or Subcutaneous Administration at a Target Dosage of Either 10,30 or 50 mg/kg in the Male Sprague-Dawley Rat. Study Number: N32017-33 and N32017-26.	
2019N406822	GSK1265744: 3-Month Intramuscular and Subcutaneous Toxicity Study in Rats	
2019N424917	GSK1265744B and Placebo Implants: Skin Sensitization Study (Maximization Method) in Guinea Pigs (ISO 10993-10).	

Early screening assays undertaken to identify pharmacological targets of opportunity, completed on multiple compounds during the candidate selection phase or to identify genotoxic impurities as well as GSK internal/status reports, have not been included in this listing of additional information. However, this information has been reviewed within GSK and is considered to have no bearing on safety.

MODULE 2.6.7. TOXICOLOGY TABULATED SUMMARY

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

1. TOXICOLOGY: OVERVIEW FOR CABOTEGRAVIR [ALSO CAB, GSK1265744]

Table 1.1 List of Single Dose Toxicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Dose escalation	Mouse (CD-1)	15M	Oral	B	10, 100, 1000, 2000	Single	No	GSK	RD2009/00691 (M42451)	m4.2.3.1
Toxicokinetic	Rat (Sprague Dawley) Rat (Sprague Dawley)	6M 6M	SC IM	A	10 10	Single	No	GSK	RD2009/00865 (R42469)	m4.2.3.1
Toxicokinetic	Rat (Sprague Dawley) Rat (Sprague Dawley)	3M 3M	SC IM	A	10, 30, 50 5, 10, 35	Single	No	GSK	RD2009/00906 (R42473)	m4.2.3.1
Toxicokinetic	Rat (Sprague Dawley) Rat (Sprague Dawley)	3M 3M	SC IM	A	10, 30, 50 5, 10, 35	Single	No	GSK	RD2009/01216 (R42506)	m4.2.3.1
Single dose	Rat (Sprague Dawley) Rat (Sprague Dawley)	10M/10F 10M/10F	SC IM	A	10, 30, 100 2.5, 10, 75	Single	Yes	GSK	RD2009/01359 (R42516)	m4.2.3.1
Toxicokinetic	Monkey (cynomolgus) Monkey (cynomolgus)	4M 4M	SC IM	A	1, 5 1, 5	Single	No	GSK	CD2009/00373 (D09052)	m4.2.3.1
Toxicokinetic	Monkey (cynomolgus) Monkey (cynomolgus)	4M 4M	SC IM	A	5 5	Single	No	GSK	CD2009/00513 (D09084)	m4.2.3.1

List of Single Dose Toxicity Studies Performed with CAB (Continued)

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Toxicokinetic	Monkey (cynomolgus)	4M 4M	SC IM	A	10 10	Single	No	GSK	CD2009/00656 (D09112)	m4.2.3.1
Dose escalation	Monkey (cynomolgus)	2M	Oral (gavage)	B	150, 300, 1000	Single	No	[redacted]	RD2007/01415 (E-265744-TF-006-R)	m4.2.3.1
Toxicokinetic	Monkey (cynomolgus)	2M 2M 4M	IM	A	10 (CAB) 60 (RPV) 10 CAB) + 60 (RPV)	Single	No	GSK	2010N105579 (8234628)	m4.2.3.1

Key:
a = Crossover design.
A = GSK1265744A, the parent form.
B = GSK1265744B, the sodium salt.

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

Table 1.2 List of Repeat Dose Toxicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
14 day	Mouse (CD-1)	10M/10F	Oral (gavage)	B	10, 75, **1000**	14 days	Yes	GSK	RD2009/00692 (M42452)	m4.2.3.2
13 week	Mouse (CD-1)	12M/12F	Oral (gavage)	B	10, **75**, 1000	13 weeks	Yes	[redacted]	2012N142081 (M42936)	m4.2.3.2
13 week	Rat (Sprague Dawley)	12M/12F	SC (monthly) IM (monthly) SC (weekly)	A	5, 30, **100** 2.5, 10, **75** **100**	13 weeks	Yes	[redacted]	2010N104820 (R42698)	m4.2.3.2
14 day	Rat (Sprague Dawley)	10M/10F[a]	Oral (gavage)	A	30, 100, **300**	14 days	Yes	GSK	RD2006/01741 (R41937)	m4.2.3.2
4 week	Rat (Sprague Dawley)	10M/10F[b]	Oral (gavage)	B	1, 75, **1000**	4 weeks	Yes	GSK	RD2008/00448 (R42288)	m4.2.3.2
26 week	Rat (Sprague Dawley)	12M/12F[b]	Oral (gavage)	B	0.5, 5, **1000**	26 weeks	Yes	GSK	RD2009/00031 (R42404)	m4.2.3.2
7 day	Monkey (cynomolgus)	1M/1F	Oral (gavage)	B	50, 150, 1000	7 days	No	GSK	CD2007/00577 (D07170)	m4.2.3.2
14 day	Monkey (cynomolgus)	3M/3F	Oral (gavage)	B	8, **25**, 1000	14 days	Yes	GSK	CD2007/00680 (G07171)	m4.2.3.2

List of Repeat Dose Toxicity Studies Performed with CAB (Continued)

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
4 week	Monkey (cynomolgus)	3M/3F[c]	Oral (gavage)	B	5, 50, **500**	4 weeks	Yes	GSK	CD2008/00632 (G08079)	m4.2.3.2
39 week	Monkey (cynomolgus)	4M/4F[d]	Oral (gavage)	B	5, 50, **500**	39 weeks	Yes	[redacted]	RD2009/00027 (P42405)	m4.2.3.2

Key:
a = An additional 3/sex/group were added for toxicokinetic evaluation.
b = An additional 6/sex/group were added at 1000 mg/kg/day as 2 week recovery animals.
c = An additional 2/sex/group were added at 500 mg/kg/day as 6 week recovery animals.
d = An additional 2/sex/group were added at 500 mg/kg/day as 6 week recovery animals.
A = GSK1265744A, the free acid. B = GSK1265744B, the sodium salt.
Note: No observed adverse effect levels (NOAELs) values are in **bold** type.

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

Table 1.3 List of Genotoxicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
CAB										
Ames test	NA	NA	In vitro	B	1.5 to 238 μg/plate[a]	NA	Yes	[redacted]	WD2007/00787 (V27580)	m4.2.3.3.1
Screening mouse lymphoma assay	NA	NA	In vitro	A	2 to 140 μg/mL[b]	NA	No	GSK	WD2007/01740 (MLA-600)	m4.2.3.3.1
Mouse lymphoma assay	NA	NA	In vitro	B	4 to 23.8 μg/mL[a]	NA	Yes	[redacted]	WD2007/00788 (V27561)	m4.2.3.3.1
Micronucleus	Rat (Sprague Dawley)	6M[c]	Oral (gavage)	B	1000, 2000	2 days	Yes	[redacted]	WD2007/00789 (R27562)	m4.2.3.3.2
Impurities[d]										
Ames test with gsk004*	NA	NA	In vitro	NA	Up to 5000 μg/plate	NA	No	GSK	2014N213336 (Ames-2047)	m4.2.3.3.1

Key:
a = Dose limited by solubility.
b = Dose limited by cytotoxicity.
c = Doses of 500, 1000 and 2000 mg/kg/dose and 3 rats/sex/group were used in the dose range finding test.
d = Listing of potential impurities that were negative for genotoxicity is provided in m2.6.6, Table 4.2.
A = GSK1265744A, the parent form.
B = GSK1265744B, the sodium salt.
NA = Not applicable.

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

*新薬承認情報提供時に置き換え

Table 1.4 List of Carcinogenicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Carcinogenicity	Mouse (CD-1)	60 9[TKa] 42[TKb]	Oral	B	M: 2.5, 10 or 75 F: 2.5, 5 or 35	104 weeks	Yes	[redacted]	2017N310750 (M30877G)	m4.2.3.4.1
Carcinogenicity	Rat (Sprague Dawley)	70 3 (TK all groups)	Oral	B	0.25, 2.5 or 75	104 weeks	Yes	[redacted]	2017N310751 (R30876G)	m4.2.3.4.1

Key:
B = CAB sodium salt.
TKa = Satellite groups for toxicokinetics analysis in vehicle control.
TKb = Satellite groups for toxicokinetics analysis in CAB dose groups.
M = Male.
F = Female.

Testing Facility:
[redacted] = [redacted]

Table 1.5 List of Reproductive and Developmental Toxicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Male fertility	Rat (Sprague Dawley)	25M	Oral (gavage)	B	0.5, 5, **1000**	64 to 66 days[a]	Yes	[redacted]	2014N207479 (R70481G)	m4.2.3.5.1
Female fertility & Embryofetal development	Rat (Sprague Dawley)	25F	Oral (gavage)	B	0.5, **5** 1000	2 weeks prior to mating, during mating and up to Day 17 pc, inclusive	Yes	GSK	CD2009/00105 (G08284)	m4.2.3.5.1
Dose range study	Rabbit (Dutch Belted, pregnant)	4F	Oral (gavage)	B	30, 250, 500, 1000, 2000[b]	13 days (Days 7 to 19 pc)	No	GSK	CD2008/01276 (D08251)	m4.2.3.5.2
Embryofetal development	Rabbit (Dutch Belted, pregnant)	22F	Oral (gavage)	B	30, 500, and **2000**	13 days (Days 7 to 19 pc)	Yes	GSK	CD2009/00842 (G08307)	m4.2.3.5.2
Pre- & post-natal development	Rat (Sprague Dawley)	24F	Oral (gavage)	B	0.5, **5**, 1000[c]	Day 6 pc to Day 20 pp	Yes	[redacted]	2015N236973 (R70586G)	m4.2.3.5.3
Investigative pre- & post-natal development	Rat (Sprague Dawley)	48F	Oral (gavage)	B	1000	Gestation Day 6 to Lactation Day 7	No	[redacted]	2016N281797 (R70909N)	m4.2.3.5.3

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

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Investigative Toxicokinetic Study	Rat (Sprague Dawley)	8F	Oral (gavage)	B	5, 1000	Gestation Day 6 and Gestation Day 6 to 20	No	[redacted]	2017N311115 (R71069N)	m4.2.3.5.3

Key:
a = Rats were dosed 15 days prior to co-habitation, through two co-habitation periods to Days 64 to 66.
b = The 2000 mg/kg/day dose was administered as a single dose and as a twice daily (BID) dose of 1000 mg/kg/dose.
c = The NOAEL for maternal reproductive function was 1000 mg/kg/day.
B = GSK1265744B, the sodium salt. pc = Post coitum.
Note: No observed adverse effect levels (NOAELs) values are in **bold** type.

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

Table 1.6 List of Local Tolerance Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Skin irritancy study	Reconstituted human skin (SkinEthic™)	NA	In vitro	16 mg/site	Up to 42 minutes	Yes	[redacted]	2019N396399 (41501616)	m4.2.3.6
Ocular irritancy study	Reconstituted human corneal model (SkinEthic™)	NA	In vitro	30 mg/site	10 or 60 minutes	Yes	[redacted]	2019N396400 (41501617)	m4.2.3.6
Local lymph node assay	Mouse (CBA/Ca)	5F	Topical	25% (25 μL/ear)	3 days	Yes	[redacted]	2019N396237 (41501619)	m4.2.3.6

Key:
All local tolerance studies were performed using the sodium salt of CAB.

Testing Facility:
[redacted] = [redacted]

Table 1.7 List of Other Toxicity Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Immunotoxicity	Rat (Sprague Dawley)	40	Oral	B	0.5, 5 or 1000	28 days	Yes	[redacted]	2013N179070	m4.2.3.7.2
Immunotoxicity	Rat (Sprague Dawley)	10	Oral	B	5 or 1000	39 days	No	[redacted]	2018N367799	m4.2.3.7.2

Key:
B = Sodium salt.

Testing Facility:
[redacted] = [redacted]

2. TOXICOKINETICS: OVERVIEW OF TOXICOKINETICS STUDIES

Table 2.1 Toxicokinetics: Overview of Toxicokinetics Studies for CAB

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Report No. (Study No.)	Location in CTD
Toxicokinetics – Single dose	Mouse (CD-1)	Oral (gavage)	10, 100, 1000, 2000	No	RD2009/00691 (M42451)	m4.2.3.1
Toxicokinetics – Single dose	Rat (Sprague Dawley)	Oral (gavage)	3, 30, 300, 1000	No	RD2008/00200 (R42257)	m4.2.2.2
Toxicokinetics – Single dose	Rat (Sprague Dawley)	Oral (gavage)	1000	No	RD2008/01308 (R42353)	m4.2.2.2
Toxicokinetics – Single dose	Rat (Sprague Dawley)	SC IM	10	No	RD2009/00865 (R42469)	m4.2.3.1
Toxicokinetics – Single dose	Rat (Sprague Dawley)	SC IM	10, 30, 50 5, 20, 35	No	RD2009/00906 (R42473)	m4.2.3.1
Toxicokinetics – Single dose	Rat (Sprague Dawley)	SC IM	10, 30, 50 5, 20, 35	No	RD2009/01216 (R42506)	m4.2.3.1
Toxicokinetics – Single dose	Rat (Sprague Dawley)	SC IM	5, 30, 100 2.5, 10, 75	Yes	RD2009/01359 (R42516)	m4.2.3.1
Toxicokinetics – Single dose	Monkey (cynomolgus)	Oral (gavage)	150, 300, 1000	No	RD2007/01415 (E-265744-TF-006-R)	m4.2.3.1
Toxicokinetics – Single dose	Monkey (cynomolgus)	Oral (gavage)	500	No	CD2008/01223 (D08226)	m4.2.2.2
Toxicokinetics – Single dose	Monkey (cynomolgus)	SC IM	1, 5 1, 5	No	CD2009/00373 (D09052)	m4.2.3.1
Toxicokinetics – Single dose	Monkey (cynomolgus)	SC IM	5 5	No	CD2009/00513 (D09084)	m4.2.3.1
Toxicokinetics – Single dose	Monkey (cynomolgus)	SC IM	10 10	No	CD2009/00656 (D09112)	m4.2.3.1

Toxicokinetics: Overview of Toxicokinetics Studies for CAB (Continued)

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Report No. (Study No.)	Location in CTD
Toxicokinetics – Single dose	Monkey (cynomolgus)	IM	10	No	2010N105579 ([redacted])	m4.2.3.1
Toxicokinetics – Repeat dose	Mouse (CD-1)	Oral (gavage)	10, 75, 1000	Yes	RD2009/00692 (M42452)	m4.2.3.2
Toxicokinetics – Repeat dose	Rat (Sprague Dawley)	Oral (gavage)	30, 100, 300	Yes	RD2006/01741 (R41937)	m4.2.3.2
Toxicokinetics – Repeat dose	Rat (Sprague Dawley)	Oral (gavage)	1, 75, 1000	Yes	RD2008/00448 (R42288)	m4.2.3.2
Toxicokinetics – Repeat dose	Rat (Sprague Dawley)	SC (monthly) IM (monthly) SC (weekly)	5, 30, 100 2.5, 10, 75 100	Yes	2010N104820 (R42698)	m4.2.3.2
Toxicokinetics –Repeat dose	Rat (Sprague Dawley)	Oral (gavage)	0.5, 5, 1000	Yes	RD2009/00031 (R42404)	m4.2.3.2
Toxicokinetics – Reproductive and Developmental Toxicity	Rabbit (Dutch Belted)	Oral (gavage)	30, 250, 500, 1000, 2000	No	CD2008/01276 D08251	m4.2.3.5.2
Toxicokinetics – Reproductive and Developmental Toxicity	Rabbit (Dutch Belted)	Oral (gavage)	30, 500, 2000	Yes	CD2009/00842 (G08307)	m4.2.3.5.2
Toxicokinetics –Repeat dose	Monkey (cynomolgus)	Oral (gavage)	50, 150, 1000	No	CD2007/00577 (D07170)	m4.2.3.2
Toxicokinetics – Repeat dose	Monkey (cynomolgus)	Oral (gavage)	8, 25, 1000	Yes	CD2007/00680 (G07171)	m4.2.3.2
Toxicokinetics – Repeat dose	Monkey (cynomolgus)	Oral (gavage)	5, 50, 500	Yes	CD2008/00632 (G08079)	m4.2.3.2
Toxicokinetics –Repeat dose	Monkey (cynomolgus)	Oral (gavage)	5, 50, 500	Yes	RD2009/00027 (P42405)	m4.2.3.2

3. TOXICOKINETICS: OVERVIEW OF TOXICOKINETICS DATA

Table 3.1 Mean Toxicokinetics Data for CAB at Steady State [AUC_{0-t} (μg.h/mL)]

Daily Dose (mg/kg/day)	Mouse		Rat		Rabbit	Monkey		Human
	Male	Female	Male	Female	Female	Male	Female	
0.5			451 [d]	675 [d]				
1			739 [c]	852 [c]				
2.5			7031 [#, h]	5500 [#, h]				
5			1861 [d]	2083 [d]		100 [c]	80.9 [c]	
5						37.7 [e]	67.8 [e]	
8						144 [b]	124 [b]	
10	552 [a]	691 [a]	26001 [#, h]	24934 [#, h]				
25						233 [b]	231 [b]	
30			1849 [b]	1605 [b]	10.5 [f]			146 [g]
50						276 [c]	279 [c]	
50						229 [e]	254 [e]	
75	1330 [a]	1360 [a]	3000 [c]	3832 [c]				
75			78051 [#, h]	107080 [#, h]				
100			2223 [b]	2435 [b]				
300			2510 [b]	3277 [b]				
400								2461 [#, i]

Mean Toxicokinetics Data for CAB at Steady State [AUC_{0-t} (μg.h/mL)] (Continued)

Daily Dose (mg/kg/day)	Mouse		Rat		Rabbit	Monkey		Human
	Male	Female	Male	Female	Female	Male	Female	
500					47.4 [f]	901 [c]	904 [c]	
500						542 [e]	552 [e]	
1000	2150 [a]	2430 [a]	3345 [c]	4125 [c]		* [,b]	946 [b]	
1000			3203 [d]	4781 [d]				
2000					96.1 [f]			

Note: All data are from oral daily administration of CAB (AUC_{0-24}), except where noted with #, which are data from IM monthly CAB (AUC_{0-t}).

Key:

= Data are from IM administered CAB.

* = AUC_{0-24} could not be calculated because the dose group was euthanized following the 4 hour sample collection time point.

a = 13 weeks dosing in mice (Report 2012N142081). AUC data from the end of the study.

b = 14 days dosing in rats and monkeys (Reports RD2006/01741 and CD2007/00680, respectively). AUC data from the end of the study.

c = 4 weeks dosing in rats and monkeys (Reports RD2008/00448 and CD2008/00632, respectively). AUC data from the end of the study.

d = 26 weeks dosing in rats (Report RD2009/00031). AUC data from the end of the study.

e = 39 weeks dosing in monkeys (Report RD2009/00027). AUC data from the end of the study.

f = Day 11 postcoitum, or dosing Day 5, in pregnant rabbits (Report CD2009/00842). AUC data from the end of the study.

g = Human data for a 30 mg oral dose given daily (Report 2018n384611).

h = 3 months IM dosing, once monthly, in rats (Report 2010n104820). AUC reported for the 3rd monthly interval, $AUC_{1440-2160h}$.

i = Human data for a 400 mg IM monthly dose (Report 2018n384611).

4. TOXICOLOGY: DRUG SUBSTANCE

Table 4.1 Toxicology: Drug Substance for CAB

Batch Number	Purity	Specified Impurities (% w/w)						Report Number	Type of Study
	(% w/w)	gsk006*	gsk007*	gsk005*	gsk002*	gsk001*	gsk003*		
PROPOSED SPECIFICATION		Not more than 0.15 for each impurity							
[redacted]	100 [a]	<0.15	<0.15	<0.15	<0.15	<0.1	<0.1	RD2008/00448	Repeat Dose Toxicity
								CD2008/00632	Repeat Dose Toxicity
[redacted]	97.9	<0.15	<0.15	<0.15	<0.15	ND	<0.05	RD2009/00692	Repeat Dose Toxicity
								2012N142081	Repeat Dose Toxicity
								RD2009/00031	Repeat Dose Toxicity
								RD2009/00027	Repeat Dose Toxicity
								CD2009/00105	Reproductive Toxicity
								CD2009/00842	Reproductive Toxicity
[redacted]	100.1	<0.15	<0.15	<0.15	<0.15	<0.1	<0.1	WD2007/00787	Genotoxicity
								WD2007/00788	Genotoxicity
								WD2007/00789	Genotoxicity
								CD2007/00268	Safety Pharmacology
								FD2007/00242	Safety Pharmacology
								CD2007/00707	Safety Pharmacology
[redacted]	99.2	≤0.15	≤0.15	≤0.15	≤0.15	ND	ND	2014N207479	Reproductive Toxicity
[redacted]	99.1	≤0.15	≤0.15	≤0.15	≤0.15	ND	ND	2013N179070	Immunotoxicity

*新薬承認情報提供時に置き換え

Toxicology: Drug Substance for CAB (Continued)

Batch Number	Purity	Specified Impurities (% w/w)						Report Number	Type of Study
	(% w/w)	gsk006*	gsk007*	gsk005*	gsk002*	gsk001*	gsk003*		
PROPOSED SPECIFICATION		Not more than 0.15 for each impurity							
[redacted]	99.8	≤0.15	≤0.15	≤0.15	≤0.15	ND	<0.05	2017N310750	Carcinogenicity
								2017N310751	Carcinogenicity
								2015N236973	Reproductive Toxicity
[redacted]	98.3	NT	NT	NT	NT	<0.05	0.59	RD2006/01741	Safety Pharmacology
[redacted] [b]	99.8	<0.05	<0.05	<0.05	<0.05	ND	ND	2010N104820	Repeat Dose Toxicity

Key:
a = Purity determined by calculation, otherwise purity determined by HPLC or external standard assay.
b = The only batch shown for CAB free acid (all other batches listed are CAB sodium salt). As a result, all impurities for this one batch have the "A" suffix, representing the free acid and thus the absence of the sodium salt.
NT = Not tested.
ND = Not detected.
gsk006* = gsk006*; gsk007* = gsk007*; gsk005* = gsk005*; gsk002* = gsk002*; gsk001* = gsk001*; gsk003* = gsk003*.

*新薬承認情報提供時に置き換え

5. SINGLE DOSE TOXICITY

Table 5.1 Single Dose Toxicity

Species/ Strain	Route: (Vehicle/ Formulation) [a]	Doses [a] (mg/kg)	Number of Animals/ Sex	Noteworthy Findings	Report/ Study No. (Module)
Mouse/ Crl:CD1(ICR)	Oral gavage/ (0.5% w/w HPMC/0.1% Tween 80 solution/ suspension)	10 100 1000 2000	15 15 15 15	One mouse given 2000 mg/kg had clinical signs of decreased activity and irregular breathing shortly after dosing. The hepatocellular necrosis noted microscopically in this animal was of uncertain relationship to test article administration. The systemic exposure (C_{max} and AUC_{0-24}) of GSK1265744 increased less than proportionally with the increase in dose. There was no difference in systemic exposure following the 2000 mg/kg dose compared to that after the 1000 mg/kg dose.	RD2009/00691 / M42451 (m4.2.3.1)
Rat/ Crl:CD (SD)	SC or IM injection: [Wet bead-milled suspensions in aqueous 1.7% (w/v) polyvinylpyrrolidone (PVP)/0.2% (w/v) polysorbate 80/ 0.18% (w/v) methylparaben/0.02% (w/v) propylparaben/ 0.004 M NaH_2PO_4 H_20/ 0.006 M Na_2HPO_4 with NaCl or aqueous 2% (w/w) pluronic F127/0.2% (w/v) polysorbate 80/0.18% (w/v) methylparaben/ 0.02% (w/v) propylparaben/0.004 M NaH_2PO_4 H_20/0.006 M Na_2HPO_4 with NaCl]	0 10 10	3[b] 6[c] 6[d]	The cause of mortality for one rat given the 10 mg/kg PVP formulation found dead on Day 44 was a neoplasm and its secondary effects and was not considered test article related. An increased severity (mild to moderate) of myocardial degeneration/necrosis (compared with concurrent control rats) was noted in one rat given the 10 mg/kg PVP formulation SC and one rat given the 10 mg/kg PVP formulation IM and was considered unlikely related to administration of the PVP formulation and GSK1265744. Injection site irritation manifested as minimal to moderate subcutaneous inflammation (predominately granulomatous) observed at the 10 mg/kg PVP formulation SC injection sites and as minimal degeneration and/or regeneration of the muscularis layer of subcutaneous tissue in one rat given the 10 mg/kg PVP formulation SC, and as minimal chronic inflammation of the adipose tissue in one rat given 10 mg/kg pluronic F formulation IM. Both GSK1265744 formulations achieved similar values for AUC_{0-t} by either route of administration, although the C_{max} was greater and was achieved faster with the pluronic F formulation than with the PVP formulation and was greater with IM administration than with SC administration.	RD2009/00865 / R42469 (m4.2.3.1)

Single Dose Toxicity (Continued)

Species/ Strain	Route: (Vehicle/ Formulation) [a]	Doses [a] (mg/kg)	Number of Animals/ Sex	Noteworthy Findings	Report/ Study No. (Module)
				On Day 64, the blood concentrations after administration of the PVP formulation were approximately 15-fold greater by the SC route and 7-fold greater by the IM route than the protein-adjusted concentration for 90% inhibition (PAIC90) of the human immunodeficiency virus, whereas GSK1265744 concentrations with the pluronic F formulation after SC and IM administration were less than or similar to the $PAIC_{90}$.	
Rat/ Crl:CD(SD)	SC or IM injection: 2% pluronic F127, 0.2% polysorbate 80, 0.18% methylparaben, 0.02% propylparaben, 0.004M sodium phosphate dibasic (NaH2PO4), 0.006M sodium phosphate monobasic (Na2HPO4) and 0.83% NaCl at a pH of 6.4	0 SC, IM 10 SC 30 SC 50 SC 5 IM 20 IM 35 IM	3 3 3 3 3 3 3	All doses by all routes of administration were well tolerated. The apparent plasma half-life of GSK1265744 following the SC and IM doses ranged from 200 to 227 hours and from 204 to 218 hours, respectively. There was no apparent difference in plasma half-life values between the dose routes, or among the dose levels.	RD2009/00906 / R42473 (m4.2.3.1)
Rat/ Crl:CD(SD)	SC or IM injection: 2% Tween 20, 2% polyethylene glycol 3350, and 4.5% mannitol in water	0 SC & IM 10 SC 30 SC 50 SC 5 IM 20 IM 35 IM	3 3 3 3 3 3 3	Swelling around the injection site occurred in one animal given 10 mg/kg SC and one animal given 50 mg/kg SC. Discoloration around the injection site occurred in one animal given 35 mg/kg IM. Slightly decreased body weights were noted in rats receiving the 50 mg/kg SC dose. Following the SC dose, plasma concentrations of GSK1265744 remained above the $PAIC_{90}$ of 0.16 μg/mL through the last time point (Day 106) for every animal. Following the IM dose, plasma concentrations remained above 0.16 μg/mL through the last time point of Day 106 in all 3 animals that received 20 mg/kg, and in 2 of the 3 animals that received 35 mg/kg. Following 5 mg/kg, the plasma concentrations remained above 0.16 μg/mL to Day 71.	RD2009/01216 / R42506 (m4.2.3.1)

Single Dose Toxicity (Continued)

Species/ Strain	Route: (Vehicle/ Formulation) [a]	Doses [a] (mg/kg)	Number of Animals/ Sex	Noteworthy Findings	Report/ Study No. (Module)
Monkey/ Cynomolgus	SC or IM injection: 1.7% PVP, 0.2% Tween 80, 0.18% methylparaben, 0.02% propylparaben, 0.004M monosodium phosphate, 0.006M disodium phosphate, and 0.84% sodium chloride in sterile water for injection, with an approximate final pH 6.8/ suspension	0 SC 0 IM 1 and 5 SC [e] 1 and 5 IM [e]	1 1 4 4	All doses were well-tolerated with no test article-related findings and no clinical observations at the injection sites. Plasma concentrations were quantifiable up to 816 and 1032 hours after dosing for monkeys given 1 and 5 mg/kg, respectively. Systemic exposure increased less than proportionally with increasing dose but was similar between SC and IM routes of administration at the same dose.	CD2009/00373 / D09052 (m4.2.3.1)
Monkey/ Cynomolgus	SC or IM injection: 1.7% polyvinylpyrrolidone (PVP), 2% Polysorbate 80, 0.18% methylparaben, 0.02% propylparaben, 0.004M monosodium phosphate, 0.006M disodium phosphate, and 0.84% sodium chloride in sterile water for injection, with an approximate final pH 6.8/ suspension.	0 SC 0 IM 5 SC 5 IM	1M 1M 4M 4M	All doses were well-tolerated with no test article-related findings and no clinical observations at the injection sites. Plasma concentrations were quantifiable up to 1344 hours in the SC and IM groups. Systemic exposure was generally higher via the IM route as compared to SC administration at 5 mg/kg.	CD2009/00513 / D09084 (m4.2.3.1)
Monkey/ Cynomolgus	SC or IM injection: 2% Pluronic F-127, 0.2% Polysorbate 80, 0.18% methylparaben, 0.02% propylparaben, 0.008M $NaH_2PO_4H_2O$, 0.006M Na_2HPO_4 and 0.81% NaCl, pH adjusted to 6.6/ suspension.	0 SC 0 IM 10 SC 10 IM	1M 1M 4M 4M	Observations of skin thickening and presence of a mass were noted at the injection sites in monkeys given 10 mg/kg via both SC and IM routes. Subcutaneous granulomatous inflammation was observed within the skin biopsy of a persistent injection site mass in 1 monkey given 10 mg/kg SC. Overall, mean C_{max} via the IM route was higher than via the SC route at a dose of 10 mg/kg. On approximately Day 49, plasma concentrations were approaching the protein-adjusted 90% inhibitory concentration ($PAIC_{90}$) of 166 ng/mL in the SC group and were below the $PAIC_{90}$ in the IM group.	CD2009/00656 / D09112 (m4.2.3.1)

Single Dose Toxicity (Continued)

Species/ Strain	Route: (Vehicle/ Formulation) [a]	Doses [a] (mg/kg)	Number of Animals/ Sex	Noteworthy Findings	Report/ Study No. (Module)
Monkey/ Cynomolgus	Oral: 0.5% w/w HPMC with 0.1% w/w Tween 80 aqueous solution	150 (Oral) 300 (Oral) 1000 (Oral)	2M 2M 2M	No CAB-related changes were evident in body weights, food consumption, hematology, or clinical chemistry at doses ≤1000 mg/kg.	RD2007/01415 E-265744-TF-006-R (m4.2.3.1)
Monkey/ Cynomolgus	IM injection: CAB - % Tween 20, 2% polyethylene glycol 3350 and 4.5% mannitol in sterile water for injection Rilpivirine (RPV) – proprietary formulation provided by Janssen.	10 (CAB) 60 (RPV) CAB + RPV (10 + 60)	2M 2M 4M	CAB was well tolerated throughout the study. RPV caused slight edema on Day 4 in 1 animal given RPV alone and in one animal given both CAB and RPV. Both CAB and RPV were well tolerated after a single dose administration.	2010N105579 8234628 (m4.2.3.1)

Key:
Oral studies were conducted using the sodium salt form of CAB and the injection studies used the free acid form.
$PAIC_{90}$ = Protein adjusted concentration for 90% inhibition of the human immunodeficiency virus.
SC = subcutaneous; IM = intramuscular; RPV = rilpivirine.
a = Dose levels are expressed in terms of the free acid.
b = One group of 3 rats was given the PVP vehicle by the SC and IM routes and another group of 3 rats was given the pluronic F vehicle by the SC and IM routes.
c = One group of 6 rats was given the PVP formulation by the SC route and another group of 6 rats by the IM route.
d = One group of 6 rats was given the pluronic F formulation by the SC route and another group of 6 rats by the IM route.
e = A dose of 1 mg/kg was administered on Day 1 and a dose of 5 mg/kg was delivered to the same monkeys on Day 43.

Table 5.2 CAB: Single Dose Subcutaneous and Intramuscular Toxicity Study in Rats Followed by at least a 74 Day Non-Treatment Period

Study Type: Single Dose Toxicity	**Report Title:** GSK1265744A: Single Dose Subcutaneous and Intramuscular Toxicity Study in Rats Followed by at least a 74 Day Non-Treatment Period	**Test Article:** GSK1265744A (parent compound) **Batch No.:** [redacted]
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** 1 day **Duration of Non-Treatment:** 75 to 76 days for Groups 1 (1st 5 rats/sex) and 5 to 7 84 to 85 days for Groups 1 (last 5 rats/sex) and 2 to 4	**Study No.:** R42516
Initial Age: Approximately 11 weeks	**Route/Frequency:** Subcutaneous and/or intramuscular / once	**GSK Document Number:** RD2009/01359
Date of Dosing: 21 January 2010	**Vehicle/Formulation:** 2% Polysorbate 20 (Tween™ 20), 2% polyethylene glycol 3350 and 4.5% Mannitol in Sterile Water for Injection, w/v	**CTD Module:** m4.2.3.1 **Study in Compliance with GLP:** Yes

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

Conclusion: There were no adverse effects noted at any dose; therefore, the no observed adverse effect levels (NOAEL) are 100 mg/kg for the SC injection and 75 mg/kg for the IM injection or greater. The systemic exposure for 100 mg/kg SC (gender averaged) is 162 μg.h/mL for mean AUC_{0-24} (range 86.8 to 266 μg.h/mL), 49508 μg.h/mL for mean AUC_{0-720} (range 38207 to 64474 μg.h/mL), 122300 μg.h/mL for mean AUC_{0-t} (range 98352 to 147837 μg.h/mL) and 101 μg/mL for mean C_{max} (range 78.4 to 133 μg/mL). The systemic exposure for 75 mg/kg IM (gender averaged) is 286 μg.h/mL for mean AUC_{0-24} (range 217 to 336 μg.h/mL), 62418 μg.h/mL for mean AUC_{0-720} (range 53582 to 70666 μg.h/mL), 96487 μg.h/mL for mean AUC_{0-t} (range 71166 to 121669 μg.h/mL) and 115 μg/mL for mean C_{max} (range 95.3 to 141 μg/mL). Test article-related injection site irritation/reactions were observed at the SC injection site of rats given ≥5 mg/kg (at doses ≥30 mg/kg histopathologically) and at the IM injection site of rats given 75 mg/kg. Minimal, non-specific test article-related changes were noted for a few clinical chemistry and urinalysis parameters.

CAB: Single Dose Subcutaneous and Intramuscular Toxicity Study in Rats Followed by at least a 74 Day Non-Treatment Period (Continued)

Study Type: Single Dose Toxicity **Study No.:** R42516

Daily Dose (mg/kg)[1]		**0 (SC and IM)**	**5 (SC)**	**30 (SC)**	**Male 100 (SC)**	**2.5 (IM)**	**10 (IM)**	**75 (IM)**
Numbers of Animals:	Main	10	10	10	10	10	10	10
	Toxicokinetic	3	3	3	3	3	3	3
AUC_{0-24} (μg.h/mL):		NA	34.9	79.5	147	86.9	164	278
AUC_{0-720} (μg.h/mL):		NA	4346	19978	47912	4321	15926	60071
AUC_{0-t} (μg.h/mL):		NA	8607	41284	117641	4617	19110	92117
C_{max} (μg/mL):		BLQ	8.36	38.7	98.3	12.6	32.4	105
Noteworthy Findings:								
Unscheduled Deaths:		0	0	0	1[2]	0	0	0
Clinical Observations:		No test article-related clinical observations were noted.						
Skin Irritation:		Very slight to well defined erythema was observed in up to 3 males given ≥30 mg/kg SC. Very slight to moderate edema was noted in up to 10 males given ≥5 mg/kg SC and very slight edema was observed in 2 males given 75 mg/kg IM. Very slight edema noted for males given 30 mg/kg and very slight to well defined edema noted for males given 100 mg/kg SC remained until termination. Generally, the number of rats affected, duration, and severity of erythema and edema increased in a dose-dependent manner for rats given ≥5 mg/kg SC.						
Body Weight:		No test article-related changes were noted.						
Food Consumption:		No test article-related changes were noted.						
Hematology:		No test article-related changes were noted.						
Coagulation:		No test article-related changes were noted.						
Clinical Chemistry:								
Calcium (mmol/L)	Week 4	2.312	2.333	2.358	2.330	2.342	2.340	2.341
	Weeks 13 (SC) or 11 (IM)	2.404	2.461	2.513	2.457	2.387	2.417	2.376
Total bilirubin (μmol/L)	Week 4	3.13	2.48*	2.36*	1.91**	2.65	2.78	1.98**
	Weeks 13 (SC) or 11 (IM)	2.30	1.90*	1.95*	1.86*	2.15	2.96	2.13

CAB: Single Dose Subcutaneous and Intramuscular Toxicity Study in Rats Followed by at least a 74 Day Non-Treatment Period (Continued)

Study Type: Single Dose Toxicity **Study No.:** R42516

Daily Dose (mg/kg)[1]		**0 (SC and IM)**	**5 (SC)**	**30 (SC)**	**Male 100 (SC)**	**2.5 (IM)**	**10 (IM)**	**75 (IM)**
Urinalysis:								
Urine volume (mL)	Week 4	8.95	13.75	10.40	10.90	12.90	13.10	13.85
	Weeks 13 (SC) or 11 (IM)	10.65	11.20	11.75	12.10	11.10	14.10	13.50
Specific gravity	Week 4	1.0340	1.0335	1.0377	1.0335	1.0331	1.0316	1.0298
	Weeks 13 (SC) or 11 (IM)	1.0314	1.0347	1.0317	1.0307	1.0328	1.0263	1.0299
Organ Weights:		No test article-related organ weight changes were noted.						
Microscopic Examination (Number of Animals):		**10**	**10**	**10**	**10**	**9**	**10**	**10**
Injection Site								
Subcutis granuloma	Mild	0	0	4	1	0	0	0
	Moderate	0	0	1	7	0	0	0
Foreign material	Minimal	0	0	0	0	0	0	1
Chronic inflammation	Mild	0	0	0	0	0	0	1
Pigmented macrophages	Minimal	0	0	0	0	0	0	4

Daily Dose (mg/kg/day)[1]		**0 (SC and IM)**	**5 (SC)**	**30 (SC)**	**Female 100 (SC)**	**2.5 (IM)**	**10 (IM)**	**75 (IM)**
Numbers of Animals:	Main	10	10	10	10	10	10	10
	Toxicokinetic	3	3	3	3	3	3	3
AUC_{0-24} (μg.h/mL):		NA	49.2	137	177	94.8	189	293
AUC_{0-720} (μg.h/mL):		NA	5367	19218	51104	4525	16464	64765
AUC_{0-t} (μg.h/mL):		NA	9400	47662	126959	4762	18663	100857
C_{max} (μg/mL):		BLQ	9.04	36.9	104	14.2	40.6	124

CAB: Single Dose Subcutaneous and Intramuscular Toxicity Study in Rats Followed by at least a 74 Day Non-Treatment Period (Continued)

Study Type: Single Dose Toxicity **Study No.:** R42516

		Female						
Daily Dose (mg/kg/day)[1]		**0 (SC and IM)**	**5 (SC)**	**30 (SC)**	**100 (SC)**	**2.5 (IM)**	**10 (IM)**	**75 (IM)**
Noteworthy Findings:								
Unscheduled Deaths:		0	0	0	0	0	0	0
Clinical Observations:		No test article-related clinical observations were noted.						
Skin Irritation (Injection Sites):		Very slight to well defined erythema was observed in up to 10 females given ≥5 mg/kg SC. Very slight erythema was observed in one female given 75 mg/kg IM. Very slight erythema for the females given ≥30 mg/kg SC remained present until termination. Very slight to moderate edema was noted in up to 10 females given ≥5 mg/kg and very slight to slight edema was observed in 2 females given 75 mg/kg IM. Very slight edema noted for females given 30 mg/kg and very slight to well defined edema noted for females given 100 mg/kg SC remained until termination. Generally, the number of rats affected, duration, and severity of erythema and edema increased in a dose-dependent manner for rats given ≥5 mg/kg SC.						
Body Weight:		No test article-related changes were noted.						
Food Consumption:		No test article-related changes were noted.						
Hematology:		No test article-related changes were noted.						
Coagulation:		No test article-related changes were noted.						
Clinical Chemistry:								
Calcium (mmol/L)	Week 4	2.354	2.388	2.438*	2.430*	2.425*	2.411*	2.421*
	Weeks 13 (SC) or 11 (IM)	2.399	2.520*	2.546*	2.587**	2.449	2.456	2.475
Total bilirubin (μmol/L)	Week 4	2.49	2.43	2.26	1.84**	2.43	2.32	2.01**
	Weeks 13 (SC) or 11 (IM)	2.29	2.22	2.17	2.16	2.39	2.37	2.35
Urinalysis:								
Urine volume (mL)	Week 4	6.90	9.90	11.15	9.80	10.40*	12.30*	12.65**
	Weeks 13 (SC) or 11 (IM)	9.40	9.00	14.50	13.20	9.70	12.70	12.75
Specific gravity	Week 4	1.0315	1.0298	1.0231	1.0226	1.0228*	1.0232*	1.0168**
	Weeks 13 (SC) or 11 (IM)	1.0260	1.0281	1.0162*	1.0176*	1.0214	1.0186*	1.0180*

CAB: Single Dose Subcutaneous and Intramuscular Toxicity Study in Rats Followed by at least a 74 Day Non-Treatment Period (Continued)

Study Type: Single Dose Toxicity **Study No.:** R42516

		Female						
Daily Dose (mg/kg/day)[1]		**0 (SC and IM)**	**5 (SC)**	**30 (SC)**	**100 (SC)**	**2.5 (IM)**	**10 (IM)**	**75 (IM)**
Organ Weights:		No test article-related organ weight changes were noted.						
Microscopic Examination (Number of Animals):		**10**	**10**	**10**	**10**	**10**	**10**	**10**
Injection Site								
Granuloma	Minimal	0	0	0	0	0	0	1
Subcutis granuloma	Minimal	0	0	1	0	0	0	0
	Mild	0	0	4	3	0	0	0
	Moderate	0	0	1	7	0	0	0
Pigmented macrophages	Minimal	0	0	0	0	0	0	2

Key:

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

2 = One toxicokinetic male was found dead on Day 39; cause of death could not be determined.

* = $p \leq 0.05$ significance level.

** = $p \leq 0.01$ significance level.

BLQ = Below limit of quantification (0.1 μg/mL).

IM = Intramuscular. SC = Subcutaneous.

NA = Not applicable. -- = Not examined.

6. REPEAT DOSE TOXICITY: NON-PIVOTAL STUDIES

Table 6.1 Repeat Dose Toxicity: Non-Pivotal Studies for CAB Sodium Salt

Species/Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report No. / Study No. (Module)
Monkey/ Cynomolgus	Oral gavage/ 0.5% (w/w) HPMC with 0.1% (w/w) Tween 80 in purified water suspension	7 Days	0 50 150 1000	1M/1F 1M/1F 1M/1F 1M/1F	Excessive salivation, emesis and abnormal feces were seen in the male given 1000 mg/kg/day. Abnormal feces were also noted in the female given 1000 mg/kg/day and in animals given 50 and 150 mg/kg/day.	CD2007/00577 / D07170 (m4.2.3.1)

Additional Information: Doses are expressed in terms of the free acid.

Table 6.2 CAB: 14 Day Oral Toxicity Study in Mice

Study Type: Repeat Dose Toxicity

Species/Strain: Mouse/Crl:CD1(ICR)
Initial Age: 11 to 12 weeks
Date of First Dose: 7 July 2009

Report Title: GSK1265744B: 14 Day Oral Toxicity Study in Mice
Duration of Dosing: 14 to 15 days
Route/Frequency: Oral by gavage, once daily
Vehicle/Formulation: 0.5% hydroxypropylmethylcellulose / 0.1% Tween™ 80 in reverse osmosis-treated water

Test Article: GSK1265744B (sodium salt)
Batch No.: [redacted]
Study No.: M42452
GSK Document Number: RD2009/00692
CTD Module: m4.2.3.2
Study in Compliance with GLP: Yes

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

Conclusion: GSK1265744B (vehicle, 10, 75 or 1000 mg/kg/day) was given orally to male and female mice for 14 days. Minimal to moderate serum enzyme (ALT, GLDH and AST) increases were noted in 2 animals administered 1000 mg/kg/day. The no observed adverse effect level (NOAEL) is 1000 mg/kg/day (mean AUC_{0-24} 2587 μg.h/mL; mean C_{max} 142 μg/mL [gender averaged based on Day 14 values]).

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**10**	**75**	**1000**	**0**	**10**	**75**	**1000**
Numbers of Animals:	Main	10	10	10	10	10	10	10	10
	Toxicokinetic	36	36	36	36	36	36	36	36
AUC_{0-24} (μg.h/mL):	Day 1	NA	427	1113	2006	NA	494	1168	2123
	Day 14	NA	681	1430	2385	NA	699	1610	2788
C_{max} (μg/mL):	Day 1	NA	27.8	66.0	118	NA	35.0	58.9	125
	Day 14	NA	38.8	84.2	132	NA	38.3	99.6	152
Noteworthy Findings:									
Clinical Chemistry:									
Glutamate dehydrogenase (U/L)		5.50	8.28	6.72	37.90	7.84	7.94	6.76	13.88
Aspartate aminotransferase (U/L)		36.0	36.8	33.6	76.6	39.8	46.4	41.0	47.6
Alanine aminotransferase (U/L)		20.6	28.8	22.4	39.6	19.8	26.2	22.6	28.2*

Key:
1 = Doses are expressed in terms of the parent compound.
* = $p<0.05$.
NA = Not applicable.

7. REPEAT DOSE TOXICITY: PIVOTAL STUDIES

Table 7.1 GSK1265744B: A 13 Week Oral (Gavage) Toxicity Study in Mice

Study Type: Repeat Dose Toxicity	**Report Title:** GSK1265744B: A 13 Week Oral (Gavage) Toxicity Study in Mice.	**Test Item:** GSK1265744B **Batch No.:** [redacted]
Species/Strain: Crl:CD1 (ICR) mouse	**Duration of Dosing:** 13 weeks	**GSK Reference No.:** M42936
Initial Age: Approximately 6 weeks old	**Route/Frequency:** Oral by gavage, once daily	**GSK Document Number:** 2012N142081
Date of First Dose: 05 July 2012	**Vehicle/Formulation:** 0.5% w/v hydroxypropylmethylcellulose (HPMC) K15M / 0.1% w/v polyoxyethylene sorbitan monooleate Tween™ 80 in Ultra Pure Water	**CTD Module**: m4.2.3.2 **Study in Compliance with GLP:** Yes

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

Conclusion: In conclusion, GSK1265744 given by oral gavage to male and female mice at doses of 0, 10, 75 or 1000 mg/kg/day for 13 weeks resulted in adverse nasal cavity lesions at 1000 mg/kg/day. One toxicology animal given 1000 mg/kg/day was euthanized on Day 68 due to moribund condition 6 hours after dosing which was consistent with gastric reflux as the cause of death. The nasal cavity lesions were considered secondary to gastric reflux of the gavage material into the nasal cavity and not a systemic effect of the test item. Single deaths in each dose group of TK animals were considered gavage dosing errors and not direct effects of the test item.

The no observed adverse effect level (NOAEL) was considered to be 75 mg/kg/day. The gender averaged mean GSK1265744 AUC_{0-t} exposure at 75 mg/kg/day for Week 13 was 1345 μg.h/mL (1330 to 1360 μg.h/mL); C_{max} 72.8 μg/mL (69.1 to 76.4 μg/mL).

GSK1265744B: A 13 Week Oral (Gavage) Toxicity Study in Mice (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** M42936

		Male				Female			
Daily Dose (mg/kg/day)		**0**	**10**	**75**	**1000**	**0**	**10**	**75**	**1000**
Numbers of Animals:	Main	12	12	12	12	12	12	12	12
	Toxicokinetic	9	54	54	54	9	54	54	54
AUC_{0-t} (μg.h/mL):	Day 1	NQ	433	971	1800	NQ	352	915	1790
	Week 4	NQ	576	1300	1710	NQ	712	1420	2300
	Week 13	NQ	552	1330	2150	NQ	691	1360	2430
C_{max} (μg/mL):	Day 1	NQ	23.6	60.2	122	NQ	23.2	44.1	103
	Week 4	NQ	34.7	68.8	108	NQ	39.4	82.0	132
	Week 13	NQ	29.8	76.4	122	NQ	35.5	69.1	133
Noteworthy Findings:									
Unscheduled Deaths (Number of Animals):		0	1 TK	1 TK	1 Main	0	0	0	1 TK
Mortality:		One toxicology group male given 1000 mg/kg/day was euthanized on Day 68, approximately 6 hours post dose, due to a rapid deteriorating clinical condition. Prior to euthanasia dosing reflux was noted. The following clinical signs were noted prior to the sacrifice: labored breathing, distended abdomen, skin purple (abdominal/lumbar), partly closed eyes, cold at the touch and suspected dehydration. Dilatation of the stomach and small intestinal tract were noted macroscopically at necropsy; there were no microscopic correlates to these specific findings. Microscopic findings consisted of marked degeneration/regeneration of the epithelium of the nasal cavity with pronounced inflammation and exudate, which had a ventral distribution. Bronze material was admixed with the exudates. The microscopic changes in the nasal cavity of this animal were also observed for animals given 1000 mg/kg/day at terminal necropsy. The dilatation of the stomach and upper intestinal tract and microscopic findings in the nasal cavity were consistent with gastric reflux, which was considered the cause of the deteriorating clinical condition leading to euthanasia. Three (two males and one female) toxicokinetic animals, one at each dose, were euthanized or found dead on Days 18, 37 and 47. One TK male given 10 mg/kg/day was euthanized due to a gavage accident. On Day 17 this animal swallowed a portion of the gavage needle, and on Day 18 had the following clinical signs: labored breathing, panting, suspected dehydration, fur erected, skin purple (on various locations) and was euthanized. At necropsy there was thickening in the ventral cervical region and a gavage needle was found in the esophagus, consistent with the gavage accident. One male given 75 mg/kg/day had the following clinical signs noted prior to euthanasia on Day 37: breathing abnormalities/panting, blue skin on the abdomen and suspected dehydration, approximately 5 hours post dose. Macroscopic and microscopic examination revealed no lesions that could have contributed to the moribundity of this animal. The lack of potentially test item-related lesions in this animal and all toxicology animals given 75 mg/kg/day suggest this was likely related to gavage dosing and not a direct test item effect. There were no clinical signs noted for female animal given 1000 mg/kg/day prior to death, however, this animal was found dead less than an hour after dosing on Day 47.							
Clinical Observations:		There were no test item-related clinical signs noted in surviving animals throughout the study.							

GSK1265744B: A 13 Week Oral (Gavage) Toxicity Study in Mice (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** M42936

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**10**	**75**	**1000**	**0**	**10**	**75**	**1000**
Body Weight (X Control[a]):								
Week 1	32.09 g	1.05X*	1.05X*	1.04X*	25.78 g	0.99X	0.97X	0.99X
Week 4	37.21 g	1.05X	1.03X	1.01X	30.20 g	0.98X	0.96X	0.97X
Week 13	45.46 g	1.03X	1.00X	0.96X	37.04 g	0.98X	0.92X	0.93X
Body Weight Gain (X Control[a]):								
Weeks -1 to 13	14.40 g	1.03X	0.95X	0.84X	12.48 g	1.01X	0.82X	0.82X
Hematology (Terminal Collection):								
Neutrophils (10^9/L)	0.744	0.798	0.764	1.275	0.654	0.516	0.496	0.640
Clinical Chemistry (Terminal Collection):								
Glucose (mmol/L)	12.360	11.699	10.876	9.508**	10.667	9.059	9.230	8.520*
Organ Weights (g):								
Heart	0.22080 g	0.21933	0.22059	0.24645*	0.17983	0.17562	0.16862	0.17281
Kidney	0.55788 g	0.56048	0.56380	0.62922*	0.37467	0.39153	0.35803	0.34319
Macroscopic Examination:	There were no test item-related macroscopic findings at terminal necropsy.							

GSK1265744B: A 13 Week Oral (Gavage) Toxicity Study in Mice (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** M42936

		Male				Female			
Daily Dose (mg/kg/day)		**0**	**10**	**75**	**1000**	**0**	**10**	**75**	**1000**
Microscopic Examination (Number of Animals):		**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
Bone Marrow									
Hypercellularity: Myeloid	Minimal	0	0	0	0	0	0	0	1
	Slight	0	0	0	0	0	0	0	1
Nasal Cavity/Sinuses									
Degeneration/Regeneration: Epithelium									
	Minimal	0	0	0	3	0	0	0	0
	Slight	0	0	0	1	0	0	0	2
	Moderate	0	0	0	0	0	0	0	1
	Marked	0	0	0	2	0	0	0	0
Inflammation: Neutrophilic cell									
	Minimal	0	0	0	0	0	0	0	1
	Slight	0	0	0	2	0	0	0	2
Exudate									
	Minimal	0	0	0	0	0	0	0	1
	Slight	0	0	0	0	0	0	0	1
	Moderate	0	0	0	2	0	0	0	0

Key:
a = For controls group means are shown, for treated groups X change as compared to controls. Statistical significance is based on actual data not change.
* = p<0.05.
** = p<0.01.
*** = p<0.001.
g = Gram.
NQ = Not quantifiable [or below the lower limit of quantification (i.e., 100 ng/mL)].
- = Not examined.

Table 7.2 GSK1265744A: A 3 Month (Weekly and Monthly Dosing) Subcutaneous (SC) and Intramuscular (IM) Toxicity Study in the Rats Followed by at least a 14 Day or 75 Day or a 51 Day (IM) Non-Treatment Period

Study Type: Repeat Dose Toxicity

Report Title: GSK1265744A: A 3 Month (Weekly and Monthly Dosing) Subcutaneous (SC) and Intramuscular (IM) Toxicity Study in the Rats Followed by at least a 14 Day or 75 Day or a 51 Day (IM) Non-Treatment Period

Test Article: GSK1265744A

Batch Nos.: [redacted] / [redacted] / [redacted] / [redacted], as pre-formulated suspensions

Species/Strain: Crl:CD(SD) rat

Duration of Dosing: 3 months/13 weeks

Duration of Recovery: 14 or 75 days (SC) or 51 days (IM)

GSK Reference No.: R42698

Initial Age: 13 to 15 weeks

Route/Frequency: Monthly intramuscular (IM) or weekly and monthly subcutaneous (SC)

GSK Document Number: 2010N104820

CTD Module: m4.2.3.2

Date of First Dose: 28 September 2010

Vehicle/Formulation: 2% w/v Polysorbate 20 (Tween™ 20), 2% w/v polyethylene glycol 3350 and 4.5% w/v Mannitol in sterile Water for Injection

Study in Compliance with GLP: Yes

Data Collected: Toxicokinetics, clinical observations and local irritation assessment (Draize scoring method), body weight, food consumption, ophthalmoscopy, hematology, coagulation, clinical chemistry, urinalysis, organ weights, macroscopic and microscopic pathology.

Conclusion: GSK1265744 was administered by monthly subcutaneous injection (vehicle control, 5, 30 and 100 mg/kg/dose); administered by monthly intramuscular injection (vehicle control, 2.5, 10 and 75 mg/kg/dose) or administered by weekly subcutaneous injection (vehicle control and 100 mg/kg/dose) to rats for up to 3 months, followed by non-dose periods of up to 75 days. Variable body weights changes were observed and did not translate into any clinical signs; therefore, they were determined to be non-adverse. Dose-proportional signs of redness and swelling were present following SC or IM injections at all dose levels. These were accompanied with local inflammatory reactions (erythema and edema graded very slight to severe) in animals given 75 mg/kg/dose (monthly IM injections), at all doses in female animals given monthly SC injections and in males given ≥30 mg/kg/month, and at a higher incidence in animals given 100 mg/kg/dose monthly and weekly SC injections.

Clinical signs, clinical and anatomic pathology changes were due to inflammation associated with the injection sites. The changes included increases in neutrophils, limited to the 100 mg/kg dose level (weekly SC injections), decreases in total bilirubin (30 and 100 mg/kg/dose given by monthly SC injection, 75 mg/kg/dose given by IM and 100 mg/kg/dose given by weekly SC injection), increases in triglyceride (males given 30 and 100 mg/kg/dose via monthly SC injections), increases in urea, creatinine and phosphorus (females given 100 mg/kg/dose weekly by SC injections) increases in phosphorus only in males given 100 mg/kg/dose) and decreases in albumin and total protein (100 mg/kg/dose given via weekly SC injections). Partial reversal during the off-treatment period was present in neutrophils, total bilirubin, triglycerides, urea, creatinine and phosphorus. Histologically, the changes were limited to granulomatous inflammation and mixed inflammatory cell infiltration at the corresponding injection sites, with correlating macroscopic changes. These changes were dose-dependent and were most severe in animals receiving 100 mg/kg/dose SC once weekly and having the shortest non-dose period.

The no observed adverse effect levels (NOAEL) for monthly administration were 100 mg/kg/dose SC and 75 mg/kg/dose IM. At the NOAEL, the mean $AUC_{1440-2160}$ at 100 mg/kg/dose (subcutaneous injection) during the 3rd dosing interval was 70494 and 116602 μg.h/mL (range of 59895 to 85122 μg.h/mL and 105082 to 124604 μg.h/mL), and the mean third dose C_{max} was 118 and 195 μg/mL (range 107 to 140 μg/mL and 172 to 208 μg/mL), for males and females, respectively. At 75 mg/kg/dose (intramuscular injection), the mean $AUC_{1440-2160}$ during the third dosing interval was 78051 and 107080 μg.h/mL (range of 74734 to 80570 μg.h/mL and 92466 to 115252 μg.h/mL) and the mean third dose C_{max} was 120 and 170 μg/mL (range 118 to 123 μg/mL and 151 to 181 μg/mL) for males and females, respectively. The NOAEL for weekly SC administration was 100 mg/kg/dose. At the NOAEL, the $AUC_{2016-2184}$ at 100 mg/kg/week was 22291 and 34315 μg.h/mL (range of 21631 to 22907 μg.h/mL and 32842 to 35565 μg.h/mL), a C_{max} of 143 and 223 μg/mL (range 141 to 144 μg/mL and 214 to 235 μg/mL).

GSK1265744A: A 3 Month (Weekly and Monthly Dosing) Subcutaneous (SC) and Intramuscular (IM) Toxicity Study in the Rats Followed by at least a 14 Day or 75 Day or a 51 Day (IM) Non-Treatment Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R42698

Monthly Subcutaneous Injections

	Male				Female			
Daily Dose (mg/kg/dose)	**0**	**5**	**30**	**100**	**0**	**5**	**30**	**100**
Numbers of Animals:	15	15	15	15	15	15	15	15
Main	12	12	12	12	12	12	12	12
Toxicokinetic	3	3	3	3	3	3	3	3
AUC (μg.h/mL): 1st dose interval (AUC_{0-720})	-	4076 [3538 - 5052]	17516 [13864 - 23636]	31464 [22594 - 41661]	-	7644 [5767 - 8775]	22304 [17866 - 27470]	58245 [52894 - 66040]
3rd dose interval ($AUC_{1440-2160}$)		11204 [8074 - 13513]	48082 [37243 - 54532]	70494 [59895 - 85122]		15238 [14303 - 16045]	55956 [41339 - 70624]	116602 [105082 - 124604]
C_{max} (μg/mL): 1st dose interval	-	7.44 [5.89 - 8.34]	33.8 [25.2 - 46.4]	62.0 [41.1 - 85.2]	-	13.3 [9.34 - 16.7	40.6 [31.3 - 51.6]	121 [107 - 137]
3rd dose interval		19.2 [13.5 - 22.6]	84.8 [66.8 - 96.3]	118 [107 - 140]		26.8 [26.0 - 27.9]	96.8 [65.3 - 132]	195 [172 - 208]
Noteworthy Findings:								
Unscheduled Deaths:	0	0	0	1[a]	0	0	0	1
Clinical Observations:	Clinical signs attributed to administration of GSK1265744 were limited to swelling and redness noted at the injection sites with dose-proportionality. These clinical signs persisted throughout the treatment and non-dose periods. Erythema and/or edema were noted following each injection, which persist during the non-treatment period. These observations were seen at 30 mg/kg/dose and at a higher incidence at 100 mg/kg/dose. The nature of the erythema and/or edema ranged mostly from very slight severity to moderate/severe. In females at 5 mg/kg, erythema and edema scores ranging from very slight to well defined, were seen at that dose level, following injection, these however did not persist after completion of the treatment period.							
Body Weight (Week 19):	700.4 g	746.4 g	735.3 g	720.9 g	376.4 g	409.3 g	359.0 g	387.1 g
Absolute Body Weight Gains (Xcontrol[b]):	159.0 g	20%	18%	10%	57.4 g	25%	-9.9%	-8.0%
Food Consumption (X Control):	1793 g	9.8%	7.9%	7.4%	1257.7 g	4.9%	-	-4.7%

GSK1265744A: A 3 Month (Weekly and Monthly Dosing) Subcutaneous (SC) and Intramuscular (IM) Toxicity Study in the Rats Followed by at least a 14 Day or 75 Day or a 51 Day (IM) Non-Treatment Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R42698

	Monthly Subcutaneous Injections							
	Male				Female			
Daily Dose (mg/kg/dose)	**0**	**5**	**30**	**100**	**0**	**5**	**30**	**100**
Clinical Chemistry:								
Total Bilirubin (μmol/L)								
Week 8	2.7	1.04X	0.81X	0.67X	3.4	0.94X	0.79X	0.62X
Week Prior Necropsy	3.9	0.82X	0.72X	0.62X	4.1	0.80X	0.78X	0.68X
Triglycerides (mmol/L)								
Week 8	1.202	1.19X	1.41X	1.20X	1.227	1.07X	1.04X	1.09X
Week Prior Necropsy	1.830	1.18X	1.15X	0.93X	1.411	1.11X	0.77X	1.04X
Macroscopic Examination (Number of Animals):	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
Injection Site 1 (Upper Left Inter-Scapula)								
Area pale	0	0	1	0	0	0	1	0
Nodule	0	1	7	9	0	0	7	10
Mass	0	0	0	3	0	0	0	0
Injection Site 2 (Upper Right Inter-Scapula)								
Area pale	0	0	0	0	0	0	0	1
Nodule	0	5	11	9	0	0	11	9
Mass	0	0	0	3	0	0	0	1
Injection Site 3 (Lower Left Inter-Scapula)								
Area pale	0	0	0	0	0	1	0	0
Nodule	0	3	5	9	0	0	11	8
Mass	0	0	0	2	0	0	0	1
Thymus								
Small	0	1	0	1	0	0	1	2

GSK1265744A: A 3 Month (Weekly and Monthly Dosing) Subcutaneous (SC) and Intramuscular (IM) Toxicity Study in the Rats Followed by at least a 14 Day or 75 Day or a 51 Day (IM) Non-Treatment Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R42698

	Monthly Subcutaneous Injections							
	Male				Female			
Daily Dose (mg/kg/dose)	**0**	**5**	**30**	**100**	**0**	**5**	**30**	**100**
Microscopic Examination (Number of Animals):	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
Injection Site 1 (Upper Left Inter-Scapula)								
Inflammation: Granulomatous	0	1	7	11	0	0	6	10
Minimal	0	1	1	0	0	0	2	1
Slight	0	0	6	11	0	0	4	8
Moderate	0	0	0	0	0	0	0	1
Infiltration: Mixed cell	0	0	1	0	0	0	1	0
Minimal	0	0	1	0	0	0	1	0
Injection Site 2 (Upper Right Inter-Scapula)								
Inflammation: Granulomatous	0	3	11	12	0	0	11	11
Minimal	0	3	1	0	0	0	0	1
Slight	0	0	10	11	0	0	10	9
Moderate	0	0	0	1	0	0	1	1
Injection Site 3 (Lower Left Inter-Scapula)								
Inflammation: Granulomatous	0	3	6	11	0	1	10	9
Minimal	0	3	1	0	0	1	3	0
Slight	0	0	5	10	0	0	7	9
Moderate	0	0	0	1	0	0	0	0

GSK1265744A: A 3 Month (Weekly and Monthly Dosing) Subcutaneous (SC) and Intramuscular (IM) Toxicity Study in the Rats Followed by at least a 14 Day or 75 Day or a 51 Day (IM) Non-Treatment Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R42698

		Monthly Intramuscular Injections							
		Male				Female			
Daily Dose (mg/kg/dose)		**0**	**2.5**	**10**	**75**	**0**	**2.5**	**10**	**75**
Numbers of Animals:		15	15	15	15	15	15	15	15
Main		12	12	12	12	12	12	12	12
Toxicokinetic		3	3	3	3	3	3	3	3
AUC_{0-t} (µg.h/mL):	1st dose interval (AUC_{0-720})	-	5588 [5386 - 5888]	18331 [16976 - 20964]	55684 [52230 - 62367]	-	5230 [5049 - 5439]	18420 [16184 - 20868]	82061 [79150 - 84534]
	3rd dose interval ($AUC_{1440-2160}$)		7031 [6945 - 7078]	26001 [21538 - 28560]	78051 [74734 - 80570]		5500 [5263 - 5622]	24934 [23435 - 27919]	107080 [92466 - 115252]
C_{max} (µg/mL):	1st dose interval	-	12.7 [11.4 - 14.1]	37.8 [34.4 - 40.8]	106 [94.6 - 116]	-	15.8 [15.1 - 16.3]	44.2 [33.7 - 49.5]	151 [150 - 152]
	3rd dose interval		16.7 [14.7 - 18.8]	49.6 [47.8 - 51.2]	120 [118 - 123]		12.4 [11.5 - 13.6]	55.2 [50.6 - 60.3]	170 [151 - 181]
Noteworthy Findings:									
Unscheduled Deaths:		0	0	0	2[a]	0	0	0	0
Clinical Observations:		Clinical signs attributed to administration of GSK1265744 were limited to swelling and redness noted at the injection sites with dose-proportionality. These clinical signs persisted throughout the treatment and non-treatment periods. Erythema and/or edema were noted following each injection, which persist during the non-treatment period. These observations were seen at 75 mg/kg/dose. The nature of the erythema and/or edema ranged mostly from very slight severity to slight/well defined.							
Body Weight (Week 15):		705.3 g	727.1 g	715.7 g	722.4 g	391.5 g	362.6 g	379.8 g	375.7 g
Absolute Body Weight Gains (X Control[b]):		168.3 g	11%	6.8%	6.8%	74.5 g	-27%	-32%	-25%
Clinical Chemistry:									
Total Bilirubin (µmol/L)									
Week 8		3.1	0.94X	0.97X	0.71X	3.7	0.89X	0.81X	0.57X
Week Prior Necropsy		3.0	0.93X	0.97X	0.83X	3.3	1.06X	1.06X	0.70X

GSK1265744A: A 3 Month (Weekly and Monthly Dosing) Subcutaneous (SC) and Intramuscular (IM) Toxicity Study in the Rats Followed by at least a 14 Day or 75 Day or a 51 Day (IM) Non-Treatment Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R42698

	Monthly Intramuscular Injections							
	Male				Female			
Daily Dose (mg/kg/dose)	**0**	**2.5**	**10**	**75**	**0**	**2.5**	**10**	**75**
Macroscopic Examination (Number of Animals):	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
Injection Site 2 (Thigh; Upper Right)								
Area pale	0	0	0	1	0	0	0	1
Nodule	0	0	0	3	0	0	0	2
Mass	0	0	0	2	0	0	0	0
Injection Site 3 (Thigh; Lower Left)								
Foci pale	0	0	0	1	0	0	0	0
Area pale	0	0	0	2	0	0	0	2
Area raised	0	0	0	1	0	0	0	0
Nodule	0	0	0	2	0	0	0	5
Mass	0	0	0	5	0	0	0	0
Thymus								
Small	0	0	0	1	0	1	1	0

GSK1265744A: A 3 Month (Weekly and Monthly Dosing) Subcutaneous (SC) and Intramuscular (IM) Toxicity Study in the Rats Followed by at least a 14 Day or 75 Day or a 51 Day (IM) Non-Treatment Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R42698

	Male				Female			
Daily Dose (mg/kg/dose)	**0**	**2.5**	**10**	**75**	**0**	**2.5**	**10**	**75**
Microscopic Examination (Number of Animals):	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
Monthly Subcutaneous Injections								
Injection Site 1 (Thigh; Upper Left)								
Inflammation: Granulomatous	0	0	0	2	0	0	0	3
Minimal	0	0	0	2	0	0	0	3
Infiltration: Mixed cell	0	0	0	0	0	0	0	1
Minimal	0	0	0	0	0	0	0	1
Injection Site 2 (Thigh; Upper Right)								
Inflammation: Granulomatous	0	0	0	7	0	0	0	5
Minimal	0	0	0	3	0	0	0	4
Slight	0	0	0	4	0	0	0	1
Infiltration: Mixed cell	0	0	1	0	0	0	0	1
Minimal	0	0	1	0	0	0	0	1
Injection Site 3 (Thigh; Lower Left)								
Inflammation: Granulomatous	0	0	0	8	0	0	0	4
Minimal	0	0	0	1	0	0	0	4
Slight	0	0	0	7	0	0	0	0
Infiltration: Mixed cell	0	0	0	0	0	0	2	2
Minimal	0	0	0	0	0	0	2	2

GSK1265744A: A 3 Month (Weekly and Monthly Dosing) Subcutaneous (SC) and Intramuscular (IM) Toxicity Study in the Rats Followed by at least a 14 Day or 75 Day or a 51 Day (IM) Non-Treatment Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R42698

		Weekly Subcutaneous Injections			
		Male		Female	
Daily Dose (mg/kg/dose)		**0**	**100**	**0**	**100**
Numbers of Animals:		15	15	15	15
Main		12	12	12	12
Toxicokinetic		3	3	3	3
$AUC_{2016-2184}$ (μg.h/mL):	Week 13	-	22291 [21631 - 22907]	-	34315 [32842 - 35565]
C_{max} (μg/mL):	Week 13	-	143 [141 - 144]	-	223 [214 - 235]
Noteworthy Findings:					
Clinical Observations:		Clinical signs attributed to administration of GSK1265744 were limited to swelling and redness noted at the injection site. These clinical signs persisted throughout the treatment and non-treatment periods. Erythema and edema were noted following each injection and would tend to persist during the non-treatment period. The nature of the erythema and/or edema ranged mostly from very slight severity to moderate/severe.			
Food Consumption:		Starting on Week 8 of treatment, the food consumption was lower than controls.			
Hematology and Coagulation:					
Neutrophils (10^9/L)					
	Week 8	1.418	1.82X	0.781	1.65X
	Week Prior Necropsy	1.658	0.97X	0.813	1.54X
Clinical Chemistry:					
Total Bilirubin (μmol/L)					
	Week 8	3.0	0.47X	2.9	0.45X
	Week Prior Necropsy	2.8	0.57X	3.5	0.31X
Urea (mmol/L)					
	Week 8	5.68	1.13X	5.71	1.23X*
	Week Prior Necropsy	5.18	1.08X	5.36	1.23X*
Creatinine (μmol/L)					
	Week 8	40.7	1.16X	46.5	1.19X**
	Week Prior Necropsy	33.0	1.18X	44.8	1.07X

GSK1265744A: A 3 Month (Weekly and Monthly Dosing) Subcutaneous (SC) and Intramuscular (IM) Toxicity Study in the Rats Followed by at least a 14 Day or 75 Day or a 51 Day (IM) Non-Treatment Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R42698

	Weekly Subcutaneous Injections			
	Male		Female	
Daily Dose (mg/kg/dose)	**0**	**100**	**0**	**100**
Clinical Chemistry (Continued):				
Phosphorus (mmol/L)				
Week 8	2.368	1.19X	1.863	1.26X***
Week Prior Necropsy	2.238	1.10X	1.694	1.18X***
Albumin (g/L)				
Week 8	46.5	0.90X	57.1	0.91X**
Week Prior Necropsy	47.6	0.97X	59.2	0.96X
Total Protein (g/L)				
Week 8	73.7	0.93X	80.5	0.94X*
Week Prior Necropsy	75.5	0.95X	81.6	0.97X
Urinalysis:	There were no GSK1265744-related urinary parameters effects.			
Organ Weights:	There were no GSK1265744-related organ weight changes.			
Macroscopic Examination (Number of Animals):	**12**	**12**	**12**	**12**
Injection Site 1 (Upper Left Inter-Scapula)				
Mass	0	12	0	11
Nodule	0	8	0	9
Injection Site 2 (Upper Right Inter-Scapula)				
Mass	0	8	0	6
Nodule	0	8	0	12
Injection Site 3 (Lower Left Inter-Scapula)				
Mass	0	10	0	8
Nodule	0	11	0	11
Injection Site 4 (Lower Right Inter-Scapula)				
Mass	0	11	0	9
Nodule	0	8	0	11
Thymus				
Small	0	1	0	0

GSK1265744A: A 3 Month (Weekly and Monthly Dosing) Subcutaneous (SC) and Intramuscular (IM) Toxicity Study in the Rats Followed by at least a 14 Day or 75 Day or a 51 Day (IM) Non-Treatment Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R42698

	Weekly Subcutaneous Injections			
	Male		Female	
Daily Dose (mg/kg/dose)	**0**	**100**	**0**	**100**
Microscopic Examination (Number of Animals):	**12**	**12**	**12**	**12**
Injections Site 1 (Upper Left Inter-Scapula)				
Inflammation: Granulomatous	0	12	0	12
Slight	0	0	0	2
Moderate	0	4	0	8
Marked	0	8	0	2
Injections Site 2 (Upper Right Inter-Scapula)				
Inflammation: Granulomatous	0	11	0	12
Slight	0	4	0	6
Moderate	0	4	0	5
Marked	0	3	0	1
Injections Site 3 (Lower Left Inter-Scapula)				
Inflammation: Granulomatous	0	12	0	12
Slight	0	3	0	4
Moderate	0	6	0	7
Marked	0	3	0	1
Infiltration: Mixed cell	0	0	0	1
Minimal	0	0	0	1
Injections Site 4 (Lower Right Inter-Scapula)				
Inflammation: Granulomatous	0	12	0	12
Slight	0	3	0	3
Moderate	0	7	0	6
Marked	0	2	0	3

Key:

a = Not test article-related.

b = At end of the dosing period. For controls, group means are shown, for treated groups, X change as compared to controls. Statistical significance is based on actual data not change.

g = Grams. * = P≤0.05. ** = P≤0.01. *** = P≤0.001. - = Could not be calculated/not measured.

Table 7.3 GSK1265744A: 14 Day Oral Toxicity Study in Rats

Study Type: Repeat Dose Toxicity

Species/Strain: Crl:CD(SD)
Initial Age: 11 to 12 weeks
Date of First Dose: 5 October 2006

Report Title: GSK1265744A: 14 Day Oral Toxicity Study in Rats
Duration of Dosing: 14 or 15 days
Route/Frequency: Oral by gavage, once daily
Vehicle/Formulation: Aqueous 0.5% hydroxypropylmethylcellulose (HPMC) with 0.1% polyoxyethylene sorbitan monooleate (Tween™ 80)

Test Article: GSK1265744A (parent compound)
Batch No.: [redacted]
Study No.: R41937
GSK Document Number: RD2006/01741
CTD Module: m4.2.3.2

Study in Compliance with GLP: Yes

Data Collected: Toxicokinetics, clinical observations, neurobehavioral assessment, body weight, food consumption, ophthalmoscopy, hematology, coagulation, clinical chemistry, urinalysis, organ weights, macroscopic and microscopic pathology (including stage-dependent evaluation of spermatogenesis) and hepatic P450 isoform evaluation (results reported separately).

Conclusion: Mild, non-adverse test article effects occurred in the kidneys ($\alpha 2\mu$-globulin- and albumin-positive eosinophilic droplets associated with proteinuria) in males given 300 mg/kg/day and the adrenal glands (cortical vacuolation) in males given ≥30 mg/kg/day. Non-adverse increases in heart and thymus weights were found in males given ≥100 mg/kg/day and ≥30 mg/kg/day, respectively, with no histopathologic correlation. Due to the absence of adverse findings, the no observed adverse effect level (NOAEL) is >300 mg/kg/day.

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**30**	**100**	**300**	**0**	**30**	**100**	**300**
Numbers of Animals:	Main	10	10	10	10	10	10	10	10
	Toxicokinetic	3	3	3	3	3	3	3	3
$AUC_{0\text{-}24}$ (ng.h/mL):	Day 1	NA	293897	489819	707628	NA	307975	471582	798517
	Day 14	NA	1849172	2222721	2510388	NA	1605280	2435243	3276967
C_{max} (ng/mL):	Day 1	NA	14438	22903	35791	NA	14368	23998	41016
	Day 14	NA	82076	98369	113659	NA	73826	110864	147098

GSK1265744A: 14 Day Oral Toxicity Study in Rats (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** R41937

	Male				Female			
Daily Dose (mg/kg/day)[1]	**0**	**30**	**100**	**300**	**0**	**30**	**100**	**300**
Noteworthy Findings:								
Clinical Chemistry:								
Total bilirubin (μmol/L)	1.71	1.52*	1.37**	1.43**	2.24	1.67**	1.52**	1.36**
Phosphorus (mmol/L)	2.363	2.500	2.467	2.599	2.221	2.271	2.151	2.518*
Urinalysis:								
Protein/creatinine ratio	0.90	0.99	0.97	1.34	0.36	0.33	0.35	0.35
Total protein excretion (mg/cp)	8.621	9.523	10.154	13.098	1.883	1.829	1.748	2.051
Organ Weights[2]:								
Heart, absolute	1.2833 g	5.16	10.47*	15.30**	0.9178 g	8.23	6.77	1.45
Heart, relative to body weight	0.312%	4.17	7.37	12.50**	0.352%	9.09	7.10	4.83
Thymus, absolute	0.3641 g	19.86	38.56*	21.18*	0.4265 g	-1.48	-1.41	4.88
Thymus, relative to body weight	0.088%	20.45*	32.95*	19.32*	0.165%	-1.21	-1.21	6.06
Microscopic Examination (Number of Animals):	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Kidney								
Eosinophilic droplets, tubule epithelium								
Minimal	6[3]	6	4	2[3]	0	0	0	0
Mild	0[3]	0	0	2[3]	0	0	0	0
Moderate	0[3]	0	0	2[3]	0	0	0	0
Adrenal Gland								
Cytoplasmic vacuolation, cortex								
Minimal	9	4	6	2	0	0	0	0
Mild	1	6	4	8	0	0	0	0

Key:

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

2 = Absolute and/or relative weights different from controls in the direction indicated. For controls, group means are shown; for treated groups, percentage change from controls is shown. Statistical significance is based on actual data, not percentage differences.

3 = Immunohistochemical analysis confirmed that the increase in renal eosinophilic droplets in the male rats was due to a combination of increased α2μ-globulin and albumin.

* = $p<0.05$. ** = $p<0.01$.

NA = Not applicable.

Table 7.4 GSK1265744B: 28 Day Oral Toxicity Study in Rats Followed by a 2 Week Recovery Period

Study Type: Repeat Dose Toxicity

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

Initial Age: Approximately 11 weeks
Date of First Dose: 27 May 2008

Report Title: GSK1265744B: 28 Day Oral Toxicity Study in Rats Followed by a 2 Week Recovery Period
Duration of Dosing: 28/29 days
Duration of Recovery: At least 14 days
Route/Frequency: Oral by gavage, once daily
Vehicle/Formulation: 0.5% hydroxypropylmethylcellulose with 0.1% polyoxyethylene sorbitan monooleate (Tween™80) in reverse osmosis-treated water

Test Article: GSK1265744B (sodium salt)
Batch No.: [redacted]
Study No.: R42288

GSK Document Number: RD2008/00448
CTD Module: m4.2.3.2

Study in Compliance with GLP: Yes

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

Conclusion: Based on the absence of adverse effects, the no observable adverse effect level (NOAEL) is 1000 mg/kg/day (mean AUC_{0-24} 3735 μg.h/mL, range 3214 to 4629 μg.h/mL; mean C_{max} 171.5 μg/mL, range 149 to 214 μg/mL [gender averaged based on Day 28 values]).

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**1**	**75**	**1000**	**0**	**1**	**75**	**1000**
Numbers of Animals:	Main	10	10	10	10	10	10	10	10
	Recovery	6	0	0	6	6	0	0	6
	Toxicokinetic	3	3	3	3	3	3	3	3
AUC_{0-24} (μg.h/mL):	Day 1	NA	70.7	1309	3368	NA	78.3	1484	3732
	Day 28	NA	739	3000	3345	NA	852	3832	4125
C_{max} (μg/mL):	Day 1	BQL	4.23	66.1	161	BQL	4.48	72.8	181
	Day 28	BQL	34.3	143	150	BQL	38.8	176	193

GSK1265744B: 28 Day Oral Toxicity Study in Rats Followed by a 2 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** R42288

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**1**	**75**	**1000**	**0**	**1**	**75**	**1000**
Noteworthy Findings:									
Body Weight[2]:	Day 28	509.16 g	0.91X**	0.95X**	0.92X**	282.39 g	1.01X	1.03X	1.00X
	Day 43	575.67 g	-	-	0.86X**	307.47 g	-	-	1.01X
Hematology:									
Absolute reticulocytes (x10^9/L)	Week 5	169.00	158.43	163.66	142.72*	145.65	145.64	152.34	154.97
	Week 7	156.22	-	-	150.72	137.92	-	-	114.84
Clinical Chemistry:									
Alanine aminotransferase (U/L)	Week 5	29.5	32.3	35.1	36.9	30.7	34.4	36.9	44.1*
	Week 7	29.3	-	-	28.2	28.0	-	-	30.8
Glutamate dehydrogenase (U/L)	Week 5	7.96	9.54	12.42	11.22	12.82	24.89	19.05	42.26**
	Week 7	8.77	-	-	4.73**	15.95	-	-	16.37
Aspartate aminotransferase (U/L)	Week 5	119.4	122.3	132.5	138.9	96.7	114.1	101.2	122.7
	Week 7	95.0	-	-	104.0	91.3	-	-	110.2
Total bilirubin (μmol/L)	Week 5	2.03	1.76*	1.86**	1.26**	2.11	1.87*	1.35**	1.34**
	Week 7	2.18	-	-	1.67	2.77	-	-	2.68
Total protein (g/L)	Week 5	60.4	60.9	60.7	60.0	66.6	63.9	66.6	67.8
	Week 7	62.3	-	-	57.2**	66.2	-	-	64.2
Globulin (g/L)	Week 5	29.3	29.6	29.2	29.3	31.6	30.3	30.5	31.1
	Week 7	30.7	-	-	26.3**	30.7	-	-	30.3
Urinalysis:									
Urine glucose:volume (μmol/cp)	Week 5	7.4	8.4	9.1	8.7	4.1	5.4*	5.5*	5.2*
	Week 7	7.3	-	-	4.3	2.8	-	-	4.3**
Urine creatinine:volume (μmol/cp)	Week 5	137.5	120.0	133.0	131.3	59.8	67.2	72.4	69.7
	Week 7	125.5	-	-	84.8*	49.2	-	-	61.8

Key:

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

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

* = $p<0.05$. ** = $p<0.01$.

BQL = Below quantifiable limit. NA = Not applicable. - = Not examined.

Table 7.5 GSK1265744: A 26 Week Oral Gavage Toxicity Study in the Rat Followed by a 6 Week Recovery Period

Study Type: Repeat Dose Toxicity

Report Title: GSK1265744: A 26 Week Oral Gavage Toxicity Study in the Rat Followed by a 6 Week Recovery Period

Test Article: GSK1265744B
Batch No.: [redacted]

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

Duration of Dosing: 26 weeks
Duration of Recovery: 6 weeks

GSK Reference No.: R42404

Initial Age: 7 weeks

Route/Frequency: Oral by gavage, once daily

GSK Document Number: RD2009/00031

Date of First Dose: 5 February 2009

Vehicle/Formulation: 0.5% w/v hydroxypropylmethylcellulose (HPMC) with 0.1% w/v Polysorbate (Tween™) 80 in deionized water

CTD Module: m4.2.3.2

Study in Compliance with GLP: Yes

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

Conclusion: Non-adverse microscopic findings related to the administration of GSK1265744 in the non-glandular stomach were noted at 5 mg/kg/day (males only) and 1000 mg/kg/day. These findings included minimal to slight increased apoptosis in the squamous mucosa with vacuolar degeneration and regenerative hyperplasia and associated submucosal infiltration of mixed inflammatory cells. These findings were still observed following the 6 week recovery period, but with a diminished incidence and severity, indicating reversibility. Due to the lack of functional changes (e.g., no fecal changes, and no negative effects on food consumption or body weight) these findings were considered not adverse. The increases in aspartate aminotransferase observed at 1000 mg/kg/day in females only was not considered adverse due to the transient nature (increases were only observed at Week 26) and absence of histology findings and other related clinical chemistry parameters. The no observed adverse effect level (NOAEL) was 1000 mg/kg/day (mean AUC_{0-24} 3992 μg.h/mL, range 3005 to 4907 and mean C_{max} 186 μg/mL, range 146 to 233 [gender averaged based on Week 26 values]).

GSK1265744: A 26 Week Oral Gavage Toxicity Study in the Rat Followed by a 6 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R42404

		Male				Female			
Daily Dose (mg/kg/day)		**0**	**0.5**	**5**	**1000**	**0**	**0.5**	**5**	**1000**
Numbers of Animals:	Main	12	12	12	12	12	12	12	12
	Recovery	6	-	-	6	6	-	-	6
	Toxicokinetic	3	3	3	3	3	3	3	3
AUC_{0-24} (µg.h/mL):	Week 4	-	329	1961	3753	-	404	1672	4403
	Week 13		491	1792	2958		659	1951	4079
	Week 26		451	1861	3203		675	2083	4781
C_{max} (µg/mL):	Week 4	-	16.2	93.2	174	-	19.4	85.1	210
	Week 13		23.1	85.6	144		30.4	94.4	190
	Week 26		23.1	91.4	148		31.6	102	224
Noteworthy Findings:									
Unscheduled Deaths:		-	-	-	1	-	-	1	-
Clinical Observations:						-			
Clinical Chemistry[a]:									
Aspartate aminotransferase (U/L)		252.9	0.59	0.61	0.56	121.8	0.83	1.05	1.24
Macroscopic Examination (Number of Animals)									
Main		**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
Recovery		**6**	**-**	**-**	**6**	**6**	**-**	**-**	**6**

GSK1265744: A 26 Week Oral Gavage Toxicity Study in the Rat Followed by a 6 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R42404

	Male				Female			
Daily Dose (mg/kg/day)	**0**	**0.5**	**5**	**1000**	**0**	**0.5**	**5**	**1000**
Microscopic Examination (Number of Animals)								
Main	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
Recovery	**6**	**-**	**-**	**6**	**6**	**-**	**-**	**6**
Main Microscopic Observations								
Stomach								
Increased apoptosis: Squamous								
mucosa Minimal	0	0	1	3	0	0	0	3
Slight	0	0	0	3	0	0	0	4
Infiltration: Mixed cell								
Minimal	0	0	1	4	0	0	0	5
Recovery Microscopic Observations								
Increased apoptosis: Squamous								
mucosa Minimal	0	-	-	1	0	-	-	1
Infiltration: Mixed cell								
Minimal	0	-	-	1	0	-	-	1

Key:
a = At Week 26. For controls, group means are shown; for treated groups, X change as compared to controls.
- = Not examined or applicable.

Table 7.6 GSK1265744B: 14 Day Oral Toxicity Study in Cynomolgus Monkeys

Study Type: Repeat Dose Toxicity

Report Title: GSK1265744B: 14 Day Oral Toxicity Study in Cynomolgus Monkeys

Test Article: GSK1265744B (sodium salt)
Batch No.: [redacted]

Species/Strain: Cynomolgus monkeys

Duration of Dosing: Approximately 14 days

Study No.: G07171

Initial Age: Males: 4.6 to 5.2 years
Females: 3.8 to 5.0 years

Route/Frequency: Oral by gavage, once daily

Study in Compliance with GLP: Yes

Date of First Dose: 9 August 2007

Vehicle/Formulation:
0.5% hydroxypropylmethylcellulose (K15M) with 0.1% Tween 80/suspensions

GSK Document Number: CD2007/00680

CTD Module: m4.2.3.2

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

Conclusion: GSK1265744 was given once daily by oral gavage to male and female cynomolgus monkeys at doses of 0 (vehicle), 8, 25 or 1000 mg/kg/day for approximately 14 days. A dose of 1000 mg/kg/day was not tolerated by males and resulted in morbidity associated with clinical signs suggestive of gastrointestinal effects including body weight loss, emesis, loose/watery feces, inappetence and moderate to severe dehydration. Microscopically, degenerative and regenerative alterations of the gastrointestinal tract were associated with the clinical signs in males given 1000 mg/kg/day. Regenerative gastric changes were also noted in a single female given 1000 mg/kg/day but were not considered adverse due to their minimal severity, limited distribution within the gastrointestinal tract and lack of accompanying clinical signs or weight loss. Bone marrow depletion with corresponding decreases in peripheral leukocyte, reticulocyte and platelet counts was present in males given 1000 mg/kg/day. Non-adverse changes that were likely exacerbated by stress were present in thymus (lymphoid atrophy) and adrenal glands (cortical hypertrophy) at doses $\geq$8 mg/kg/day.

Due to the minimal nature of the microscopic findings in males given 25 mg/kg/day this was considered the male NOAEL (mean AUC_{0-24} 233252 ng.h/mL, range 198017 to 256532 ng.h/mL; mean C_{max} 22699 ng/mL, range 20086 to 24603 ng/mL [based on Day 14 values]).

Based on the lack of adverse clinical or microscopic findings in females given 1000 mg/kg/day this was considered the female no observed adverse effect level (NOAEL) (mean AUC_{0-24} 945723 ng.h/mL, range 777889 to 1073887 ng.h/mL; mean C_{max} 65870 ng/mL, range 57623 to 71165 ng/mL [based on Day 14 values]).

GSK1265744B: 14 Day Oral Toxicity Study in Cynomolgus Monkeys (Continued)

		Male				Female			
Daily Dose (mg/kg/day)[a]		**0**	**8**	**25**	**1000**	**0**	**8**	**25**	**1000**
Numbers of Animals:		3	3	3	3	3	3	3	3
$AUC_{(0-24)}$ (ng.h/mL)	Day 1	NC	128174	233423	1050958	NC	104228	233973 [b]	961322 [b]
	Day 14	NC	144252 [b]	233252	ND [c]	NC	124431	231169	945723
C_{max} (ng/mL)	Day 1	NQ	12167	20754	66974	NQ	11755	23573	59156
	Day 14	NQ	14568	22699	ND [c]	NQ	15517	22169	65870
Noteworthy Findings:									
Unscheduled Deaths:		0	0	0	3	0	0	0	0
Clinical Observations: (including qualitative assessment of food consumption)		All males given 1000 mg/kg/day were euthanized in moribund condition on Day 14. Body weight loss, emesis, loose/watery feces, inappetence, salivation and discolored feces (yellow, tan and/or orange) preceded morbidity which was generally characterized by moderate to severe dehydration, decreased activity, hunched posture, and/or reluctance to move. Clinical observations in surviving monkeys that could be attributed to test article administration included tan discolored feces for females given 1000 mg/kg/day and slight to moderate salivation for females given ≥8 mg/kg/day. One female given 1000 mg/kg/day had emesis on two occasions during the first week of treatment that were considered test article-related.							
Body Weight[d]:		0.98X	1.00X	1.02X	0.94X	0.97X	1.00X	1.01X	1.01X
Hematology:									
Reticulocyte Count ($x10^9$/L)									
	Day -7	43.27	53.27	53.43	25.97	66.93	24.67	42.73	26.80
	Day 13	70.57	64.73	55.80	5.90	92.37	53.07	55.23	56.57
Platelet Count ($x10^9$/L)									
	Day -7	562.3	470.3	548.7	457.0	425.3	512.0	446.3	620.3
	Day 13	555.3	396.0	415.0	204.3	331.0	513.0	361.7	524.7
White Blood Cell Count ($x10^9$/L)									
	Day -7	14.903	12.533	13.110	14.023	9.303	8.087	8.340	11.907
	Day 13	13.507	11.743	15.123	8.133	10.783	7.360	7.733	8.130

GSK1265744B: 14 Day Oral Toxicity Study in Cynomolgus Monkeys (Continued)

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**8**	**25**	**1000**	**0**	**8**	**25**	**1000**
Numbers of Animals:	3	3	3	3	3	3	3	3
Lymphocyte Count (x10^9/L)								
Day -7	8.060	7.533	7.403	7.450	4.390	3.343	4.727	3.517
Day 13	8.210	6.243	5.980	2.427	5.533	4.233	3.563	4.517
Monocytes (x10^9/L)								
Day -7	0.293	0.243	0.320	0.333	0.263	0.230	0.333	0.300
Day 13	0.383	0.367	0.383	0.150	0.380	0.210	0.317	0.370
Basophils (x10^9/L)								
Day -7	0.080	0.080	0.077	0.073	0.047	0.030	0.053	0.060
Day 13	0.083	0.067	0.073	0.033	0.173	0.350	0.203	0.030
Large Unstained Cells (x10^9/L)								
Day -7	0.183	0.100	0.133	0.113	0.100	0.060	0.140	0.077
Day 13	0.180	0.113	0.127	0.043	0.130	0.090	0.130	0.217
Eosinophils (x10^9/L)								
Day -7	0.240	0.120	0.313	0.093	0.077	0.080	0.397	0.157
Day 13	0.183	0.200	0.390	0.010	0.173	0.350	0.203	0.093
Clinical Chemistry								
Serum Urea (mmol/L)								
Day -7	6.63	7.47	5.47	8.93	7.20	8.13	7.30	6.20
Day 13	6.70	7.33	5.67	13.60	5.80	6.50	5.43	5.83
Macroscopic Examination								
number of animals examined	3	3	3	3	3	3	3	3
Cecum								
Discoloration; red	0	0	0	1	0	0	0	0
Duodenum								
Focus; red; mucosa; multifocal	0	0	0	1	0	0	0	0
Stomach								
Focus; red; mucosa; multiple	0	0	0	1	0	0	0	0
Gastrointestinal Tract								
General Comment - Distension	0	0	0	3	0	0	0	0

GSK1265744B: 14 Day Oral Toxicity Study in Cynomolgus Monkeys (Continued)

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**8**	**25**	**1000**	**0**	**8**	**25**	**1000**
Numbers of Animals:	3	3	3	3	3	3	3	3
Microscopic Examination								
number of animals examined	3	3	3	3	3	3	3	3
Stomach								
Degeneration/regeneration; glandular region; fundic region (characterized by glandular dilation and mucous depletion in males and edema and fibrin deposition in the lamina propria and loss of glands in the female)								
Minimal	0	0	0	2	0	0	0	1
Moderate	0	0	0	1	0	0	0	0
Duodenum								
Atrophy; villi	0	0	0	2	0	0	0	0
Jejunum								
Atrophy; villi	0	0	0	1	0	0	0	0
Ileum								
Atrophy; villi	0	0	0	1	0	0	0	0
Cecum								
Degeneration/regeneration; lamina propria (characterized by glandular dilation, goblet cell hypertrophy and increased thickness)	0	0	0	3	0	0	0	0
Colon								
Degeneration/regeneration; lamina propria (characterized by glandular dilation, goblet cell hypertrophy and increased thickness)	0	0	0	2	0	0	0	0

GSK1265744B: 14 Day Oral Toxicity Study in Cynomolgus Monkeys (Continued)

	Male				Female			
Daily Dose (mg/kg/day)[a]	**0**	**8**	**25**	**1000**	**0**	**8**	**25**	**1000**
Numbers of Animals:	3	3	3	3	3	3	3	3
Microscopic Examination								
number of animals examined	3	3	3	3	3	3	3	3
Bone Marrow								
Cellularity decreased	0	0	0	3	0	0	0	0
Liver								
Vacuolation, microvesicular	0	0	0	1	0	0	0	0
Thymus								
Atrophy; lymphoid	1	1	3	3	0	0	0	0
Not examined; No section	0	1	0	0	0	0	0	0
Adrenal Glands								
Hypertrophy; cortex; bilateral; diffuse	0	0	3	3	0	1	3	3
Kidney								
Dilation; distal tubule; unilateral	0	0	0	1	0	0	0	0
Salivary Gland - Mandibular								
Atrophy	0	0	0	2	0	0	0	0
Not Examined: No section	0	0	0	0	0	1	0	0
Salivary Gland – Parotid								
Atrophy	0	0	0	2	0	0	0	0

Key: NC = Not calculable

NQ = Not Quantifiable. Below the lower limit of quantification (LLQ = 100 ng/mL for a 25 μL plasma sample).

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

b. Emesis was observed in one animal in this dose group.

c. ND = Not Determined. $AUC_{0\text{-}24}$ and a definitive C_{max} were not determined on Day 14 for males given 1000 mg/kg/day due to their early termination.

d. At end of dosing period, change from Day 1 values are shown.

Table 7.7 GSK1265744B: 4 Week Oral Gavage Toxicity Study in Monkeys Followed by a 2 Week Recovery Period

Study Type: Repeat Dose Toxicity

Report Title: GSK1265744B: 4 Week Oral Gavage Toxicity Study in Monkeys Followed by a 2 Week Recovery Period

Test Article: GSK1265744B, the sodium salt of GSK1265744A
Batch No.: [redacted]

Species/Strain: Monkey/cynomolgus; all Mauritian origin)

Duration of Dosing: 4 weeks
Duration of Recovery: 2 weeks

Study No.: G08079

Initial Age: Males - Approximately 4.18 to 5.76 years old.
Females - Approximately 3.78 to 5.73 years old

Route/Frequency: Oral by gavage, once daily

GSK Document Number: CD2008/00632

CTD Module: m4.2.3.2

Date of First Dose: 12 June 2008

Vehicle/Formulation:
0.5% hydroxypropylmethylcellulose (HPMC; K15M) with 0.1%% polyoxyethylene sorbitan monooleate (Tween™ 80) in water

Study in Compliance with GLP: Yes

Data Collected: Toxicokinetics, clinical observations, body weight, food consumption, ophthalmoscopy, electrocardiography, hematology, coagulation, clinical chemistry, urinalysis, organ weights, electron microscopy, stage-dependent spermatogenesis, viral serology (treatment period animals), macroscopic and microscopic pathology.

Conclusion: All doses were well tolerated. Intermittent excessive salivation and discolored feces (tan) were observed in monkeys given 500 mg/kg/day. Based on the lack of test article-related adverse clinical or microscopic findings in males and females given 500 mg/kg/day this was considered the no observed adverse effect level (NOAEL) (mean AUC_{0-24} 902.5 μg.h/mL, range 792 to 1114 μg.h/mL; mean C_{max} 61.6 μg/mL, range 50.3 to 79.1 μg/mL [based on Day 28 values]).

GSK1265744B: 4 Week Oral Gavage Toxicity Study in Monkeys Followed by a 2 Week Recovery Period (Continued)

Study Type: Repeat Dose Toxicity **Study No.:** G08079

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**5**	**50**	**500**	**0**	**5**	**50**	**500**
Numbers of Animals:	Main	3	3	3	3	3	3	3	3
	Recovery	2			2	2			2
AUC_{0-24} (μg.h/mL):	Day 1	NQ	115	311	697	NQ	85.3	311	664
	Day 28	NQ	100	276	901	NQ	80.9	279	904
C_{max} (μg/mL):	Day 1	NQ	12.6	20.8	38.2	NQ	10.4	23.9	39.1
	Day 28	NQ	10.0	17.4	58.1	NQ	9.07	20.0	65.0
Noteworthy Findings:									
Clinical Observations:		Intermittent episodes of discolored feces and excessive salivation in males and females given 500 mg/kg/day during the treatment period.							

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

Table 7.8 GSK1265744B: 39 Week Oral Gavage Toxicity Study in Monkeys Followed by a 2 Week Recovery Period

Study Type: Repeat Dose Toxicity

Report Title: GSK1265744B: A 39 Week Oral Gavage Toxicity Study in the Cynomolgus Monkey with a 6 Week Recovery Period

Test Article: GSK1265744B
Batch No.: [redacted]

Species/Strain: Cynomolgus monkey

Duration of Dosing: 39 weeks
Duration of Recovery: 6 weeks

GSK Reference No.: P42405

Initial Age: At least 2 years

Route/Frequency: Oral by gavage, once daily

GSK Document Number: RD2009/00027

Date of First Dose: 18 February 2009

Vehicle/Formulation: 0.5% w/v hydroxypropylmethylcellulose (HPMC) with 0.1% w/v Polysorbate (Tween™) 80 in deionized water

CTD Module: m4.2.3.2

Study in Compliance with GLP: Yes

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

Conclusion: GSK1265744 (vehicle, 5, 50 or 500 mg/kg/day) was given orally to male and female monkeys for 39 weeks followed by a 6 week recovery period. There were no test article-related changes noted in any parameter. Consequently, the no observed adverse effect level (NOAEL) was 500 mg/kg/day (C_{max} of 34.6 μg/mL [range 23.9 to 57.2 μg/mL] and AUC_{0-24} of 547 μg h/mL [range 359 to 781 μg.h/mL] for males and females combined at Week 39) in this study.

		Male				Female			
Daily Dose (mg/kg/day)[1]		**0**	**5**	**50**	**500**	**0**	**5**	**50**	**500**
Numbers of Animals:	Main	4	4	4	4	4	4	4	4
	Recovery	2	-	-	2	2	-	-	2
AUC_{0-24} (μg.h/mL):	Week 4	-	62.1	251	644	-	69.6	303	807
	Week 26	-	90.4	296	575	-	65.7	255	678
	Week 39	-	37.7	229	542	-	67.8	254	552
C_{max} (μg/mL):	Week 4	-	7.15	22.1	45.3	-	8.77	27.3	56.4
	Week 26	-	10.3	25.1	37.3	-	5.87	22.4	40.8
	Week 39	-	3.37	21.1	36.8	-	6.33	17.4	32.4
Noteworthy Findings:		None.							

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

8. GENOTOXICITY: IN VITRO

Table 8.1 GSK1265744B: Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

Genotoxicity: In Vitro

Report Title: GSK1265744B: Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli*

Test Compound: GSK1265744B (sodium salt)

Batch Number: [redacted]

Test for Induction of: Reverse mutation in bacterial cells

No. of Independent Assays: 2

[redacted] **Study No.:** 2990/141

GSK Reference No.: V27560

GSK Document Number: WD2007/00787

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

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

Location in CTD: m4.2.3.3.1

Metabolising System: Aroclor-induced rat liver S9-mix containing 50 μL S9 fraction/plate (final)

Vehicles: Test Article: Dimethylsulphoxide (DMSO) **Positive Controls:** DMSO or water

GLP Compliance: Yes

Treatment: Plate incorporation for 3 days

Date of Treatment: May to June 2007

Cytotoxic Effects: None

Mutagenic Effects: Negative

Metabolic Activation	Test Compound	Concentration (μg/plate)[1]	Main Plate Incorporation (Ames) Test 1 Mean Number of Revertant Colonies Per Plate				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* (pKM101)
Without Activation	DMSO	100 μL/plate	29	105	24	14	181
	GSK1265744	1.5	28	106	21	13	126
	GSK1265744	5	26	117	25	12	127
	GSK1265744	15	28	123	27	13	132
	GSK1265744	50	29	115	30	12	143
	GSK1265744	150	29	119	25	9	123
	GSK1265744	238	33	104	23	15	99
	2-nitrofluorene	5	469[2]	NT	NT	NT	NT
	Sodium azide	2	NT	427[2]	377[2]	NT	NT
	9-aminoacridine	50	NT	NT	NT	232[2]	NT
	4-nitroquinoline-1-oxide	2	NT	NT	NT	NT	785[2]

Key:

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

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

NT = Not tested.

GSK1265744B: Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Metabolic Activation	Test Compound	Concentration (μg/plate)[1]	Main Plate Incorporation (Ames) Test 1 Mean Number of Revertant Colonies Per Plate				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* (pKM101)
With Activation	DMSO	100 μL/plate	34	118	24	18	196
	GSK1265744	1.5	40	102	23	11	143
	GSK1265744	5	34	98	22	16	124
	GSK1265744	15	28	106	22	8	132
	GSK1265744	50	29	101	23	11	122
	GSK1265744	150	30	106	24	12	124
	GSK1265744	238	29	92	17	9	109
	Benzo[a]pyrene	10	333[2]	NT	NT	NT	NT
	2-aminoanthracene	5	NT	976[2]	308[2]	107[2]	NT
	2-aminoanthracene	10	NT	NT	NT	NT	585[2]

Key:

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

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

NT = Not tested.

GSK1265744B: Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Metabolic Activation	Test Compound	Concentration (μg/plate)[1]	Main Plate Incorporation (Ames) Test 2 Mean Number of Revertant Colonies Per Plate				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* (pKM101)
Without Activation	DMSO	100 μL/plate	24	95	13	11	150
	GSK1265744	1.5	26	100	15	9	110
	GSK1265744	5	28	99	19	12	137
	GSK1265744	15	27	105	16	12	132
	GSK1265744	50	29	97	20	15	128
	GSK1265744	150	28	93	24	9	125
	GSK1265744	238	22	91	24	15	108
	2-nitrofluorene	5	1062[2]	NT	NT	NT	NT
	Sodium azide	2	NT	644[2]	604[2]	NT	NT
	9-aminoacridine	50	NT	NT	NT	162[2]	NT
	4-nitroquinoline-1-oxide	2	NT	NT	NT	NT	978[2]

Key:

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

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

NT = Not tested.

GSK1265744B: Bacterial Mutation Assay (Ames Test) with *Salmonella typhimurium* and *Escherichia coli* (Continued)

Metabolic Activation	Test Compound	Concentration (μg/plate)[1]	Main Plate Incorporation (Ames) Test 2 Mean Number of Revertant Colonies Per Plate				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* (pKM101)
With Activation	DMSO	100 μL/plate	32	111	19	15	170
	GSK1265744	1.5	32	103	16	17	139
	GSK1265744	5	33	115	22	15	147
	GSK1265744	15	34	90	24	14	159
	GSK1265744	50	32	106	26	13	141
	GSK1265744	150	33	101	19	9	138
	GSK1265744	238	26	101	19	11	139
	Benzo[a]pyrene	10	331[2]	NT	NT	NT	NT
	2-aminoanthracene	5	NT	891[2]	268[2]	109[2]	NT
	2-aminoanthracene	10	NT	NT	NT	NT	514[2]

Key:

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

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

NT = Not tested.

Table 8.2 GSK1265744B: In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus

Genotoxicity: In Vitro

Report Title: GSK1265744B: In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus

Test Article: GSK1265744B (sodium salt)

Batch Number: [redacted]

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

No. of Independent Tests: 3

[redacted] **Study No.:** 2990/142

GSK Ref. No.: V27561

GSK Document Number: WD2007/00788

Cell Type: L5178Y mouse lymphoma cells

No. of Replicate Cultures: 4 (vehicle); 2 (treatment and positive controls)

Location in CTD: m4.2.3.3.1

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

Vehicles: Test Article: Dimethylsulphoxide (DMSO) **Positive Controls:** DMSO

GLP Compliance: Yes

Treatment: 3 hour treatment with and without S9-mix; treatment for 24 hours without S9-mix.

Date of Treatment(s): May to June 2007

Cytotoxic Effects: Some evidence of cytotoxicity observed (maximum concentration limited by solubility in DMSO)

Genotoxic Effects: Negative

Test Article	Dose Level[1] µg/mL	3 Hour Treatment -S9-Mix		3 Hour Treatment +S9-Mix		24 Hours 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	90.58	100	77.05	100	89.18
GSK1265744	4	92	115.55	116	79.56	NE	NE
GSK1265744	8	102	90.35	114	70.84	94	92.78
GSK1265744	12	67	79.69	91	78.94	75	111.83
GSK1265744	14	NT	NT	NT	NT	50	94.66
GSK1265744	16	53	90.81	98	72.68	NE	NE
GSK1265744	18	NT	NT	NT	NT	35	149.46
GSK1265744	20	47	76.35	110	67.54	34	141.60
GSK1265744	23.8	57	78.71	109	69.96	33	135.86
Methyl methane sulphonate	20	43	814.32	NT	NT	NT	NT
Methyl methane sulphonate	5	NT	NT	NT	NT	56	711.39
Benzo[a]pyrene	3	NT	NT	14	984.63	NT	NT

Key:

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

NE = Not evaluated. NT = Not tested.

Table 8.3 GSK1265744A: In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus

Study Type: Genetic Toxicology In Vitro
Test for Induction of: Forward mutation at the TK$^{+/-}$ locus
Cell Type: L5178Y Mouse Lymphoma Cells

Report Title: GSK1265744A: In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus
No. of Independent Tests: 2
No. of Replicate Cultures: 2 (vehicle); 1 (treatment and positives

Test Article: GSK1265744A
Batch Number: [redacted]
Study No: MLA-600
GSK Document No.: WD2007/01740
Location in CTD: m4.2.3.3.1

Metabolising System: Phenobarbital –5,6-Benzoflavone -induced rat liver S9-mix containing 1% v/v S9-fraction (final)
Vehicles **Test Article:** DMSO **Positive Controls:** DMSO
Treatment: 3 hr treatment with S9-mix; treatment for 24 hr without S9-mix
Cytotoxic Effects: Reduction in RTG
Genotoxic Effects: Positive
Study Type: Genetic Toxicology In Vitro

GLP Compliance: No
Date of Treatment(s): July, 2006

Test Article	Dose Level[1] mcg/mL	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})
DMSO	0	100	122.25	100	105.41
GSK1265744A	2			85	120.56
GSK1265744A	12.5			39	179.32
GSK1265744A	20	102	132.81	14	317.26[1]
GSK1265744A	60	47	164.76		
GSK1265744A	100	33	176.10		
GSK1265744A	140	26	127.68		
Methyl methane sulphonate	5			63	557.55[1]
Dimethylbenzanthracene	1	58	871.46[1]		

1. Mean mutant frequency exceeds the sum of the mean control mutant frequency plus Global Evaluation Factor (126x10^{-6})

9. GENOTOXICITY: IN VIVO

Table 9.1 GSK1265744B: Oral Bone Marrow Micronucleus Assay in Rats

Genetic Toxicology: In Vivo

Test for Induction of: Structural chromosomal damage and/or aneuploidy

Species/Strain: Rat: (Hsd:SD)
Approximate Age: 8 weeks at time of dosing

Cells Evaluated: Polychromatic erythrocytes (PCE)
No. of Cells Analysed/Animal: 2000 PCE

Report Title: GSK1265744B: Oral Bone Marrow Micronucleus Assay in Rats
Treatment Schedule: Two doses 24 hours apart (vehicle & test compound).
Positive control dosed once only.
Sampling Time: 24 hours after final dose
Method of Administration: Oral gavage
Dose Volume: 15 mL/kg (10 mL/kg for positive control)
Vehicle/Formulation: 0.5% w/w hydroxypropylmethylcellulose (HPMC K15M Premium) with 0.1% w/w Polysorbate (Tween™) 80 in reverse osmosis (deionized) water/suspension

Test Article: GSK1265744B (sodium salt)
Batch Number: [redacted]
PCS-MTL Study No.: 961509
GSK Reference No.: R27562
GSK Document No.: WD2007/00789
Location in CTD: m4.2.3.3.2

GLP Compliance: Yes
Date of Dosing: May/June 2007

Special Features: None
Toxic/Cytotoxic Effects: None
Genotoxic Effects: Negative
Evidence of Exposure: Mean plasma concentration (range 152932 to 157162 ng/mL)

Test Compound	Dose[1] (mg/kg/day)	No. of Animals Analysed[2]	Group Mean % PCE	Group Mean MPCE[3]
Vehicle	0	6M	49.2	1.2
GSK1265744	1000	6M	50.4	2.2
GSK1265744	2000	6M	44.8	1.8
Cyclophosphamide	20	3M	49.0	62.7

Key:
1 = All doses/concentrations are expressed in terms of parent compound.
2 = M = Male.
3 = Group mean number of micronucleated polychromatic erythrocytes (MPCE) per 2000 PCE analyzed.

10. CARCINOGENICITY

Table 10.1 Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks

Study Type: Carcinogenicity	**Report Title:** GSK1265744B: A 2-Year Oral (Gavage) Carcinogenicity Study in Mice	**Test Item:** GSK1265744B (sodium salt) **Batch No.:** [redacted]
Species/Strain: Mouse/Crl:CD1 (ICR)	**Duration of Dosing:** At least 104 weeks	**GSK Reference No.:** M30877G
Initial Age: 7 weeks	**Route/Frequency:** Oral by gavage, once daily	**GSK Document Number:** 2017N310750
Date of First Dose: 18 September 2014	**Vehicle/Formulation:** 0, 0.25, 0.5, 1, 3.5 or 7.5 mg/mL in 0.5% (w/v) Hydroxypropylmethylcellulose (K-15M) / 0.1% (w/v) Tween 80 in Ultra Pure Water.	**Location in CTD**: m4.2.3.4.1 **Study in Compliance with GLP:** Yes

Data Collected: Toxicokinetics, clinical observations (including mass palpation), body weight, food consumption, and ophthalmoscopy. Blood smears (not evaluated), macroscopic and microscopic pathology.

Basis for high dose selection: 75 mg/kg/day in males and 35 mg/kg/day in females were selected since both doses were anticipated to provide similar exposures and were well tolerated in the preceding 13 week study. In addition, exposure plateaus occur between 10 and 75 mg/kg/day.

Conclusion: GSK1265744B was given to mice (60/sex/group) at 0 (vehicle), 2.5, 10 or 75 mg/kg/day (males) and at 0 (vehicle), 2.5, 5 or 35 mg/kg/day (females) once daily for a minimum of 104 weeks by oral gavage. Statistical analyses showed no increases in mortality in animals given GSK1265744.

There were no test item effects on the distribution of non-neoplastic or neoplastic lesions contributing to early death or preterminal euthanasia and overall there were no GSK1265744-related non-neoplastic or neoplastic macroscopic or microscopic findings.

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

		Male				Female			
Daily Dose (mg/kg/day) [a]		0	2.5	10	75	0	2.5	5	35
Numbers of Animals:	**Main**	60	60	60	60	60	60	60	60
	Toxicokinetic [b]	9	42	42	42	9	42	42	42
$AUC_{(0-t)}$ (µg.h/mL)	**Week 4**	NA	250	583	1290	NA	306	538	1370
	Week 26	NA	230	574	1140	NA	296	532	1060
C_{max} (µg/mL)	**Week 4**	NQ	13.5	33.3	67.5	NQ	18.8	31.8	70.9
	Week 26	NQ	12.3	32.6	65.4	NQ	17.1	28.8	70.2
Noteworthy Findings									
Number of Surviving Mice at Week 104		35	27	29	30	23	35	31	20
Survival at Week 104 (%)		58	45	48	50	38	58	52	33
Total Decedents (number killed/died)		25	33	31	30	37	25	29	40
Cause of demise									
Undetermined		2	5	3	0	2	1	3	6
Accidental[c]		0	1	1	0	1	0	0	0
Bronchioloaveolar carcinoma		11	5	8	6	3	2	2	3
Lymphoma		2	3	2	3	9	7	2	9
Amyloidosis		0	3	1	1	4	2	4	4
Obstructive uropathy		4	6	4	9	0	0	0	0

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

		Male				Female			
Daily Dose (mg/kg/day) [a]		0	2.5	10	75	0	2.5	5	35
Mean Bodyweight (X control) [d]	**Week 13**	43.95 g	1.00	1.02	1.02	35.65 g	0.99	1.00	0.98
	Week 52	52.15 g	1.01	1.03	1.01	45.11 g	0.98	0.98	0.95
	Week 80	53.69 g	1.00	1.00	0.99	48.50 g	0.97	0.95	0.90
	Week 104	51.05 g	0.98	1.01	0.99	43.44 g	1.05	0.96	0.94
Mean Body Weight Change (Xcontrol) [d]			1.03						
Weeks -1 to 13 (Day -1 to 91)		11.30 g		1.11	1.10	10.14 g	1.00	1.06	0.94
Weeks 13 to 28 (Days 91 to 196)		4.81 g	0.98	1.10	0.88	5.05 g	1.00	0.62 [e]	0.82
Weeks 28 to 52 (Days 196 to 364)		3.39 g	1.19	1.04	1.09	4.70 g	0.83	0.99	0.84
Weeks 52 to 80 (Days 364 to 560)		1.15 g	0.87	0.43	0.18	3.04 g	0.99	0.58	0.24 [f]
Weeks 80 to 104 (Days 560 to 728)		-2.95 g	1.03	0.93	0.75	-4.84 g	0.41	0.78	0.52
Overall mean bodyweight change (Xcontrol) [d]		18.32 g	0.96	1.05	0.99	17.95 g	1.17	0.91	0.86
Weeks -1 to Week 104									
Mean Food Consumption		There was a slight reduction in food consumption for GSK1265744-treated females when compared to controls, however the values (mean g/animal/day) were very variable and generally not dose-dependent.							
Microscopic examination - Neoplastic lesions (without consideration of cause of relevance)		Statistical analysis: Peto analysis, trend test							
Adipose Tissue (no. examined)		2	4	3	6	6	8	7	7
M-bronchioloalveolar carcinoma		1	1	0	1	0	0	0	0
M-histiocytic sarcoma		0	0	0	0	0	0	0	1
M-malignant lymphoma		1	1	0	1	4	5	1	4

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-adenocarcinoma	0	0	0	1	0	0	0	0
M-sarcoma	0	1	0	0	0	1	2	0
B-hemangioma	0	0	0	0	1	0	0	0
M-osteosarcoma	0	0	1	0	0	0	0	0
M-granulocytic leukemia	0	0	0	0	0	0	0	1
M-hemangiosarcoma	0	0	0	0	1	0	0	0
M-malignant thymoma	0	0	0	0	0	0	1	0
Aorta (no. examined)	60	60	60	60	60	60	59	60
M-malignant lymphoma	2	2	1	0	3	5	2	6
M-bronchioloalveolar carcinoma	0	0	3	1	0	0	0	0
M-sarcoma	0	0	1	0	0	0	0	0
M-malignant thymoma	0	0	1	0	0	1	0	0
M-granulocytic leukemia	0	0	0	0	1	0	0	0
M-histiocytic sarcoma	0	0	0	0	1	0	0	1
M-osteosarcoma	0	0	1	0	0	0	0	0
Body cavity, abdominal (no. examined)	4	0	2	6	9	5	3	6
M-malignant lymphoma	2	0	1	1	4	5	1	1
M-granulocytic leukemia	1	0	0	0	1	0	0	1
B- benign neuroendocrine cell tumor	0	0	0	1	0	0	0	0
M-adenocarcinoma	0	0	0	1	0	0	0	0

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-sarcoma	0	0	0	0	0	0	2	0
M-osteosarcoma	0	0	1	0	0	0	0	0
M-malignant mesothelioma	0	0	0	1	0	0	0	0
Body cavity, cranial (no. examined)	0	1	0	1	0	0	0	2
M-malignant lymphoma	0	0	0	1	0	0	0	0
Body cavity, nasal (no. examined)	60	60	60	60	60	60	60	60
M-malignant lymphoma	2	0	0	0	0	3	1	2
M-granulocytic leukemia	1	0	0	0	0	0	0	1
M-histiocytic sarcoma; bilateral	0	0	0	0	1	0	0	0
Body cavity, oral (no. examined)	0	0	0	0	0	0	1	0
B-papilloma	0	0	0	0	0	0	1	0
Body cavity, pelvic (no. examined)	2	2	1	4	2	1	0	1
M-granulocytic leukemia	1	0	0	0	0	0	0	0
M-malignant lymphoma	0	0	0	0	1	1	0	1
Body cavity, thoracic (no. examined)	6	3	5	4	11	4	2	4
M-malignant lymphoma	1	2	1	2	5	3	1	4
M-granulocytic leukemia	1	0	0	0	1	0	0	0
M-bronchioloalveolar carcinoma	1	0	0	1	1	1	0	0
M-adenocarcinoma	0	0	0	1	0	0	0	0
M-sarcoma	0	1	1	0	0	0	0	0

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-malignant mesothelioma	0	0	1	0	0	0	0	0
Bone (no. examined)	0	1	1	1	0	1	0	1
M-hemangiosarcoma	0	0	0	1	0	0	0	0
M-sarcoma	0	0	0	0	0	1	0	0
M-osteosarcoma	0	0	1	0	0	0	0	0
M-squamous cell carcinoma	0	1	0	0	0	0	0	0
Bone, calvarium (no. examined)	1	0	0	0	0	0	0	0
M-malignant lymphoma	1	0	0	0	0	0	0	0
Bone, femur (no. examined)	60	60	60	60	60	60	60	60
M-granulocytic leukemia	0	0	0	0	0	0	0	1
M-osteosarcoma	0	0	1	0	0	0	0	0
M-malignant lymphoma	1	0	1	0	0	2	0	3
Bone, sternum (no. examined)	60	60	59	60	60	59	59	60
M-malignant lymphoma	2	1	1	0	2	1	0	5
M-granulocytic leukemia	0	0	0	0	0	0	0	1
M-sarcoma	0	0	1	0	0	0	0	0
M-histiocytic sarcoma	0	0	0	0	0	0	1	2
M-malignant mesothelioma	0	0	1	0	0	0	0	0
Bone marrow (no. examined)	60	60	60	60	60	60	60	60
M-malignant lymphoma	2	0	1	1	2	4	3	8

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-granulocytic leukemia	2	0	0	0	3	0	1	3
M-histiocytic sarcoma	0	1	0	0	1	0	1	0
M-osteosarcoma	0	0	1	0	0	0	0	0
Brain (no. examined)	60	60	60	60	60	60	60	60
M-malignant lymphoma	2	2	2	0	0	1	0	4
M-carcinoma	0	0	0	1	0	1	0	0
M-granulocytic leukemia	0	0	0	0	1	0	0	1
Cervix (no. examined)	-	-	-	-	60	60	59	60
M-leiomyosarcoma	-	-	-	-	0	3	1	0
M-histiocytic sarcoma	-	-	-	-	2	0	1	3
B-leiomyoma	-	-	-	-	0	0	0	1
M-malignant lymphoma	-	-	-	-	5	6	1	3
M-adenocarcinoma	-	-	-	-	0	0	1	0
M- granulocytic leukemia	-	-	-	-	2	0	0	2
B-endometrial stromal polyp	-	-	-	-	1	0	0	0
B-polyp	-	-	-	-	0	1	0	0
Ear (no. examined)	0	0	0	0	0	1	0	0
B-hair follicle tumor; multiple; pilomatrixoma	0	0	0	0	0	1	0	0
Epididymus (no. examined)	60	60	60	60	-	-	-	-
M-malignant mesothelioma; bilateral	0	0	0	1	-	-	-	-

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-adenocarcinoma	0	0	0	1	-	-	-	-
M-adenocarcinoma; bilateral	1	0	0	0	-	-	-	-
M-granulocytic leukemia	1	0	0	0	-	-	--	-
M-malignant lymphoma; bilateral	1	4	1	2	-	-	-	-
M-bronchioloalveolar carcinoma; bilateral	0	0	1	0	-	-	-	-
B- inerstitial (leydig) cell adenoma; unilateral	0	0	1	0	-	-	-	-
Esophagus (no. examined)	60	60	60	60	60	59	60	60
M-granulocytic leukemia	0	0	0	0	2	0	0	0
M-malignant lymphoma	1	1	0	0	1	2	0	0
M-bronchioloalveolar carcinoma	0	0	1	0	0	0	0	0
M-malignant mesothelioma	0	0	1	0	0	0	0	0
Eye (no. examined)	60	60	60	60	60	60	60	60
M-malignant schwannoma; unilateral	0	0	0	0	0	1	0	0
M-malignant lymphoma; bilateral	1	0	2	1	1	6	0	4
M-granulocytic leukemia; bilateral	0	0	0	0	1	0	1	2
Gallbladder (no. examined)	60	59	59	60	59	60	60	60
M-malignant lymphoma	1	0	1	2	3	6	2	2
M-histiocytic sarcoma	0	0	0	0	0	0	2	0
M-sarcoma	0	0	0	0	0	0	1	0
M-granulocytic leukemia	0	0	0	0	0	0	0	1

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
Galt (no. examined)	2	0	0	3	7	0	2	5
M-malignant lymphoma	2	0	0	2	3	0	1	2
M-granulocytic leukemia	0	0	0	0	0	0	0	1
Gland, Adrenal (no. examined)	60	60	60	60	60	60	60	60
B-benign pheochromocytoma; unilateral	0	0	0	0	0	0	1	0
B-cortical adenoma; unilateral	0	1	1	1	0	0	0	0
B-cortical adenoma subcapsular; unilateral	0	0	0	0	0	0	0	2
M-granulocytic leukemia; bilateral	0	0	0	0	3	0	1	3
M-bronchioloalveolar carcinoma; unilateral	0	0	1	0	0	0	0	0
M-adenocarcinoma	0	0	0	0	1	0	0	0
M-malignant lymphoma; unilateral	0	1	0	0	2	0	0	1
M-malignant lymphoma; bilateral	1	2	2	2	1	7	0	5
M-sarcoma; unilateral	0	0	0	0	0	0	1	0
M-histiocytic sarcoma; unilteral	0	0	0	0	0	0	0	2
M-histiocytic sarcoma; bilateral	0	0	0	0	1	0	0	0
M-carcinoma	0	0	1	0	0	0	0	0
M-carcinoma;unilateral	0	0	0	0	0	0	1	0
M-subcapsular carcinoma;unilateral	0	0	0	0	0	1	0	0
M-paraganglioma; unilateral	0	0	0	1	0	0	0	0
Gland, clitoral (no. examined)	-	-	-	-	59	59	59	60

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-granulocytic leukemia	-	-	-	-	2	0	1	1
M-malignant lymphoma	-	-	-	-	0	5	0	2
M-adenocarcinoma	-	-	-	-	0	0	1	0
M-histiocytic sarcoma	-	-	-	-	0	0	1	0
Gland, harderian (no. examined)	60	60	60	60	60	60	60	60
B-multiple adenoma; unilateral	0	1	0	0	0	0	0	0
B-adenoma; unilateral	10	4	10	6	3	7	2	3
M-adenocarcinoma	0	0	0	0	0	0	1	0
M-malignant lymphoma; unilateral	1	0	0	0	0	0	0	0
M-malignant lymphoma; bilateral	1	1	2	0	0	5	0	3
M-granulocytic leukemia; bilateral	0	0	0	0	3	0	1	2
M-histiocytic sarcoma; bilateral	0	0	0	0	1	0	0	0
M-malignant thymoma; bilateral	0	0	0	0	1	0	0	0
Gland, lacrimal (no. examined)	0	3	1	0	0	3	1	1
M-malignant lymphoma; bilateral	0	0	1	0	0	1	0	1
Gland, mammary (no. examined)	13	6	8	15	57	59	59	58
B-adenoma	0	0	0	0	0	0	1	0
M-adenocarcinoma	0	0	1	1	4	0	1	0
M-granulocytic leukemia	0	0	0	0	1	0	0	3
M-malignant lymphoma	0	0	0	0	2	4	1	3

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-malignant thymoma	0	0	0	0	1	0	0	0
M-histiocytic sarcoma	0	0	0	0	0	0	1	0
Gland, pituitary (no. examined)	60	60	58	60	59	60	58	60
B-adenoma	0	1	0	0	2	2	1	0
M-carcinoma	0	0	0	1	1	1	0	0
M-malignant lymphoma	2	0	0	0	0	0	0	0
Gland, preputial (no. examined)	60	59	60	60	-	-	-	-
M-granulocytic leukemia; unilateral	1	0	0	0	-	-	-	-
M-adenocarcinoma; unilateral	0	0	0	1	-	-	-	-
M-malignant lymphoma; unilateral	1	3	1	0	-	-	-	-
Gland, prostate (no. examined)	60	60	60	60	-	-	-	-
M-adenocarcinoma	1	0	0	0	-	-	-	-
M-granulocytic leukemia	1	0	0	0	-	-	-	-
M-malignant lymphoma	2	3	1	3	-	-	-	-
M-osteosarcoma	0	0	1	0	-	-	-	-
M-malignant mesothelioma	0	0	0	1	-	-	-	-
Gland salivary, mandibular (no. examined)	60	60	60	60	60	60	60	60
M-malignant lymphoma; unilateral	2	1	1	2	4	5	3	3
M-malignant lymphoma; bilateral	0	0	1	0	0	0	0	0
M-granulocytic leukemia	0	0	0	0	1	0	0	0

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-granulocytic leukemia; unilateral	0	0	0	0	1	0	0	2
M-histiocytic sarcoma; unilateral	0	0	0	0	1	0	1	0
M-osteosarcoma	0	0	1	0	0	0	0	0
M-malignant thymoma	0	0	0	0	0	0	1	0
Gland salivary, parotid (no. examined)	59	60	60	60	60	60	60	60
M-malignant lymphoma; unilateral	2	2	1	2	4	6	1	3
M-malignant lymphoma; bilateral	0	0	1	0	0	1	0	0
M-granulocytic leukemia; unilateral	0	0	0	0	3	0	1	1
M-malignant thymoma; unilateral	0	0	0	0	1	0	0	0
Gland salivary, sublingual (no. examined)	60	60	60	60	60	60	60	60
M-malignant lymphoma; unilateral	2	0	0	1	3	5	2	3
M-granulocytic leukemia	0	0	0	0	0	0	0	1
M-granulocytic leukemia; unilateral	0	0	0	0	2	0	0	1
M-histiocytic sarcoma; unilateral	0	0	0	0	0	0	1	0
M-osteosarcoma	0	0	1	0	0	0	0	0
Gland, seminal vesicle (no. examined)	60	60	60	60	-	-	-	-
B-adenoma	0	0	1	0	-	-	-	-
M-adenocarcinoma; unilateral	0	0	0	1	-	-	-	-
M-adenocarcinoma; bilateral	1	0	0	0	-	-	-	-
M-malignant lymphoma; unilateral	1	0	1	2	-	-	-	-

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-malignant lymphoma; bilateral	1	2	1	1	-	-	-	-
M-adenosquamous carcinoma; unilateral	0	1	0	0	-	-	-	-
M-bronchioloalveolar carcinoma; bilateral	0	0	1	0	-	-	-	-
Gland, thyroid (no. examined)	60	60	60	60	59	60	60	60
B-follicular cell adenoma; unilateral	1	0	0	1	0	0	0	0
M-follicular cell carcinoma; unilateral	0	0	0	0	1	0	0	0
B-adenoma; unilateral	0	1	1	0	0	1	0	0
M-malignant lymphoma; unilateral	0	0	0	0	0	1	1	2
M-malignant lymphoma; bilateral	0	1	1	2	2	5	0	1
M-histiocytic sarcoma; unilateral	0	0	0	0	0	0	1	0
M-adenocarcinoma; bilateral	0	0	0	1	0	0	0	0
M-granulocytic leukemia; bilateral	0	0	0	0	1	0	0	0
M-malignant thymoma	0	0	0	0	0	1	0	0
Heart (no. examined)	60	60	60	60	60	60	60	60
M-malignant mesothelioma	0	0	1	0	0	0	0	0
M-granulocytic leukemia	1	0	0	0	2	0	0	3
M-sarcoma	0	1	1	0	0	1	0	0
M-bronchioloalveolar carcinoma	2	2	2	1	0	1	0	0
M-malignant lymphoma	2	4	2	4	6	7	2	7
M-histiocytic sarcoma	0	0	0	0	1	0	0	0

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-adenocarcinoma	0	0	0	1	0	0	0	0
M-malignant thymoma	0	0	0	0	1	0	0	0
M-osteosarcoma	0	0	1	0	0	0	0	0
Hemolymphoreticular tissue (no. examined)	60	60	60	60	60	60	60	60
M-histiocytic sarcoma	0	1	2	0	2	1	2	4
M-granulocytic leukemia	2	0	0	0	3	0	1	3
M-malignant lymphoma	4	7	2	4	10	11	7	12
M-malignant mast cell tumor	0	1	0	0	0	0	0	0
Joint (no. examined)	0	0	0	0	4	0	1	3
M-granulocytic leukemia	0	0	0	0	1	0	0	0
Kidney (no. examined)	60	60	60	60	60	60	60	60
B-adenoma; unilateral	1	1	0	1	0	0	0	0
M-carcinoma; unilateral	1	0	0	0	0	0	0	0
M-histiocytic sarcoma	0	0	1	0	0	0	1	0
M-histiocytic sarcoma; unilateral	0	0	0	0	0	1	0	1
M-histiocytic sarcoma; bilateral	0	0	0	0	1	0	0	2
M-granulocytic leukemia	0	0	0	0	0	0	0	1
M-granulocytic leukemia; bilateral	1	0	0	0	3	0	1	1
M-malignant lymphoma; unilateral	0	0	0	1	0	1	0	1
M-malignant lymphoma; bilateral	1	3	2	2	4	6	3	6

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-bronchioloalveolar carcinoma; unilateral	0	0	1	0	0	0	0	0
M-bronchioloalveolar carcinoma; bilateral	0	1	1	0	0	0	0	0
M-osteosarcoma; bilateral	0	0	1	0	0	0	0	0
Larynx (no. examined)	60	60	60	60	59	60	60	60
M-granulocytic leukemia	0	0	0	0	1	0	0	2
M-malignant lymphoma	1	1	2	1	1	5	0	3
Large intestine, cecum (no. examined)	60	60	60	60	60	60	60	60
B-leiomyoma	0	0	0	0	0	0	1	0
M-malignant lymphoma	2	1	1	0	2	2	0	2
M-granulocytic leukemia	0	0	0	0	2	0	1	0
M-histiocytic sarcoma	0	0	0	0	0	0	0	2
Large intestine, colon (no. examined)	60	60	60	60	60	60	60	60
M-granulocytic leukemia	0	0	0	0	2	0	0	0
M-malignant lymphoma	0	0	0	0	0	2	0	1
M-malignant lymphoma; bilateral	2	1	1	0	1	0	0	3
M-histiocytic sarcoma	0	0	0	0	0	0	1	1
B-hemangioma	1	0	0	0	0	0	0	0
Large intestine, rectum (no. examined)	59	59	60	59	60	60	60	60
M-granulocytic leukemia	0	0	0	0	1	0	1	1
M-malignant lymphoma	0	1	2	1	4	6	1	3

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-sarcoma	0	0	0	0	0	0	2	0
M-adenocarcinoma	0	0	0	0	0	0	1	0
M-histiocytic sarcoma	0	0	0	0	0	0	0	2
Liver (no. examined)	60	60	60	60	60	60	60	60
M-hepatocellular carcinoma	1	1	1	2	0	0	0	0
M-multiple hepatocellular carcinoma	0	1	0	0	0	0	0	1
B-hepatocellular adenoma	12	5	8	7	1	1	2	0
B-multiple hepatocellular adenoma	7	6	7	3	0	0	0	0
M-malignant lymphoma	3	2	2	3	6	8	5	10
M-granulocytic leukemia	2	0	0	0	3	0	1	3
M-multiple hepatocholangiocellular carcinoma	0	0	0	1	0	0	0	0
M-histiocytic sarcoma	0	1	1	0	2	1	2	3
M-adenocarcinoma	0	0	0	1	0	0	0	0
M-sarcoma	0	0	0	0	0	1	1	0
M-hemangiosarcoma	1	2	1	1	0	0	1	2
M-bronchioloalveolar carcinoma	0	1	1	0	0	0	0	0
M-osteosarcoma	0	0	1	0	0	0	0	0
Lung (no. examined)	60	60	60	60	60	60	60	60
M-histiocytic sarcoma	0	0	1	0	2	0	2	2
M-malignant mesothelioma	0	0	1	0	0	0	0	0

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M- Bronchioloalveolar carcinoma	13	8	5	12	3	3	4	5
M- Bronchioloalveolar carcinoma; multiple	6	3	6	3	2	0	3	0
M-granulocytic leukemia	2	0	0	0	3	0	1	3
B-bronchioloalveolar adenoma	16	7	16	13	8	8	13	5
B-bronchioloalveolar adenoma; multiple	6	5	5	6	0	3	2	0
M-malignant lymphoma	2	3	2	2	9	6	2	10
M-adenocarcinoma	0	0	0	1	3	0	0	0
M-fibrosarcoma	0	1	0	0	0	0	0	0
M-sarcoma	0	1	1	0	0	1	1	0
M-malignant thymoma	0	0	0	0	1	0	0	0
Lymph node (no. examined)	16	13	14	1	18	19	19	20
M-malignant lymphoma	2	3	1	1	8	8	2	9
M-granulocytic leukemia	0	0	0	0	1	0	0	2
M-bronchioloalveolar carcinoma	2	1	2	0	1	0	0	0
M-adenocarcinoma	0	0	0	0	1	0	0	0
B-hemangioma	0	1	0	0	0	0	0	0
M-sarcoma	0	1	0	0	0	0	1	1
M-histiocytic sarcoma	0	0	1	0	0	0	1	1
M-malignant thymoma	0	0	0	0	1	1	1	0
M-osteosarcoma	0	0	1	0	0	0	0	0

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
Lymph node, mandibular (no. examined)	60	59	59	60	60	59	58	59
M-granulocytic leukemia; unilateral	0	0	0	0	3	0	0	1
M-granulocytic leukemia; bilateral	0	0	0	0	0	0	0	1
M-malignant lymphoma; unilateral	1	4	0	0	5	2	3	1
M-malignant lymphoma, bilateral	2	0	2	3	3	6	1	9
M-histiocytic sarcoma	0	0	0	0	1	0	0	0
M-histiocytic sarcoma; unilateral	0	0	1	0	0	0	1	0
M-histiocytic sarcoma; bilateral	0	0	0	0	1	0	1	1
M-osteosarcoma	0	0	1	0	0	0	0	0
M-malignant thymoma	0	0	0	0	0	0	1	0
Lymph node, mesenteric (no. examined)	60	59	60	60	59	60	57	60
M-malignant lymphoma	3	4	2	2	8	7	5	10
M-sarcoma	0	0	0	0	0	0	1	0
M-granulocytic leukemia	0	0	0	0	3	0	1	3
M-histiocytic sarcoma	0	1	2	0	1	0	2	3
M-osteosarcoma	0	0	1	0	0	0	0	0
Muscle, skeletal (no. examined)	60	60	60	58	59	60	60	59
M-hemangiosarcoma	0	1	0	1	1	0	0	0
M-granulocytic leukemia	0	0	0	0	2	0	0	1
M-osteosarcoma	0	1	1	0	0	0	0	0

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-adenocarcinoma	0	0	0	1	0	0	0	0
M-malignant lymphoma	0	1	1	0	2	4	0	6
M-sarcoma	0	2	0	0	0	0	1	0
M-bronchioloalveolar carcinoma	0	0	1	0	0	0	0	0
Nerve, optic (no. examined)	59	57	58	59	58	57	59	58
M-malignant lymphoma; bilateral	1	0	1	0	0	0	0	2
Nerve, sciatic (no. examined)	60	60	60	60	60	60	60	60
M-malignant lymphoma	0	0	1	0	0	2	0	3
M-granulocytic leukemia	0	0	0	0	0	0	1	0
M-fibrosarcoma	0	1	0	0	0	0	0	0
Ovary (no. examined)	-	-	.	.	60	60	60	60
M-adenocarcinoma; bilateral	-	-	-	-	0	0	1	0
B-cystadenoma; unilateral	-	-	-	-	2	1	1	0
M-cystadenocarcinoma; unilateral	-	-	-	-	1	0	0	0
B-granulosa cell tumor; unilateral	-	-	-	-	0	0	1	0
B-thecoma;unilateral	-	-	-	-	0	0	0	1
B-adenoma; unilateral	-	-	-	-	1	0	0	0
M-malignant lymphoma; unilateral	-	-	-	-	1	1	1	0
M-malignant lymphoma; bilateral	-	-	-	-	6	6	3	7
M-granulocytic leukemia; bilateral	-	-	-	-	3	0	1	3

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-histiocytic sarcoma	-	-	-	-	1	0	0	0
M-histiocytic sarcoma; unilateral	-	-	-	-	0	0	0	2
M-histiocytic sarcoma; bilateral	-	-	-	-	1	0	2	1
M-leiomyosarcoma; unilateral	-	-	-	-	1	0	0	0
M-sarcoma	-	-	-	-	0	0	1	0
B-Sertoli cell tumor; unilateral	-	-	-	-	0	2	0	1
B-luteoma; unilateral	-	-	-	-	0	1	0	0
Pancreas (no. examined)	60	60	60	60	60	60	60	60
M-malignant lymphoma	3	1	2	1	6	7	2	7
M-histiocytic sarcoma	0	1	1	0	1	0	0	3
M-granulocytic leukemia	0	0	0	0	3	0	1	3
M-adenocarcinoma	0	0	0	1	0	0	0	0
M-bronchioloalveolar carcinoma	0	1	2	0	0	0	0	0
M-sarcoma	0	0	0	0	0	0	1	0
M-malignant thymoma	0	0	0	0	1	0	0	0
M-carcinoma	0	0	1	0	0	0	0	0
B-islet cell adenoma	0	0	2	0	0	0	0	0
M-islet cell carcinoma	1	0	0	0	0	0	0	0
Pericardium (no. examined)	0	0	3	1	0	0	1	0
M-malignant mesothelioma	0	0	1	0	0	0	0	0

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
Site, uncertain primary (no. examined)	0	0	0	0	0	0	0	1
M-sarcoma	0	0	0	0	0	0	0	1
Skin (no. examined)	60	60	60	60	60	60	60	60
B-papilloma	0	1	0	0	0	0	0	0
B-squamous cell papilloma	0	0	0	0	0	1	0	0
B-fibroma	0	0	1	0	0	0	0	0
B-basal cell tumor	0	1	0	0	0	0	0	0
M-granulocytic leukemia	1	0	0	0	1	0	0	3
M-malignant lymphoma	1	2	2	2	4	7	0	7
M-sarcoma	0	0	0	0	0	0	1	0
M-histiocytic sarcoma	0	0	0	0	0	0	1	1
M-malignant thymoma	0	0	0	0	1	0	0	0
Small intestine, duodenum (no. examined)	60	60	60	60	60	60	60	60
M-malignant lymphoma	1	0	0	0	1	0	0	2
M-histiocytic sarcoma	0	0	0	0	0	0	0	1
Small intestine, ileum (no. examined)	60	60	60	60	60	60	60	60
M-malignant lymphoma	0	1	1	0	0	3	0	4
M-granulocytic leukemia	0	0	0	0	0	0	0	1
M-histiocytic sarcoma	0	0	0	0	0	0	0	1
Small intestine, jejunum (no. examined)	60	59	60	60	60	60	60	60

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-adenocarcinoma	1	0	0	0	0	0	0	0
M-malignant lymphoma	1	0	0	0	1	0	0	2
M-granulocytic leukemia	0	0	0	0	0	0	0	1
M-histiocytic sarcoma	0	0	0	0	0	0	1	2
M-sarcoma	0	0	0	0	0	0	1	0
Spinal cord, lumbar (no. examined)	60	60	60	59	60	60	60	60
M-malignant lymphoma	1	1	2	0	0	2	0	4
M-granulocytic leukemia	0	0	0	0	1	0	0	1
B-hemangioma	0	0	0	0	1	0	0	0
Spleen (no. examined)	60	59	60	60	60	60	60	60
M-hemangiosarcoma	1	0	1	0	1	0	0	0
M-malignant lymphoma	3	3	2	3	8	7	7	11
M-granulocytic leukemia	2	0	0	0	3	0	1	3
M-histiocytic sarcoma	0	1	1	0	1	0	2	3
M-sarcoma	0	0	0	0	0	0	1	0
Stomach (no. examined)	60	60	60	60	60	60	60	60
M-adenocarcinoma	0	0	1	1	0	0	0	0
M-carcinoma	0	0	1	0	0	0	0	0
B-leiomyoma	1	0	0	0	0	0	0	0
M-malignant lymphoma	2	3	2	0	7	6	2	3

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-histiocytic sarcoma	0	0	0	0	0	0	0	2
M-granulocytic leukemia	0	0	0	0	2	0	1	2
M-squamous cell carcinoma	0	0	0	0	0	0	1	0
M-sarcoma	0	0	0	0	0	0	1	0
B-non glandular squamous cell papilloma	0	0	0	0	0	0	1	0
Subcutis (no. examined)	2	10	6	5	7	10	8	8
M-histiocytic sarcoma	0	0	1	0	0	0	0	1
M-adenocarcinoma	0	0	0	1	0	0	1	0
M-fibrosarcoma	0	1	1	0	1	0	0	1
M-osteosarcoma	0	1	0	0	0	0	0	0
M-sarcoma	1	2	0	0	0	3	1	0
M-malignant lymphoma	0	2	0	0	0	2	0	1
M-bronchioloalveolar carcinoma	0	0	0	0	1	0	0	0
M-hemangiosarcoma	0	0	0	0	0	0	1	0
M-malignant basal cell tumor	0	0	0	1	0	0	1	0
B-adnexal cystadenoma	0	0	0	1	0	0	0	0
B-benign hair follicle tumor	0	0	0	0	0	1	0	0
B-benign hair follicle tumor; pilomatrixoma	0	1	0	0	0	0	0	0
M-myxosarcoma	0	0	0	0	0	0	1	0
Tail (no. examined)	2	1	0	0	4	1	0	0

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-hemangiosarcoma	0	0	0	0	1	0	0	0
Testis (no. examined)	60	60	60	60	-	-	-	-
B-multiple interstitial (leydig) cell adenoma; bilateral	0	0	0	1	-	-	-	-
B-interstitial (leydig) cell adenoma; unilateral	2	0	0	2	-	-	-	-
M-interstitial (leydig) carcinoma	0	1	0	0	-	-	-	-
M-granulocytic leukemia; bilateral	1	0	0	0	-	-	-	-
M-malignant lymphoma; unilateral	0	1	1	1	-	-	-	-
M-bronchioloalveolar carcinoma; bilateral	0	0	1	0	-	-	-	-
Thymus (no. examined)	60	59	58	59	59	59	59	58
M-malignant lymphoma	4	3	2	3	9	8	3	12
M-malignant thymoma	0	0	1	0	1	1	1	0
M-bronchioloalveolar carcinoma	0	0	4	0	0	0	0	1
M-leukemia granulocytic	1	0	0	0	2	0	0	1
M-histiocytic sarcoma	0	0	0	0	1	0	1	1
M-carcinoma	0	0	0	0	0	0	0	1
M-hemangiosarcoma	0	0	0	0	0	0	0	1
Tongue (no. examined)	60	60	60	60	59	60	60	60
M-granulocytic leukemia	0	0	0	0	3	0	1	1
M-malignant lymphoma	0	1	1	2	2	4	1	4
Trachea (no examined)	60	60	60	60	60	60	60	60

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-histiocytic sarcoma	0	0	0	0	1	0	0	0
M-granulocytic leukemia	0	0	0	0	1	0	0	0
M-malignant lymphoma	1	3	2	1	1	5	1	2
Ureter (no. examined)	2	2	6	3	0	1	0	3
M-malignant lymphoma; unilateral	0	0	0	0	0	0	0	1
M-granulocytic leukemia; bilateral	0	0	0	0	0	0	0	1
Urinary bladder (no. examined)	60	60	60	60	57	60	60	60
M-transitional cell carcinoma	0	1	0	0	1	0	0	0
M-granulocytic leukemia	1	0	0	0	1	0	1	2
M-malignant lymphoma	1	1	1	1	8	7	1	7
M-histiocytic sarcoma	0	0	0	0	1	0	1	3
Uterus (no examined)	-	-	-	-	60	60	60	60
M-histiocytic sarcoma	-	-	-	-	2	0	2	3
B-leiomyoma	-	-	-	-	0	1	2	0
B-leiomyoma; unilateral	-	-	-	-	1	0	0	0
M-leiomyosarcoma	-	-	-	-	0	4	1	1
M-endometrial stromal sarcoma	-	-	-	-	1	1	0	0
B-endometrial stromal polyp	-	-	-	-	2	1	0	0
B-adenoma	-	-	-	-	0	1	0	0
M-adenocarcinoma	-	-	-	-	2	0	1	1

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
M-malignant lymphoma	-	-	-	-	7	8	2	6
M-granulocytic leukemia	-	-	-	-	2	0	1	3
M-sarcoma	-	-	-	-	0	1	1	0
B-polyp	-	-	-	-	0	2	1	0
M-hemangiosarcoma	-	-	-	-	0	0	1	0
B-cystadenoma; unilateral	-	-	-	-	0	0	1	0
Vagina (no. examined)	-	-	-	-	59	60	60	59
M-malignant lymphoma	-	-	-	-	5	4	0	4
M-granulocytic leukemia	-	-	-	-	3	0	0	3
M-leiomyosarcoma	-	-	-	-	0	1	0	0
M-sarcoma	-	-	-	-	0	0	1	0
M-adenocarcinoma	-	-	-	-	0	0	1	0
M-histiocytic sarcoma	-	-	-	-	1	0	1	2

Carcinogenicity Study of CAB Sodium in Mice for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** M30877G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	2.5	10	75	0	2.5	5	35
Vessel blood (no. examined)	0	0	0	0	0	0	1	0
M-bronchioloalveolar carcinoma	0	0	0	0	0	0	1	0

1. NQ = Not quantifiable; NA= Not applicable; g = grams; M = Malignant; B = Benign; - = Not examined.

a. Doses are expressed in terms of the parent compound GSK1265744.

b. For Toxicokinetic groups given GSK1265744, 3/sex/ group were designated as 'spare' animals for replacement when required.

c. Accidental deaths due to gavage dosing incidents.

d. For controls group means are shown, for Test Item-treated groups fold (X) change as compared to controls.

e. Statistically significantly different from control Group 1 ($p<0.01$). Statistical significance is based on actual data, not fold change.

f. Statistically significantly different from control Group 1 ($p<0.05$). Statistical significance is based on actual data, not fold change.

Table 10.2 Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks

Study Type: Carcinogenicity	**Report Title:** GSK1265744B: A 2-year Oral (Gavage) Carcinogenicity Study in Rat	**Test Item:** GSK1265744B (sodium salt) **Batch No.:** [redacted]
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** Up to 102 completed weeks for males; up to 101 completed weeks for females	**GSK Reference No.:** R30876G
Initial Age: 7 weeks	**Route/Frequency:** Oral by gavage, once daily	**GSK Document Number:** 2017N310751
Date of First Dose: 02 October 2014	**Vehicle/Formulation:** Suspension in 0.5% (w/v) Hydroxypropylmethylcellulose (K-15M) / 0.1% (w/v) Tween 80 in Ultra Pure Water.	**Location in CTD**: m4.2.3.4.1 **Study in Compliance with GLP:** Yes

Data Collected: Toxicokinetics, clinical observations (including mass palpation), body weight, food consumption and ophthalmoscopy; blood smears (not evaluated), macroscopic and microscopic observations.

Basis for high dose selection: 75 mg/kg/day was selected as the high dose since saturation of absorption occurs between 75 mg/kg/day and 1000 mg/kg/day. 1000 mg/kg/day was the no observed adverse effect level in a 26 week study.

Additional information: Females were terminated after 101 weeks dosing when the number of survivors in the control group reached 20. Males were terminated after 102 weeks dosing when the number of survivors in the high dose group reached 15.

Conclusion: GSK1265744B was given to rats (70/sex/group) at 0 (vehicle/Reference Item), 0.25, 2.5 or 75 mg/kg/day once daily by oral gavage for a minimum of 100 or 101 completed weeks for females or males respectively. There was no GSK1265744-related effect on mortality and there were no GSK1265744-related non-neoplastic or neoplastic macroscopic or microscopic findings.

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

		Male				Female			
Daily Dose (mg/kg/day) [a]		0	0.25	2.5	75	0	0.25	2.5	75
Numbers of Animals: Main		70	70	70	70	70	70	70	70
	Toxicokinetic [d]	6	6	6	6	6	6	6	6
$AUC_{(0-t)}$ (µg.h/mL)	**Week 4**	NQ	206	1260	3360	NQ	295	1620	4010
	Week 26	NQ	277	1470	2840	NQ	428	1980	4810
C_{max} (µg/mL)	**Week 4**	NQ	9.97	59.6	160	NQ	14.2	76.3	181
	Week 26	NQ	13.1	73.1	137	NQ	19.7	92.0	230
Noteworthy Findings									
Terminal Euthanasia (TE): Number of Surviving Rats [Week of TE]		25 [102]	19 [102]	25 [102]	15 [102]	20 [101]	18 [101]	20 [101]	19 [101]
Survival at Terminal Euthanasia (%)		36	27	36	21	29	26	29	27
Decedents		45	51	45	55	50	52	50	51
Clinical Observations									
Skin dryness (Day 195 to termination)									
	Number of observations	26	20	120	175	18	213	102	108
	Number of animals	4	7	19	21	10	22	18	15
Body Weight Gain (Xcontrol) [b]									
Weeks -1 to 13 (Day -1 to 91)		419.63 g	0.99X	1.01X	1.00X	159.56 g	1.01X	1.02X	1.06X
Weeks 13 to 28 (Days 91 to 196)		158.3 g	0.89X [c]	0.97X	0.90X [c]	71.31 g	1.04X	1.04X	1.01X
Weeks 28 to 52 (Days 196 to 364)		131.05 g	1.05X	1.01X	1.01X	115.36 g	1.07X	0.99X	1.01X
Weeks 52 to 80 (Days 364 to 560)		81.37 g	1.10X	0.87X	0.91X	100.79 g	1.01X	1.22X	1.40X

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
Weeks 80 to 100 (Days 560 to 700)	-6.39 g	18.26 g	-0.31 g	-59.33 g	37.55 g	1.22X	1.04X	0.41X
Overall mean bodyweight change (Xcontrol) [b] **Weeks -1 to 100**	756.07 g	1.01X	1.04X	0.88X	432.27 g	1.17X	1.09X	1.18X
Food Consumption	Lower food consumption for males given 75 mg/kg/day over last 13 weeks of study (down to 0.87X control)							
Neoplastic lesions (Not Test Item- related)								
Adipose tissue (no. examined)	4	4	2	3	6	0	1	3
M-leiomyosarcoma	0	0	0	0	1	0	0	0
M-adenocarcinoma	0	0	0	0	0	0	0	1
M-fibrosarcoma	1	0	0	0	0	0	0	0
M-histiocytic sarcoma	0	1	0	0	0	0	1	0
Body cavity, abdominal (no. examined)	2	2	1	1	0	1	1	0
M-sarcoma	0	0	1	0	0	0	0	0
M-fibrosarcoma	2	1	0	1	0	0	0	0
B-lipoma	0	0	0	0	0	0	1	0
M-histiocytic sarcoma	0	1	0	0	0	0	0	0
M-malignant mesothelioma	0	0	0	0	0	1	0	0
Body cavity, nasal (no. examined)	70	70	70	70	70	69	70	70
M-malignant lymphoma	0	1	1	1	0	0	0	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-histiocytic sarcoma	0	0	2	1	0	1	0	0
M-granulocytic leukemia	1	2	3	5	0	1	0	0
M-squamous cell carcinoma	1	0	0	0	0	0	0	0
B-glandular adenoma	0	1	1	0	0	0	0	0
Body cavity, oral (no. examined)	0	0	0	2	1	1	0	0
M-squamous cell carcinoma	0	0	0	2	1	1	0	0
Body cavity, thoracic (no. examined)	0	3	2	3	0	1	0	2
M-osteosarcoma	0	0	1	0	0	0	0	0
M-granulocytic leukemia	0	0	0	0	0	1	0	0
M-malignant mesothelioma	0	0	0	1	0	0	0	0
M-sarcoma	0	1	1	0	0	0	0	0
Bone (no. examined)	2	3	4	2	0	1	2	1
M-granulocytic leukemia	0	1	2	2	0	1	0	0
B-osteoma	2	0	0	0	0	0	0	0
M-osteosarcoma	0	1	2	0	0	0	1	1
M-fibrosarcoma	0	1	0	0	0	0	1	0
Bone, femur (no. examined)	70	70	70	70	69	70	70	70
M-granulocytic leukemia	1	3	4	5	0	1	0	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-histiocytic sarcoma	0	1	1	1	0	0	0	0
Bone sternum (no. examined)	70	70	70	70	70	70	70	70
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-histiocytic sarcoma	0	0	1	1	0	0	0	0
M-granulocytic leukemia	1	3	4	5	0	1	0	0
Bone marrow (no. examined)	70	70	70	70	70	70	70	70
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-histiocytic sarcoma	1	1	3	2	0	0	0	0
M-granulocytic leukemia	1	3	4	5	0	1	0	0
M-malignant pheochromocytoma	0	0	1	0	0	0	0	0
Brain (no. examined)	70	70	70	70	70	70	70	70
M-malignant astrocytoma	2	1	0	1	3	0	0	0
M-malignant granular cell tumor	0	1	0	0	0	0	0	0
M-malignant meningioma	0	0	1	0	0	0	0	0
M-histiocytic sarcoma	0	0	2	0	0	0	0	0
M-malignant lymphoma	0	0	1	1	0	0	0	0
M-granulocytic leukemia	1	1	1	1	0	0	0	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
B-hemangioma	0	0	1	0	0	0	0	0
Cervix (no. examined)	-	-	-	-	70	70	70	70
M-leiomyosarcoma	-	-	-	-	1	0	0	0
M-granulocytic leukemia	-	-	-	-	0	1	0	0
B-polyp	-	-	-	-	0	1	0	0
Ear (no. examined)	1	1	1	1	0	0	1	0
M-sebaceous cell carninoma	1	1	1	1	0	0	0	0
M-sarcoma	1	0	0	0	0	0	0	0
Epididymis (no. examined)	70	70	70	70	-	-	-	-
M-histiocytic sarcoma	0	1	0	0	-	-	-	-
M-granulocytic leukemia	1	0	1	0	-	-	-	-
M-fibrosarcoma	1	0	0	0	-	-	-	-
Esophagus (no. examined)	69	70	70	70	70	70	70	70
M-histiocytic sarcoma	0	0	1	0	0	0	0	0
Eye (no. examined)	70	70	70	70	70	70	70	70
M-malignant lymphoma	0	1	0	0	0	0	0	0
M-granulocytic leukemia	1	3	4	3	0	1	0	0
Gland, adrenal (no. examined)	70	70	70	70	70	70	70	70

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
B-benign pheochromocytoma	10	11	5	1	1	1	1	1
B-benign pheochromocytoma; multiple	1	0	0	0	0	0	0	0
B-cortical adenoma	0	0	1	0	1	1	0	1
M-malignant pheochromocytoma	2	1	2	1	0	1	0	0
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-granulocytic leukemia	1	2	3	1	0	1	0	0
M-leiomyosarcoma	0	0	0	0	1	0	0	0
M-fibrosarcoma	1	0	0	0	0	0	0	0
Gland, harderian (no. examined)	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	0	0	1	0	0	1	0	0
M-granulocytic leukemia	1	2	4	4	0	1	0	0
M-malignant lymphoma	0	1	1	0	0	0	0	0
M-squamous cell carcinoma	0	0	0	1	0	0	0	0
Gland, mammary (no. examined)	65	62	60	63	70	70	70	70
B-fibroadenoma	2	5	2	4	19	14	13	19
B-fibroadenoma; multiple	0	0	0	0	27	28	33	30
B-adenoma	1	0	0	0	6	7	6	3
B-adenoma; multiple	0	0	0	0	1	0	0	3

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-adenocarcinoma	0	2	1	0	13	21	13	12
M-adenocarcinoma; multiple	0	0	0	1	5	8	10	7
M-histiocytic sarcoma	0	0	1	0	0	0	0	0
M-granulocytic leukemia	1	2	3	1	0	1	0	0
Gland, parathyroid (no. examined)	66	69	64	66	66	67	67	68
B-adenoma	0	1	0	0	0	1	0	0
M-granulocytic leukemia	1	1	1	1	0	1	0	0
Gland, pituitary (no. examined)	70	70	70	70	70	69	69	68
B-pars intermedia adenoma	0	0	1	1	0	0	0	0
B-pars distalis adenoma	22	23	24	23	41	45	44	45
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-granulocytic leukemia	1	2	4	4	0	1	0	0
M-malignant astrocytoma	0	0	0	0	1	0	0	0
M-pars distalis carcinoma	2	0	0	1	0	2	1	0
Gland, preputial (no. examined)	70	70	70	70	-	-	-	-
M-histiocytic sarcoma	1	0	0	0	-	-	-	-
M-granulocytic leukemia	1	3	1	0	-	-	-	-
Gland, prostate (no. examined)	69	69	70	70	-	-	-	-

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-histiocytic sarcoma	1	0	1	0	-	-	-	-
M-granulocytic leukemia	1	3	4	4	-	-	-	-
M-malignant lymphoma	0	1	0	0	-	-	-	-
Gland salivary, mandibular (no. examined)	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	0	0	1	0	0	0	0	0
M-granulocytic leukemia	1	3	2	1	0	1	0	0
Gland salivary, parotid (no. examined)	69	70	70	70	70	70	70	69
M-histiocytic sarcoma	0	0	1	0	0	0	0	0
M-granulocytic leukemia	1	2	2	0	0	1	0	0
Gland salivary, sublingual (no. examined)	70	70	70	69	70	70	70	70
M-histiocytic sarcoma	0	0	1	0	0	0	0	0
M-granulocytic leukemia	1	3	3	1	0	1	0	0
Gland, seminal vesicle (no. examined)	69	69	70	70	-	-	-	-
M-histiocytic sarcoma	1	1	1	0	-	-	-	-
M-granulocytic leukemia	1	2	2	1	-	-	-	-
Gland thyroid (no. examined)	69	70	70	70	70	70	70	70
B-follicular cell adenoma	4	1	0	2	1	2	0	1
M-follicular cell carcinoma	0	1	1	0	0	0	0	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-c-cell carcinoma	1	3	0	0	0	2	1	0
B-c-cell adenoma	7	6	4	10	5	6	6	8
B-c-cell adenoma; multiple	1	1	2	2	0	0	1	1
M-histiocytic sarcoma	0	0	1	0	0	0	0	0
M-granulocytic leukemia	1	3	2	2	0	1	0	0
Head (no. examined)	0	0	0	1	0	0	0	0
M-fibrosarcoma	0	0	0	1	0	0	0	0
Heart (no. examined)	70	70	70	70	70	70	70	70
M-granulocytic leukemia	1	3	2	3	0	1	0	0
Hemolymphoreticular tissue (no. examined)	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	2	2	4	3	2	2	1	1
M-granulocytic leukemia	1	3	4	5	0	1	0	0
M-malignant lymphoma	0	1	1	2	0	1	0	0
Joint (no. examined)	4	5	3	5	3	2	2	1
M-granulocytic leukemia	0	1	0	0	0	0	0	0
Kidney (no. examined)	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	0	0	2	0	0	0	0	0
M-granulocytic leukemia	1	3	4	5	0	1	0	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-tubular cell carcinoma	3	1	1	2	1	3	1	0
M-tubular cell carcinoma; multiple	1	3	4	3	1	1	1	3
M-liposarcoma	1	0	0	0	1	0	0	0
M-leiomyosarcoma	0	0	0	0	1	0	0	0
B-tubular cell adenoma	0	1	1	0	0	1	1	1
B-lipoma	0	0	0	0	0	1	0	0
M-pars distalis carcinoma	1	0	0	0	0	0	0	0
M-fibrosarcoma	1	0	0	0	0	0	0	0
Larynx (no. examined)	69	70	70	70	70	70	70	69
M-histiocytic sarcoma	0	0	1	0	0	0	0	0
M-granulocytic leukemia	1	2	3	3	0	1	0	0
M-malignant lymphoma	0	1	1	0	0	0	0	0
B-polyp	0	0	0	0	1	0	0	0
Large intestine, cecum (no. examined)	70	70	70	70	70	70	70	70
B-leiomyoma	0	0	0	0	0	1	0	0
M-malignant lymphoma	0	1	1	0	0	0	0	0
M-granulocytic leukemia	0	0	0	1	0	1	0	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-hemangiosarcoma; multiple	1	0	0	0	0	0	0	0
M-hystiocytic sarcoma	0	0	0	0	0	0	1	0
Large intestine, colon (no. examined)	70	70	70	70	70	70	70	70
M-malignant lymphoma	0	1	0	0	0	1	0	0
M-granulocytic leukemia	0	0	0	0	0	1	0	0
M-histiocytic sarcoma	1	0	0	0	0	0	1	0
Large intestine, rectum (no. examined)	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	1	0	0	0	0	0	0	0
M-granulocytic leukemia	1	0	1	2	0	1	0	0
M-malignant lymphoma	0	1	0	0	0	0	0	0
M-hemangioma	0	0	0	0	0	0	1	0
M-hemangiosarcoma	0	0	0	0	0	0	0	1
B-polyp	0	0	0	0	1	0	0	0
Liver (no. examined)	70	70	69	70	70	70	70	70
M-hepatocellular carcinoma	0	1	0	0	0	0	0	0
M-hepatocellular adenoma	2	3	1	0	0	0	0	0
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-granulocytic leukemia	1	3	4	5	0	1	0	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
B-cholangioma	0	0	0	0	0	1	1	0
M-histiocytic sarcoma	1	1	2	2	0	0	1	1
M-hemangiosarcoma	0	0	1	0	0	0	0	0
M-fibrosarcoma	1	0	0	0	0	0	0	0
Lung (no. examined)	70	70	70	70	70	70	70	70
M-hemangiosarcoma	0	1	0	0	0	0	0	1
M-histiocytic sarcoma	1	1	3	2	1	0	1	1
M-granuloctytic leukemia	1	3	4	5	0	1	0	0
M-malignant lymphoma	0	1	1	0	0	0	0	0
M-adenocarcinoma	0	0	0	0	0	1	0	1
M-osteosarcoma	0	1	2	0	0	0	1	0
M-pars distalis carcinoma	1	0	0	1	0	0	0	0
M-fibrosarcoma	0	0	0	1	0	0	0	0
B-adenoma	0	0	1	0	0	0	0	0
M-sarcoma	0	0	0	0	0	1	0	0
M-liposarcoma	0	0	0	0	0	0	0	1
M-follicular cell carcinoma	0	0	1	0	0	0	0	0
Lymph node (no. examined)	14	12	18	16	14	15	14	14

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-malignant lymphoma	0	0	1	1	0	0	0	0
M-granulocytic leukemia	0	0	2	4	0	1	0	0
M-histiocytic sarcoma	1	1	3	2	0	1	1	0
M-malignant astrocytoma	0	0	0	0	1	0	0	0
M-leiomyosarcoma	0	0	0	0	1	0	0	0
B-hemangioma	0	0	0	0	0	0	1	0
M-myxosarcoma	0	0	1	0	0	0	0	0
M-osteosarcoma	0	0	1	0	0	0	0	0
M-sarcoma	0	0	0	1	0	0	0	0
M-c-cell carcinoma	0	0	0	0	0	1	0	0
M-adenocarcinoma	0	0	0	0	0	1	0	0
M-islet of Langerhans adenocarcinoma	1	0	0	0	0	0	0	0
Lymph node mandibular (no. examined)	70	70	70	70	70	70	70	70
M-granulocytic leukemia	1	3	4	5	0	1	0	0
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-histiocytic sarcoma	0	0	3	0	0	1	0	0
M-malignant astrocytoma	0	0	0	0	1	0	0	0
Lymph node, mesenteric (no. examined)	70	70	69	70	70	70	70	70

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-granulocytic leukemia	1	3	4	3	0	1	0	0
M-histiocytic sarcoma	0	0	1	0	0	0	1	0
M-hemangiosarcoma	2	2	4	0	1	0	1	0
Meninges (no. examined)	2	3	3	5	0	1	0	0
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-granulocytic leukemia	1	2	2	2	0	1	0	0
Mesentery (no. examined)	0	0	0	0	0	1	0	0
M-malignant granulosa cell tumor	0	0	0	0	0	1	0	0
Muscle, skeletal (no. examined)	70	69	70	70	69	70	70	70
B-fibroma	0	0	1	0	0	0	0	0
M-fibrosarcoma	1	0	1	0	0	0	0	0
M-histiocytic sarcoma	1	1	0	0	0	0	0	0
M-leiomyosarcoma	0	0	0	0	1	0	0	0
M-granulocytic leukemia	1	3	3	0	0	0	0	0
M-malignant lymphoma	0	0	1	0	0	0	0	0
M-liposarcoma	0	0	0	0	0	0	0	1
Nerve, optic (no. examined)	70	70	70	70	69	70	70	70

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-malignant lymphoma	0	1	0	0	0	0	0	0
M-granulocytic leukemia	1	3	4	2	0	1	0	0
Nerve, sciatic (no. examined)	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	1	0	0	0	1	0	0	0
M-granulocytic leukemia	1	3	2	0	0	0	0	0
Ovary (no. examined)	-	-	-	-	70	70	70	70
M-malignant granulosa cell tumor	-	-	-	-	0	1	0	0
M-granulocytic leukemia	-	-	-	-	0	1	0	0
M-histiocytic sarcoma	-	-	-	-	0	0	1	0
Pancreas (no. examined)	70	70	69	70	70	70	70	70
M-histiocytic sarcoma	0	1	1	1	0	0	0	0
M-malignant lymphoma	0	1	0	0	0	0	0	0
M-granulocytic leukemia	1	3	4	5	0	1	0	0
M-islet of langerhans adenocarcinoma	1	0	0	1	2	1	0	0
M-islet of Langerhans adenocarcinoma: multiple	1	0	0	0	0	0	0	0
M-leiomyosarcoma	0	0	0	0	1	0	0	0
B-islet of Langerhans adenoma	4	9	7	8	3	4	3	7
M-acinar carcinoma	0	1	0	0	0	0	0	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-fibrosarcoma	1	0	0	0	0	0	0	0
B-acinar adenoma	0	2	0	1	0	0	0	0
Pericardium (no. examined)	0	0	0	1	1	1	0	1
M-granulocytic leukemia	0	0	0	0	0	1	0	0
Skin (no. examined)	70	70	70	70	70	70	70	70
B-squamous cell papilloma	0	3	1	2	1	0	0	0
B-benign hair follicle tumor	0	1	2	0	2	0	0	0
M-malignant basal cell	0	0	1	0	0	0	0	0
M-squamous cell carcinoma	1	1	0	0	3	0	0	1
M-histiocytic sarcoma	1	1	1	1	0	0	0	0
M-Keratoacanthoma	4	4	8	4	1	0	0	0
M-granulocytic leukemia	1	2	1	1	0	0	0	0
B-fiobroepithelial polyp	0	0	0	2	1	0	0	0
M-squamous cell carcinoma	0	1	0	0	0	1	1	0
B-sebaceous cell adenoma	0	1	0	0	0	0	0	0
Small intestine, duodenum (no examined)	70	70	69	70	70	70	70	70
M-histiocytic sarcoma	0	1	0	1	0	0	0	0
M-granulocytic leukemia	0	1	1	1	0	0	0	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
Small intestine, ileum (no. examined)	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	1	0	0	0	0	0	0	0
M-granulocytic leukemia	0	0	1	2	0	1	0	0
M-malignant lymphoma	0	1	0	0	0	0	0	0
Small intestine, jejunum (no. examined)	70	70	70	70	70	70	69	70
M-adenocarcinoma	0	1	0	0	0	0	0	0
M-histiocytic sarcoma	0	1	1	0	0	0	0	0
M-granulocytic leukemia	1	1	3	1	0	1	0	0
M-malignant lymphoma	0	1	0	0	0	0	0	0
M-liposarcoma	0	0	0	0	0	1	0	0
Spinal cord, lumbar (no. examined)	70	69	69	70	69	68	70	70
M-malignant astrocytoma	0	0	0	0	1	0	0	0
M-malignant lymphoma	0	0	1	1	0	0	0	0
M-histiocytic sarcoma	0	0	1	0	0	0	0	0
Spleen (no. examined)	70	70	70	70	69	70	70	70
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-granulocytic leukemia	1	3	4	5	0	1	0	0
M-histiocytic sarcoma	1	1	1	1	0	0	1	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
M-sarcoma	0	0	1	0	0	0	0	0
Stomach (no. examined)	70	70	69	70	70	70	70	70
M-leiomyosarcoma	0	0	0	1	1	0	0	0
M-histiocytic sarcoma	1	1	1	0	0	0	1	0
M-granulocytic leukemia	1	2	3	3	0	1	0	0
Subcutis (no. examined)	17	18	21	26	10	8	12	12
M-hemangiosarcoma	1	0	0	0	0	0	0	1
M-histiocytic sarcoma	2	2	3	2	0	2	0	0
M-fibrosarcoma	5	4	4	10	3	5	2	4
M-fibrosarcoma; multiple	0	2	0	2	1	0	0	0
B-fibroma	7	4	11	5	2	2	3	4
B-fibroma; multiple	0	0	0	0	0	1	0	0
B-lipoma	3	1	2	4	2	0	6	2
M-myxosarcoma	1	2	1	0	0	0	1	0
M-sarcoma	1	0	0	2	1	0	0	0
B-fibrolipoma	0	0	1	0	0	0	0	0
B-hemangioma	0	0	0	1	0	0	0	0
M-liposarcoma	0	0	1	0	0	0	0	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
B-myxoma	0	0	0	1	0	0	0	0
M-granulocytic leukemia	0	1	0	0	0	0	0	0
Testis (no. examined)	70	70	70	70	-	-	-	-
B-hemangioma	0	0	1	0	-	-	-	-
B-interstitial (leydig) cell adenoma	3	1	2	2	-	-	-	-
M-granulocytic leukemia	0	1	0	0	-	-	-	-
Thymus (no. examined)	69	70	70	69	70	70	70	70
M-malignant lymphoma	0	1	1	1	0	0	0	0
M-histiocytic sarcoma	0	0	2	1	0	0	0	0
M-granulocytic leukemia	1	3	4	4	0	1	0	0
Tongue (no. examined)	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	0	0	0	0	0	1	0	0
M-granulocytic leukemia	1	1	0	1	0	1	0	0
Trachea (no. examined)	70	70	70	70	70	70	70	70
M-histiocytic sarcoma	0	0	1	0	0	0	0	0
M-granulocytic leukemia	1	3	2	2	0	0	0	0
Ureter (no. examined)	1	0	0	1	2	0	0	0
M-histiocytic sarcoma	1	0	0	0	0	0	0	0

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
Urinary bladder (no. examined)	69	69	70	70	69	70	70	70
B-transitional cell papilloma	0	1	0	0	0	0	0	1
M-histiocytic sarcoma	0	0	0	0	1	0	1	0
M-granulocytic leukemia	1	1	3	1	0	1	0	0
B-polyp	0	1	0	0	0	0	0	0
Uterus (no. examined)	-	-	-	-	70	70	70	70
M-histiocytic sarcoma	-	-	-	-	0	0	1	0
B-leiomyoma	-	-	-	-	1	0	0	0
M-leiomyosarcoma	-	-	-	-	1	0	0	0
M-endometrial stromal sarcoma	-	-	-	-	1	1	2	0
M-adenocarcinoma	-	-	-	-	0	0	1	0
B-hemangioma	-	-	-	-	1	0	0	1
B-fibroma	-	-	-	-	0	0	0	1
M-tubular cell carcinoma	-	-	-	-	0	1	0	0
M-granulocytic leukemia	-	-	-	-	0	1	0	0
B-polyp	-	-	-	-	3	3	3	4

Carcinogenicity Study of CAB Sodium in Rats for 104 Weeks (Continued)

Study Type: Carcinogenicity **GSK Reference No.:** R30876G

	Male				Female			
Daily Dose (mg/kg/day) [a]	0	0.25	2.5	75	0	0.25	2.5	75
Vagina (no. examined)	-	-	-	-	70	70	70	70
M-leiomyosarcoma	-	-	-	-	53	49	48	60
B-polyp	-	-	-	-	0	1	0	0

NQ = Not quantifiable; - = Not applicable; B = benign; M = malignant; g = grams

a. Doses are expressed in terms of the parent compound GSK1265744.

b. For control group mean is shown, for treated group X change as compared to control.

c. Statistically significantly different from control Group 1 ($p<0.05$). Statistical significance is based on actual data, not fold change.

d. 3 animal/sex/group were used for TK sampling and 3 animals/sex/group were used as replacement if required.

11. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: NON-PIVOTAL STUDIES

Table 11.1 GSK1265744B: Oral Dose Range Study in Female Rabbits

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Dose Levels[a] (mg/kg/day)	Number of Females/ Group	Noteworthy Findings	GSK Document Number/ Study No. (Module)
Rabbit / Dutch Belted [Haz:(DB)SPF]	Oral (0.5% hydroxypropyl methylcellulose (HPMC) / 0.1% Tween 80 in purified water / suspension)	13 days	(Round 1) 0 30 250 (Round 2) 0 500 1000 (Round 3) 0 2000 (once daily) 2000 (1000 twice daily)	 2 4 4 2 4 4 2 4 4	There were no effects on maternal body weight or food consumption at any dose level. The clinical observation of pale feces at 2000 mg/kg/day was presumed to be test article in the feces. The maximal systemic exposure was achieved with a single oral dose of 2000 mg/kg/day.	CD2008/01276 D08251 (m4.2.3.5.2)

Key:

a. Dose levels of CAB are expressed in terms of the free acid.

12. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: FERTILITY AND EARLY EMBRYONIC DEVELOPMENT TO IMPLANTATION (PIVOTAL)

Table 12.1 GSK1265744B: Oral Female Fertility, Early Embryonic and Embryofetal Development Study in Rats

Study Type: Reproductive and Developmental Toxicology

Report Title: GSK1265744B: Oral Female Fertility, Early Embryonic and Embryofetal Development Study in Rats

Test Article: GSK1265744 sodium salt
(Lot/Batch No.): [redacted]

Design Similar to ICH 4.1.1: Yes

Duration of Dosing: 2 weeks prior to mating, during mating and up to Day 17 pc, inclusive.

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

Study No.: G08284

Initial Age: 10 weeks

Route/Frequency: Oral, once daily

GSK Document Number: CD2009/00105

Day of Sperm/Plug Present: Day 0 post coitum (pc)

Location in CTD: m4.2.3.5.1

Date of First Dose: 23 March 2009

Day of C-Section: Day 21 pc

GLP Compliance: Yes

Special Features: None

Method of Administration: Gavage

No Observed Adverse Effect Level:
F_0 Reproductive Effects: 1000 mg/kg/day
F_1 Litters: 5 mg/kg

Vehicle/Formulation: 0.5% hydroxypropylmethylcellulose with 0.1% polyoxyethylene sorbitan monooleate (Tween 80) in purified water

Data Collected: F_0 females: Mortality, clinical observations, body weight, food consumption, estrous cycle, mating, fertility, necropsy, corpora lutea and uterine weight; F_1 litters: Implantations, resorptions, live and dead fetuses, fetal weight, sex, and placental and fetal morphology (external, visceral and skeletal).

Conclusion: GSK1265744 at 0.5, 5 and 1000 mg/kg/day (doses expressed as parent compound) was given orally by gavage to female rats for 15 days prior to co-habitation, through mating and from Days 0 to 17 pc. There were no test article-related effects on female fertility at any dose. Therefore, the no observed adverse effect level (NOAEL) for female fertility was 1000 mg/kg/day, however, as male and female fetal weights were decreased at 1000 mg/kg/day, the NOAEL for rat embryofetal development was 5 mg/kg/day.

GSK1265744B: Oral Female Fertility, Early Embryonic and Embryofetal Development Study in Rats (Continued)

Study Type: Reproductive and Developmental Toxicology **Study No.:** G08284

Daily Dose (mg/kg)		0 (Control)	0.5	5	1000
F_0 Females:	No. Animals/Group	25	25	25	25
	No. Euthanized Pregnant[a]	0	1	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Pre-Mating Body Weight Gain (Days 1 to 15)[b]	12 g	-33.3%	0%	0%
	Gestation Body Weight Gain (Days 0 to 18 pc)[b]	116 g	3.4%	-1.7%	-2.6%
	Food Consumption (Days 1 to 15)[b]	261 g	-3.1%	1.5%	1.1%
	Food Consumption (Days 0 to 18 pc)[b]	436 g	0.2%	-0.9%	-1.1%
	Mean No. of Times in Estrus/15 Days of Treatment	3.6	3.6	3.5	3.5
	Mean No. Days Needed to Mate	2.2	2.1	2.1	2.2
	Mating Index (%)[c]	100	100	100	96
	Fertility Index (%)[d]	100	92	100	95.8
	No. of Females Mated	25	25	25	24
	No. of Pregnant Females	25	23	25	23
	No. of Pregnant Females Evaluated	25	23	25	23
	Mean No. Corpora Lutea	16.2	16.5	15.3	16.4
	Mean No. Implantations	15.2	15.6	14.8	15.8
	Mean % Pre-Implantation Loss	6.7	5.1	2.7	3.6

GSK1265744B: Oral Female Fertility, Early Embryonic and Embryofetal Development Study in Rats (Continued)

Study Type: Reproductive and Developmental Toxicology **Study No.:** G08284

Daily Dose (mg/kg)		0 (Control)	0.5	5	1000
Litters:	**No. Litters Evaluated[e]**	25	22	25	23
	Mean No. Live Fetuses	14.3	15.0	14.0	15.0
	Mean Total Post-Implantation Loss - No. (%)	6.0	4.8	5.9	5.5
	Mean Fetal Body Weight (g) - Males	5.81 g	5.70 g	5.83 g	5.47* g
	Mean Fetal Body Weight (g) - Females	5.46 g	5.41 g	5.52 g	5.15* g
	% Male Fetuses	48.3	54.0	50.3	46.3
	Fetal Malformations or Variations:				
	External anomalies	-	-	-	-
	Visceral anomalies	-	-	-	-
	Skeletal anomalies	-	-	-	-

Key:
a = Evidence for a positive mating of one female (R09F7788) was missed and as per protocol this female was euthanized 8 days after the end of the co-habitation period.
b = For controls, group means are shown. For treated groups, change from controls is shown.
c = Mating index = (Number mated/Total number co-habited) x 100.
d = Fertility index = (Number pregnant/Number mated) x 100.
e = Method of fetal evaluation [external, visceral, skeletal].
* = Statistical significance ($p \leq 0.05$) is based on raw data (not on the change from controls).
- = No noteworthy findings.

Table 12.2 GSK1265744B: Oral Male Fertility Study in Rats

Study Type: Reproductive and Developmental Toxicology

Report Title: GSK1265744B: Oral Male Fertility Study in Rats

Test Article (Batch No.): GSK1265744B ([redacted])

Design similar to ICH 4.1.1. Yes

Duration of Dosing: 15 days prior to cohabitation, through two cohabitation periods to Day 64 to 66

Study No. 20052742

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

GSK Reference No. R70481G

Initial Age: ~ 9 weeks

Route/Frequency: Oral, once daily

Day of Sperm/Plug Present: Day 0 postcoitum

GSK Document Number: 2014N207479

Date of First Dose: 07 January 2014

Day of C-Section: Day 20 pc

Location in CTD: m4.2.3.5.1

Special Features: None

Method of Administration: Gavage

GLP Compliance: Yes

No Observed Adverse-Effect Level:

Vehicle/Formulation: 0.5 % (w/v) Hypromellose Methocel K15M Premium and 0.1% (v/v) TWEEN® 80 in reverse osmosis membrane-processed deionized water/Suspension

F_0 Reproductive Effects: 1000 mg/kg/day

F_1 Litters: 1000 mg/kg/day

Data Collected: Treated F0 males: viability, clinical observations, body weight, food consumption, mating, fertility, necropsy and male reproductive organ weights, sperm concentration, sperm motility; untreated F0 females: viability, clinical observations, body weight, macroscopic observation of uterus and cervix, corpora lutea and uterine weight; F1 litters: implantations, resorptions, live and dead fetuses, fetal weight, sex, and placental and fetal external morphology

Conclusion: At 1000 mg/kg/day, clinical observations of excess salivation and urine-stained abdominal fur occurred. Body weight gains were transiently reduced at 1000 mg/kg/day, which correlated with food consumption reductions. There were no effects on male mating and fertility parameters or embryo-fetal development of offspring of untreated females mated to GSK1265744-treated males. Therefore, the NOAEL for reproductive effects in the male rat was 1000 mg/kg/day, the highest dose tested.

GSK1265744B: Oral Male Fertility Study in Rats (Continued)

Daily Dose (mg/kg)	0 (Control)	0.5	5	1000
Males:				
No. Animals/Group	25	25	25	25
Clinical Observations (total no. of observations/no. of males with observation)				
Excess salivation, slight	0/0	1/1	0/0	24/11
Urine-stained abdominal fur	0/0	5/1	0/0	3/3
Necropsy Observations	-	-	-	-
Body Weight Gain (Day 1 to 15)[a]	81.7 g	0.96X	1.04X	0.90X
Body Weight Gain (Day 1 to 22)[a]	104.1 g	0.96X	1.06X	0.91X
Food Consumption (Day 1 to 8)[a]	25.4 g/day	0.95X	0.97X	0.94X
Food Consumption (Day 8 to 15)[a]	25.5 g/day	0.98X	1.00X	0.95X
Mean No. Days Needed to Mate – First Cohabitation	3.4	3.4	2.7	2.3*
Mating Index (%)[b] – First Cohabitation	100	100	100	100
Fertility Index (%)[c] – First Cohabitation	100	96.0	100	84.0
Mean No. Days Needed to Mate – Second Cohabitation	2.4	2.3	2.8	2.9
Mating Index (%)[b] – Second Cohabitation	100	100	100	96.0
Fertility Index (%)[c] – Second Cohabitation	92.0	96.0	100	91.7
Organ Weights	-	-	-	-
Absolute Testis Left[a]	1.9389 g	0.97X	1.03X	1.00X
Absolute Testis Right[a]	1.9471 g	0.98X	1.04X	0.99X
Absolute Epididymis Left[a]	0.7164 g	1.01X	1.03X	1.01X
Absolute Epididymis Right[a]	0.7370 g	1.00X	1.01X	0.97X
Relative Seminal Vesicles (%)[a]	0.398	1.01X	0.97X	1.06X
Relative Prostate (%)[a]	0.256	0.95X	1.02X	0.99X
Vas Deferens Sperm Motility (% Motile)	89.9	88.5	90.9	90.8
Cauda Epididymal Sperm Count (Sperm Density)	1330.42	1227.94	1162.18	1091.79

GSK1265744B: Oral Male Fertility Study in Rats (Continued)

Daily Dose (mg/kg)	0 (Control)	0.5	5	1000
Females (First Cohabitation):				
No. Mated Females Evaluated	25	25	25	25
Gestation Body Weight Gain (Day 0 to 20)[a]	154.8 g	0.98X	1.02X	0.98X
No. of Pregnant Females	25	24	25	21
No. of Pregnant Females Evaluated	25	24	25	21
Mean No. Corpora Lutea	16.2	15.8	15.2	15.2
Mean No. Implantations	14.5	14.6	14.6	14.3
Mean % Preimplantation Loss[d]	10.1	7.3	4.0	5.2
Mean Total Postimplantation Loss (%)[e]	6.8	5.5	4.6	5.6
Mean No. Live Fetuses	13.6	13.8	14.0	13.5
Mean Fetal Body Weight (g) - Male	4.03	4.10	4.04	4.08
Mean Fetal Body Weight (g) - Female	3.81	3.94	3.86	3.86
% Live Males	49.8	51.2	46.2	49.6
External Fetal Malformations or Variations	-	-	-	-

GSK1265744B: Oral Male Fertility Study in Rats (Continued)

Daily Dose (mg/kg)	0 (Control)	0.5	5	1000
Females (Second Cohabitation):				
No. Mated Females Evaluated	25	25	25	25
Gestation Body Weight Gain (Day 0 to 20)[a]	154.6 g	1.01X	1.05X	0.97X
No. of Pregnant Females	23	24	25	22
No. of Pregnant Females Evaluated	23	24	25	22
Mean No. Corpora Lutea	15.7	16.0	16.6	15.9
Mean No. Implantations	14.9	15.3	15.2	14.8
Mean % Preimplantation Loss[d]	4.8	4.3	8.0	6.6
Mean Total Postimplantation Loss (%)[e]	4.3	5.5	3.6	3.5
Mean No. Live Fetuses	14.3	14.4	14.6	14.3
Mean Fetal Body Weight (g) - Male	3.97	4.00	3.94	4.02
Mean Fetal Body Weight (g) - Female	3.74	3.74	3.71	3.82
% Live Males	46.6	52.4	49.5	48.4
External Fetal Malformations or Variations	-	-	-	-

Key:

a. For controls, group means are shown. For treated groups, change from controls are shown.

b. Mating index = (Number mated/Total number cohabited) x 100.

c. Fertility index = (Number pregnant/Number mated) x 100.

d. % Preimplantation Loss = [(Number of corpora lutea - Number of implantations) / Number of corpora lutea] x 100

e. % Total Postimplantation Loss = [(Number of implantations - Number of live fetuses) / Number of implantations] x 100

- = no noteworthy findings

* = Statistical significance ($p \leq 0.05$) is based on raw data (not on the change from controls).

13. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: EFFECTS ON EMBRYOFETAL DEVELOPMENT (PIVOTAL)

Note: For results of embryofetal development effects in rats, please refer to Table 12.1.

Table 13.1 GSK1265744B: Embryofetal Development Study in Rabbits

Study Type: Reproductive and Developmental Toxicology

Report Title: GSK1265744B: Embryofetal Development Study in Rabbits

Test Article (Lot/Batch No.): GSK1265744B (Batch No. [redacted])

Design Similar to ICH 4.1.3: Yes

Duration of Dosing: Days 7 to 19 pc

Study No.: G08307

Day of Mating: Day 0 post coitum (pc)

GSK Document Number: CD2009/00842

Species/Strain: Rabbit/Dutch Belted [Haz:(DB)SPF]

Day of C-Section: Day 29 pc

Location in CTD: m4.2.3.5.2

Initial Age: 6 months

Method of Administration: Gavage

Date of First Dose: 18 October 2009

Vehicle/Formulation:
0.5% hydroxypropylmethylcellulose K15M /
0.1% Tween™ 80 in purified water / suspension

GLP Compliance: Yes

Special Features: None

Route/Frequency: Oral, once daily

No Observed Adverse Effect Level:
F_1 Litters: 2000 mg/kg

Data Collected: F_0 females: Mortality, clinical observations, body weight, food consumption, toxicokinetics, necropsy, uterine weight and corpora lutea; F_1 litters: Implantations, resorptions, live and dead fetuses, fetal weight, sex, and placental and fetal morphology (external, visceral and skeletal) and fetal photographs.

Conclusion: There was maternal toxicity at 2000 mg/kg/day evidenced as transient decreases in body weight and food consumption at the onset of dosing. There were no effects on developmental parameters at any dose level. Thus, the no observed adverse effect level (NOAEL) for rabbit embryofetal development is 2000 mg/kg/day, the highest dose tested; the AUC_{0-24} was 96.1 μg.h/mL and the C_{max} was 7.5 μg/mL at this dose.

GSK1265744B: Embryofetal Development Study in Rabbits (Continued)

Study Type: Reproductive and Developmental Toxicology **Study No.:** G08307

Daily Dose (mg/kg)		0 (Control)	30	500	2000
Does:	Toxicokinetics: AUC (μg.h/mL)	0	10.5	47.4	96.1
	C_{max} (μg/mL)	0	0.95	3.39	7.51
	No. Animals/Group	22	22	22	22
	No. Pregnant	22	21	22	22
	No. Pregnant Evaluated	20	21	21	22
	No. Died or Euthanized Moribund	0	0	0	0
	No. Aborted or Naturally Delivered	2	0	1	0
	No. with Total Resorption of Litter	0	0	0	1
	Clinical Observations	-	-	-	Pale feces
	Necropsy Observations	-	-	-	-
	Body Weight Gain (Days 7 to 20 pc)[a]	130 g	0.92X	1.00X	0.85X*
	Body Weight Gain (Day 7 to 8 pc)[a]	0 g	1.00X	Loss 10 g	Loss 40 g
	Food Consumption (Days 7 to 20 pc)[a]	65	1.00X	1.00X	0.93X
	Food Consumption (Days 7 to 8 pc)[a,b]	63	1.03X	1.02X	0.84X*
	Mean No. Corpora Lutea	8.4[c]	8.7	9.0	8.2
	Mean No. Implantations	7.7[c]	7.9	8.0	7.7
	Mean % Pre-Implantation Loss	8.9%[c]	9.6%	11.0%	6.3%
Litters:	**No. Litters Evaluated**	21[c]	21	21	22
	Mean No. Live Fetuses	7.3	7.2	7.6	6.7
	Mean Total Post-Implantation Loss - No. (%)	0.4 (5.2%)	0.7 (8.1%)	0.4 (5.0%)	1.3 (16.6%)
	Mean Fetal Body Weight (g) - Males	35.7	35.9	33.5	33.7
	Mean Fetal Body Weight (g) - Females	34.3	34.3	32.9	33.8
	% Male Fetuses	49%[c]	41%	54%	49%
	Fetal Malformations or Variations[d]	-	-	-	-

Key: * = Statistical significance ($p \leq 0.05$) is based on raw data (not on the change from controls). - = No noteworthy findings.

a = For control the group, mean values are shown. For the treated groups, change from control mean is shown. Statistical significance ($p \leq 0.05$) is based on raw data (not on the percent differences).

b = This interval represents the largest difference from control (Days 7 to 8 pc). Statistical analysis was performed on individual days.

c = Includes data from one female that naturally delivered kits on Day 29 pc; visceral and skeletal evaluations were not performed on any fetuses or kits in this litter.

d = External, visceral and skeletal fetal evaluations were performed.

14. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: EFFECTS ON PRE- AND POST-NATAL DEVELOPMENT INCLUDING MATERNAL FUNCTION (PIVOTAL)

Table 14.1 GSK1265744B: Oral Pre- and Postnatal Development Study in Rats

Study Type: Reproductive and Developmental Toxicology
Design similar to ICH 4.1.2.? Yes
Species/Strain: Rat/Sprague-Dawley [Crl:CD(SD)]
Initial Age: ~66 days
Date of First Dose: 25 August 2014
Special Features: F_1 Toxicokinetic evaluation (C_{max} only) on PND 10

Report Title: GSK1265744B: Oral Pre- and Postnatal Development Study in Rats
Duration of Dosing: Day 6 pc to 20 pp
Day of Mating: Day 0 pc
Method of Administration/Frequency: Oral Gavage/Once Daily
Vehicle/Formulation: 0.5 % (w/v) Hydroxypropylmethylcellulose (HPMC; Grade K15M Premium) and 0.1% (v/v) TWEEN™ 80 in reverse osmosis membrane-processed deionized water/Suspension
Litters Culled/Not Culled: Culled at weaning on Postnatal Day (PND) 21

Test Article: GSK1265744B, the sodium salt **Batch No.:** [redacted]
GSK Reference No.: R70586G
Study No.: 20063353
Location in CTD:
GSK Document Number: 2015N236973
CTD Module: m4.2.3.5.3
GLP Compliance: Yes

No Observed Adverse-Effect Level:

F0 Females:	1000 mg/kg/day	**F1 Males:**	5 mg/kg/day	**F1 Females:**	5 mg/kg/day

Data Collected: F_0 females: mortality, clinical observations, body weight, food consumption, parturition, lactation, maternal behavior, and necropsy; F_1 offspring: viability, gender, external morphology, clinical observations, body weight, GSK1265744 exposure in plasma of pups via mother's milk (PND 10), food consumption (starting on PND 29), physical development landmarks of sexual maturation (including vaginal opening in females and balano-preputial skin fold separation in males), neurobehavioral development (acoustic startle habituation, locomotor activity, and Morris water maze), estrous cycling, reproductive performance, parturition, maternal behavior, and necropsy; F_2 litters: viability, gender, external morphology, clinical observations and body weight.

Conclusion: There was no test article-related effect on F_0 female body weight, food consumption, parturition, or lactation at any dose. However, at 1000 mg/kg/day, there were test article-related decreases in F_1 pup survival and viability that resulted in reduced litter sizes during the first 4 days of life. Similar findings were not observed among litters at 0.5 or 5 mg/kg/day. There was no test article-related effect on F_1 growth and development, including pre- and post-weaning body weight, sexual maturation, neurobehavioral function, reproductive performance, or survival, growth, and development of F_2 generation offspring. Based on these findings, the no observed adverse effect level (NOAEL) for maternal (F_0) reproductive function was 1000 mg/kg/day and for the pre- and postnatal development of the offspring in rats (F_1) was 5 mg/kg/day. At 5 mg/kg/day, the C_{max} in F_1 pups on PND 10 was 58400 ng/mL in males and 52600 ng/mL in females, indicating the presence of GSK1265744 in maternal milk.

GSK1265744B: Oral Pre- and Postnatal Development Study in Rats (Continued)

Study Type: Reproductive and Developmental Toxicology **GSK Reference No.:** R70586G

Daily Dose (mg/kg/day)	0 (Control)	0.5	5	1000
F_0 Females:				
No. Animals/Group	24	24	24	24
No. Pregnant	24	23	23	23
No. Pregnant Survivors to Term	24	23	23	23
No. Died or Euthanized	0	0	1[b]	0
Clinical Observations	-	-	-	-
Gestation Body Weight Change – Days 6 to 21 pc[a]	156.9 g	1.04X	1.04X	1.01X
Lactation Body Weight Change – Days 1 to 21 pp[a]	43.5 g	1.07X	0.90X	0.97X
Gestation Food Consumption – Days 6 to 21 pc[a]	22.9 g/day	1.00X	1.03X	1.00X
Lactation Food Consumption – Days 1 to 14 pp[a]	49.0 g/day	1.03X	0.98X	0.93X
Mean Duration of Gestation (days)[a]	22.2	22.2	22.4	22.7**[c]
Mean No. of Implantation Sites per Delivered Litter	12.5	12.9	12.4	12.4
Average Pup Delivery Time (min)[d]	10.6	10.2	11.6	9.8
Gestation Index (%)[e]	100	100	100	100
Necropsy Observations	-	-	-	-
F_1 Litters (Preweaning):				
GSK1265744 Toxicokinetics:				
C_{max} (ng/mL) – PND 10[f] Males	NC	15600	58400	72500
C_{max} (ng/mL) – PND 10[f] Females	NC	15700	52600	78300
No. Viable Litters at Birth (Day 1)	24	23	23	23
No. Viable Litters at Weaning (Day 21)	24	23	23	23
Mean No. Liveborn Pups/Litter	11.7	12.2	11.6	11.4[g]
Total No. Liveborn Pups (No. [%])	280 (99.3%)	280 (99.6%)	268 (98.9%)	263 (96.3%)**[g]
Mean No. Stillborn Pups/Litter	0.1	0.0	0.1	0.3[g]
Total No. Stillborn Pups (No. [%])	2 (0.7%)	1 (0.4%)	3 (1.1%)	8 (2.9%)**[g]
Pup Sex Ratio at PND 1 (% Males)	50.4	47.7	50.6	49.8
No. Pups Found Dead or Presumed Cannibalized on PND 1 (%)[h]	1 (0.4%)	1 (0.4%)	0 (0%)	7 (2.7%)**
No. Pups Found Dead or Presumed Cannibalized on PND 2 to 4 (%)	2 (0.7%)	4 (1.4%)	2 (0.7%)	26 (10.2%)**

GSK1265744B: Oral Pre- and Postnatal Development Study in Rats (Continued)

Study Type: Reproductive and Developmental Toxicology **GSK Reference No.:** R70586G

Daily Dose (mg/kg/day)	0 (Control)	0.5	5	1000
Postnatal Survival PND 4 (Viability Index; PND 1 to 4)	98.9%	98.2%	99.2%	87.4%**
Postnatal Survival to Weaning (Lactation Index; PND 4 to 21)[i]	99.2%	99.6%	100%	100%
Weight at PND 1[a]	6.9 g	0.99X	1.00X	1.01X
Weight at PND 4[a]	9.7 g	1.00X	1.01X	0.99X
Weight at PND 7[a]	14.0 g	1.01X	1.04X	1.00X
Weight at PND 14[a]	28.3 g	1.00X	1.01X	1.03X
Weight at Weaning (PND 21)[a]	40.6 g	1.01X	1.01X	1.05X*[j]
F_1 Males (Postweaning):				
No. Evaluated	72	72	72	72
Mean Body Weight at PND 71[a]	414.0 g	1.00X	1.01X	1.01X
Mean Food Consumption - PND 29 to 71[a]	49.7 g/day	0.99X	1.00X	1.01X
Mean Age of Balano-Preputial Separation (days)	44.5	44.0	44.4	44.4
Acoustic Startle Habituation	-	-	-	-
Motor Activity	-	-	-	-
Morris Water Maze	-	-	-	-
Mean No. Days Needed for Mating	2.9	2.8	2.3	2.6
No. of Males that Mated (% Mating Index)[k]	23/24 (95.8%)	24/24 (100%)	24/24 (100%)	24/24 (100%)
Fertility Index (%; No. Pregnancies/No. Males That Mated)	91.3	87.5	87.5	91.7
Clinical/Necropsy Observations	-	-	-	-
F1 Females (Postweaning):				
No. Evaluated	72	72	72	72
Mean Body Weight at PND 71[a]	252.1 g	1.00X	1.01X	0.96X
Mean Food Consumption - PND 29 to 71[a]	34.8 g/day	1.01X	1.03X	0.99X
Mean Age of Vaginal Patency (days)	32.8	32.8	33.4	33.0
Acoustic Startle Habituation	-	-	-	-
Motor Activity	-	-	-	-
Morris Water Maze	-	-	-	-

GSK1265744B: Oral Pre- and Postnatal Development Study in Rats (Continued)

Study Type: Reproductive and Developmental Toxicology **GSK Reference No.:** R70586G

Daily Dose (mg/kg/day)	0 (Control)	0.5	5	1000
Mean No. of Estrous Cycles Premating	2.2	1.8	2.2	2.1
Mean No. Days Needed for Mating	2.9	2.8	2.3	2.6
No. of Females with Evidence of Mating (% Mating Index)[k]	23/24 (95.8%)	24/24 (100%)	24/24 (100%)	24/24 (100%)
Gestation Body Weight Change - Day 0 to 21 pc[a]	179.0 g	1.10X	1.06X	1.05X
Lactation Body Weight Change - Day 1 to 7 pp[a]	12.5 g	1.50X	1.71X	1.97X
Mean Gestation Food Consumption - Day 0 to 21 pc[a]	26.8 g/day	1.06X	1.04X	1.03X
Mean Lactation Food Consumption - Day 1 to 7 pp[a]	39.8 g/day	1.08X	1.07X	1.08X
Fertility Index (%; No. Pregnancies/No. Females That Mated)	21 (91.3%)	21 (87.5%)	21 (87.5%)	22 (91.7%)
Clinical/Necropsy Observations	-	-	-	-
Mean Duration of Gestation (days)	22.3	22.5	22.6	22.4
Average Pup Delivery Time (min)	14.2	11.3	10.3	13.0
Mean No. of Implantations per Delivered Litter	16.1	17.3	17.1	15.4
Gestation Index (%)[e]	100	100	100	100

GSK1265744B: Oral Pre- and Postnatal Development Study in Rats (Continued)

Study Type: Reproductive and Developmental Toxicology **GSK Reference No.:** R70586G

Daily Dose (mg/kg/day)	0 (Control)	0.5	5	1000
F_2 Litters:				
No. Litters Evaluated	21	21	21	22
Mean No. Liveborn Pups/Litter	13.8	15.5	15.8	14.5
Mean No. Stillborn Pups/Litter	0.1	0.2	0.3	0.3
Postnatal Survival to PND 4 (Viability Index; PND 1 to 4)	97.2%	98.8%	98.2%	98.8%
Postnatal Survival to PND 7 (Lactation Index; PND 4 to 7)	98.6%	99.1%	99.7%	99.0%
Pup Sex Ratio at PND 1 (% Males)	48.3	47.9	50.5	50.8
Weight at PND 1[a]	6.6 g	0.98X	1.00X	1.02X
Weight at PND 7[a]	14.0 g	0.92X	0.94X	0.96X
Clinical/Necropsy Observations	-	-	-	-

Key: - No noteworthy findings pp postpartum pc postcoitum PND postnatal day NC not calculated

a. For controls, group means are shown. For treated groups, change from controls is shown.
b. Dam 1355 was found dead after dosing on Day 18 pp, and death was attributed to pyometra (necropsy examinations: pyometra (i.e., infection of uterus), cloudy brown fluid [approximately 6 mL] in the left horn of the uterus, additional cloudy brown fluid in the abdominal cavity [approximately 18 mL], and red-colored large and small intestines. This occurrence was isolated and not considered test article related. The litter of 8 live offspring were culled to 3 pups/sex and assigned to post-weaning testing subsets.
c. Not considered test article related because the difference from control was considered minimal and because both individual gestation lengths and group mean values were considered normal based on the range of gestation lengths recorded historically at the Test Facility.
d. Natural deliveries that required more than a single day for completion (includes deliveries initiated between 0800 and 1800 hours and completed overnight) or deliveries that were unobserved (initiated outside of the daily observation period) were not included in delivery time calculations. Delivery time calculations were restricted to litters that had delivery of at least two pups observed.
e. Gestation Index = number of females with live offspring/number of pregnant females.
f. Following maternal (F_0) dose administration on Day 10 pp.
g. Excludes two pups for which maternal cannibalization or autolysis precluded determination of vital status at birth.
h. After litter weighing.
i. Excludes pups that were euthanized on Day 10 or 11 pp (PND 10) for toxicokinetic sample collection.
j. This difference was considered secondary to the reduced number of live pups in some of the litters and was not considered directly related to GSK1265744 treatment, as Chahoud and Paumgartten [2009] and Romero and colleagues [1992] have found there to be an inverse relationship between rate of growth and development of rat pups and litter size during the lactation period.
k. Mating Index = number of rats that mated/number rats cohabited.

* = Statistical significance ($p \leq 0.05$) is based on raw data (not on the change from controls).
** = Statistical significance ($p \leq 0.01$) is based on raw data (not on the change from controls).

Table 14.2 GSK1265744B: Oral Investigative Pre- and Postnatal Development Study in Rats

Study Type: Reproductive and Developmental Toxicology

Design Similar to ICH 4.1.3. No

Day Sperm/Plug Present: Gestation Day (GD) 0

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

Initial Age: ~68 days

Date of First Dose: 01 Feb 2016

Special Features: None

Report Title: GSK1265744B: Oral Investigative Pre- and Postnatal Development Study in Rats

Duration of Dosing: GD 6 through Lactation Day (LD) 7

Method of Administration/Frequency: Oral gavage, once daily

Vehicle/Formulation: 0.5 % (w/v) Hypromellose Methocel K15M Premium and 0.1% (v/v) Tween™80 in R.O. deionized water/Suspension

Litters Culled/Not Culled: Not Culled

Day of Necropsy: LD 8

Test Article (Batch No.): GSK1265744B, sodium salt of GSK1265744 (Batch [redacted])

Study No. 20091536

GSK Reference No. R70909N

Location in CTD:

GSK Document Number: 2016N281797_01

GLP Compliance: No

Data Collected: F_0 females: viability, clinical observations, body weight, food consumption, natural delivery, maternal behavior, necropsy, and pregnancy status; F_1 pups: viability, external morphology, clinical observations (including examination for presence/absence of milk in stomach), and body weight.

Conclusion: There were no GSK1265744-related effects on mean maternal body weight or body weight gains during the gestation periods in the 1000 mg/kg/day group compared to vehicle-treated dams; however, a decrease in body weight gain was evident between LD1 and 4. There were no effects on mean maternal food consumption, or lactation between the GSK1265744-treated F_0 females and the vehicle control F_0 females. While there was no apparent treatment-related effect on the act of parturition itself (i.e. values for average pup delivery times were similar to vehicle control group) there was a delay in onset of parturition at 1000 mg/kg/day as the majority of females in this group initiated delivery on GD 23 compared to vehicle treated females that initiated delivery primarily on GD 22. Test article-related decreases in F1 pup viability and corresponding decreases in live litter size, due to an increase in stillbirths and early postnatal deaths during the first 4 days of life, was observed for dams given GSK1265744 regardless of whether the pups were exposed to the test article during gestation only or during gestation and lactation. As no treatment-related deaths occurred in pups that were exposed to GSK1265744 via the milk, and as there was no apparent exacerbation of deaths among pups that were exposed to GSK1265744 both *in utero* and via milk, compared to pups exposed *in utero* only, this weight of evidence suggests that the increase in stillbirths and early postnatal deaths are related to gestational exposure to GSK1265744 and not lactational exposure.

GSK1265744B: Oral Investigative Pre- and Postnatal Development Study in Rats (Continued)

Study Type: Reproductive and Developmental Toxicology	Study No. 20091536	
Daily Dose (mg/kg)	**0 (Vehicle Control)**	**1000**
F_0 Females and F1 Litters:		
No. Pregnant	36	48
No. Natural Delivered	36	48[b]
No. F0 Females/Litters Survived to LD7	35[n]	43[n]
Treatment-related Clinical Observations	-	-
Mean Gestation Body Weight Change (%[a]) (GD 6 to 21)	156.4 g	0.92X
Mean Lactation Body Weight Change (%[a]) (LD 1 to 4)	9.1 g	0.32X
Mean Lactation Body Weight Change (%[a]) (LD 4 to 8)	13.2 g/day	1.69X
Mean Gestation Food Consumption (%[a]) (GD 6 to 21)	25.6	0.98X
Mean Duration of Gestation (days)	22.3	22.8[h]
Average Pup Delivery Time (min)	10.1	10.0
Total Number of Pups Born		
GD22 Delivery	328	88
GD23 Delivery	129	489
Mean No. Stillborn Pups /Litter (Total No.)[k]	0.0 (2)	0.5 (24)
No. Females with Stillborn Pups	2	7
No. Stillborn Pups on GD22	0 (0.0%)	2 (2.3%)
No. Stillborn Pups on GD23	2 (1.6%)	22 (4.5%)
Gestation Index (%)[i]	100.0	100.0
Mean No. Live Pups Born/Litter	12.3	11.8[j]
No. Pup Deaths on PND 1 (prior to Subset Assignment)		
GD22 Delivery	5[l]	1
GD23 Delivery	0	18[l]

GSK1265744B: Oral Investigative Pre- and Postnatal Development Study in Rats (Continued)

Study Type: Reproductive and Developmental Toxicology	Study No. 20091536			
F1 Postnatal Subsets & Survival	GSK1265744 Gestational Exposure[m]	GSK1265744 Lactational Exposure	Control Litters-Not fostered	GSK1265744-Treated Litters-Not fostered[m]
	Subset A[c]	**Subset C[d]**	**Subset B[e]**	**Subset D[f]**
No. F0 Dams and Litters on PND1	**24**	**24**	**12**	**23**
No. F0 Dams and Litters on PND 2	**23**	**24**	**12**	**20**
No. Pups Found Dead, or Cannibalized PND 1[o]	8/297	3/308	3/145	17/244
No. Pups Found Dead, or Cannibalized PND 2 to 4[o]	48/289	3/305	1/142	39/227
No. Pups Found Dead or Cannibalized PND 5 to 8[o]	1/241	1/302	0/141	1/188
Mean No. Live Pups/Litter PND 1	12.4	12.9	12.1	10.6
Mean No. Live Pups/Litter PND 4	10.0	12.6	11.8	8.2
Mean No. Live Pups/Litter PND 8	10.0	12.5	11.8	8.1
Postnatal Survival % (Viability Index on PND 1 to 8)	80.8	98.0	97.2	77.0
Mean Pup Weight at PND 1 (g)[p]	6.6	6.8	6.6	6.8
Mean Pup Weight at PND 4 (g)[p]	8.9	9.9	9.3	9.3
Mean Pup Weight at PND 8 (g)[p]	14.5	15.8	15.3	15.2
Treatment-related Clinical Observations (PND 1 to 8)	-	-	-	-
Treatment-related necropsy Observations (PND 1 to 8)	-	-	-	-

GSK1265744B: Oral Investigative Pre- and Postnatal Development Study in Rats (Continued)

l. For controls, group means are shown. For treated groups, percent differences from controls are shown.
m. Female 9852 and her litter (13 pups, including 2 stillbirths) was euthanized on Day 22 of gestation due to prolapsed uterus during delivery.
n. Subset A identified in data as Control Females Given GSK1265744 Treated Litters – GSK1265744 Exposure During Gestation Only.
o. Subset C identified in data as GSK1265744 Treated Females Given Control Litters – GSK1265744 Exposure During Lactation Only
p. Subset B identified in data as Natural Control Females and Litters – No Fostering.
q. Subset D identified in data as Natural GSK1265744 Treated Females and Litters – No Fostering
r. Decrease in lactational weight gain considered related to reduced live litter sizes due to decreased pup survival during the first few days of life resulting in less physiological burden on F0 female for maintenance of litters.
s. Majority of GSK1265744 (41 of 48 dams) delivered litters on GD23 compared to majority of controls that delivered on GD22. Treated females that delivered on GD23 seemed to have an increase in number of stillbirths and early postnatal deaths compared to females that delivered earlier.
t. Gestation Index = number of females with live offspring/number of pregnant females.
u. Due to increased number of stillbirths.
v. Viability status confirmed based on results of lung floatation test.
w. Pups were born alive but died a short time after delivery completion. At 1000 mg/kg/day, value excludes 11 liveborn pups from litter 9852 that were euthanized along with their natural mother on GD22 due to prolapsed uterus during delivery.
x. As there were no deaths of fostered control pups exposed to GSK1265744 via milk and there was no apparent difference in the overall number of postnatal deaths among GSK1265744 natural litters that were fostered or not fostered, it is unlikely that the increase in stillbirths and early postnatal deaths at 1000 mg/kg/day is related to lactational exposure to GSK1265744 but more likely related to gestational exposure to GSK1265744.
y. One control female euthanized due to non-viable GSK1265744 foster litter on LD2 and 4 GSK1265744-treated dams euthanized on LD1, 2 or 3 due to non-viable natural born litters.
z. F1 clinical and necropsy observations indicate the pups that died had no treatment-related external or visceral abnormalities to indicate a cause of death. Also, F1 postnatal deaths are not likely to be related to poor maternal care by natural or foster dams as most of the pups that died had milk in their stomach when given enough time to nurse.
aa. Combined sexes.

- = No noteworthy findings
NA = Not Applicable to litters that were cross fostered.
* = Statistical significance ($p \leq 0.05$) is based on raw data (not on the percent differences).

Table 14.3 GSK1265744B: Oral Investigative Toxicokinetics Study in Rats

Study Type: Investigative Reproductive and Developmental Toxicokinetics Study

Report Title: GSK1265744B: Oral Investigative Toxicokinetics Study in Rats

Test Article: GSK1265744B
Lot Number: [redacted]

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses[a] (mg/kg)	Number of Animals/Group	Noteworthy Findings	GSK Document Number/ [redacted] Study No. (Module)
Sprague-Dawley Rat/ Crl:CD(SD)	Oral/0.5 % (w/v) Hypromellose Methocel K15M Premium and 0.1% (v/v) TWEEN® 80 in Reverse Osmosis membrane-processed deionized water/ Suspension)	1 day (GD 20)	5 1000	8 8	Mean C_{max} and AUC_{0-8} values for maternal plasma were approximately 5.0-fold higher at 1000 mg/kg/day after a single dose on GD 20 when compared to values for female rats given a single dose of 5 mg/kg/day. However, following repeat dosing throughout pregnancy, the same toxicokinetic parameters remained relatively unchanged for females given 1000 mg/kg/day from GD 6 to 20, while at 5 mg/kg/day, maternal exposures increased approximately 3.0-fold during the same period resulting in mean C_{max} and AUC_{0-8} values on GD 20 that were nearly similar to values reported for the 1000 mg/kg/day group (<2.0-fold difference between groups). Fetal tissue to corresponding maternal plasma ratios for single and repeat dose cohorts were comparable across the different groups.	2017N311115/ 20104116 (m4.2.3.5.3)
		15 Days GD 6 to 20	5 1000	8 8		

GSK1265744B: Oral Investigative Toxicokinetics Study in Rats (Continued)

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses[a] (mg/kg)	Number of Animals/Group	Noteworthy Findings	GSK Document Number/ [redacted] Study No. (Module)
					Similar to maternal plasma levels, mean fetal tissue concentrations at 1000 mg/kg/day, on GD 20 after repeat gestational exposure, were relatively the same as values reported for the single exposure cohort whereas mean fetal tissue concentrations at 5 mg/kg/day increased after repeat exposure (mean litter concentrations were up to 6.0-fold higher than single dose data) with very little intra- or inter-litter variability. The increase in fetal tissue concentrations at 5 mg/kg/day after repeat gestational exposure resulted in mean values that were within 2.0-fold of values reported for fetuses at 1000 mg/kg/day on GD 20. All of these data indicate that fetal concentrations increased proportionally with an increase in maternal plasma levels and that there was no evidence of preferential accumulation of GSK1265744 within individual fetal compartments at either dose.	

Key:

a. Doses expressed as parent compound, GSK1265744.

b. Total of 8 pregnant female rats per dosing cohort were used in the determination of plasma drug concentrations after single and repeat dosing during gestation. Fetuses were delivered by caesarean section at approximately 9 hours after the last maternal dose on GD 20 and all 32 litters were used to determine fetal tissue concentrations of GSK1265744.

c. GD = Gestation Day

15. STUDIES IN JUVENILE ANIMALS

No studies relevant to this category have been conducted with CAB.

16. LOCAL TOLERANCE

Table 16.1 Local Tolerance Studies

Species/Strain	Route (Vehicle/ Formulation)	Doses (mg/kg)	Number of Animals/Sex	Noteworthy Findings	Report / Study No. (Module)
Mouse (CBA/Ca)	Topical (propylene glycol)	25 μL/site (25% w/w) (sodium salt)	5F	No signs of systemic toxicity or changes in body weights were noted. CAB was a non-sensitizer under the conditions of this test with a Stimulation Index (SI) of 1.27.	2019N396237 41501619 (m4.2.3.6)
Reconstituted human skin (SkinEthic™)	In vitro (NA)	16 mg/site	NA	CAB was classified as non-irritant.	2019N396399 41501616 (m4.2.3.6)
Reconstituted human corneal model (SkinEthic™)	In vitro (NA)	30 mg/site	NA	CAB was considered not to be a significant irritant.	2019N396400 41501617 (m4.2.3.6)

17. OTHER TOXICITY STUDIES

Table 17.1 GSK1265744B: A 28-Day Oral Gavage T Cell-Dependent Antibody Response (TDAR) Study in the Rat

Study Type: Repeat Dose Toxicity	**Report Title:** GSK1265744B: A 28-Day Oral Gavage T Cell-Dependent Antibody Response (TDAR) Study in the Rat	**Test Item:** GSK1265744B **Batch No.:** [redacted]
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** 28 days	**GSK Reference No.:** R70426G
Initial Age: 12 weeks	**Route/Frequency:** Oral by gavage, once daily	**GSK Document Number:** 2013N179070 **CTD Module**: m4.2.3.7.2
Date of First Dose: 31 October 2013 (Replicate 1) and 01 November 2013 (Replicate 2)	**Vehicle/Formulation:** 0.5% (w/v) Hydroxypropylmethylcellulose and 0.1% (w/v) Tween 80 in Ultra Pure Water	**Study in Compliance with GLP:** Yes

Data Collected: Clinical observations, body weight, macroscopic observations and T cell-dependent (i.e. anti-keyhole limpet hemocyanin [KLH]) antibody response (TDAR).

Conclusion: GSK1265744B was given once daily by oral gavage to male and female rats at doses of 0 (reference item/vehicle), 0.5, 5 or 1000 mg/kg/day for 28 days. Rats were immunized with a single intravenous dose of the T cell-dependent antigen, keyhole limpet hemocyanin (KLH), following 12 daily doses of GSK1265744B. A GSK1265744B-related decrease in the anti-KLH IgG antibody response was observed in males given 1000 mg/kg/day. Since the effect in males at 1000 mg/kg/day was minimal, and no effects were observed on the female anti-KLH IgG response or on the anti-KLH IgM response in either sex, GSK1265744B is not considered immunosuppressive under the conditions of this study. Based on the T cell-dependent antibody response assessment, the no observed effect level (NOEL), under the conditions of this study, is considered to be 5 mg/kg/day in males and 1000 mg/kg/day in females.

GSK1265744B: A 28-Day Oral Gavage T Cell-Dependent Antibody Response (TDAR) Study in the Rat (Continued)

Study Type: Repeat Dose Toxicity **GSK Reference No.:** R70426G

	Male				Female			
Daily Dose (mg/kg/day)	0	0.5	5	1000	0	0.5	5	1000
Number of Animals:	10	10	10	10	10	10	10	10
Noteworthy Findings								
TDAR (Group Median, µg/mL)								
Anti-KLH IgM								
Day 1 (pre-KLH)	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]
Day 17 (5 days post KLH)	38.1	35.8	41.3	31.9	39.2	104	66.5	73.8
Day 18 (6 days post KLH)	33.1	31.1	41.0	29.9	40.0	114	65.9	85.9
Day 19 (7 days post KLH)	25.2	26.7	39.1	28.6	33.4	112	43.9	57.8
Anti-KLH IgG								
Day 1 (pre-KLH)	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]	<LLOQ[a]
Day 26 (14 days post KLH)	9.87	4.19	6.96	2.94*	7.57	12.7	9.84	2.64
Day 29 (17 days post KLH)	29.9	6.26	15.0	4.20*	12.4	25.1	17.7	4.18

Key: * Significant difference from control group ($p \leq 0.05$).

a. Group median is below the assay lower limit of quantitation (LLOQ; 0.782 µg/mL for IgM, 0.391 µg/mL for IgG).

Table 17.2 GSK1265744B: A 39-Day Oral (Gavage) T Cell Dependent Antibody Response (TDAR) Study in the Rat followed by an 8-Week Off-Dose Period

Study Type: T Cell-Dependent Antibody Response (TDAR)

Report Title: GSK1265744B: A 39-Day Oral (Gavage) T Cell Dependent Antibody Response (TDAR) Study in the Rat followed by an 8-Week Off-Dose Period

Test Item/Batch: GSK1265744B (sodium salt)/[redacted]

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses[a] (mg/kg/day)	Number of Animals/Sex	Noteworthy Findings[a]	GSK Document Number/ Reference No. (Module)
Rat/ Sprague-Dawley Crl:CD(SD)	Oral Gavage (0.5% w/v Hydroxypropyl-methylcellulose [HPMC; K-15M] + 0.1% w/v Tween® 80™ in Ultra Pure Water)	39 days	0 (vehicle)	10M/10F[b]	GSK1265744 was given to Sprague-Dawley Crl:CD(SD) rats (10/sex/group) at doses of 0, 5, or 1000 mg/kg/day once daily for 39 days by oral gavage. Ten animals/sex/group were added to the 0 and 1000 mg/kg/day groups as recovery animals. Two additional groups of rats (10/sex/group) received the positive control for immunosuppression, cyclosporine (SandImmune Oral Solution; Novartis), at 0 or 5 mg/kg/day once daily by oral gavage from Days 8 to 39. Rats were immunized with intravenous doses (300 μg/animal) of the T cell-dependent antigen, keyhole limpet hemocyanin (KLH), on Days 12 and 26 (3 hours ± 15 minutes after GSK1265744, cyclosporine, or respective vehicle; main study animals) and following a 4-week off-dose period on Days 68	2018N367799/ R71343N (m4.2.3.7.2)
			5	10M/10F		
			1000	10M/10F[b]		

Study Type: T Cell-Dependent Antibody Response (TDAR) | **Report Title:** GSK1265744B: A 39-Day Oral (Gavage) T Cell Dependent Antibody Response (TDAR) Study in the Rat followed by an 8-Week Off-Dose Period | **Test Item/Batch:** GSK1265744B (sodium salt)/[redacted]

Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses[a] (mg/kg/day)	Number of Animals/Sex	Noteworthy Findings[a]	GSK Document Number/ Reference No. (Module)
					and 82 (recovery animals) for evaluation of T cell-dependent antibody response (TDAR). No GSK1265744-related effects on anti-KLH IgM or IgG antibody response were observed during the dosing period; therefore, TDAR samples collected during the off-dose period were not evaluated. In males given cyclosporine, statistically-significant decreases were observed in anti-KLH IgG, but not IgM, response. In females given cyclosporine, statistically-significant decreases were observed in both anti-KLH IgM and IgG responses. Based on the TDAR assessment, the no observed effect level (NOEL) under the conditions of this study is considered to be 1000 mg/kg/day GSK1265744.	

Key:

a. Daily doses are expressed in terms of the parent compound, GSK1265744.

b. 10M/10F were added as recovery animals.