CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202834Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA: 202-834
Submission date:12/22/2011
Drug: perampanel
Applicant: Eisai, Inc.
Indication: Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years or older
Reviewing Division: Division of Neurology Products

Introductory Comments:
The pharmacology/toxicology reviewer and supervisor have determined that the nonclinical information is adequate to support approval of this NDA for the indication noted above.

Discussion:
The pharmacology/toxicology reviewer recommended that the potential for perampanel to bind to the human aorta should be assessed in vitro as a post marketing requirement. This recommendation was based on the finding that perampanel covalently bound to the aorta in rats. However, significant covalent binding to the aorta did not appear to occur in monkeys and there was no nonclinical evidence of toxicity related to this finding in rats. Based on these data and the uncertain utility of data derived from an in vitro study in human aorta, the pharmacology supervisor did not recommend any further nonclinical studies.

Carcinogenicity studies of perampanel were conducted in mice and rats. These studies were reviewed by the Executive Carcinogenicity Assessment Committee. The studies were found to be adequate and no drug-related neoplasms were noted.

Pharmacology data demonstrate that perampanel is a noncompetitive AMPA glutamate receptor antagonist. An established pharmacologic class does not exist for this mechanism, but use of this term as the established pharmacologic class in labeling appears appropriate.

Conclusions:
The pharmacology/toxicology reviewer and supervisor conducted a thorough evaluation of the nonclinical information submitted in support of this NDA. I agree that perampanel may be approved for the above indication from a nonclinical perspective. No additional nonclinical studies are recommended. Labeling changes as suggested by the pharmacology/toxicology supervisor appear acceptable.

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/s/

PAUL C BROWN
10/18/2012

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: August 29, 2012

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 202-834 (perampanel)

NDA 202-834 was submitted on May 25, 2011 by Eisai Inc. for perampanel for the treatment of partial-onset seizures with or without secondarily generalized seizures in epilepsy patients at least 12 years of age. The Agency issued a Refusal-to-File letter (dated July 21, 2011) due to clinical and nonclinical deficiencies. The nonclinical deficiencies consisted of missing individual animal line listings, missing signed and dated pathology reports, and/or missing pages for several pivotal toxicity (embryo-fetal development, carcinogenicity, or chronic toxicity) studies. The NDA was resubmitted on December 22, 2011 and filed (*Agency letter, dated 03/02/2012*); one potential nonclinical review issue was identified: the Pathologist Report for the carcinogenicity study in mouse needs to be revised to incorporate comments that were handwritten in the margins of the report, as submitted to the NDA.

A full battery of nonclinical studies in adult animals and toxicology studies in juvenile animals were conducted under INDs 68368 (b) (4), in support of the NDA. These studies have been reviewed in detail by Dr. Toscano (*Pharmacology/Toxicology Review and Evaluation NDA 202-834, Christopher D. Toscano, Ph.D., 8/22/2012*). Based on his review, Dr. Toscano has concluded that the nonclinical data submitted in support of the NDA are adequate and recommends approval, with one postmarketing requirement (PMR) for an *in vitro* study to assess the potential for perampanel to bind to human aorta.

This memo includes a brief summary of the nonclinical data, with a focus on a few nonclinical issues (e.g., behavioral effects of perampanel and retention of drug-related material in aorta). Dr. Toscano's review should be consulted for a detailed presentation and discussion of the nonclinical data.

Pharmacology

The pharmacological activity of perampanel was characterized in a series of *in vitro* and *in vivo* studies. Based on these data, the sponsor has concluded that perampanel is a "highly selective" noncompetitive antagonist of the AMPA receptor. In *in vitro* assays, perampanel exhibited minimal inhibition of AMPA binding in rat brain membranes; however, perampanel binding was inhibited by noncompetitive AMPA receptor antagonists (IC_{50}'s of 21.1 nM for CP465022 and 23.3 µM for GYKI52466). Perampanel exhibited minimal, if any, binding affinity in two separate panels of *in vitro* binding sites. *In vitro* binding to the kainate receptor was assessed (using kainate as ligand) in only one of these panels; both panels assessed *in vitro* binding to the NMDA receptor, using CGP 39653 (an NMDA receptor antagonist that binds to the agonist site) or CGS019755 (a competitive NMDA receptor antagonist), glycine (an NMDA receptor allosteric modulator), and MK-801 (an NMDA channel blocker).

In *in vitro* functional studies, perampanel inhibited AMPA-induced increases in Ca^{2+} in E18 rat cortical neurons (IC_{50} = 93 and 66 nM in separate assays). These data are included in a published study, cited by the sponsor, reporting that perampanel exhibited minimal inhibition of NMDA-induced increases in Ca^{2+} (18% at 30 µM, the highest concentration tested) (Hanada T *et al*. *Epilepsia* 52(7):1331-1340, 2011). A number of perampanel metabolites were also tested this assay; all except one also inhibited AMPA-induced increases in Ca^{2+}, although with higher IC_{50} values compared to perampanel (E2007). The data are summarized in the following sponsor's table:

	E2007	M1	M2	M3	M4	M5	M7
IC_{50} (µmol/L)	0.066	2.9	>10	0.20	0.25	0.51	1.8
95% CI	0 056–0 079	1 5–5 4	–	0 055–0 73	0 071–0 87	0 21–1 3	1 5–2 2
vs E2007 ratio	1.0	44	>150	3.0	3.8	7.7	27

Perampanel was tested in a variety of *in vivo* animal models used to assess efficacy against epileptic seizures: audiogenic seizures in the genetically susceptible DBA/2J mouse (ED_{50} = 0.47 mg/kg PO), MES in ddY mouse (ED_{50} = 1.6 mg/kg PO), PTZ in ICR mouse (ED_{50} = 0.94 mg/kg PO), corneal kindling in C57BL/6 mouse (at all dose tested, 0.75-3 mg/kg PO), amygdala-kindled Sprague-Dawley rat (at 5 and 10 mg/kg PO but not at 1.25 or 5 mg/kg PO), and a genetic animal model (GAERS) of absence epilepsy. Perampanel exhibited efficacy in all animal models tested, with the exception of the GAERS model (doses: 1, 3, or 10 mg/kg PO). Perampanel also inhibited AMPA-induced clonic convulsions in ddY mouse, indicating AMPA antagonist effects, at oral doses of 2.5 and 5 mg/kg but not at 1.25 mg/kg.

One concern regarding use of AMPA antagonists for treatment of epilepsy is the potential for adverse CNS effects at doses or plasma exposures within the therapeutic range (*cf*. Rogawski M *Epilepsy Currents* 11(2):56-63, 2011; Russo E *et al*. *Expert Opin Investig Drugs* [Early Online], 2012). Therefore, the sponsor tested perampanel in the rotorod test in ICR mouse and Sprague-Dawley rat. In both species, perampanel increased motor incoordination when tested one hour post dose (ED_{50}'s of 1.8 and 9.14 mg/kg PO in

mouse and rat, respectively). These data suggest a fairly narrow therapeutic window, with protective indexes of 1.1-3.8 in mouse and 0.8-1.6 in rat.

In a core battery of safety pharmacology studies, perampanel was demonstrated to have adverse effects on rotorod performance in male ICR mice (>0.5 mg/kg PO) and male Sprague-Dawley rat (>2 mg/kg PO), CNS depressant effects in Sprague-Dawley rat (>0.3 mg/kg PO), minimal effects on cardiovascular parameters in conscious Beagle dog and in the *in vitro* hERG assay (IC_{50} = 15.8 μM), and to decrease respiratory frequency in Sprague-Dawley rat (considered by the sponsor to be secondary to CNS depression) at all doses tested (0.3-5 mg/kg PO).

The data provided by the sponsor demonstrate that perampanel is a noncompetitive antagonist of the AMPA receptor. While the data suggest that perampanel is selective for the AMPA receptor, they are not sufficient to rule out other pharmacological activity. (Clinical signs observed in toxicity studies suggest the possibility of pharmacological effects via other receptor systems.) The data also indicate a narrow therapeutic window for adverse CNS effects. The most common adverse effects reported in humans at therapeutic doses (8, 12 mg) are CNS-related, and are consistent with those reported in animals (e.g., gait disturbance and somnolence). Clinical data suggest an association between perampanel administration and aggressive behavior. There was no report of aggressive behavior in animals. Animals were individually housed in the pivotal toxicity studies, so there was no opportunity to observe aggressive interactions, but there was no report of difficulty in handling or dosing. Data from published literature suggest involvement of AMPA receptors in aggressive behavior; however, inhibition of AMPA receptors (e.g., administration of AMPA antagonists) or lack of AMPA receptors (e.g., AMPA receptor knockout mice) are reported to reduce, not increase, consummate aggressive behavior ("throws, fighting, bites, [and] boxing") in mice (Vekovischeva OY *et al*. *Genes Brain Behav* 3:253-265, 2004; Vekovischeva OY *et al*. *Pharm Biochem Behav* 87:241-249, 2007). [Additional discussion of the behavioral effects of perampanel is included in the General Toxicology section of this memo.]

PK/ADME

The PK/ADME of perampanel was characterized in CD-1 (ICR) mouse, Sprague-Dawley rat, Beagle dog, cynomolgus monkey, and human. Absorption was estimated to be nearly complete, with absolute oral bioavailability of 40, 50, and 75% in rat, dog, and monkey, respectively. In rat, tissue distribution of radioactivity was widespread following oral administration of radiolabeled perampanel. Highest levels of radioactivity were detected in liver and GI tract, adipose tissue, and adrenal gland; radioactivity in aorta was ≈50-80% higher than in plasma at the T_{max} for both (1 hr post dose). Tissue retention was prolonged in liver and aorta in albino and pigmented rat, and in eye of pigmented rat. In pigmented rat, radioactivity was still detected in aorta and eye up to 106 weeks post dose (the latest time point sampled); the $t_{1/2}$ of radioactivity in eye and aorta was 45 and 110 weeks, respectively. In monkey, radioactivity at 7 days post dose was below the limit of quantitation in all tissues except for eye (iris and ciliary body, retina, and chorioides), liver, and gallbladder; radioactivity in aorta was 1 ng-eq/g (compared to 22 and 108 ng-

eq/g in liver and gallbladder, respectively). The prolonged $t_{1/2}$ in rat aorta and liver was demonstrated to represent covalent binding of drug-related material to endogenous macromolecules (elastin in aorta). In published studies, covalent binding of drug-related material to aorta has been demonstrated to induce angiopathy and clear evidence of myocardial damage in rats, presumably by inhibiting crosslinking of collagen and elastin in the aortic wall (*cf*. Boor PJ, Nelson TJ *J Mole Cell Cardiol* 14:679-682, 1982; Boor PJ *Toxicol* 35:167-177, 1985; Junker P *et al*. *Atherosclerosis* 45:17-31, 1982; Ohta K *et al*. *Drug Metab Disp* 24(12): 1291-1297, 1996). Rofecoxib (or metabolites) has been shown to covalently bind to rat and human aorta *in vitro* and to induce histopathological changes (e.g., "disruption and swelling of the elastic lamellae"; "marked degeneration of the elastic fibers in the aorta") in aortic wall when administered orally to Sprague-Dawley rat daily for 4 weeks (Oitate M *et al*. *Drug Metab Dispos* 34:1417-1422, 2006; Oitate M *et al*. *JPET* 320:1195-1203, 2007a; Oitate M *et al*. *Drug Metab Dispos* 35:1846-1852, 2007b). Oitate *et al*. (2006) have suggested that this binding may be involved in the adverse cardiovascular effects of rofecoxib (Vioxx) in humans, although there appears to be no evidence that rofecoxib induces histopathological changes in human aorta *in vitro* or *in vivo*. It does not appear that nonclinical data submitted to support clinical development and approval of rofecoxib identified any toxicity to aorta or any associated toxicity, although it is unclear to what extent aorta was examined in those studies. Direct toxicity to the aorta or any toxicity suggestive of arterial damage (or damage to other tissues [e.g., skin (except for that associated with behavioral effects), joints, respiratory tract] containing elastin and/or collagen) was not reported in the nonclinical studies of perampanel; however, it is possible that the methodologies used were not adequate to detect more subtle toxicity to aorta or other elastin/collagen-containing tissues. Dr. Toscano has recommended that the sponsor be required to conduct, postmarketing, an *in vitro* assay to assess the potential for perampanel to bind covalently to human aorta.

In vitro and *in vivo* metabolism data suggest a qualitatively similar metabolic profile in the animals used for toxicity testing and human. In all species, perampanel appears to be the major drug-related material in circulation. The sponsor reports the results of a mass balance study in humans that suggest no major human metabolites, based on recovery of 70% of dose-related radioactivity. At this time, there is no concern regarding nonclinical assessment of circulating metabolites, as the OCPB review team has concluded that there are no major circulating metabolites in humans. However, clinical data indicate that concomitant use of drugs that induce CYP enzymes (including CYP3A4) may alter plasma levels of parent compound and/or metabolites. Since a number of perampanel metabolites may have pharmacological activity *in vivo* (based on *in vitro* assays), it is unclear what effects changes in the extent of metabolism would have on safety and efficacy. It is possible that additional safety (e.g., *in vitro* receptor binding, *in vitro* hERG) data may be warranted if and when additional clinical PK data become available.

General Toxicology:

The pivotal general toxicity studies of perampanel were conducted in ICR/CD-1 mouse (13-week), Sprague-Dawley rat (4-, 13-, and 26-week), Beagle dog (4-, 13-week), and cynomolgus monkey (4-, 39-, and 52-week). In all studies, perampanel was administered

QD by oral gavage. The primary finding in all species was effects on CNS. Abnormal gait, reduced motor activity, and/or prostration were observed in all species tested; some evidence of tolerance was observed, particularly at low doses. Based on plasma perampanel exposure, dog was the most sensitive species for these clinical signs. In the carcinogenicity bioassays, clinical signs consisted of abnormal gait in mouse (doses >3 mg/kg/day) and abnormal gait, reduced motor activity, and prostration/lateral position in rat (all doses tested); evidence of tolerance was observed in both studies, except for abnormal gait, which persisted or increased over the duration of the study in rat.

Clinical signs consistent with excessive grooming and/or self-mutilation were observed in mouse, rat, and rabbit; the most severe effects were observed in mouse. In mouse, skin lesions and/or loss of digits or fore/hindlimbs, leading to death, were observed at doses of 30 mg/kg and above in the general toxicity studies. In the carcinogenicity study in mouse, similar clinical signs ("loss of the fore-/hindlimbs, and loss of digits of fore-/hindlimbs and a part of skin/muscle), attributed to "self-trauma" by the sponsor, were observed at doses >3 mg/kg/day in males and females; however, trauma-related injury (considered by the sponsor to be "associated with excessive grooming and self-trauma") resulting in death was increased in males at ≥3 mg/kg and in females at all doses. (The sponsor did not consider the increase in low-dose females [7 vs 3 in control] to be drug-related.) In rat, evidence of self-mutilation (or self-trauma) was noted only in the 13-week oral toxicity study in male rats, the only study in rat to test a dose as high as 300-mg/kg/day; hemorrhage, crust, and/or swelling of the forelimbs were noted in 2 males receiving the 300-mg/kg/day dose. The sponsor stated that the findings in one HDM were "probably due to severe/excessive behavioral changes such as frequent licking and/or biting of digits or limbs"; however, it is not clear that excessive grooming/licking/biting was actually observed in any animal. "Increase in grooming" was reported in the fertility and early embryonic development and embryo-fetal development studies in rat, and in an embryo-fetal dose-range finding study in rabbit; only in the pivotal embryo-fetal development study in rat was the increased grooming associated with gross changes (i.e., swelling of limbs); there was no evidence of self-mutilation. Signs of increased grooming and/or self-mutilation were not observed in (adult) dog or monkey. (Excessive grooming, without evidence of self-mutilation, was reported in a 13-week phototoxicity study of perampanel in hairless mouse.)

The sponsor considers the clinical signs observed in animals (including the excessive grooming and/or self-mutilation) a reflection of the pharmacological activity of perampanel. Whereas the abnormal gait, reduced motor activity, and prostration are clearly consistent with previous reports of the pharmacological effects of AMPA antagonists (*cf.* Russo E *et al*. *Exp Opin Investig Drugs [Early Online]*, 2012), the association is less clear for the excessive grooming and self-mutilation. It is also unclear whether the signs of self-mutilation are an extension of the excessive grooming or a separate behavioral effect. An examination of individual animal data suggests that loss of digits and/or fore or hindlimbs were observed in the absence of skin lesions and it does not appear that excessive grooming was observed in any of the mouse studies (except in hairless mouse). Excessive (or increased) grooming was reported only in rat and rabbit, and, with possibly one exception, only in studies in which self-mutilation was not

observed. Considering the severe signs of self-mutilation in mouse, it is difficult to understand how instances of excessive grooming could have been missing in this species.

Genetic manipulation (knock-out mouse models) and pharmacological induction of stereotypies and self-mutilation in animals, including mouse, are widely considered animal models of obsessive-compulsive and/or self-injurious behavior in humans (Andersen SL *et al*. *Biol Psychiat* 68:741-747, 2010; Feusner J *et al*. *CNS Spectr* 14(9):503-513, 2009; Yang XW, Lu X-H *Cur Opin Neurol* 24:114-118, 2011). Published studies in these animal models suggest involvement of dopaminergic, serotonergic (Sivam SP *Life Sci* 58(26):2367-2375, 1996), and, possibly, glutamatergic receptor systems (Wu K *et al*. *Pharm Biochem Behav* 100:726-735, 2012) in the development of these behaviors. What, if any, implications these findings have to possible effects of perampanel on human behavior is unknown.

One other finding was an increase in convulsions only at the low dose in the carcinogenicity study in rat; individual low-dose animals clearly had recurring convulsions. As noted by Dr. Toscano, the lack of dose-dependency may be due to anticonvulsant effects of perampanel at higher doses.

Reproductive and Developmental Toxicology:

A standard battery of reproductive and developmental toxicity studies was conducted for perampanel.

In the fertility and early embryonic development study (oral doses of 0, 1, 10, 30 mg/kg/day), there was no clear adverse effect on fertility. Prolonged and/or irregular estrus cycles were observed primarily at the highest dose tested (60% of high-dose females exhibited consecutive diestrus), although prolonged estrus was also evident at the lower doses but to a much lesser extent. A clear no-effect dose was not identified in this study.

To assess embryo-fetal development in pregnant Sprague-Dawley rat, dose-ranging (0, 10, 30, 60 mg/kg/day) and pivotal (0, 1, 3, 10 mg/kg/day) studies were conducted. In both studies, perampanel was administered orally on gestation days (GD) 6-17. In the dose-ranging study (n = 7/group), increases in post-implantation loss and decreases in fetal body weight were observed at the mid and high doses. The pivotal study confirmed the lack of these findings at 10 mg/kg. The only finding observed in the pivotal study was an increase in a single abnormality, diverticulum of the intestine, at all doses tested (0/137, 1/133, 2/128, 3/137 for C, LD, MD, HD, respectively). A no-effect dose for developmental toxicity was not identified in this study

Dose-ranging (0, 10, 30, 60 mg/kg/day) and pivotal (0, 1, 3, 10 mg/kg/day) embryo-fetal development studies were also conducted in pregnant New Zealand White rabbit. In both studies, perampanel was administered orally on GD 6-18. In the dose-ranging study, all high-dose does died during the dosing period. At the mid dose, 2 does died, one had total litter loss, and 100% post-implantation loss was observed in the remaining does. At the

low dose, post-implantation loss was increased, resulting in fewer live fetuses. In the pivotal study, total litter loss (spontaneous abortion) occurred in 3 high-dose does (GD 26-27, just before scheduled sacrifice on GD28). In remaining does, post-implantation loss was increased at the mid and high doses, although the number of live fetuses was clearly reduced only at the high dose. The lowest dose tested was the no-effect dose in this study.

Pre- and postnatal development was assessed in dose-ranging and pivotal studies (0, 1, 3, 10 mg/kg/day) in Sprague-Dawley rat. In the dose-ranging study, perampanel was administered orally from GD 6 to postnatal day (PND) 6; in the pivotal study, the oral dosing period was from GD 6 to PND 20 (weaning). In the dose-ranging study (n = 8/group), no developmental toxicity was observed. In the pivotal study, the number of stillbirths was increased and the viability index was decreased at the mid and high doses. Developmental delay was noted in both males (preputial separation) and females (vaginal opening) at the high dose, but no adverse effects on learning and memory tasks or on reproductive performance were observed. The lowest dose tested was the no-effect dose for developmental toxicity in this study.

[Behavioral effects observed in these studies are discussed under the General Toxicology section of this memo.]

Juvenile animal toxicology

The potential for perampanel to induce developmental toxicity was assessed in juvenile Sprague-Dawley rat (12-week, starting PND 7) and juvenile Beagle dog (33-week, starting PND 42). Perampanel was administered by oral gavage in the dose-ranging and pivotal studies in both species.

In juvenile rat, drug-related death occurred at >3 mg/kg/day. In the pivotal study (oral doses of 0, 1, 3, 3/10/30 mg/kg/day; the high dose was increased on PNDs 28 and 56), clinical signs (reduced activity, incoordination, excessive grooming and/or scratching) occurred at 3 mg/kg/day prior to weaning but at all doses post weaning. Reduced pup body weight and growth (crown-to-rump length), delayed sexual maturation (preputial separation, vaginal opening), reduced hindlimb grip strength, and adverse effects on learning and memory (impaired performance in the Cincinnati water maze) were observed in mid- and high-dose animals; hindlimb splay was reduced at all doses. Effects on body weight and growth and hindlimb grip strength persisted through the recovery period. Reproductive performance was not affected.

In juvenile dog, morbidity leading to premature sacrifice occurred following an acute oral dose of 40 mg/kg. Clinical signs (including incoordination, excessive grooming/licking/scratching, head shaking, spatial disorientation, and/or ataxic gait) were observed at all doses (1-40 mg/kg). In the pivotal study (oral doses of 0, 1, 5, 5/10 mg/kg/day; the high dose was increased on PND 56), clinical signs were the prominent drug-related effects; there were no adverse effects on the FOB or neurological examinations or on bone density. Learning and memory were not assessed.

Juvenile rat and dog appeared to be more sensitive to the behavioral effects of perampanel, compared to adults. In juvenile rat, this may be due to the higher plasma exposure, particularly during the lactation period, at similar doses. However, in juvenile rat, there seemed to be no evidence of the self-mutilation observed in adults. Plasma exposures in juvenile dog were fairly similar to those in adult dog, comparing oral doses up to 10 mg/kg/day; however, excessive grooming/scratching/licking were observed only in juvenile dog.

Carcinogenic Potential

The carcinogenic potential of perampanel was assessed in lifetime carcinogenicity bioassays in CD-1 mouse and Sprague-Dawley rat. In mouse, increased mortality resulted in dose discontinuation in mid- and high-dose males (Week 87 and 85, respectively) and at all doses in females (Week 101 at low and mid doses; Week 92 at the high dose); all survivors were sacrificed at Week 104 (males) or Week 103 (females). Survival was not affected in rat. Both studies were reviewed by Dr. Toscano and discussed with the Executive CAC (*Meeting Minutes, 7/5/2012*) and found to be adequate and negative for drug-related neoplasms.

[Behavioral effects observed in the mouse study are discussed under the General Toxicology section of this memo.]

Genotoxicity

Perampanel was negative in an adequately conducted standard battery of genetic toxicology studies (*in vitro* Ames assay, *in vitro* mouse lymphoma *tk* assay, *in vivo* micronucleus assay in rat).

Recommendations: I agree with Dr. Toscano's conclusion that the nonclinical studies of perampanel submitted to NDA 202-834 are adequate to support approval, with appropriate labeling. However, in my opinion, an *in vitro* study to assess potential binding of perampanel-related material to human aorta is not necessary. While Dr. Toscano's recommendation is reasonable, I do not believe that the results of such a study would be of benefit from a regulatory standpoint or to the prescribing physician (if included in labeling). The most informative result would be if the *in vitro* assay demonstrated prolonged binding to human aorta, and if follow-up *in vitro* studies identified perampanel-related damage to the aorta. Even with these results, it is unclear what, if any, clinical action would be indicated, with no nonclinical evidence of related toxicity or clinical signal warranting investigation.

Draft labeling recommendations are provided below but may be modified following further internal discussion and receipt of comments from the sponsor. Safety margins are based on body surface area comparisons, using a human dose of 8 mg/day. If the maximum recommended human dose (MRHD) is changed (to 12 mg/day) and/or if steady-state plasma exposure (AUC) data are available at the MRHD, then safety margins will need to be revised accordingly. A pharmacologic class has not yet been established

for perampanel; the available data support the term, "noncompetitive ionotropic AMPA glutamate receptor antagonist."

The CNS stimulatory effects of perampanel observed in several species, and presumed to be responsible for the severe self-mutilation observed in mouse at clinically relevant doses, are of concern. Although wording has not been provided, consideration should be given to including a description of the findings in labeling.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LOIS M FREED
08/29/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	202-834
Supporting document/s:	1, 11
Applicant's letter date:	5/25/2011, 12/22/2011
CDER stamp date:	5/25/2011, 12/22/2011
Product:	FYCOMPA (perampanel; E2007; ER-155055-90)
Indication:	Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years or older
Applicant:	Eisai, Inc.; Woodcliff Lake, NJ
Review Division:	Neurology Products (DNP), HFD-120
Reviewer:	Christopher D. Toscano, Ph.D., DABT
Supervisor/Team Leader:	Lois M. Freed, Ph.D.
Division Director:	Russell G. Katz, M.D.
Project Manager:	Stephanie N. Parncutt

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 202-834 are owned by Eisai, Inc. or are data for which Eisai, Inc has obtained a written right of reference. Any information or data necessary for approval of NDA 202-834 that Eisai, Inc does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are for descriptive purposes only and are not relied upon for approval of NDA 202-834.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Perampanel (FYCOMPA) is a noncompetitive AMPA receptor (AMPAR) antagonist developed by Eisai as a treatment for partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years or older. AMPAR, along with the two other ionotropic glutamate receptors, NMDA and kainate receptors, allow for the transmembrane flow of cations such as K^+, Na^+, and Ca^{2+}. Activation of this ion flux by glutamate, the main excitatory neurotransmitter in the brain, facilitates depolarization of the neuron. Being the main excitatory neurotransmitter in the brain, glutamate and its receptors are logical targets for the development of antiepileptic medications, such as perampanel. The nonclinical studies submitted to support the approval of FYCOMPA are reviewed in this document.

1.2 Brief Discussion of Nonclinical Findings

Perampanel exhibited the ability to noncompetitively antagonize the activation of AMPA receptors *in vitro*. *In vivo* studies performed in several animal models of epilepsy have demonstrated the ability of perampanel to abrogate seizures. The results of the pharmacology studies performed with perampanel suggest that this compound may be useful as an antiepileptic medication in humans.

The main findings of concern in the nonclinical studies are the prolonged residence of perampanel in the aorta due to covalent binding to elastin, delayed-onset convulsions observed in rats dosed with low levels of perampanel for greater than 6-months, cognitive dysfunction observed in the juvenile toxicology study, and teratogenicity (i.e. diverticulum of the intestine) observed in the rat embryo-fetal development study.

1.3 Recommendations

1.3.1 Approvability

NDA 202-834 contains an adequate nonclinical assessment of the pharmacology and toxicology of perampanel. The overall nonclinical toxicity profile of this compound is not markedly different than other FDA-approved antiepileptics and would not preclude the approval of FYCOMPA for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years or older.

1.3.2 Additional Non Clinical Recommendations

Due to the unusual finding of covalent binding of perampanel to the aorta resulting in a residence time of at least 2 years in rat, it is recommended that additional studies be performed to determine if this finding is of clinical concern. Rofecoxib (Vioxx), a cyclooxygenase-2 (COX-2) inhibitor withdrawn from the market due to adverse cardiovascular findings in humans, is also known to covalently bind the aorta of rats and humans. It is recommended that the Sponsor investigate, as a post marketing requirement (PMR), the ability of perampanel to bind to the human aorta; details regarding studies from the peer-reviewed literature that have performed similar *in vitro* assessments with rofecoxib are described in Section 11 of this Review.

1.3.3 Labeling:

The Sponsor has proposed (b) (4)

Therefore, the safety margins in the draft labeling below have been calculated based on dose per body surface area, using 12 mg as the MRHD.

The labeling provided below (in italics) is the Reviewer's draft recommendation for labeling:

Highlights of Prescribing Information:

Indications and Usage:
FYCOMPA is a noncompetitive AMPA receptor (AMPAR) antagonist indicated for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

Use in Specific Populations:
Pregnancy: Based on animal data, may cause fetal harm.

1.1 Indications and Usage:
FYCOMPA (perampanel) is a noncompetitive AMPA receptor antagonist indicated for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

8.1 Pregnancy
Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Perampanel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (b) (4)

Perampanel, when administered at doses of 1, 3, or 10 mg/kg to pregnant rats during the period of organogenesis, resulted in diverticulum of the intestine, (b) (4)

In pregnant rabbits given daily oral doses of 1, 3, or 10 mg/kg perampanel during organogenesis, (b) (4)

(b) (4)

(b) (4)

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years of age have not been established.

(b) (4)

12.1 Mechanism of Action

The mechanism by which perampanel exerts its (b) (4) *effect has not been fully elucidated.* (b) (4)

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenesis

(b) (4)

Mutagenicity

(b) (4)

Perampanel was not mutagenic in the Ames test or the in vitro mouse lymphoma assay. Perampanel was negative in the in vivo mouse micronucleus assay.

(b) (4)

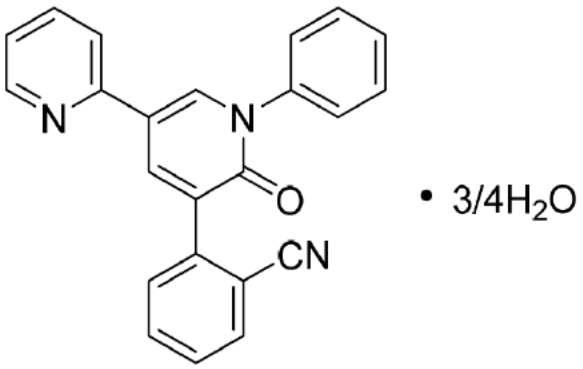
Impairment of Fertility

Fertility was not impaired in male and female rats given daily oral doses of 1, 10, 30 mg/kg (b) (4) *days prior to mating, continuing through mating and, in females, up to Day 6 of gestation. Female rats dosed with 30 mg/kg exhibited prolonged and irregular estrous cycles.*

2 Drug Information

2.1 Drug

CAS Registry Number:	380917-97-5
Generic Name:	Perampanel
Code Name:	E2007; ER-155055-90
Chemical Name:	2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile hydrate (4:3)
Molecular Formula:	$C_{23}H_{15}N_3O$
Molecular Weight:	(b) (4) 362.9 (3/4 hydrate)
Pharmacologic Class:	Antiepileptic, noncompetitive AMPA antagonist
Structure:	



• $3/4H_2O$

2.2 Relevant INDs and DMFs:

IND 68368, (b) (4); DMFs (b) (4) (b) (4) Letters of authorization to the DMFs ((b) (4) are provided in the NDA; the INDs listed here are owned by the Sponsor.

2.3 Drug Formulation

The formulation of the 2, 4, 6, 8, 10, and 12 mg tablets of FYCOMPA is provided in the Sponsor's table, below.

Table 3.2.P.1-2 Components and Composition of Perampanel Film-coated Tablets

Ingredient	Dosage Strength of Perampanel Film-coated Tablets						Function	Specification
	2 mg	4 mg	6 mg	8 mg	10 mg	12 mg		
	Amount (mg)							
[redacted]							(b) (4)	In-house (E2007)
								NF
								NF
								USP
								USP
								NF
								NF
								NF
								-
								In-house (03F43101
								In-house (03F45059
								In-house (03F44071
								In-house (03F40008
								In-house (03F41127
								In-house (03F40557
								USP
Total Weight (mg)	105	210	210	210	210	210	-	-

NF = National Formulary (U.S.), q.s. = quantum sufficit, USP = United States Pharmacopeia.

(b) (4)

(b) (4)

b: Name as listed in European Pharmacopoeia.

(b) (4)

(b) (4)

2.4 Comments on Novel Excipients

All excipients included in the drug product are listed in the Inactive Ingredient Database for Approved Drug Products and are present at levels lower than those found in previously approved drug products.

2.5 Comments on Impurities/Degradants of Concern

There are no impurities or degradants of concern.

2.6 Proposed Clinical Population and Dosing Regimen

Perampanel is to be used for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. Treatment will be initiated at a daily dose of 2 mg. Based on clinical response and tolerability the dose can be increased in increments of 2 mg with at least one week between increases. The maximum recommended daily dose is 12 mg.

2.7 Regulatory Background

FYCOMPA was developed under IND 68368, which was first submitted to the FDA on 10/7/2003. Shortly after this IND was opened, carcinogenicity SPAs were received (11/6/2003). The Executive CAC did not agree with the Sponsor regarding the study design and suggested that the Sponsor conduct additional studies in rat and mouse.

An End of Phase 2 meeting was held on 12/5/2007 in which the Sponsor was informed that the chronic nonrodent study was inadequate due to insufficient exposure relative to the human. In addition, the Sponsor was informed that it appeared that novel human metabolites may exist that are not produced in rodents. The Sponsor was encouraged to characterize both qualitatively and quantitatively the *in vivo* metabolism of the drug in animals and humans. The Sponsor was also informed that the mass balance study was inadequate given that only 70% of the drug was recovered.

DNP refused to file NDA 202-834 when it was submitted on 5/25/2011. The nonclinical deficiencies in the initial application included pivotal studies without signed and dated pathology reports and missing line listings for several pivotal studies. The Sponsor addressed all of the nonclinical deficiencies in the version submitted on 12/22/2011; this version of the application was accepted for review. (b) (4)

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

Primary Pharmacology

1) M00025- Effect of E2D07 and ER-179392 on AMPA-induced intracellular free calcium elevation in rat cortical neurons
2) M09014- E2007: Effects of E2007 metabolites on AMPA-induced intracellular calcium elevation in rat cortical neurons
3) M00031- E2007: *In vivo* suppression of AMPA-induced seizure in mice
4) M01029- E2007 Effects on audiogenic seizures in DBA/2J mice
5) M01033- E2007: Effects on maximal electroshock seizures in mice
6) M01031- E2007: Effects on pentylenetetrazole-induced seizures in mice
7) M01034- E2007: Effect on seizure parameters in amygdale-kindled rats
8) JP06ei01004- E2007: Effect of 2007 and valproate on the genetic model of absence epilepsy in the rat (GAERS)
9) EIS072811-2- Ion channel profilier data report
10) M11016- Effects of E2007 on seizure development in mouse corneal kindling model.

Secondary Pharmacology

11) T/O 00-6870- E2007: *In vitro* specificity of binding
12) 929001- *In vitro* pharmacology- study of compound E2007
13) 929005- *In vitro* pharmacology- study of E2007 on cytokine and chemokine production and immunosuppresion

Safety Pharmacology

14) M01036- E2007: Effects on Rotarod test in mice
15) W20010415- Effect of E2007 on rotarod test
16) DJNR1008- Effect of E2007 on hERG tail current recorded from stably transfected HEK293 cells
17) G00006- Effects of oral administration of E2007 on heart rate, blood pressure and electrocardiogram in conscious dogs
18) B010484- Effect of orally administered E2007 on general physical condition and behavior (Irwin's method) in rats
19) B010485- Effect of orally administered E2007 on body temperature in rats
20) B010486- Effect of orally administered E2007 on respiratory function in rats

Pharmacokinetics

Analytical Methods

1) TKV0004- Validation of the bioanalytical method for the measurement of E2007 in rat plasma
2) A1437- Validation of analytical method for determination of in mouse plasma using HPLC
3) A1438- Validation of analytical method of determination of E2007 in rat plasma using

HPLC
4) A2043- Validation of analytical method for determination of E2007 in rabbit plasma using HPLC
5) TKV0005- Validation of the bioanalytical method for the measurement of E2007 in monkey plasma
6) SBL4746- Analytical method validation for the determination of E2007 in monkey plasma
7) B01028- E2007: Identification of chemical structure and determination of radiochemical purity and specific activity of 14C labeled E2007
8) CP3071- Purification of 14C-E2007

Absorption

1) B00023- E2007: Pharmacokinetic profile of E2007 after a single oral and intravenous administration to rats
2) B00027- Pharmacokinetic profile of E2007 after a single oral and intravenous administration to dogs
3) BSBL4758- E2007: Pharmacokinetic profile of E2007 after a single oral and intravenous administration to monkeys

Distribution

1) B01032- E2007: Blood level, distribution, metabolism and excretion of radioactivity after an oral administration of 14C-E2007 to rats
2) AE3690g- E2007: Distribution of radioactivity in tissues after an oral administration of 14C-E2007 to pigmented rats
3) B04002- E2007: Blood, aorta, eye and skin concentrations of radioactivity after an oral administration of 14C-E2007 to pigmented rats
4) AE3321g- E2007: Absorption, distribution and excretion in Cynomolgus monkeys after single oral administration of 14C-E2007
5) B02010- E2007: Protein binding of 14C-E2007 in mouse and monkey plasma
6) AE4736g- Pharmacokinetic study of E2007-Placental transfer after a single oral administration of 14C-E2007 in pregnant rats

Metabolism

1) AE3427- E2007: Metabolism of 14C-E2007 in Cynomolgus monkeys after single oral administration
2) B00034- E2007: Structural analysis of E2007 metabolites in dog liver microsomes

Excretion

1) AE4735g- Radioactive concentration in milk after single oral administration of 14C-E2007 to lactating rats

Toxicology

General Toxicology

Mouse

Single Dose

1) C-B062- E2007: Single oral dose range toxicity study in mice

Repeat Dose

2) CB063- E2007: A 2 week oral dose range toxicity study in mice
3) B5121- E2007: A 4-week oral dose range toxicity study in mice (additional study)
4) B4954- E2007: A 13-week oral dose range toxicity study in mice

Rat

Single Dose

1) TKB00005- E2007 and (b) (4) Single oral dose range study in rats
2) S05092- E2007: Single oral dose toxicity study in rats

Repeat Dose

3) TKB00006- E2007 and (b) (4) A 4-day dose range oral study in rats
4) S00009- E2007: A 4-week oral toxicity study in rats
5) S01008- E2007: A 13-week oral toxicity study in rats
6) S04007- A 13-week oral toxicity study in male rats (additional study)
7) S02002- E2007: A 26-week oral toxicity study in rats
8) S05107- E2007: A 26-week oral toxicity study in male rats (additional study)

Rabbit

Single Dose

1) S00619- E2007: MTD study in non-pregnant rabbits

Dog

Single Dose

1) TKB00007- E2007 and (b) (4) Dose escalation oral toxicity study in dogs

Repeat Dose

2) TKB00008- E2007: A 7-day oral range toxicity study in dogs
3) S00010- E2007: A4-week oral toxicity study in dogs
4) S01009- E2007: A 13-week oral toxicity study in dogs

Non-Human Primate

Single Dose

1) TKB01011- E2007: Dose escalation oral toxicity study in monkeys

Repeat Dose

2) TKB01016- E2007: A 2-week oral repeat dose toxicity study in monkeys
3) SBL4747- A 4-week oral toxicity study in monkeys
4) SBL038024- E2007: A 39-week oral toxicity study in monkeys
5) SBL4761- E2007: A 52-week oral toxicity study in monkeys

Genotoxicity

1) S00604- E2007 and (b) (4) preliminary reverse mutation assay in bacteria
2) S00612- E2007: Reverse mutation assay in bacteria
3) S00613- E2007: Mouse lymphoma TK assay

4) S01620- E2007: Micronucleus assay in rats following oral administration
5) 12546: Mutagenicity study of [redacted] (b) (4)
6) Derek Analysis of Specified Impurities
7) Derek Analysis of Unspecified Impurities

Carcinogenicity

1) B4955- E2007: A 24-month oral carcinogenicity study in mice
2) S04063- E2007: An oral carcinogenicity study in rats

Reproductive and Development Toxicity

1) S01011- E2007: An oral fertility study in rats
2) 200420p- E2007: Dose range toxicity study in pregnant rats
3) 200420- E2007: Oral embryo-fetal development study in rats
4) 250520p- E2007: Dose range toxicity study in pregnant rabbits
5) 250520- E2007: Oral embryo-fetal development study in rabbits
6) 091027- E2007: An oral TK study in pregnant rabbits
7) 300326p- E2007: An oral dose range toxicity study of effects on pre- and postnatal development, including maternal functions, in rats
8) 300326- E2007: An oral toxicity study of effects on pre- and postnatal development, including maternal functions, in rats

Juvenile Toxicity

1) 901162- E2007: A dose range-finding oral toxicity study in the juvenile rat
2) 901163- E2007: A 12-week oral gavage toxicity study in the juvenile rat followed by a 4-week recovery period
3) 901978- E2007: An oral dose range-finding toxicity study in juvenile dogs
4) 901979- A 33-week oral gavage toxicity study in the juvenile dog followed by a 4-week recovery period

Other Toxicity Studies

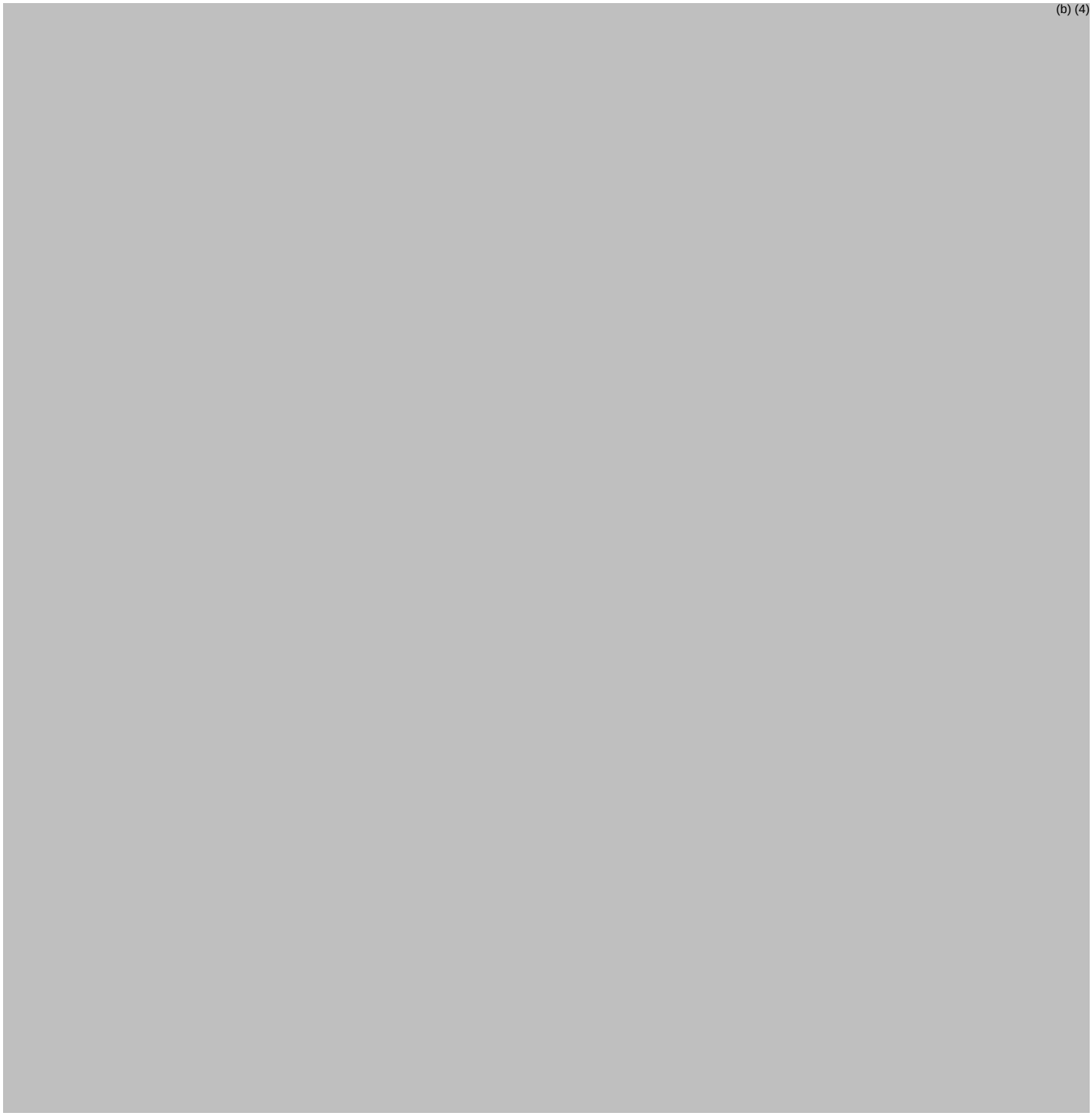
Phototoxicity

1) F06003- E2007: Phototoxicity test using BALB/3T3 cells
2) 1060501- Photomutagenicity in a Salmonella typhimurium reverse mutation assay with E2007
3) 1060502- Chromosome aberration test *in vitro*: Photomutagenicity in Chinese hamster V79 cells with E2007
4) LFA00042- Topical photoallergy test of E2007 in albino hairless guinea pigs
5) LFA00036- 13-week oral range finding study of W2007 in hairless mice, with or without simulated sunlight
6) CK-168: Immunohistochemical biomarkers study using skin tissues from study SBL038024

3.2 Studies Not Reviewed

The four nonclinical abuse liability studies contained in this application are not reviewed here. In addition, the following primary pharmacology and toxicology studies involve disease models and study designs that are not pertinent to the indication of this NDA

(i.e., epilepsy) and were, therefore, not reviewed:



3.3 Previous Reviews Referenced

1) Toscano CD, Nonclinical Review, (b) (4) (b) (4)
2) Elayan IM, SPA Carcinogenicity Protocol Review, IND 68368 (DARRTS, 2/17/2004)
3) Seifried AS et al., Faxed CAC Report for SPA, IND 68368 (DARRTS, 12/18/2003)

4 Pharmacology

4.1 Primary Pharmacology

In vitro:

The ability of perampanel and one of its metabolites (ER-179392-00 or M1) to alter AMPA-induced intracellular calcium levels was tested in rat cortical neurons (Study M00025). Perampanel exhibited an IC_{50} value of 93 nM in the presence of 2 μM AMPA; the IC_{50} value for ER-179392 was 17-fold higher (1.6 μM). When this study was repeated with additional metabolites of perampanel (Study M09014), it was determined that most are also potent antagonists of the AMPA receptor, in the presence of 2 μM AMPA (Sponsor's table, below). These findings suggest that perampanel and its metabolites (M1, M3, M4, M5, and M7) are antagonists of the AMPA receptor.

	E2007	M1	M2	M3	M4	M5	M7
IC_{50} (μmol/L)	0.066	2.9	>10	0.20	0.25	0.51	1.8
95% CI	0 056−0 079	1 5−5 4	–	0 055−0 73	0 071−0 87	0 21−1 3	1 5−2 2
vs E2007 ratio	1.0	44	>150	3.0	3.8	7.7	27

Sponsor's Table: The metabolites of perampanel (E2007) are as follows: M1 (ER-179392-00), M2 (ER-260862-00), M3 (ER-260860-00), M4 (ER-390105-00), M5 (ER-464998-00), M7 (ER-497647-00).

Perampanel (0.3 μM to 30 μM) did not modulate GABA-mediated current *in vitro* when assessed in cell lines expressing $GABA_A$ α1β3γ2, $GABA_A$ α3β3γ2, $GABA_A$ α2β3γ2, or $GABA_A$ α5β3γ2 (Study EIS072811-2).

In vivo:

The ability of perampanel to abrogate seizures was investigated in several mouse and rat models of epilepsy (AMPA-induced, audiogenic, electroshock, pentylenetetrazole-induced, corneal kindling, amygdala kindling, and a genetic model of absence epilepsy). Oral pre-treatment of mice with up to 5 mg/kg perampanel one hour before intracerebral infusion of AMPA resulted in a dose-dependent increase in latency to seizure (Study M00031). Specifically, 2.5 and 5 mg/kg perampanel increased latency to seizure onset by 2 to 3 fold, relative to control (0 mg/kg= 42 sec; 1.25 mg/kg= 68 sec; 2.5 mg/kg= 87 sec; 5 mg/kg= 142 sec.). Oral treatment with perampanel was also observed to abrogate pentylenetetrazole (PTZ)-induced seizure (Study M01031) with an ED_{50} value of 940 μg/kg; the ED_{50} for sodium valproate (VA) and carbamazepine (CBZ) in PTZ-exposed mice was 350 and >100 mg/kg, respectively. The ED_{50} for perampanel (oral) and the positive controls carbamazepine and valproate in the maximal electroshock-induced seizure test were 1.6, 21, and 460 mg/kg, respectively (Study M01033). Perampanel also exhibited efficacy in a model of audiogenic seizure (DBA/2J mice; Study M01029). The ED_{50} for perampanel (oral), carbamazepine, and valproate in abrogating audiogenic seizures was 470 μg/kg, 6.1 mg/kg, and 160 mg/kg, respectively. Perampanel (1.5 mg/kg and 3 mg/kg, p.o.) prevented kindling in the mouse model of corneal kindling (Study M11016). Perampanel (5 and 10 mg/kg, p.o.) decreased the average motor seizure duration and seizure severity score by 50% in amygdala-kindled

rats (Study M01034). The ability of perampanel and VA to abrogate seizures was tested in the genetic model of absence epilepsy in the rat (GAERS; Study JP06EI01-004). Rats genetically susceptible to epilepsy were dosed by oral gavage with perampanel (1, 3, 10 mg/kg, single dose) or intraperitoneal injection with VA (200 mg/kg) and spike and wave discharge (SWD) was monitored by intracranial electrodes implanted into the frontal and parietal cortices. SWD was not affected in rats dosed with perampanel; however, VA decreased SWD by 72-95%, relative to control. Overall, perampanel was more potent than CBZ and VA in several mouse and rat models of seizure but not in the rat model of absence seizure.

The pharmacodynamics of perampanel were also studied in several other animal models of disease (b) (4) Given that the current NDA has been submitted for the approval of perampanel for treatment of epilepsy, detailed discussion of these additional primary pharmacology studies is considered to be beyond the scope of this review.

4.2 Secondary Pharmacology

Several screening studies to investigate the binding of perampanel to targets other than the AMPA receptor were performed (Studies T-0-00-6870, 929001, and 929005). When tested at 250 nM and 1.25 µM (concentrations that are 2.7- and 13-fold higher, respectively, than the IC_{50} for AMPAR) in a Novascreen assay (63 receptors, enzymes and other targets), marked binding was not observed for any of the targets in this assay (Study T-0-00-6870). Importantly, perampanel did not compete with ligands for the AMPA (^{3}H-AMPA, agonist), kainate (^{3}H-kainic acid, agonist), or NMDA (^{3}H-CGP39653, competitive antagonist [1] or CGS19755 competitive antagonist [2]) glutamate receptors which suggests that this compound is not a competitive antagonist of these glutamate receptors and may affect the activity of AMPA receptors (as observed in Study M09014) in a noncompetitive manner. To provide further evidence that perampanel is a noncompetitive antagonist of AMPA, the Sponsor cites a peer-reviewed publication which demonstrates that perampanel binding in rat forebrain membranes can be displaced by the noncompetitive AMPA antagonists CP465022 and GYK152466 [3]. Furthermore, this study shows that the IC_{50} of perampanel for Ca^{2+} flux in rat cortical neurons is approximately 100 nM. This publication also demonstrates that perampanel does exhibit extremely weak activity at the NMDA receptor at high concentrations (~20% inhibition of calcium flux at 30 µM perampanel compared to > 80% inhibition at 1 µM MK-801). These data suggest that perampanel may act as a selective, noncompetitive antagonist of the AMPAR. When tested in an expanded *in vitro* screen of 86 targets, the lack of perampanel (2.8 and 28 µM) interaction with cellular targets, as observed in the previous study (Study 929001). Perampanel (0.1, 1, 10 µM) did not inhibit the production of chemokines or cytokines (IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10) by peripheral blood monocytes in an *in vitro* assay (Study 929005).

4.3 Safety Pharmacology

4.3.1 Cardiovascular

A) Study DJNR1008: "Effect of E2007 on HERG Tail Current Recorded from Stably Transfected HEK293 Cells"

In this study, which was initiated on 5/8/2001, the hERG tail current was recorded from hERG-transfected HEK293 cells in the presence of 0, 1, 3, 10, or 30 μM perampanel dissolved in 0.1% DMSO. Perampanel (E2007) inhibited hERG in a concentration-dependent manner (Sponsor's Table 1) with an IC_{50} of 15.8 μM. The positive control (100 nM E-4031) markedly inhibited hERG to a level that was 7% of the control. Overall, this study demonstrates that perampanel does inhibit hERG activity but is not as potent as the positive control E-4031.

Table 1 Concentration-Response Relationship for E2007 on HERG Tail Current

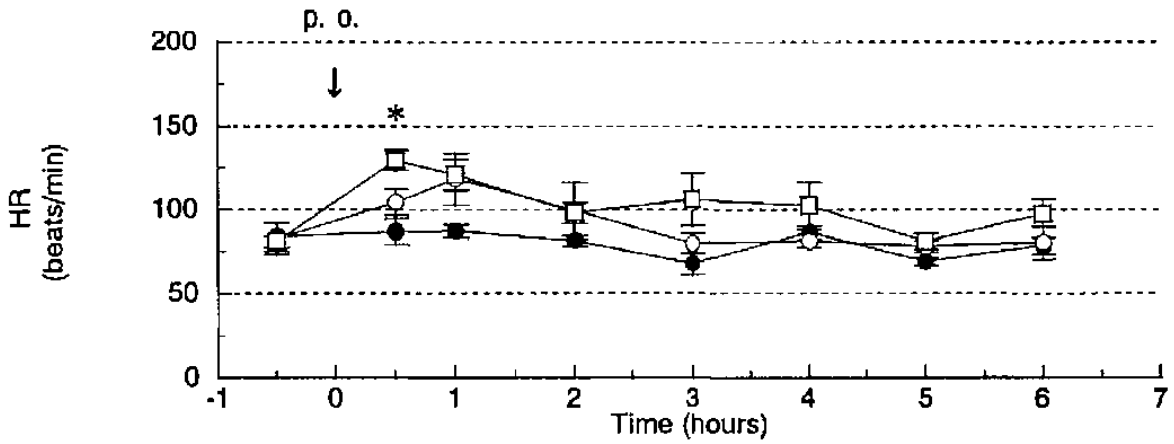
Concentration (μM)	Tail Current (% Control)	Tail Current (% Control) Vehicle Corrected
1	91.6 ± 3.5	115.9 ± 4.4
3	84.9 ± 4.1	107.5 ± 5.2
10	52.1 ± 5.4 ##	65.9 ± 6.8
30	16.4 ± 3.9 ##	20.7 ± 4.9

$P < 0.01$; ANOVA followed by Dunnett's test.
Data are given as mean ± s.e. mean for n = 4 cells per group before and after correction for mean vehicle rundown.

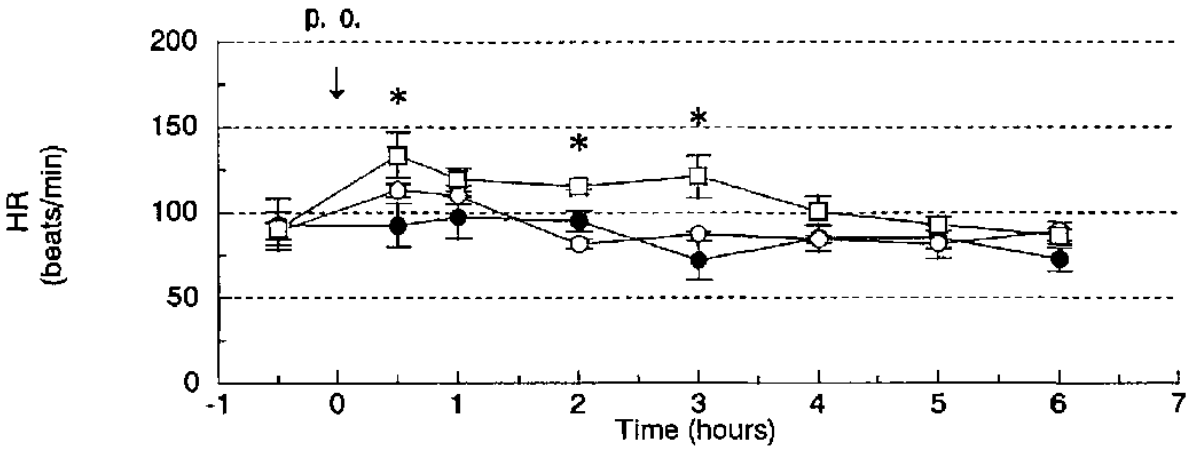
B) Study G00006: "Effects of Oral Administration of E2007 on Heart Rate, Blood Pressure and Electrocardiogram in Conscious Dogs"

Beagle dogs (n=3/sex) were administered a single oral dose of 0, 1, and 10 mg/kg perampanel in 0.5 % methyl cellulose with a 7-day washout period between the 0 and 1 mg/kg doses and a 14-day washout period between the 1 and 10 mg/kg doses. Heart rate, mean arterial blood pressure, PQ interval, QRS interval, and QT interval were measured 0.5, 1, 2, 3, 4, 5, and 6 hours after dosing. The study was initiated on 11/13/2000. An increase in heart rate, which lasted for up to 4 hours after dosing, was observed in male and female dogs dosed with 10 mg/kg (Sponsor's Figures below). There were no drug-related changes observed in the other cardiac parameters, including QT interval.

Males



Females



●: Vehicle (0.5% methyl cellulose solution), ○: E2007 (1 mg/kg), □: E2007 (10 mg/kg), HR: heart rate, MBP: mean blood pressure. Each point and bar represents mean ± S.E.M. (n=3). *: $p<0.05$ compared to the control group.

4.3.2. Respiratory

A) Study B010486: "Effect of Orally Administered E2007 on Respiratory Function in Rats"

Using whole body plethysmography, respiratory parameters (respiratory frequency, tidal volume, and minute volume) were measured in male SD rats (n=6/group) administered a single oral dose of 0, 0.3, 1, and 5 mg/kg perampanel in 0.5% methyl cellulose. Respiratory rate was decreased by up to 17% and 19%, relative to predosing, in MD and HD, respectively, for up to 2 hours after dosing (Sponsor's Table, below). Respiratory rate resolved to control levels within 4 hours of dosing. There were no test

article-related changes observed in any of the other respiratory parameters that were assessed.

Table 1 Effect of E2007 on respiratory frequency (% to before) in rats

Test substance	Dose (mg/kg p.o.)	No. of animals	Respiratory frequency (% to before)				
			Before	Time after administration (hour)			
				0.5	1	2	4
Control[1)]	---	6	100.0	98.2 ± 3.8	99.8 ± 4.0	94.7 ± 4.4	87.2 ± 3.6
E2007	0.3	6	100.0	91.6 ± 2.1	93.1 ± 2.3	89.5 ± 2.8	84.9 ± 2.7
	1	6	100.0	91.4 ± 1.9	83.1 ± 2.1 *	88.9 ± 1.6	83.5 ± 1.6
	5	6	100.0	85.1 ± 2.9 *	81.1 ± 3.1 *	84.3 ± 3.3	93.3 ± 4.2

Each value represents the mean±S.E.
1) 0.5% methyl cellulose
* : Significantly different from the control group by parametric Dunnett's test, $p<0.05$

4.3.3 Central Nervous System

A) Study B010485: "Effect of Orally Administered E2007 on Body Temperature in Rats"

In male SD rats (n=6/group) administered a single oral dose of 0, 0.3, 1, and 5 mg/kg perampanel, body temperature was not altered in a test article-related manner when assessed at 0.5, 1, 2 and 4 hours after dosing.

B) Study M01036: "E2007: Effects on Rotarod in Mice"

When male ICR mice (n=9/group) were given a single oral dose of 0, 0.5, 1, 2, and 4 mg/kg perampanel one hour before testing on the rotarod, a dose-related increase in the number of animals that could not remain on the rotarod for 120 seconds was observed for doses > 0.5 mg/kg (Sponsor's Table, below).

Table2. The effect of E2007 in the rotarod test

Treatment	% of motor uncoordinated mice
Vehicle (control)	11.1
E2007- 0.5 mg/kg	0
E2007- 1 mg/kg	22.2
E2007- 2 mg/kg	55.6
E2007- 4 mg/kg	100

C) Study W-20010415: "Effect of E2007 on Rotarod Test"

When male SD rats (n=8/group) were given a single oral dose of 0, 2, 4, 8, or 16 mg/kg perampanel one hour before testing on the rotarod, a dose-related increase in the number of animals that could not remain on the rotarod for 120 seconds was observed for doses > 2 mg/kg (Sponsor's Table, below).

Table1. The effect of E2007 in the rotarod test

Treatment	Latency (sec)	% of motor incoordinated rats
Vehicle (control)	115.1±4.9	0
E2007- 2 mg/kg	117.1±2.0	0
E2007- 4 mg/kg	78.0±11.4*	37.5
E2007- 8 mg/kg	57.6±14.6*	75
E2007- 16 mg/kg	46.5±20.5*	62.5

Results are expressed as mean ± SEM (n=?). *p<0.05 vs. the control group (one-way ANOVA followed by Dunnett type multiple comparison test)

D) Study B010484: "Effect of Orally Administered E2007 on General Physical Condition and Behavior (Irwin's Method) in Rats"

Male SD rats (n=6/group) were assessed for general physical condition and behavior by the Irwin method at 0.5, 1, 2, 4, and 6 hours after a single oral dose of 0, 0.3, 1, and 5 mg/kg perampanel in 0.5% methylcellulose. There were no perampanel-related effects observed in rats dosed with 0.3 mg/kg. One of the six MDM exhibited a slight decrease in abdominal tone up to 2 hours after dosing. A decrease in alertness, spontaneous activity, touch response, limb tone, grip strength, body tone, and abdominal tone as well as an increase in staggering gait and palpebral closure were observed at the HD from 0.5 to 4 hours after dosing (Sponsor's Table, below). Clinical signs were not observed in any dose group at 6 hours after dosing. The NOEL in this study was 0.5 mg/kg, with higher doses resulting in depression of CNS function.

Table 1 Effect of E2007 on general physical condition and behavior in rats

Test substance	Dose (mg/kg p.o.)	Signs	Normal score	Score	Time after administration (hour)					
					Before	0.5	1	2	4	6
Control[1)]	---	No abnormal signs	—	—	6/6 [2)]	6/6	6/6	6/6	6/6	6/6
E2007	0.3	No abnormal signs	—	—	6/6	6/6	6/6	6/6	6/6	6/6
	1	No abnormal signs	—	—	6/6	6/6	5/6	5/6	6/6	6/6
		Abdominal tone	4	3			1/6	1/6		
	5	No abnormal signs	—	—	6/6		1/6	2/6	4/6	6/6
		Alertness	4	3		3/6	4/6	2/6		
		Spontaneous activity	4	3		4/6	4/6	1/6		
		Touch response	4	3		3/6	4/6	2/6		
		Body position	4	3		5/6	4/6	2/6		
		Staggering gait	0	1		2/6	2/6	2/6	1/6	
				2		3/6	2/6	1/6		
		Limb tone	4	3		3/6	5/6	2/6		
		Grip strength	4	3		1/6				
		Body tone	4	3		5/6	2/6	2/6		
		Abdominal tone	4	3		6/6	4/6	3/6	2/6	
				2			1/6	1/6		
		Palpebral opening	4	3		1/6	2/6	2/6		

1) 0.5 % methyl cellulose

2) Number of animals showing the sign / Number of animals tested.

5 Pharmacokinetics

5.1 PK/ADME

5.1.1 Analytical Methods and Validation

Analytical methods for detecting and quantifying perampanel in rat, mouse, rabbit, dog, and monkey plasma were validated by the Sponsor in studies that were GLP compliant. Using HPLC with fluorescence detection, calibration curves for perampanel spiked into rat plasma exhibited linearity (r >0.999) over a range of 0.3 to 3000 ng/ml, which represented the lower and upper limits of quantification, respectively (Studies TKV0004 & A-1438). There were no peaks that interfered with the detection of perampanel (RT= 10.5 min) in rat plasma. The recovery of perampanel from rat plasma ranged from 97.1-100.9% of the initial concentration when stored at -20 to -30^{o}C for up to 59 days. Similar findings for range of linearity in HPLC with fluorescence detection (0.3 to 3000 ng/ml; r >0.999), limit of quantification (0.3 ng/ml), and stability at -30^{o}C (94.7-102.5% sixty days after spiking) were observed for perampanel spiked into mouse plasma (Study A-1437). There were no peaks that interfered with the detection of perampanel in mouse plasma (RT=10.3 min). When perampanel was spiked into rabbit plasma, calibration curves were linear over the concentration range of 0.3 to 3000 ng/ml, with a limit of quantification of 0.3 ng/ml (Study A-2043). Perampanel was stable in rabbit plasma stored at -30^{o}C for up to 28 days (96.1 to 101.7%, relative to initial concentration). There were no peaks that interfered with the detection of perampanel in rabbit plasma (RT=11.1 min). The calibration curve for perampanel in dog plasma was linear between 0.3 ng/ml, the limit of quantification, and 3000 ng/ml (Study TKV0005). Perampanel was stable (96.4- 108.2% of initial concentration) in dog plasma for up to 4 weeks when stored below -15^{o}C. There were no peaks that interfered with the detection of perampanel in dog plasma (RT=10.6 min). Perampanel was stable (94.2-96.6%) in Cynomolgus monkey plasma for up to 4 weeks at -15^{o}C (Study SBL-47-46). The calibration curve for perampanel in monkey plasma was linear between 0.3 ng/ml, the limit of quantification, and 3000 ng/ml. There were no peaks that interfered with the detection of perampanel in monkey plasma (RT=12.6 min).

5.1.2. Absorption

A) Study B00023: “Pharmacokinetic Profile of E2007 After a Single Oral and Intravenous Administration to Rats”

Fasted male Sprague-Dawley rats (n=4/group) were dosed intravenously with 1 mg/kg or orally with 1, 3, or 10 mg/kg perampanel. Blood was then sampled at 0.8, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours post-dose to calculate PK parameters of perampanel (Sponsor’s Table 2, below). Perampanel demonstrated an oral bioavailability that ranged from 36.7-47.8% and a half-life that ranged from 1.3 to 2.1 hours in rats.

Table 2 Pharmacokinetic parameters of E2007 after a single oral and intravenous administration to rats

Route	Dose (mg/kg)	t_{max} (hr)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	MRT (hr)	AUC (ng · hr/mL)	CL (mL/hr/kg)	V_{ss} (mL/kg)	B.A. (%)
iv	1	-	-	1.36 ± 0.15	1.29 ± 0.14	836.21 ± 95.91	1238.6 ± 125.4	1560.0 ± 121.6	-
po	1	1.00 (0.50–1.00)	100.350 ± 16.926	1.65 ± 0.13	3.19 ± 0.20	385.75 ± 24.62	-	-	46.1
po	3	1.00 (0.50–1.00)	353.090 ± 63.747	1.45 ± 0.09	2.27 ± 0.13	920.94 ± 81.50	-	-	36.7
po	10	0.75 (0.25–6.00)	778.830 ± 85.656	2.15 ± 0.27	4.02 ± 0.76	3998.73 ± 533.55	-	-	47.8

Each parameter, except for t_{max} and B.A., represents the mean ± S.E.M. of four rats.
t_{max} is shown as the median and the range, and B.A. is estimated by the mean AUC values.
-: not calculated.

B) Study B00027: "Pharmacokinetic Profile of E2007 After a Single Oral and Intravenous Administration to Dogs"

Male beagle dogs (n=4) were dosed intravenously with 0.1 mg/kg or orally with 0.1, 0.3, or 1 mg/kg perampanel with a 7-day washout period between doses. PK parameters for perampanel are provided in the Sponsor's Table, below. Perampanel exhibited an oral bioavailability of 49-53% and a half life of 5.3-5.8 hours in dogs.

Table 2 Pharmacokinetic parameters of E2007 after a single oral and intravenous administration to dogs

Route	Dose (mg/kg)	t_{max} (hr)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	MRT (hr)	AUC (ng · hr/mL)	CL (mL/hr/kg)	V_{ss} (mL/kg)	B.A. (%)
iv	0.1	-	-	6.87 ± 0.7	5.78 ± 0.75	131.72 ± 15.23	779.8 ± 89.8	4423.5 ± 461.4	-
po	0.1	0.50 (0.25–0.50)	25.934 ± 3.925	5.34 ± 0.7	4.88 ± 0.34	69.55 ± 5.31	-	-	53.5 ± 3.9
po	0.3	0.50 (0.25–0.50)	69.656 ± 12.614	5.47 ± 0.3	4.81 ± 0.54	199.90 ± 13.44	-	-	51.5 ± 5.0
po	1	0.50 (0.50–1.00)	133.249 ± 21.307	5.80 ± 0.9	5.96 ± 1.18	649.88 ± 72.29	-	-	49.4 ± 1.8

Each parameter, except for t_{max}, represents the mean ± S.E.M. of three dogs.
t_{max} is shown as the median and the range.
-: not calculated.

C) Study SBL-47-58: "E2007: Pharmacokinetic Profile of E2007 After a Single Oral and Intravenous Administration to Monkeys"

Male Cynomolgus monkeys (n=4) were administered an oral dose of 0.03 mg/kg perampanel followed two weeks later by an intravenous dose of 0.03 mg/kg perampanel. PK parameters were calculated for each monkey and are provided in the Sponsor's tables, below. Bioavailability was determined to be 75% and the half-life for perampanel was similar between the intravenous and oral dosing (6.9 hrs vs. 7.5 hrs, respectively).

Table 3 Plasma concentrations and pharmacokinetic parameters of E2007 after oral administration of E2007 to monkeys

Dose (mg/kg)	Animal No.	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24hr} (ng·hr/mL)	$AUC_{0-\infty hr}$ (ng·hr/mL)	MRT (hr)	$t_{1/2}$ (hr)
0.03	1	12.03	1.00	85.30	93.23	7.06	7.23
	2	13.35	2.00	129.10	148.82	8.46	8.44
	3	16.06	1.00	179.60	205.79	8.47	8.37
	4	10.56	2.00	78.67	83.41	6.75	6.19
	Mean	13.00	1.50	118.17	132.81	7.69	7.56
	SD	2.34	0.58	46.67	56.54	0.91	1.07

Table 4 Plasma concentrations and pharmacokinetic parameters of E2007 after intravenous administration of E2007 to monkeys

Dose (mg/kg)	Animal No.	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24hr} (ng·hr/mL)	$AUC_{0-\infty hr}$ (ng·hr/mL)	MRT (hr)	$t_{1/2}$ (hr)	CLtot (mL/hr/kg)	V_{ss} (mL/kg)
0.03	1	24.90	0.0833	109.44	121.05	7.08	7.45	247.83	2412.46
	2	25.72	0.0833	163.06	184.22	8.25	7.76	162.85	1847.44
	3	21.79	0.0833	223.71	250.44	8.33	7.35	119.79	1333.76
	4	24.52	0.0833	138.11	143.86	6.98	5.18	208.54	1659.31
	Mean	24.23	0.0833	158.58	174.89	7.66	6.94	184.75	1813.24
	SD	1.70	0.00	48.63	56.73	0.73	1.18	55.51	452.34

Table 5 Bioavailability of E2007 in monkeys

Dose (mg/kg)	Animal No.	Oral administration $AUC_{0-\infty hr}$ (ng·hr/mL)	Intravenous administration $AUC_{0-\infty hr}$ (ng·hr/mL)	BA (%)
0.03	1	93.23	121.05	77.02
	2	148.82	184.22	80.78
	3	205.79	250.44	82.17
	4	83.41	143.86	57.98
	Mean	132.8	174.9	74.50
	SD	56.54	56.73	11.22

BA: Bioavailability

5.1.3. Distribution

A) Study B02010: "E2007: Protein Binding of ^{14}C-E2007 in Mouse and Monkey Plasma"

Plasma from male CD-1 mice and male Cynomolgus monkeys was incubated with 20, 200, or 2000 ng/ml radiolabeled perampanel to determine the plasma protein binding capacity of perampanel. Perampanel exhibited robust binding to both mouse (>94%) and monkey (>90%) plasma proteins.

Summary Table Protein binding of ^{14}C-E2007 in mouse and monkey plasma

Added conc. (ng/mL)	Plasma protein binding (%)	
	Mouse	Monkey
20	94.1 ± 0.2	90.2 ± 0.3
200	94.3 ± 0.1	90.6 ± 0.3
2000	94.6 ± 0.1	90.1 ± 0.3

Each value represents the mean ± S.E.M. (n=3 or 4)

B) Study AE-4736-G: "E2007: Placental Transfer After Single Oral Administration of ^{14}C-E2007 in Pregnant Rats"

Female Crl:CD(SD) rats were given a single oral dose of 1 mg/kg radiolabeled-perampanel on gestational day (GD) 13 or 19 to determine the magnitude of placental transfer of perampanel. Dams were euthanized at 0.5, 6, or 24 hours after dosing and distribution of perampanel was assessed by scintillation counting of selected maternal and fetal tissues (Sponsor's Tables, below). The data demonstrate that there is placental transfer of perampanel to fetal blood (34-48% of maternal levels), fetal brain (59-88% of maternal levels), fetal heart (41-44% of maternal levels), fetal lung (33-59% of maternal levels), fetal liver (5-15% of maternal levels), and fetal kidney (13-23% of maternal levels).

Table Exp.1-1 Radioactive concentration in tissue after single oral administration of ^{14}C-E2007 to fasting rats on day 13 of pregnancy (dose: 1 mg/kg)

Tissue	Radioactive concentration (ng eq. of E2007/g or mL)		
	0.5 hr	6 hr	24 hr
Plasma	400.64 ± 35.50 (1.00)	111.09 ± 28.11 (1.00)	8.33 ± 1.48 (1.00)
Blood	311.88 ± 24.05 (0.78)	88.52 ± 21.41 (0.80)	7.82 ± 0.56 (0.94)
Cerebrum	272.64 ± 5.18 (0.68)	55.87 ± 18.13 (0.50)	0.65 ± 0.39 (0.08)
Heart	619.14 ± 20.18 (1.55)	158.82 ± 47.14 (1.43)	5.41 ± 1.06 (0.65)
Lung	555.90 ± 23.87 (1.39)	154.54 ± 42.70 (1.39)	11.90 ± 1.08 (1.43)
Liver	2699.43 ± 327.64 (6.74)	991.68 ± 154.10 (8.93)	152.15 ± 7.49 (18.27)
Kidney	836.38 ± 20.99 (2.09)	304.33 ± 69.30 (2.74)	41.00 ± 5.32 (4.92)
Adrenal gland	1734.38 ± 40.03 (4.33)	503.20 ± 158.44 (4.53)	11.83 ± 2.62 (1.42)
Uterus	325.51 ± 15.59 (0.81)	103.71 ± 38.29 (0.93)	6.96 ± 0.60 (0.84)
Ovary	835.22 ± 33.98 (2.08)	293.64 ± 123.22 (2.64)	5.99 ± 1.99 (0.72)
Mammary gland	1228.15 ± 132.82 (3.07)	464.25 ± 115.67 (4.18)	8.99 ± 1.55 (1.08)
Placenta	335.61 ± 11.65 (0.84)	96.11 ± 35.59 (0.87)	4.35 ± 0.69 (0.52)
Fetal membrane	252.38 ± 7.00 (0.63)	85.17 ± 22.30 (0.77)	43.55 ± 6.90 (5.23)
Yolk sac fluid	31.27 ± 2.44 (0.08)	9.00 ± 2.62 (0.08)	0.60 ± 0.30 (0.07)
Fetus	97.56 ± 7.90 (0.24)	29.98 ± 9.51 (0.27)	0.96 ± 0.41 (0.12)

Data are expressed as the mean values ± S.E.M. of three animals.
Figures in parentheses are expressed as the ratio of concentration in tissue relative to plasma.

Table Exp.1-3 Radioactive concentration in tissue after single oral administration of ^{14}C-E2007 to fasting rats on day 19 of pregnancy (dose: 1 mg/kg)

Tissue	Radioactive concentration (ng eq. of E2007/g or mL)		
	0.5 hr	6 hr	24 hr
Maternal			
Plasma	267.02 ± 24.62 (1.00)	135.47 ± 20.61 (1.00)	14.68 ± 4.39 (1.00)
Blood	217.58 ± 15.50 (0.81)	117.36 ± 17.62 (0.87)	14.06 ± 3.20 (0.96)
Cerebrum	229.09 ± 8.92 (0.86)	94.71 ± 25.25 (0.70)	4.86 ± 2.12 (0.33)
Heart	499.57 ± 19.89 (1.87)	250.60 ± 56.83 (1.85)	18.48 ± 6.30 (1.26)
Lung	474.03 ± 15.92 (1.78)	220.61 ± 43.81 (1.63)	22.28 ± 4.78 (1.52)
Liver	2634.57 ± 264.00 (9.87)	1147.18 ± 89.30 (8.47)	212.11 ± 8.20 (14.45)
Kidney	727.47 ± 21.33 (2.72)	428.91 ± 52.46 (3.17)	71.22 ± 9.73 (4.85)
Adrenal gland	1391.14 ± 72.85 (5.21)	702.78 ± 164.85 (5.19)	52.65 ± 20.71 (3.59)
Uterus	197.49 ± 15.44 (0.74)	122.18 ± 15.15 (0.90)	11.46 ± 2.26 (0.78)
Ovary	846.25 ± 53.36 (3.17)	377.99 ± 93.90 (2.79)	25.59 ± 10.47 (1.74)
Mammary gland	1317.59 ± 79.94 (4.93)	941.12 ± 260.94 (6.95)	50.11 ± 20.47 (3.41)
Placenta	309.33 ± 21.92 (1.16)	171.72 ± 29.54 (1.27)	17.46 ± 5.11 (1.19)
Fetal membrane	228.85 ± 20.19 (0.86)	170.78 ± 24.17 (1.26)	104.39 ± 14.49 (7.11)
Amniotic fluid	34.54 ± 1.84 (0.13)	23.86 ± 3.09 (0.18)	12.10 ± 2.21 (0.82)
Fetus	158.14 ± 4.06 (0.59)	86.45 ± 18.71 (0.64)	10.44 ± 2.76 (0.71)
Fetal			
Blood	93.41 ± 10.57 (0.35)	56.06 ± 9.06 (0.41)	7.15 ± 1.87 (0.49)
Brain	135.88 ± 4.87 (0.51)	77.12 ± 16.96 (0.57)	4.29 ± 1.53 (0.29)
Heart	207.20 ± 11.00 (0.78)	110.74 ± 26.38 (0.82)	7.86 ± 3.07 (0.54)
Lung	161.31 ± 6.01 (0.60)	85.37 ± 16.91 (0.63)	7.62 ± 2.34 (0.52)
Liver	302.92 ± 11.45 (1.13)	172.03 ± 40.79 (1.27)	12.16 ± 3.48 (0.83)
Kidney	170.10 ± 5.66 (0.64)	102.09 ± 19.03 (0.75)	9.46 ± 2.41 (0.64)
Digestive tract	173.08 ± 5.06 (0.65)	124.87 ± 29.42 (0.92)	120.50 ± 45.52 (8.21)

Data are expressed as the mean values ± S.E.M. of three animals.
Figures in parentheses are expressed as the ratio of concentration in tissue relative to plasma.

C) Study B01032: "E2007: Blood Level, Distribution, Metabolism and Excretion of Radioactivity After an Oral Administration of ^{14}C-E2007 to Rats"

Male Sprague Dawley rats were given a single oral dose of 1 mg/kg ^{14}C-radiolabeled perampanel in order to assess blood levels, distribution, metabolism, and excretion of the test article. Blood samples were collected at several intervals up to 168 hours after dosing and animals were euthanized 1, 6, 24, 168 hours, and 21 days after dosing to assess for tissue distribution. Urine and feces were examined for radioactivity up to 7 days after dosing and biliary excretion was assessed by cannulation of the bile duct, 48 hours after dosing.

The plasma half-life calculated for radiolabeled perampanel was 8.3 hours in this study (Sponsor's Table 2, below). The majority of the radioactivity was eliminated in the bile (87%) with the remainder being eliminated via the urine (11.7%; Sponsor's Table 5, below); 99.5% of the radioactive dose was recovered in urine and feces by Day 7 of the study (Sponsor's Table 5, below). A similar ratio of elimination was found in the cannulated rats with 92% of the radioactivity being recovered in the bile within 48 hours of dosing (Sponsor's Table 6, below). Within one hour of dosing, the tissues demonstrating the highest levels of radiolabeled perampanel were the Harderian gland, thyroid, adipose tissue, vein, adrenal gland, liver, stomach, and small intestine (Sponsor's Table 3, below). Within 24 hours after exposure, radioactivity levels were at

or below the limit of detection for most tissues except the aorta, kidney, liver, cecum, and large intestine. Detectable levels of radioactivity were present in the kidney, liver, and aorta 21 days after dosing, suggesting a substantially longer half life in these tissues. Attempts to extract the radioactivity from the liver were generally unsuccessful with up to 62% of the radioactivity remaining with the pellet after centrifugation, suggesting covalent binding of perampanel to endogenous macromolecules (Sponsor's Table 8).

Regarding metabolism of perampanel, the parent compound ("Fraction 1") represented 85% of the radioactivity detected in plasma at one hour after dosing, with "Fraction 6" (ER-260862-00) and "Fraction 7" (glucuronide of 4'-hydroxy-perampanel) accounting for the balance of extractable metabolites (5.6% and 1.4%, respectively; Sponsor's Table 10). At 6 hours after dosing, the majority of the radioactivity (70%) was associated with "Fraction 7"; the parent compound represented the balance of extractable radioactivity in the plasma (16%). Perampanel represented 93% of the radioactivity found in the brain at one hour after dosing. The main component of radioactivity in bile was the glucuronide of the 4'-hydroxylated form of perampanel; however, the 4'-OH form of perampanel (ER-179392-00; Sponsor's Figure 19) was the predominant component of radioactivity in feces, which suggests deconjugation by enteric bacteria.

Table 2. Pharmacokinetic parameters of radioactivity in blood after an oral administration of ^{14}C-E2007 at 1 mg/kg to SD rats

Parameters		mean ± S.E.M.
AUC	(ng eq.·hr/mL)	963 ± 88
$t_{1/2}$	(hr)	8.3 ± 0.2
t_{max}	(hr)	1.0 ± 0.2
C_{max}	(ng eq./mL)	161 ± 21

Each value was expressed as the mean ± S.E.M. of four animals.

Table 5. Cumulative excretion of radioactivity in urine and feces after an oral administration of ^{14}C-E2007 at 1 mg/kg to SD rats

Time	Cumulative excretion of radioactivity (% of dose)		
	Urine	Feces	Total
1 day	10.88 ± 0.86	76.89 ± 5.09	87.77 ± 4.46
2 days	11.62 ± 0.97	83.30 ± 4.65	94.92 ± 3.98
3 days	11.71 ± 0.98	84.03 ± 4.69	95.74 ± 4.03
5 days	11.77 ± 0.99	84.29 ± 4.71	96.05 ± 4.05
7 days	11.78 ± 0.99	87.71 ± 1.82	99.49 ± 1.19

Each value represents the mean ± S.E.M. of four animals.

Table 6. Cumulative excretion of radioactivity in urine and bile after an oral administration of ^{14}C-E2007 at 1 mg/kg to SD rats canulated to bile duct

Time	Cumulative excretion of radioactivity (% of dose)	Time	Cumulative excretion of radioactivity (% of dose)	
	Urine		Bile	Total
0-24 hr	5.44 ± 1.02	0-2 hr	27.38 ± 16.40	27.38 ± 16.40
0-48 hr	6.69 ± 1.26	0-4 hr	43.25 ± 17.82	43.25 ± 17.82
		0-6 hr	56.39 ± 17.60	56.39 ± 17.60
		0-24 hr	86.08 ± 8.27	91.52 ± 8.41
		0-48 hr	92.33 ± 2.79	99.01 ± 2.33

Each value represents the mean ± S.E.M. of three animals.

Table 3. Tissue distribution of radioactivity after an oral administration of ^{14}C-E2007 at 1 mg/kg to SD rats

Tissue	Concentration of radioactivity (ng eq./g or mL)				
	1 hr	6 hr	24 hr	168 hr[a)]	21 days[a)]
Blood	162 ± 11	43 ± 6	7 ± 1	BQL	N.T.
Plasma	212 ± 21	62 ± 10	7 ± 0	BQL	N.T.
RBC	108 ± 7	25 ± 1	4 ± 0	BQL	N.T.
Cerebrum	142 ± 26	14 ± 3	BQL	BQL	N.T.
Cerebellum	140 ± 29	13 ± 2	BQL	BQL	N.T.
Hypophysis	304 ± 68	38 ± 4	BQL	BQL	N.T.
Medulla oblongata	160 ± 41	16 ± 4	BQL	BQL	N.T.
Spinal cord	164 ± 34	14 ± 3	BQL	BQL	N.T.
Eye	70 ± 3	15 ± 1	2 ± 0	BQL	N.T.
Harderian gland	590 ± 80	75 ± 11	5 ± 0	BQL	N.T.
Lymph node	212 ± 26	35 ± 5	BQL	BQL	N.T.
Submaxillary gland	317 ± 33	48 ± 10	BQL	BQL	N.T.
Thyroid	404 ± 87	64 ± 2	15 ± 8	BQL	N.T.
Trachea	285 ± 87	49 ± 10	10 ± 1	BQL	N.T.
Heart	312 ± 43	40 ± 7	3 ± 2	BQL	N.T.
Lung	277 ± 19	51 ± 8	9 ± 2	2 ± 1	N.T.
Thymus	162 ± 22	29 ± 5	BQL	BQL	N.T.
Adipose Tissue	1702 ± 479	390 ± 84	6 ± 4	BQL	N.T.
Skin	310 ± 50	65 ± 10	6 ± 1	BQL	N.T.
Muscle	142 ± 17	26 ± 3	BQL	BQL	N.T.
Sciatic nerve	247 ± 77	28 ± 14	BQL	BQL	N.T.
Bone marrow	254 ± 77	22 ± 11	BQL	BQL	N.T.
Testis	151 ± 26	26 ± 3	BQL	BQL	N.T.
Aorta	384 ± 71	118 ± 13	89 ± 35	44 ± 9	96 ± 17
Vein	642 ± 205	229 ± 154	BQL	9 ± 5	N.T.
Prostate	203 ± 26	41 ± 1	BQL	BQL	N.T.
Urinary bladder	225 ± 8	68 ± 17	6 ± 4	BQL	N.T.
Spleen	258 ± 52	36 ± 2	3 ± 2	BQL	N.T.
Pancreas	376 ± 64	72 ± 19	5 ± 3	BQL	N.T.
Adrenal gland	1025 ± 164	160 ± 26	4 ± 2	BQL	N.T.
Kidney cortex	757 ± 61	190 ± 21	51 ± 6	11 ± 1	2 ± 1
Kidney medulla	483 ± 35	233 ± 65	13 ± 9	BQL	N.T.
Liver	3194 ± 405	907 ± 86	207 ± 91	27 ± 1	4 ± 0
Stomach	3155 ± 718	241 ± 85	6 ± 1	BQL	N.T.
Small intestine	2634 ± 486	836 ± 340	13 ± 0	BQL	N.T.
Caecum	315 ± 104	4462 ± 895	179 ± 75	BQL	N.T.
Large intestine	338 ± 87	97 ± 10	62 ± 38	BQL	N.T.

Each data represents the mean ± S.E.M. of three animals. a): the mean ± S.E.M. of four animals.
NT: not tested, BQL: below quantitation limit (<30 dpm/sample)

Table 8. Extraction recovery (%) of radioactivity in plasma, kidney and liver after an oral administration of ^{14}C-E2007 at 1 mg/kg to SD rats

Tissue	Time	Extraction recovery of radioactivity			
		MeOH	15% TCA	Hot MeOH	Pellet
Plasma	6 hr	85.8 ± 1.8	0.4 ± 0.2	6.0 ± 0.8	7.8 ± 1.2
Kidney	6 hr	83.8 ± 0.9	1.5 ± 0.2	2.9 ± 0.5	11.8 ± 0.7
	24 hr	72.3 ± 0.9	1.8 ± 1.1	7.9 ± 3.4	17.9 ± 4.6
Liver	6 hr	59.5 ± 1.2	2.0 ± 0.2	3.7 ± 0.4	34.8 ± 1.0
	24 hr	27.0 ± 2.1	2.8 ± 0.1	7.5 ± 0.9	62.8 ± 2.5

Each value represents the mean ± S.E.M. of three animals.

Table 10. Metabolic profile of radioactivity in plasma after an oral administration of ^{14}C-E2007 at 1 mg/kg to SD rats

Metabolites	1 hr	6 hr
Fraction 1 (E2007)	180 ± 27	10 ± 6
Fraction 2	4 ± 2	0 ± 0
Fraction 3	0 ± 0	0 ± 0
Fraction 4	2 ± 1	0 ± 0
Fraction 5 (4'-OH)	0 ± 0	0 ± 0
Fraction 6	12 ± 2	0 ± 0
Fraction 7	3 ± 2	44 ± 9
Origin	0 ± 0	0 ± 0
Others	1 ± 1	0 ± 0
Unextracted	9 ± 1	8 ± 0

Each value was expressed as ng eq./mL and represents the mean ± S.E.M. of three animals.

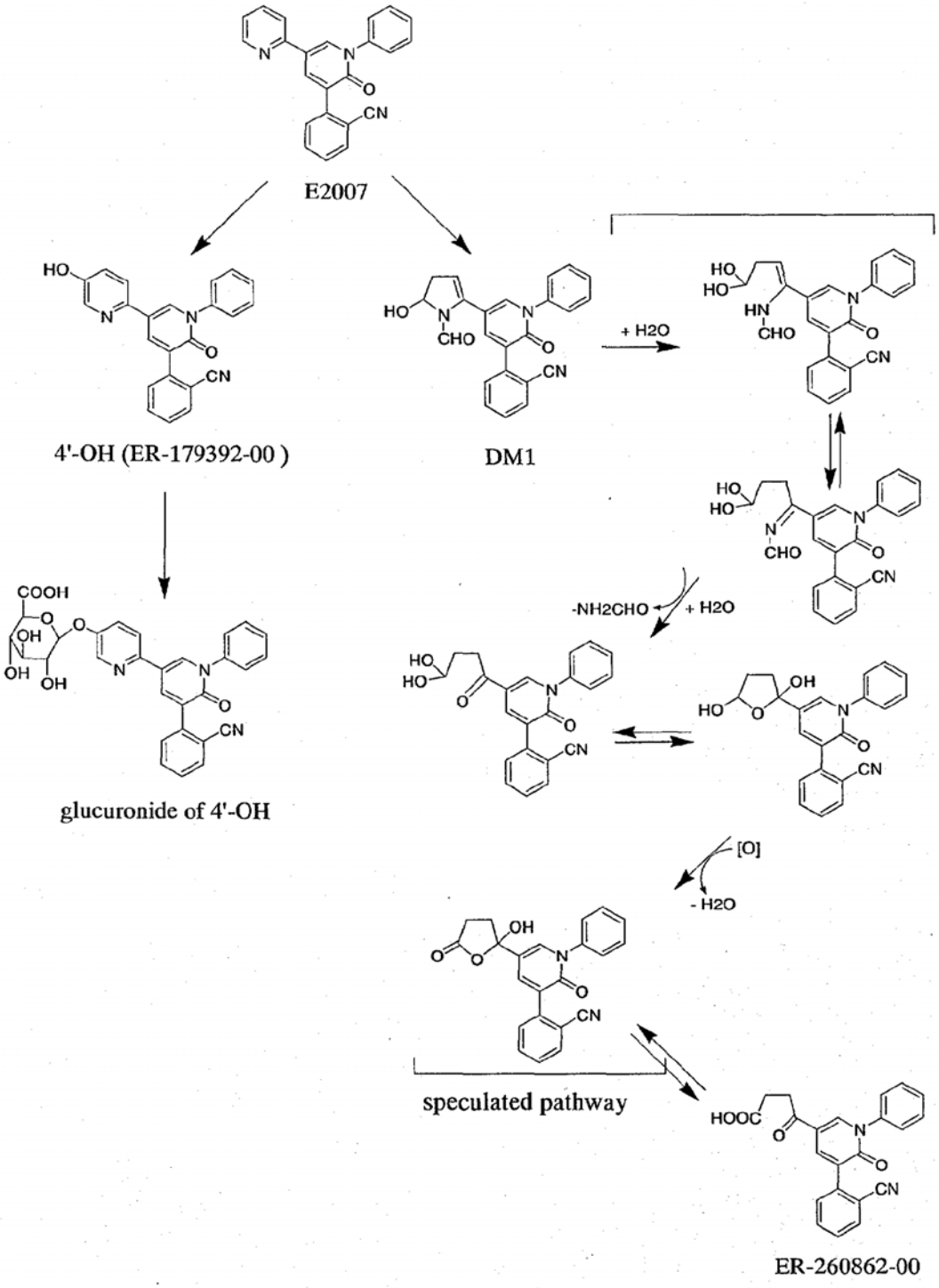


Figure 19. Proposed metabolic pathways of E2007 in rat

Table 14. Metabolic profile of radioactivity in urine after an oral administration of ^{14}C-E2007 at 1 mg/kg to SD rats

Metabolites	0~1 day
Fraction 1 (E2007)	0.00 ± 0.00
Fraction 2	0.00 ± 0.00
Fraction 3	0.00 ± 0.00
Fraction 4	0.00 ± 0.00
Fraction 5 (4'-OH)	0.35 ± 0.21
Fraction 6	6.53 ± 0.69
Fraction 7	3.60 ± 0.24
Origin	0.00 ± 0.00
Others	0.41 ± 0.17

Each value was expressed % of dose and represents the mean ± S.E.M. of four animals.

Table 15. Metabolic profile of radioactivity in feces after an oral administration of ^{14}C-E2007 at 1 mg/kg to SD rats

Metabolites	0~1 day	1~2 day
Fraction 1 (E2007)	0.51 ± 0.22	0.00 ± 0.00
Fraction 2	0.39 ± 0.08	0.00 ± 0.00
Fraction 3	0.26 ± 0.04	0.00 ± 0.00
Fraction 4	1.58 ± 0.13	0.00 ± 0.00
Fraction 5 (4'-OH)	20.84 ± 0.87	5.22 ± 0.26
Fraction 6	6.53 ± 0.69	0.27 ± 0.12
Fraction 7	4.77 ± 0.61	0.02 ± 0.02
Origin	0.87 ± 0.16	0.00 ± 0.00
Others	28.13 ± 1.85	0.00 ± 0.00
Unextracted	13.03 ± 1.12	0.91 ± 0.14

Each value was expressed as % of dose and represents the mean ± S.E.M. of four animals.

D) Study AE-3690-G: "E2007: Distribution of Radioactivity in Tissues After an Oral Administration of ^{14}C-E2007 in Pigmented Rats"

Male pigmented SPF/VAF/BN/Crj rats (Brown Norway) were given a single oral dose of 1 mg/kg ^{14}C-radiolabeled perampanel in order to assess distribution of the test article. Blood samples were collected at several intervals up to 168 hours after dosing and animals were euthanized 1 hr, 24 hrs or 1, 3, 6, or 9 weeks after dosing. Due to a triphasic decrease in blood and plasma levels, three separate half-life values were calculated (Sponsor's Table 3).

Table Exp.3 Radioactive concentration and pharmacokinetic parameters in blood and plasma after single oral administration of ^{14}C-E2007 to fasting male pigmented rats (dose: 1 mg/kg)

			Radioactivity concentration (ng eq. of E2007/mL)	
			Blood	Plasma
Detection limit			1	1
tmax (hr)			1 ± 0	1 ± 0
Cmax (ng eq./mL)			141 ± 10	183 ± 14
$t_{1/2}$	(2-6hr)	(hr)	2.1 ± 0.1	2.1 ± 0.1
	(8-24hr)	(hr)	11 ± 1	10 ± 1
	(48-72,96,144hr)	(day)	4.8 ± 0.5	2.1 ± 0.7
AUC		(0-time)	1.20 ± 0.03	1.30 ± 0.03
(μg eq.·hr/mL)		(0-∞)	1.60 ± 0.10	1.44 ± 0.07

Data are expressed as the mean values ± S.E. of three animals.
N.D. : Not detected

Although the highest levels of radioactivity detected in plasma, blood, eyeball, liver, and aorta occurred at 1 hour after dosing, detectable levels of radioactivity were measured in liver up to 6 weeks after dosing and in eye and aorta at the final sampling time (Sponsor's Table 4-1, below). The levels of radioactivity detected in the liver at 6 weeks after dosing and the eye and aorta at 9 weeks after dosing were 0.03%, 4.4% and 5%, respectively, of the levels detected at 1 hour after dosing. When treated with either elastase or pronase, 100% of the radioactivity present in the aorta at 1 week after dosing was extractable with methanol (Sponsor's Table 5), suggesting a covalent interaction of the perampanel or a related metabolite with the macromolecules of the aorta. Retention of radioactivity in the eye of the pigmented rat was longer than in the albino rats in Study B01032 suggesting that perampanel and/or its metabolites may have an affinity for melanin.

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Table Exp.4-1 Radioactive concentration in tissue after single oral administration of ^{14}C-E2007 to fasting male pigmented rats (dose: 1 mg/kg)

Tissue	Radioactivity concentration (ng eq. of E2007/g or mL)											
	1 hr		24 hr		1 week		3 weeks		6 weeks		9 weeks	
Plasma	241 ± (1.00)	16	7 ± (1.00)	0	N.D.		N.D.		N.D.		N.D.	
Blood	194 ± (0.80)	9	7 ± (1.00)	0	1 ±	0	1 ±	0	N.D.		N.D.	
Eyeball	269 ± (1.12)	16	24 ± (3.43)	2	18 ±	2	15 ±	1	12 ±	1	12 ±	0
Liver	2630 ± (10.91)	24	151 ± (21.57)	3	28 ±	1	4 ±	0	1 ±	0	0 ±	0
Aorta	361 ± (1.50)	48	36 ± (5.14)	3	24 ±	5	17 ±	4	18 ±	5	18 ±	5

Data are expressed as the mean values ± S.E. of three animals.
Figures in parentheses are expressed as the ratio of concentration in tissue relative to plasma.
N.D. : Not detected

Table Exp.5 Recovery of radioactivity from aorta, 168 hr after single oral administration of ^{14}C-E2007 to fasting male pigmented rats (dose: 1 mg/kg)

	Recovery (%) of radioactivity
Methanol extract	0.0 [1)]
Enzyme treatment	
Elastase treatment	100.0
Control[2)]	0.0 [1)]
Pronase treatment	100.0
Control[2)]	0.0 [1)]

Sample was extracted with methanol.

1) : Sample radioactivity are below the 2 × background value

2) : Aorta were incubated without enzymes

E) Study B04002: "E2007: Blood, aorta, eye and skin concentrations of radioactivity after an oral administration of ^{14}C-E2007 to pigmented rats"

Male pigmented, Brown Norway rats were given a single oral dose of 1 mg/kg ^{14}C-radiolabeled perampanel in order to assess distribution of the test article to aorta, eye, and skin. Blood samples were collected at 1 hour after dosing and animals were

euthanized 6, 9, 12, 24, 38, 55, and 106 weeks after dosing to assess for tissue distribution of the test article. Blood levels of radioactivity at one hour after dosing (141 ng-eq/ml) were similar to those observed in Study AE-3690-G (141 ng-eq/ml). Elimination of radioactivity from the aorta and eye was slow, with an estimated half-life of 110 weeks in aorta and 45 weeks in eye (Sponsor's Table 2 & 3). Radioactivity was detected in the skin of rats up to 12 weeks after dosing.

Table 2 Tissue concentration of radioactivity after an oral administration of ^{14}C-E2007 at 1 mg/kg to pigmented rats

Tissue	Concentration (ng E2007 eq./g or mL)						
Time (weeks)	6	9	12	24	38	55	106
Blood	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Aorta	16 ± 0 (100)	15 ± 2 (94)	11 ± 1 (69)	11 ± 2 (69)	10 ± 2 (63)	8 ± 2 (50)	7 ± 1 (44)
Eyeball	11 ± 0 (100)	10 ± 1 (91)	10 ± 1 (91)	4 ± 0 (36)	8 ± 1 (73)	5 ± 0 (45)	3 ± 0 (27)
Skin	2 ± 1	4 ± 1	2 ± 0	BQL	BQL	BQL	BQL

Each data represents the mean ± S.E.M. of three animals.
BQL: below the quantitation limit (<30 dpm/sample).
These parentheses were ratio to concentration of sixth weeks in aorta and eyeball, respectively.

Table 3 Half-life of radioactivity in aorta and eyeball after an oral administration of ^{14}C-E2007 at 1 mg/kg to pigmented rats

Tissue	Estimated $t_{1/2}$ (weeks)
Aorta	110
Eyeball	45

F) Study AE-3321-G: "E2007: Absorption, Distribution, and Excretion in Cynomolgus Monkeys after a Single Oral Administration of ^{14}C-E2007"

Male Cynomolgus monkeys (n=4) were given a single oral dose of 0.3 mg/kg ^{14}C-radiolabeled perampanel in order to assess absorption, distribution, and excretion of the test article. Blood, plasma, urine, and feces were collected at several intervals up to 168 hours, which was the time of euthanasia and tissue collection in this study.

Blood and plasma levels of radioactivity peaked at 5 hours after dosing and declined in a biphasic manner that resulted in a half-life of 11 hrs for the first phase (α) and 2.2 days for the second phase (β) of elimination (Sponsor's Table 2, below). The excretion of radioactivity via urine (36.9%) and feces (56.7%) reached a plateau by Day 7 of the study, with 93.6% of the total dose recovered by this time point (Sponsor's Table 3, below).

At seven days after dosing, 90% of the remaining radioactivity was detected in the following tissues: gallbladder (33%), retina and choroids (23%), iris and ciliary body (19%), liver (6%), cecum (6%), renal cortex (3%; Sponsor's Table 4-1, below). The

amount of radioactivity remaining in the aorta was <1% of the radioactivity present in all tissues on day 7. Overall, this study and those performed in rats (Studies B04002, AE-3690-G, AE-4736-G) demonstrate that although some of the tissues in which perampanel exhibits long residence times are similar between monkey and rat (eye, liver, and kidney), there is a marked difference in the perampanel residence time in the aorta of monkeys and rats.

Table Exp.2 Radioactivity concentration in blood, plasma and blood cell after single oral administration of ^{14}C-E2007 to male cynomolgus monkeys (dose: 0.3mg/kg)

			Radioactivity concentration (ng eq. of E2007/g or mL)		
			Blood	Plasma	Blood Cell
Detection limit			1	1	1
tmax	(hr)		5 ± 2	5 ± 2	4 ± 2
Cmax	(ng eq./g or mL)		116 ± 11	131 ± 11	97 ± 13
$t_{1/2}$	(hr)	α	11 ± 1	12 ± 1	10 ± 1
	(day)	β	2.2 ± 0.1	3.0 ± 0.5	1.6 ± 0.2
	AUC	(0-finite)	2.16 ± 0.30	2.58 ± 0.36	1.50 ± 0.14
(μg eq.·hr/g or mL)		(0-∞)	2.23 ± 0.30	2.75 ± 0.37	1.55 ± 0.15

Data are expressed as the mean values ± S.E. of four animals.
^{14}C-E2007 was administered 12hr before feeding.
N.D. : Not detected

Table Exp.3 Cumulative excretion of radioactivity in urine and feces after single oral administration of ^{14}C-E2007 to male cynomolgus monkeys (dose: 0.3mg/kg)

Time (hr)	Excretion of radioactivity (% of dose)		
	Urine	Feces	Total
0 - 8	11.4 ± 2.7	–	–
24	25.2 ± 4.4	7.5 ± 1.8	32.6 ± 3.5
48	31.7 ± 4.7	36.2 ± 4.6	68.0 ± 3.5
72	34.6 ± 5.1	48.3 ± 4.5	82.9 ± 2.7
96	35.9 ± 5.1	53.1 ± 3.9	89.0 ± 1.9
120	36.4 ± 5.1	55.2 ± 3.9	91.6 ± 1.6
144	36.7 ± 5.2	56.2 ± 3.9	92.9 ± 1.5
168	36.9 ± 5.2	56.7 ± 3.9	93.6 ± 1.4
Cage washing (168hr)			1.7 ± 0.8

Data are expressed as the mean values ± S.E. of four animals.
^{14}C-E2007 was administered 12hr before feeding.
– : Not determined

Table Exp.4-1 Radioactivity concentration in tissue 168 hr after single oral administration of ^{14}C-E2007 to male cynomolgus monkeys (dose: 0.3mg/kg)

Tissue	Radioactivity concentration (ng eq. of E2007/g or mL)
Plasma	1 ± 0 (1.00)
Blood	1 ± 0 (1.00)
Blood cell	N.D.
Cerebral cortex	N.D.
Cerebral medulla	N.D.
Mesencephalon	N.D.
Cerebellum	N.D.
Pituitary gland	N.D.
Medulla oblongata	N.D.
Spinal cord	N.D.
Aqueous humor	N.D.
Cornea	N.D.
Lens	1 ± 0 (1.00)
Iris & ciliary body	62 ± 4 (62.00)
Vitreous body	N.D.
Retina & chorioides	77 ± 19 (77.00)
Sclera	3 ± 1 (3.00)
Optic nerve	N.D.
Thyroid gland	2 ± 0 (2.00)
Trachea	1 ± 0 (1.00)
Mandibular gland	N.D.
Mandibular lymph node	N.D.
Thymus	N.D.
Heart	N.D.
Lung	1 ± 0 (1.00)
Liver	22 ± 2 (22.00)
Renal cortex	9 ± 1 (9.00)
Renal medulla	2 ± 0 (2.00)
Adrenal gland	2 ± 0 (2.00)
Spleen	N.D.
Pancreas	N.D.
Fat	1 ± 0 (1.00)
Skeletal muscle	N.D.
Bone marrow	1 ± 0 (1.00)
Skin	3 ± 0 (3.00)

continued

Table Exp.4-1 continued

Tissue	Radioactivity concentration (ng eq. of E2007/g or mL)
Sciatic nerve	N.D.
Aorta	1 ± 0 (1.00)
Vein	N.D.
Testis	1 ± 0 (1.00)
Prostate gland	N.D.
Stomach	3 ± 2 (3.00)
Small intestine	3 ± 1 (3.00)
Cecum	20 ± 6 (20.00)
Large intestine	4 ± 1 (4.00)
Urinary bladder	1 ± 0 (1.00)
Gall bladder	108 ± 8 (108.00)

Data are expressed as the mean values ± S.E. of four animals.
^{14}C-E2007 was administered 12hr before feeding.
Data were obtained by dry or wet method.
Figures in parentheses are expressed as the ratio of concentration in tissue relative to plasma.

5.1.4. Metabolism

A) Study AE-3427: "E2007: Metabolism of ^{14}C-E2007 in Cynomolgus Monkeys After Single Oral Administration"

Male Cynomolgus monkeys (n=4) were given a single oral dose of 0.3 mg/kg radiolabeled perampanel to assess the concentration of metabolites in the plasma, liver, gallbladder, urine, and feces. Blood samples were collected at several intervals up to 168 hours after dosing. Urine and feces were examined for radioactivity up to 3 days after dosing. Bile was sampled from monkeys at 168 hours after dosing.

Up to 48 hours after dosing, the parent compound accounted for most of the radioactivity (75.2 to 88%) detected in the plasma; all other metabolites detected in the plasma were considered to be minor (Sponsor's Tables 1A & 1B, below).

Table 1A Concentration of E2007 and its metabolites in monkey plasma

	Concentration (ng eq. of E2007/mL)				
Metabolite	15 min	30 min	1 hr	2 hr	4 hr
E2007	7 ± 3	21 ± 16	75 ± 29	80 ± 17	88 ± 4
4'-OH	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
SP1	–	–	1 ± 0	2 ± 1	3 ± 1
SP2	–	–	1 ± 0	1 ± 0	2 ± 1
SP3	–	–	1 ± 0	1 ± 0	1 ± 0
SP4	–	–	1 ± 1	1 ± 0	1 ± 0
SP5	–	1 ± 0	1 ± 0	1 ± 0	1 ± 0
SP6	–	0 ± 0	1 ± 0	1 ± 0	1 ± 0
Origin	1 ± 0	0 ± 0	0 ± 0	0 ± 0	1 ± 1
Total conc.[1)]	9 ± 5	29 ± 19	84 ± 32	95 ± 19	104 ± 5

Table 1B Concentration of E2007 and its metabolites in monkey plasma

	Concentration (ng eq. of E2007/mL)				
Metabolite	6 hr	8 hr	12 hr	24 hr	48 hr
E2007	86 ± 10	79 ± 9	66 ± 14	23 ± 5	4 ± 2
4'-OH	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
SP1	2 ± 0	2 ± 0	3 ± 0	1 ± 0	1 ± 0
SP2	1 ± 0	1 ± 0	1 ± 0	–	–
SP3	1 ± 0	1 ± 0	1 ± 0	–	–
SP4	1 ± 0	1 ± 0	1 ± 0	0 ± 0	–
SP5	1 ± 0	1 ± 0	1 ± 0	–	–
SP6	1 ± 0	–	–	–	–
Origin	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Total conc.[1)]	97 ± 10	92 ± 9	81 ± 15	30 ± 7	10 ± 2

Data are expressed as the mean values ± S.E. of four animals.

– : Not detected

1) : Total radioactivity concentration in plasma

When bile was sampled 168 hours after dosing, SB1 (a glucuronide conjugate of the 4'-OH metabolite of perampanel) accounted for 88.9% of the radioactivity detected in the gallbladder (Sponsor's Table 3). SB2 was determined to be the sulfate conjugate of the 4'-OH metabolite. Most of the excretion of perampanel and its related metabolites

occurred during the time of the first urine sample (Sponsor's Table 5). Although SB1 accounted for most of the radioactivity in the gallbladder, this metabolite was not detected in the feces which suggested that it may have been deconjugated by enteric bacteria (Sponsor's Table 7, below).

Table 3 Concentration of E2007 and its metabolites in monkey bile[1)] collected at 168 hr

Metabolite	Concentration (ng eq. of E2007/g)
E2007	0 ± 0
4'-OH	112 ± 22
SB1	1851 ± 145
SB2	105 ± 21
Origin	13 ± 4
Total conc.[2)]	2181 ± 194

Data are expressed as the mean values ± S.E. of four animals.

1) : In gall bladder

2) : Total radioactivity concentration in bile

Table 5 Excretion of E2007 and its metabolites in monkey urine

	% of dose		
Metabolite	0-24 hr	24-48 hr	48-96 hr
E2007	4.1 ± 3.9	0.1 ± 0.1	0.2 ± 0.2
4'-OH	0.2 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
SU1	3.6 ± 0.6	1.5 ± 0.3	1.0 ± 0.2
SU2	1.7 ± 0.3	0.6 ± 0.1	0.6 ± 0.2
SU3	1.4 ± 0.3	0.2 ± 0.0	0.2 ± 0.0
SU4	4.3 ± 0.2	1.1 ± 0.2	0.6 ± 0.1
SU5	4.5 ± 0.2	1.3 ± 0.2	0.5 ± 0.0
SU6	2.6 ± 0.2	0.7 ± 0.1	0.4 ± 0.1
Origin	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Excretion (%)	25.2 ± 4.4	6.6 ± 1.1	4.2 ± 0.7

Table 7 Excretion of E2007 and its metabolites in monkey feces

	% of dose		
Metabolite	0-24 hr	24-48 hr	48-96 hr
E2007	0.3 ± 0.0	0.6 ± 0.0	0.2 ± 0.0
4'-OH	0.2 ± 0.0	2.3 ± 0.6	2.8 ± 0.2
SF1	0.4 ± 0.1	1.2 ± 0.1	0.6 ± 0.1
SF2	1.5 ± 0.5	4.5 ± 0.5	2.6 ± 0.4
SF3	0.9 ± 0.2	1.9 ± 0.6	1.6 ± 0.1
SF4	0.3 ± 0.1	1.1 ± 0.2	1.0 ± 0.3
Origin	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Excretion (%)	7.5 ± 1.8	28.8 ± 4.2	16.9 ± 1.6

Data are expressed as the mean values ± S.E. of four animals.

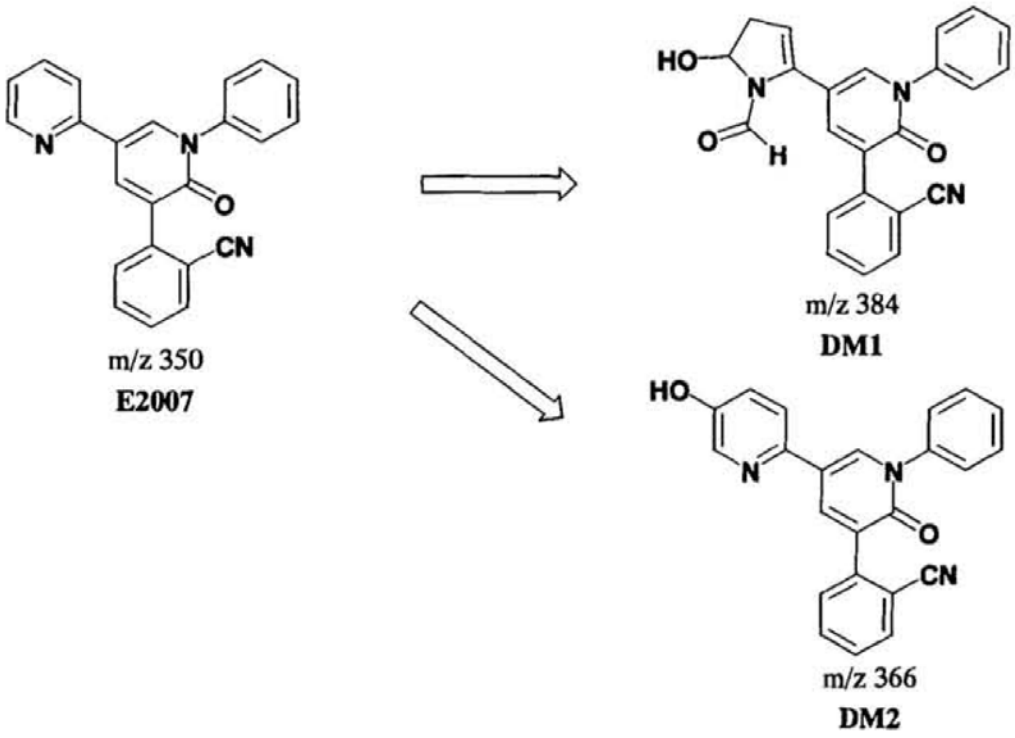
Correlation of Metabolites

Plasma	Bile in gall bladder	Urine	Feces
SP1	SB1	SU1	
		SU2	
SP2			
	SB2	SU3	SF1
SP3		SU4	SF2
SP4		SU5	SF3
SP5			
SP6		SU6	SF4

B) Study B00034: "Structural Analysis of E2007 Metabolites in Dog Liver Microsomes"

Dog liver microsomes were incubated with perampanel in the presence of NADPH for 4 hours at 37°C. The resulting metabolites were identified using LC-MS. Metabolites DM1 and DM2 were the predominant metabolites isolated from the microsomal incubation (Sponsor's Figure 5, below). However, these metabolites were not present in the plasma of dogs dosed orally with 1 mg/kg perampanel.

5. Metabolic Pathways



5.1.5. Excretion

A) Study AE-4735: "E2007: Radioactive Concentration in Milk After Single Oral Administration of ^{14}C-E2007 to Lactating Rats"

Lactating Crl:CD(SD) rats (4 days post parturition; n=3) were given a single dose of radiolabeled perampanel and radioactivity was measured in milk and plasma up to 24 hours after dosing. The levels of radioactivity detected in milk were 2.5-3.9-fold higher than those found in plasma (Sponsor's Table 1-1, below). Up to 4 hours after dosing, most of the radioactivity in milk (79-92%) was associated with the parent compound. At 24 hours after dosing, perampanel accounted for 21.4% of the radioactivity found in milk. Overall, this study demonstrates that perampanel is excreted into milk for at least 4 hours after dosing.

Table Exp.1-1 Radioactive concentrations in milk and plasma after single oral administration of ^{14}C-E2007 to non-fasting lactating rats (dose: 1 mg/kg)

Time (hr)	Radioactive concentration (ng eq. of E2007/mL)	
	Milk	Plasma
0.5	573.27 ± 73.32 (3.10)	184.97 ± 21.46
1	591.87 ± 82.91 (3.65)	162.03 ± 3.31
2	581.72 ± 60.25 (3.92)	148.24 ± 2.43
4	567.87 ± 30.91 (4.73)	120.08 ± 13.70
24	64.12 ± 7.22 (2.48)	25.87 ± 3.91

Data are expressed as the mean values ± S.E.M. of three animals.
Figures in parentheses are expressed as the ratio of concentration in milk relative to plasma.

Table Exp.1-2 Concentrations of E2007 and its metabolites in milk after single oral administration of ^{14}C-E2007 to non-fasting lactating rats (dose: 1 mg/kg)

Metabolite	Concentration (ng eq. of E2007/mL)				
	0.5 hr	1 hr	2 hr	4 hr	24 hr
E2007	527.41	519.07	496.79	446.35	13.72
E2007 4' -OH	1.72	N.D.	N.D.	N.D.	N.D.
LRMi1	1.15	2.96	2.91	3.41	3.46
LRMi2	9.75	24.86	35.48	50.54	18.47
LRMi3	2.29	N.D.	N.D.	N.D.	N.D.
LRMi4	10.32	13.02	16.29	19.31	2.63
Origin	0.57	N.D.	N.D.	0.57	N.D.
Total conc.[1)]	573.27	591.87	581.72	567.87	64.12

Milk was analyzed by TLC.
1): Total radioactive concentration in milk
N.D. : Not detected

6 General Toxicology

6.1 Single-Dose Toxicity

Mouse: Study C-B062: "E2007: Single Oral Dose Range Toxicity Study in Mice"

Male and female CD-1 mice (n=5/sex/group) were administered a single dose of 0, 100, 300, 1000, or 1500 mg/kg E2007 in 0.5% methylcellulose by oral gavage. Clinical signs, body weight, and food consumption were observed daily until necropsy of all animals, 5 days after dosing. Clinical signs, such as decreased activity and abnormal gait, were observed in mice at oral doses of ≥ 100 mg/kg.

Rat: Study S05092: "E2007: Single Oral Dose Toxicity Study in Rats"

Male and female Sprague-Dawley rats (n=5/group/sex) were administered, by oral gavage, a single dose of 0, 500, 1000, or 2000 mg/kg E2007 (Lot # 13022002) in 0.5% methylcellulose. Clinical signs, body weight, and food consumption were observed daily until necropsy, 15 days after dosing. The MTD was 1000 mg/kg. When rats were given a single dose of 10, 100, or 1000 mg/kg perampanel in 0.5% methylcellulose (Study TKB-00005), clinical signs such as abnormal gait, prostration, and decreased activity were observed at all dose levels.

Rabbit: Study S00619: "E2007: MTD Study in Non-Pregnant Rabbits"

Two female Kbl:NZW rabbits were dosed once per day, by oral gavage, in a dose-escalating study design (1 mg/kg on Day 1, 10 mg/kg on Day 5, 30 mg/kg on Day 8, 100 mg/kg on Day 10, 300 mg/kg on Day 13). Animals were euthanized for necropsy on Day 14 of the study. The MTD was determined to be 100 mg/kg and the NOAEL was 10 mg/kg, with abnormal gait and decreased activity observed at higher doses.

Dog: Study TKB00007: "E2007: Dose Escalation Oral Toxicology Study in Dogs"

Male and female beagle dogs (n=2/sex) were dosed once daily, by oral gavage, in a dose-escalating study design (Days 1-2= 0.3 mg/kg, Days 3-4= 1 mg/kg, Days 5-6= 3 mg/kg, Days 7-8= 10 mg/kg E2007 in 0.5% methylcellulose). A control group received an equivalent volume of 0.5% methylcellulose (5 ml/kg). Dogs were euthanized on Day 8 at 30 minutes after dosing due to extreme clinical signs. The MTD was determined to be 3 mg/kg and the NOAEL was 1 mg/kg, with vomiting, abnormal gait, decreased activity, and euthanasia *in extremis* occurring at higher doses.

Monkey: Study TKB01011: "E2007: Dose Escalation Oral Toxicity Study in Monkeys"

Cynomolgus monkeys (n=1/sex) were dosed orally once a week with 0.3, 1, or 2 mg/kg E2007 in a dose escalation study design. A separate pair of monkeys was used for the 4-mg/kg dose. The NOAEL in the single dose (oral) study performed in Cynomolgus monkeys was 0.3 mg/kg with ataxia, prostration, and drowsiness observed at higher doses.

6.2. Repeat-Dose Toxicity

6.2.1 Mouse

Study title: E2007: A 2-Week Oral Dose Range Toxicity Study in Mice

Study no.:	C-B063
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6/24/2002
GLP compliance:	No GLP compliance statement provided
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 11070303, Purity 99.6%

Key Study Findings

- **Clinical signs such as abnormal gait, decreased activity, dyspnea, and prostration were observed for up to 2 hours after dosing.**
- **T_{max} was markedly shortened on Day 12 (0.5-2 hrs), relative to Day 1 of dosing (2-8 hrs).**

Methods

Doses:	0, 100, 300, 1000 mg/kg
Frequency of dosing:	Once/day
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% (w/v) methylcellulose
Species/Strain:	ICR (Crj:CD-1(ICR)) mice; (b) (4) (b) (4)
Number/Sex/Group:	5/sex/group
Age:	6 weeks
Weight:	M= 26.0-34.6 g; F= 20.2-27.4 g

Dosing Solution Analysis: Dosing solutions were within +/- 5% of the nominal concentration.

Mortality & Clinical Signs: There were no deaths during the treatment period. On Days 1-2, 5-9, and 12-14, animals were observed prior to dosing, immediately after dosing, 15-30 minutes after dosing, and 2 hours after dosing. On the remaining days (weekend), mice were only observed immediately before and immediately after dosing. Abnormal gait and decreased activity were observed in all dosing groups. In HD animals, dyspnea, and prostration were also observed.

Body Weights & Feed Consumption: Beginning on Day 3 of the study and lasting until study termination, body weight was decreased, relative to controls, in all dose groups (Sponsor's table, below). Food consumption was decreased in all dose groups (~20-40%) during the course of the dosing period.

Table Summary of mean body weight changes

Sex	Male				Female			
Dose (mg/kg)	0	100	300	1000	0	100	300	1000
No. of animals	5	5	5	5	5	5	5	5
Body weight change (on Day 14) [a)]	-	-6	-12*	-10*	-	-4	-12**	-8
Body weight gain (Day 1 - 14) [b)]	2.1	-0.5	-2.5**	-2.1**	2.2	0.7	-0.8**	-0.2*

a): Values are expressed percentage of change against the control mean.
b): gram
*: $p<0.05$, **: $p<0.01$, Significant difference from the control group

Hematology & Clinical Chemistry: There were no dose-related effects observed when blood was sampled on Day 12 of the study.

Gross Pathology: A raised focus was observed in the forestomach of one HDF.

Toxicokinetics: T_{max} was markedly shortened at all dose levels on Day 12, relative to Day 1 of dosing. AUC and C_{max} increased in a less-than-linear manner with respect to dose and were markedly lower on Day 12 when compared with Day 1 (Sponsor's Table 3, below).

Table 3 Toxicokinetic parameters obtained from mean plasma levels of E2007 following repeated oral administration of E2007 for 2 weeks in mice

Dose (mg/kg)		Male			Female		
		C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
100	Day 1	1344.85	4	15298.53	2532.76	4	28505.93
	Day 12	1750.10	0.5	11466.00	1953.87	1	11364.39
300	Day 1	2964.42	4	42061.28	3772.57	2	45679.30
	Day 12	2425.42	2	20970.26	2131.78	1	19988.29
1000	Day 1	3992.46	8	55284.3	5522.23	8	75186.7
	Day 12	3354.2	1	33037.3	2314.7	2	36521.8

Values in table were determined using mean plasma concentrations of 3 animals.

Study title: E2007: A 4-week oral dose range toxicity study in mice (additional study)

Study no.:	B-5121
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5/22/2003
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 11070303, Purity 99.6%

Key Study Findings

- **The NOAEL in this study is 3 mg/kg with higher doses exhibiting clinical signs, decreased BW gain, findings in the gross pathology, hematology, and clinical pathology assessments.**
- **Deaths were observed in animals dosed with ≥ 30 mg/kg.**
- **Excoriations and trauma to the genitalia, possibly secondary to excessive grooming, were observed in HD animals.**

Methods

Doses:	0, 3 (LD), 10 (MD1), 30 (MD2), 60 (HD) mg/kg
Frequency of dosing:	Daily for 4 weeks
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Vehicle:	0.5% methylcellulose
Species/Strain:	Mice /ICR (Crj:CD-1(ICR))
Number/Sex/Group:	10 in main group; 38 in TK group
Age:	6 weeks
Weight:	M= 26.5-36.1 g; F= 19.7-28.0 g
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study

Dosing Solution Analysis: Dosing solutions were within ± 10% of the nominal concentration.

Mortality: 1 HDM and 1 HDF from the TK group were found dead on Day 20 and Day 8, respectively. One HDM (5007) from the main group was euthanized *in extremis* on Day 20. One MD2M from the TK group was found dead 1 hour after dosing on Day 9. The Sponsor stated that this animal experienced abnormal gait and decreased activity before dosing and subcutaneous edema was observed upon necropsy. There was no evidence of dosing-related trauma in this animal.

Clinical Signs: Abnormal gait was observed in both sexes after administration of each daily dose of ≥ 10 mg/kg E2007. MD2M, HDF, and HDM exhibited excoriation secondary to excessive, but unobserved, grooming, beginning on Day 16 of dosing. One HDM (5010) also exhibited prolapse of the penis. There were no test article-related clinical signs observed in LD animals.

Body Weights: A dose-dependent reduction in body weight gain, relative to control, was observed in MD2M, HDM, MD1F, MD2F, and HDF (Sponsor's Table 1, below). There were no effects on BW or BW gain at the LD.

Text Table 1. Summary of body weight.

Sex	Dose (mg/kg/day)	No. of animals	Mean body weight at the end of administration	Body weight gain (1-4w)
Male	3	10	+1%	+18%
	10	10	+2%	+27%
	30	10	-6%	-48%
	60	9	-8%	-79%
Female	3	10	0%	-2%
	10	10	-3%	-34%
	30	10	-1%	-32%
	60	10	-4%	-54%*

Values in the table indicate percentage of change against the mean control value.

-: Decrease

* (**): p<0.05 (0.01) (significantly different from the control group)

Feed Consumption: A slight decrease in food consumption was observed on Days 3 and 7 in MD2 (Male= 12 %, Female= 21 %) and HD (Male= 19 %, F= 30 %) animals, relative to controls.

Hematology and Clinical Chemistry: Blood samples were collected on the final day of the study. There were no test article-related findings in female animals. HDM exhibited a decrease in RBC, hemoglobin, hematocrit, and an increase in WBC (Sponsor's Table 4). Increases in AST and ALT and decreases in glucose and albumin were also observed in HDM (Sponsor's Table 5). These findings in HDM were driven by one male (5010), which exhibited a 4-fold decrease in RBC, a 3.3-fold decrease in hemoglobin, a 3-fold decrease in hematocrit, a 12-fold increase in WBC, a 5-fold increase in AST, a 9-fold increase in ALT, a 5-fold decrease in glucose and a 40% decrease in albumin, relative to other HDM. This animal exhibited excoriation and prolapse of the penis beginning on Day 15.

Table 4 E2007 : A 4-week oral dose range finding toxicity study in mice (Additional study)

Hematology

Sex	Dose mg/kg/day	No.		RBC X10⁴/μL	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC %	Plate-let X10⁴/μL	WBC X10³/μL
	0	10	Mean	905	15.5	48	52.9	17.1	32.4	136.0	31
			S.D.	29	0.4	2	2.2	0.4	0.7	11.8	19
	3	10	Mean	860	14.7	45	52.7	17.1	32.6	133.7	25
			S.D.	85	1.1	3	2.2	0.7	0.3	10.8	20
Male	10	10	Mean	851	14.5	45	53.2	17.1	32.2	125.6	28
			S.D.	130	2.1	7	1.4	0.4	0.5	15.6	16
	30	10	Mean	861	14.6	45	51.9	16.9	32.6	140.8	30
			S.D.	68	1.2	4	1.7	0.2	0.8	21.2	25
	60	9	Mean	767	13.0	40	54.2	17.2	31.9	147.0	99
			S.D.	219	3.5	10	6.6	1.2	1.4	35.3	212

Table 5 E2007 : A 4-week oral dose range finding toxicity study in mice (Additional study)

Blood chemistry

Sex	Dose mg/kg/day	No.		ASAT (GOT) IU/L	ALAT (GPT) IU/L	Glucose mg/dL	BUN mg/dL	TP g/dL	Albumin g/dL	A/G
	0	10	Mean	48	18	160	37	5.1	3.2	1.71
			S.D.	10	4	28	9	0.1	0.1	0.07
	3	10	Mean	57	23	178	43	4.9	3.0	1.61
			S.D.	23	9	29	15	0.2	0.2	0.08
Male	10	10	Mean	46	18	171	35	4.9	3.0	1.63
			S.D.	14	5	35	12	0.2	0.1	0.09
	30	10	Mean	49	27	168	32	5.0	3.1	1.60
			S.D.	20	22	41	7	0.2	0.1	0.11
	60	9	Mean	75	55	161	37	4.8	2.8	1.48
			S.D.	90	103	62	19	0.5	0.3	0.15

Gross Pathology: HDM # 5007 (euthanized *in extremis*) exhibited prolapse of penis, "loss of skin in the scrotum and caudal epididymis", discoloration of the testes, and enlarged spleen. HDM #5010, which survived until the end of the study, also exhibited prolapse of the penis and loss of digits. 4 HDF exhibited excoriation. The Sponsor attributes the excoriation and the findings of genital trauma to excessive grooming; however, excessive grooming was not reported in these animals. The thymus was considered to be small in 3/10 HDM and 1/10 HDF. There were no findings in LD or MD1 animals.

Organ Weights: Absolute and relative liver and kidney weights were increased in HDM and HDF (Sponsor's Table 2, below).

Text Table 2. Summary of organ weights.

Sex		Male				Female			
Dose (mg/kg/day)		3	10	30	60	3	10	30	60
No. of animals		10	10	10	9	10	10	10	10
Body weight at necropsy		+3%	+7%*	+1%	-2%	+3%	+2%	+6%	0%
Liver	Absolute	N	N	N	+15%*	N	N	N	+10%
	Relative	N	N	N	+20%**	N	N	N	+9%*
Kidney	Absolute	N	N	N	+15%	N	N	N	N
	Relative	N	N	N	+17%**	N	N	N	N

Values in the table indicate percentage of change against the mean control value.

N: Not remarkable changes, +: Increase, -: Decrease

* (**): $p<0.05$ (0.01) (significantly different from the control group)

Toxicokinetics: $AUC_{0\text{-}24hr}$ and C_{max} increased in a less-than-linear manner in relation to dose. T_{max} occurred between 0.5 to 4 hours on Day 1 and 0.5 to 1 hour on Day 25. There were no sex-related effects on TK.

Table Toxicokinetic Summary of E2007

Dose (mg/kg)		Male		Female	
		C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)
3	Day 1	344.25	1404.44	413.52	1306.59
	Day 25	454.09	1258.75	639.64	1478.84
10	Day 1	727.70	4005.90	792.95	7164.36
	Day 25	1190.89	3507.42	1078.97	3887.39
30	Day 1	989.35	9386.24	996.63	10975.38
	Day 25	1394.65	7721.39	2286.93	9676.59
60	Day 1	1320.57	20571.50	1420.89	17195.31
	Day 25	2213.05	11146.42	2232.95	9286.79

Study title: E2007: A 13-week oral dose range toxicity study in mice

Study no.:	B-4954
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8/21/2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot# 11070303, Purity 99.6%

Key Study Findings

- **Deaths were observed in each dose group. The Sponsor attributed these deaths to infections that were secondary to excoriation of the skin and urogenital area. Although unobserved, the Sponsor supposed that the excoriations were due to excessive grooming.**
- **One HDM exhibited clonic convulsions prior to death.**
- **Clinical signs such as abnormal gait were observed in all dose groups. Prostration and dyspnea were observed in animals dosed with 1000 mg/kg.**
- **A NOAEL was not determined in this study.**

Methods

Doses:	0, 100 (LD), 300 (MD), 1000 (HD) mg/kg
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% Methylcellulose
Species/Strain:	Mice /ICR (Crj:CD-1(ICR))
Number/Sex/Group:	Main group= 10; TK group = 57
Age:	6 weeks
Weight:	M=26.7-34.8 g; F=19.9-28.1 g
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study

Dosing Solution Analysis: Dosing solutions were within ± 10% of the nominal concentration.

Mortality: When the data from the TK and main groups are combined, it is clear that deaths occurred in a dose-dependent manner, LD= 4 (3 M, 1F), MD= 5 (2 M, 3 F), HD= 8 (7 M, 1 F). The death of all animals, except one HDM that died after clonic convulsions, was attributed to excessive (unobserved) grooming that resulted in infection from excoriation of the urogenital region and skin. The Sponsor provides evidence of infection in these animals in the histopathology report (see below). One male in each dose group exhibited prolapse of the penis (Sponsor's Table 1-1, below).

Table 1-1 E2007 : A 13-week oral dose range finding toxicity study in mice

Clinical signs (Dead animals)

Sex	Dose mg/kg/day	Animal number	Day of death	Week of administration 1	2	3	4	5	6	7	8	9	10	11	12
	100	2006	72	A	A	A	A	A	A	A	ACM	ABM	ABCDLM	ALM+	
		2008	53	AB	ABH	AH	AH	ABCH	ABH	ABHL	ACDHL+				
Male	300	3004	73	ABC	AB	AB	A	A	A	A	A	A	ABM	ABCDFMN+	
	1000	4005	85	ABC	AB	AB	A	AB	A	A	A	A	A	AC	ABCM
		4008	26	AB	AB	AB	AJ+								
		4010	4	ABCDEF+											

A : Abnormal gait
B : Decreased activity
C : Prostration
D : Dyspnea
E : Wound
F : Hypothermia
H : Excoriation
J : Clonic convulsion
L : Emaciation
M : Prolapse of penis
N : Pale skin
+ : Dead/Sacrificed

Clinical Signs: Abnormal gait and decreased activity were observed in all dose groups. (Sponsor's Table 1-2, below). Prostration was also observed in all female groups and in MDM and HDM. Dyspnea observed in the HD group occurred mostly during the first week of dosing. The eyeballs of two HDM were found to be opaque beginning at week 5. Besides abnormal gait, the incidence of the other clinical signs observed in this study decreased over time suggesting the development of tolerance to E2007-induced clinical signs.

Table 1-2 E2007 : A 13-week oral dose range finding toxicity study in mice

Clinical signs (Survivors)

Sex	Dose mg/kg/day	Findings	Week of administration 1	2	3	4	5	6	7	8	9	10	11	12	13
	0	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10
		No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10
	100	No. of animals	8	8	8	8	8	8	8	8	8	8	8	8	8
		No abnormality	0	0	0	0	0	0	0	0	0	0	0	0	0
		Abnormal gait	8	8	8	8	8	8	8	8	8	8	8	8	8
		Decreased activity	3	0	0	0	0	0	0	0	0	0	0	2	1
		Loss of finger, forelimb	0	0	0	0	0	0	0	1	1	1	1	1	1
Male	300	No. of animals	9	9	9	9	9	9	9	9	9	9	9	9	9
		No abnormality	0	0	0	0	0	0	0	0	0	0	0	0	0
		Abnormal gait	9	9	9	9	9	9	9	9	9	9	9	9	9
		Decreased activity	9	4	5	2	0	0	0	1	1	1	1	1	2
		Prostration	3	1	0	1	0	0	0	0	0	1	1	0	0
		Excoriation	0	0	0	0	0	0	0	0	0	1	1	1	1
		Loss of finger, forelimb	0	0	0	1	1	1	1	1	1	1	1	1	1
	1000	No. of animals	7	7	7	7	7	7	7	7	7	7	7	7	7
		No abnormality	0	0	0	0	0	0	0	0	0	0	0	0	0
		Abnormal gait	7	7	7	7	7	7	7	7	7	7	7	7	7
		Decreased activity	7	5	4	6	2	0	1	2	1	2	0	0	3
		Prostration	5	2	1	1	0	0	1	1	0	1	1	1	0
		Dyspnea	3	0	0	1	0	0	0	1	0	0	0	0	0
		Excoriation	0	0	0	1	1	1	1	1	1	1	1	1	2
		Opacity of eyeball	0	0	0	0	1	2	2	2	2	2	2	2	2
	0	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10
		No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10
	100	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10
		No abnormality	0	0	0	0	0	0	0	0	0	0	0	0	0
		Abnormal gait	10	10	10	10	10	10	10	10	10	10	10	10	10
		Decreased activity	5	2	0	0	0	0	0	0	1	0	0	0	0
		Prostration	1	0	0	0	0	0	0	0	0	0	0	0	0
Female	300	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10
		No abnormality	0	0	0	0	0	0	0	0	0	0	0	0	0
		Abnormal gait	10	10	10	10	10	10	10	10	10	10	10	10	10
		Decreased activity	8	1	1	0	0	0	0	0	1	0	0	0	0
		Prostration	1	0	0	0	0	0	0	0	0	0	1	0	0
		Excoriation	0	0	0	0	1	1	1	1	1	1	1	1	1
	1000	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10
		No abnormality	0	0	0	0	0	0	0	0	0	0	0	0	0
		Abnormal gait	10	10	10	10	10	10	10	10	10	10	10	10	10
		Decreased activity	10	6	6	4	2	0	0	0	1	1	2	0	0
		Prostration	9	2	0	1	0	0	0	0	0	0	1	0	0
		Dyspnea	6	0	0	0	0	0	0	0	0	0	0	0	0

Body Weights: Body weight gain and absolute BW, relative to controls, were decreased in a dose-dependent manner (Sponsor's Table 2, below).

Text Table 2. Summary of body weight.

Sex	Dose (mg/kg/day)	No. of animals	Mean body weight at the end of administration	Body weight gain (1-13w)
Male	100	8	-5%	-24%
	300	9	-10%*	-56%**
	1000	7	-12%**	-63%**
Female	100	10	-4%	-17%
	300	10	-4%	-28%
	1000	10	-10%*	-45%*

Values in the table indicate percentage of change against the mean control value.

-: Decrease

* (**): p<0.05 (0.01) (significantly different from the control group)

Feed Consumption: A transient decrease in food consumption was observed in all dose groups during the first week of the study (LD= 20-30%; MD= 29-46%; HD= 29-36%, relative to control).

Hematology: MDM and HDM exhibited a decrease in RBC, hemoglobin, and hematocrit (Sponsor's Table 3, below). The Sponsor suggests that the slight decrease in these measurements were due to the excoriations observed in animals in these dose groups. Some of the animals that exhibited decreases in RBC, hematocrit, and hemoglobin also exhibited excoriations (4003, 3003); however, some of the animals with the largest decreases in these measures (3004 and 3005) did not exhibit excoriations. Therefore, the plausibility of the Sponsor's explanation for a decrease in these measures is questionable.

Text Table 3. Summary of hematology.

Sex	Male			Female		
Dose (mg/kg/day)	100	300	1000	100	300	1000
No. of animals	8	9	6 a)	10	10	10
RBC	N	-8%	-10%	N	N	N
Hb	N	-6%	-6%	N	N	N
Ht	N	-5%	-9%	N	N	N
WBC	N	N	N	N	N	+106%

a): Examination was not done on one male because a sufficient amount of blood sample was not obtained due to moribund condition.

Values in the table indicate percentage of change against the mean control value.

N: Not remarkable changes, -: Decrease, +: Increase

Clinical Chemistry: Glucose was decreased in all male dose groups, MDF, and HDF (Sponsor's Table 4, below). A decrease in the ratio of albumin to globulin was observed in MDM and HDM.

Text Table 4. Summary of blood chemistry.

Sex	Male			Female		
Dose (mg/kg/day)	100	300	1000	100	300	1000
No. of animals	8	9	7	10	10	10
Glucose	-19%	-31%	-25%	N	-10%	-9%
A/G	N	-17%	-16%	N	N	N

Values in the table indicate percentage of change against the mean control value.

N: Not remarkable changes, -: Decrease, +: Increase

Gross Pathology: Wounding and/or prolapse of the penis and bladder distension with urine retention were observed in all male dose groups (1 LDM, 1 MDM, 2 HDM). Eye opacity was observed in 2 HDM (1 bilateral, 1 unilateral).

Organ Weights: A dose-dependent increase in relative liver weights was observed in all dose groups. An increase in kidney weight that was not dose-dependent was observed in all male dose groups (Sponsor's Table 5, below). A dose-dependent decrease in absolute (247, 232, 214, 205 mg; C, LD, MD, HD, respectively) and relative (755, 730, 724, 717 mg; C, LD, MD, HD, respectively) testes weight was observed in all male dose groups.

Text Table 5. Summary of organ weights.

Sex		Male			Female		
Dose (mg/kg/day)		100	300	1000	100	300	1000
No. of animals		8	9	7	10	10	10
Body weight at necropsy		-4%	-9%	-12%*	N	N	-10%*
Liver	Absolute	+7%	+4%	+4%	+6%	+18%*	+11%
	Relative	+11%*	+14%*	+19%**	+10%*	+20%*	+23%**
Kidney	Absolute	+31%**	+16%	+16%	N	N	N
	Relative	+36%**	+28%**	+33%**	N	N	N

Values in the table indicate percentage of change against the mean control value.

N: Not remarkable changes, +: Increase, -: Decrease

* (**): $p<0.05$ (0.01) (significantly different from the control group)

Histopathology: *Adequate Battery*: No, nasal passages/ turbinates were not examined; *Peer Review*: No; *Signed and Dated Pathology Report*: Yes

Test article-related findings were observed in the adrenal, eye, ovary, skin, marrow of the sternum, and thymus of animals surviving until the end of the dosing phase (Sponsor's Table 8-3, below). Some of the same organs were affected in early decedents (adrenal, penis, marrow of the sternum, thymus). Excoriations of the skin or penis were characterized by loss of epidermis with bacterial infection which resulted in inflammation that extended to the urethra, prostate, and seminal vesicle. Similar excoriations of the urogenital area were observed in previous studies and were attributed by the Sponsor to unobserved excessive grooming. The urogenital lesions occurred in all male dose groups. There was no histopathological correlate for the

urinary bladder distension and urine retention; however the animals that exhibited the urine retention also exhibited lesions of the penis (# 2006, 3004, 4005, 4010), suggesting the cause of retention was associated with the urogenital lesions.

Table 8-3 E2007 : A 13-week oral dose range finding toxicity study in mice

Histopathological findings (Survivors)

Organs / Findings	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg/day):	0	100	300	1000	0	100	300	1000
	Number:	10	8	9	7	10	10	10	10
Adrenal									
Number examined		10	8	9	7	10	0	0	10
Hypertrophy, cortical cell		0	1	2	2	0	0	0	0
slight		0	1	2	0	0	0	0	0
mild		0	0	0	2	0	0	0	0
Eye									
Number examined		10	0	0	7	10	0	0	10
Mineralization, corneal		0	0	0	0	0	0	0	1
mild		0	0	0	0	0	0	0	1
Phthisis bulbi		0	0	0	1	0	0	0	0
present		0	0	0	1	0	0	0	0
Keratitis		0	0	0	1	0	0	0	0
mild		0	0	0	1	0	0	0	0
Panophthalmitis		0	0	0	1	0	0	0	0
mild		0	0	0	1	0	0	0	0
Ovary									
Number examined		-	-	-	-	10	10	10	10
Decrease, corpus luteum		-	-	-	-	0	4	5	7
slight		-	-	-	-	0	2	2	2
mild		-	-	-	-	0	2	3	5
Skin									
Number examined		0	0	1	2	0	0	2	0
Ulcer		0	0	1	2	0	0	2	0
mild		0	0	1	2	0	0	2	0
Sternum + marrow									
Number examined		10	8	9	7	10	0	0	10
Granulopoiesis, increased		1	1	1	3	0	0	0	0
slight		0	1	0	1	0	0	0	0
mild		0	0	1	2	0	0	0	0
moderate		1	0	0	0	0	0	0	0
Thymus									
Number examined		10	8	9	7	10	0	0	10
Atrophy		0	1	2	2	0	0	0	0
mild		0	0	0	1	0	0	0	0
moderate		0	1	2	1	0	0	0	0

Table 8-1 E2007 : A 13-week oral dose range finding toxicity study in mice

Histopathological findings (Dead animals)

Organs / Findings	Sex:	M	M	M
	Dose(mg/kg/day):	100	300	1000
	Number:	2	1	3
Adrenal				
Number examined		2	1	3
Hypertrophy, cortical cell		1	1	1
mild		1	1	1
Penis				
Number examined		1	1	2
Ulcer		1	1	2
moderate		0	1	2
severe		1	0	0
Sternum + marrow				
Number examined		2	1	3
Granulopoiesis, increased		2	0	1
slight		1	0	0
mild		1	0	1
Thymus				
Number examined		2	1	3
Atrophy		2	1	2
moderate		0	1	1
severe		2	0	1

Toxicokinetics: $AUC_{0\text{-}24hr}$ and C_{max} increased in a less-than-linear manner in relation to dose. T_{max} occurred between 4 to 8 hours on Day 1 and 1 to 2 hours on Day 89.

Table 3 Toxicokinetic parameters obtained from mean plasma levels of E2007 following repeated oral administration of E2007 for 13 weeks in mice

Dose (mg/kg)		Male			Female		
		Cmax (ng/mL)	Tmax (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
100	Day 1	1820.47	4	16053.39	2061.33	8	30552.05
	Day 25	1724.48	2	9978.51	1822.28	0.5	9880.33
	Day 89	1976.50	1	12976.07	2193.91	1	10011.66
300	Day 1	2139.80	4	29876.36	3012.32	4	39842.22
	Day 25	1994.03	1	14385.77	2119.83	1	14587.95
	Day 89	2308.17	1	18665.47	2747.57	2	16163.45
1000	Day 1	3481.96	8	47708.6	4524.95	8	62413.6
	Day 25	3282.4	2	29817.4	2377.0	1	26726.8
	Day 89	2573.6	1	14893.2	2899.6	2	30534.1

6.2.2 Rat

Study title: E2007: A 4-Day Dose Range Oral Toxicity Study in Rats

Study no.:	TKB00006
Study report location:	EDR
Conducting laboratory and location:	Eisai Co, Ltd; Ibaraki, Japan
Date of study initiation:	9/4/2000
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	E2007, Lot #08066-007211, Purity not provided

Key Study Findings

- **The NOAEL in this study was < 10 mg/kg E2007.**
- **Abnormal gait and decreased activity were observed in all dose groups. Females, but not males, exhibited tremors at ≥ 100 mg/kg.**
- **A dose-dependent decrease in lymphocytes was observed in all male dose groups and in females dosed with ≥ 100 mg/kg.**
- **On the final dosing day, plasma levels of E2007 were 3 to 5-fold higher in females than in males.**

Methods

Doses:	0, 10, 100, 300 mg/kg
Frequency of dosing:	Once daily for 4 days
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Sprague-Dawley (IGS) rat
Number/Sex/Group:	Main= 3; TK= 3
Age:	6 weeks

Mortality and Clinical Signs: There were no test article-related deaths in this study. Abnormal gait and decreased activity were observed in all dose groups. Prostration was observed at ≥100 mg/kg. Clinical signs were more severe in females. Specifically, tremors were observed at ≥100 mg/kg in females but were not observed in males dosed at the highest dose of 300 mg/kg.

Body Weights and Food Consumption: BW loss, relative to predosing values, was observed in MDF (-9%), HDF (-4%), and HDM (-2%). Decreased BW gain, relative to control, was observed in LDM (-48%) and LDF (-31%). Food consumption was decreased in HD animals (33-35%) and in MDF (81%). There was no effect on food consumption in MDM and LD animals.

Hematology and Clinical Chemistry: A dose-dependent decrease in WBC (-23%, -28%, -36%; LD, MD, HD, respectively) and lymphocyte count was observed in all male dose groups (-22%, -27%, -45%; LD, MD, HD, respectively), in MDF (-43%), and HDF (-49%). There were no test article-related effects on clinical chemistry parameters when assessed at the end of the dosing phase.

Gross Pathology and Histopathology: There were no abnormal findings in the gross pathology or histopathology assessments. There was no signed and dated pathology report provided in this study.

Toxicokinetics: Plasma concentrations of E2007 were markedly higher in females (5-, 3-fold, 2.7-fold; LD, MD, HD, respectively), relative to males, on Day 4 of the study.

Dose (mg/kg)		Day	Males		Females	
			C_{max} (ng/mL)	$AUC_{0\text{-}24hr}$ (ng·hr/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24hr}$ (ng·hr/mL)
E2007	10	1	133	692	341	1883
		4	168	603	351	3087
E2007	100	1	949	15525	1071	13853
		4	965	8790	1987	27567
E2007	300	1	949	18497	1181	18267
		4	1735	15023	3950	40950

Study title: E2007: A 4-Week Oral Toxicity Study in Rats

Study no.: S00009
Study report location: EDR
Conducting laboratory and location: Eisai Co., Ltd.; Gifu, Japan
Date of study initiation: 10/25/2000
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: E2007, Lot 10092507, Purity 99.6%

Key Study Findings

- **The NOAEL in this study was 3 mg/kg for males and 1 mg/kg for females. Higher doses resulted in abnormal clinical signs.**
- **Urine volume was increased and osmolality was decreased in males (≥ 30 mg/kg) and in females (≥ 10 mg/kg).**
- **Females exhibited plasma concentrations of E2007 that were 2.2 to 3.6-fold higher than in males at the same dose level.**

Methods

Doses: M= 0, 3, 30, 100 mg/kg; F= 0, 1, 10, 30 mg/kg
Frequency of dosing: Once daily for 4 weeks
Route of administration: Oral gavage
Dose volume: 10 ml/kg
Formulation/Vehicle: 0.5% methylcellulose
Species/Strain: Sprague-Dawley (Crj:CD(SD)IGS) rats
Number/Sex/Group: Main group= 10; TK= 4
Age: 8 weeks
Weight: M= 226-265 g; F= 152-171 g
Deviation from study protocol: There were no deviations that compromised the validity of the study.

Mortality: HDM # 03M04 was euthanized *in extremis* on Day 9 due to BW loss, decreased food consumption, and marked clinical signs (abnormal gait, decreased activity, and prostration).

Clinical Signs: There were no test article-related clinical signs in LDM (3 mg/kg) or LDF (1 mg/kg). Males dosed with ≥ 30 mg/kg exhibited abnormal gait, decreased activity, and prostration. Abnormal gait (≥ 10 mg/kg) and decreased activity (30 mg/kg) were observed in females. The one HDM that was euthanized *in extremis* on Day 9 exhibited emaciation beginning on Day 8.

Body Weights and Food Consumption: Relative to control, there was no clear dose-dependent effect on absolute BW or food consumption during the dosing phase.

Ophthalmoscopy: There were no test article-related findings when performed on Day 23 of dosing.

Hematology and Clinical Chemistry: A slight, but dose-dependent, decrease in WBC (-4%, -7%, -15%; LD, MD, HD, respectively) and lymphocyte count was observed in all male dose groups (-6%, -11%, -19%; LD, MD, HD, respectively). There were no test article-related effects observed on clinical chemistry parameters when assessed on Day 29-30 of the study.

Urinalysis: Urine volume was increased (MDM= 1.8-fold, HDM= 1.9-fold; MDF= 1.6-fold, HDF= 2.5-fold) and urine osmolality was decreased (MDM= -35 %, HDM= -43 %; MDF= -18 %, HDF= -64 %) in a dose-dependent manner, relative to control, when assessed on Day 29-30 of the study.

Gross Pathology and Organ Weights: There were no test article-related findings.

Histopathology: Adequate Battery: No, nasal passages/ turbinates were not examined; Peer Review: No; Signed and Dated Pathology Report: Yes. There were no test article-related findings.

Toxicokinetics: Plasma levels of E2007 in females were 2.2 to 3.6-fold higher than in males at the only dose level (30 mg/kg) administered to both.

Table 4 Mean values of pharmacokinetic parameters obtained from plasma levels of E2007 following repeated oral administration of E2007 for 4 weeks in rats

Sex	Dose (mg/kg)	Day	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0\text{-}24hr}$ (ng·hr/mL)
Male	3	Day 1	228.57 ± 122.99	1 (0.5-1)	896.49 ± 553.70
		Day 7	238.94 ± 133.16	0.75 (0.5-1)	922.42 ± 712.27
		Day 27	208.39 ± 68.79	0.75 (0.5-1)	857.37 ± 498.72
	30	Day 1	348.2 ± 46.1	1 (1-1)	2722.6 ± 1268.8
		Day 7	494.35 ± 184.89	1 (0.5-2)	4569.67 ± 4039.03
		Day 27	535.84 ± 226.91	1.5 (0.5-2)	2979.45 ± 1193.13
	100	Day 1	758.8 ± 283.3	3 (2-8)	10901.7 ± 4050.7
		Day 7	1561.4 ± 314.3	2.5 (1-8)	17994.7 ± 9549.6
		Day 27	948.8 ± 526.2	2 (1-4)	11855.1 ± 15282.5
Female	1	Day 1	191.93 ± 40.56	0.75 (0.5-1)	616.73 ± 223.83
		Day 7	208.46 ± 41.40	0.5 (0.5-0.5)	606.55 ± 223.61
		Day 27	195.97 ± 23.98	1.25 (0.5-2)	759.36 ± 289.29
	10	Day 1	909.2 ± 579.7	1.5 (1-4)	9796.5 ± 10730.3
		Day 7	1022.9 ± 932.6	2 (1-2)	10425.8 ± 12703.9
		Day 27	1278.8 ± 1209.5	2 (2-4)	11267.3 ± 15365.3
	30	Day 1	912.1 ± 318.0	3 (1-8)	9826.8 ± 5588.5
		Day 7	1301.2 ± 522.8	2 (1-2)	10155.4 ± 4942.3
		Day 27	1201.4 ± 438.3	2 (0.5-2)	10287.1 ± 3150.8

C_{max} and $AUC_{0\text{-}24hr}$ values represent the mean ±SD of 4 animals.
t_{max} values represent the medium and range of 4 animals.

Study title: E2007: A 13-Week Oral Toxicity Study in Rats

Study no.:	S01008
Study report location:	EDR
Conducting laboratory and location:	Eisai Co., Ltd.; Gifu, Japan
Date of study initiation:	5/29/2001
GLP compliance:	No GLP certification provided
QA statement:	QA certification is provided
Drug, lot #, and % purity:	E2007, Lot 10092507, Purity 99.6%

Key Study Findings

- **The NOAEL in this study was 1 mg/kg in both sexes. Clinical signs were observed at higher doses.**
- **Urine volume was increased and osmolality was decreased in males at 30 mg/kg and in females at ≥ 10 mg/kg**

Methods

Doses:	0, 1 (LD), 10 (MD), 30 (HD) mg/kg
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Sprague-Dawley (Crj:CD(SD)IGS) rats
Number/Sex/Group:	Main= 10; TK=4
Age:	8 weeks
Weight:	M= 222-271 g; F= 161-188 g
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Dosing Solution Analysis: Dosing solutions were ± 5% of the nominal concentration.

Mortality & Clinical Signs: There were no deaths during the dosing phase of the study. There were no test article-related clinical signs in LD animals (Sponsor's Table, below). Generally, the incidence of clinical signs (i.e. abnormal gait, decreased activity, and prostration) decreased over the course of the dosing period, suggesting the development of tolerance. Mydriasis was observed in MDF, HDF, and HDM during the first week of dosing.

Table. Incidence of abnormal gait, decreased activity and prostration

Sex	Dose (mg/kg)	Clinical sign	No. of animals observed Week 1	Week 4	Week 8	Week 12
Male	1	Abnormal gait	0	0	0	0
		Decreased activity	0	0	0	0
		Prostration	0	0	0	0
	10	Abnormal gait	8	0	0	0
		Decreased activity	0	0	0	0
		Prostration	0	0	0	0
	30	Abnormal gait	10	10	2	1
		Decreased activity	3	0	0	0
		Prostration	0	0	0	0
Female	1	Abnormal gait	0	0	0	0
		Decreased activity	0	0	0	0
		Prostration	0	0	0	0
	10	Abnormal gait	10	9	5	5
		Decreased activity	4	1	0	0
		Prostration	0	0	0	0
	30	Abnormal gait	10	10	6	8
		Decreased activity	10	3	1	1
		Prostration	4	0	0	0

Body Weights & Feed Consumption: Absolute BW was decreased by 7-9% in HDM and HDF, relative to controls, beginning at Day 14 and lasting until the end of the dosing period. Absolute BW was decreased by 7-9% in MDF, relative to control, beginning on Day 28 and lasting until the end of dosing. There was no test article-related effect on food consumption.

Ophthalmoscopy: When assessed on Day 87 of the study, there was no test article-related effect observed.

Hematology & Clinical Chemistry: When assessed on Day 92-93 of the study, there were no test article-related effects.

Urinalysis: Urine volume was increased (HDM= 1.8-fold; MDF= 1.6-fold, HDF= 2.5-fold) and urine osmolality was decreased (HDM= -55 %; MDF= -23 %, HDF= -22 %) in a dose-dependent manner, relative to control, when assessed on Day 90-91 of the study.

Gross Pathology: There were no test article-related abnormalities observed.

Organ Weights: Absolute spleen (-19 to -21 %) and heart (-9% to -12%) weights were decreased in MDF and HDF.

Histopathology: Adequate Battery: No, nasal passages/turbinates were not assessed; Peer Review: No; Signed and Dated Pathology Report: Yes.

Slight degeneration of the hepatic artery was observed in 1/10 CM and 2/10 HDM. Moderate chronic pericarditis was observed in 1/10 HDF.

Toxicokinetics: Plasma levels of E2007 in females were 1.3 to 1.5-fold higher than in males (Sponsor's Table, below)

		Male			Female		
Dose (mg/kg)	Day	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0\text{-}24hr}$ (ng·hr/mL)	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0\text{-}24hr}$ (ng·hr/mL)
1	Day 1	150.00 ± 50.40	0.75 (0.5-1)	473.65 ± 270.19	201.03 ± 45.31	1.25 (0.5-2)	851.55 ± 244.92
	Day 28	168.20 ± 52.66	0.5 (0.5-0.5)	557.93 ± 301.78	226.31 ± 57.17	0.5 (0.5-0.5)	834.15 ± 296.31
	Day 85	167.28 ± 58.82	0.5 (0.5-0.5)	631.80 ± 389.39	255.64 ± 90.99	0.75 (0.5-2)	998.50 ± 317.30
10	Day 1	471.81 ± 62.02	2 (2-2)	3125.49 ± 431.84	611.2 ± 104.9	2 (0.5-2)	3866.7 ± 827.9
	Day 28	540.55 ± 117.86	0.5 (0.5-0.5)	3278.53 ± 600.43	1010.0 ± 230.8	2 (1-2)	4079.2 ± 810.0
	Day 85	460.98 ± 68.39	1 (0.5-1)	3243.16 ± 524.81	902.7 ± 147.1	2 (1-2)	4318.9 ± 1411.4
30	Day 1	413.16 ± 61.40	2 (1-4)	4100.80 ± 1812.28	877.4 ± 446.1	3 (2-4)	11107.5 ± 4434.2
	Day 28	548.58 ± 172.88	1 (0.5-2)	3837.80 ± 2007.69	1241.3 ± 555.1	1.5 (0.5-2)	8488.6 ± 5352.1
	Day 85	501.96 ± 261.13	1 (0.5-2)	5638.33 ± 7436.26	1137.9 ± 336.4	0.75 (0.5-2)	8454.1 ± 3886.7

C_{max} and $AUC_{0\text{-}24hr}$ values represent the mean ±SD of 4 animals.

t_{max} values represent the median and range of 4 animals.

Study title: A 13-Week Oral Toxicity Study in Male Rats (Additional Study)

Study no.:	S04007
Study report location:	EDR
Conducting laboratory and location:	Eisai Co., Ltd; Gifu, Japan
Date of study initiation:	12/2/2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, 13022022, Purity 100%

Key Study Findings

- **The MTD in male rats was determined to be 100 mg/kg due to deaths, weight loss, and extreme clinical signs at 300 mg/kg.**
- **Abnormal gait and decreased activity were observed in all E2007 dose groups (≥ 6 mg/kg).**

Methods

Doses:	0, 6, 100, 300 mg/kg
Frequency of dosing:	Once daily for 13 weeks, except HDM which were euthanized on Day 44 due to extreme clinical signs.
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Sprague-Dawley (Crj:CD(SD)IGS), males only
Number/Sex/Group:	Main= 10; TK= 4
Age:	8 weeks
Weight:	250.8-278.6 g
Deviation from study protocol:	Deviations were minor and did not impact the validity of the study.

Dosing Solution Analysis: Dosing formulations were within +/- 5% of the nominal value.

Mortality: A total of 7 HDM (5/10 main group; 2/4 TK group) were either euthanized *in extremis* or found dead between Day 14 and 41 of the study. Clinical signs such as bradypnea, arched back, tremor, and lateral recumbence were observed before death. BW was decreased by 20 to 40% relative to control males.

Clinical Signs: The main clinical signs were abnormal gait in LDM, abnormal gait and decreased activity in MDM. HDM exhibited prostration, clonic convulsion, tremors, lateral recumbence, bradypnea, arched back, excessive grooming, and excessive grooming-related injuries such as swollen and bleeding forelimbs. Due to the extreme clinical signs in HDM, dosing was discontinued at Day 42.

Body Weights and Food Consumption: Absolute BW at the end of the study were decreased in all dose groups (LDM= 6%, MDM= 12%, HDM= 24%). Food consumption was markedly decreased in HDM only.

Hematology & Clinical Chemistry: Blood was sampled from LDM and MDM on Day 91 and from HDM on Day 44. There was no test article-related effect on hematology parameters. AST (2.9-fold) and ALT (11-fold) were increased in HDM.

Gross Pathology: There were no findings in the LD and MD animals that survived until

the end of the dosing period. In HDM survivors, small liver (1/5), small and discolored spleen (2/5), and small thymus (1/5) were observed. In animals that died or were euthanized *in extremis* during the dosing period, enlarged adrenals (1/5), small epididymides (1/5), distended small intestine with blood contents (4/5), discolored liver (1/5), small prostate (4/5), small testes (1/5), and small thymus (5/5) were observed.

Organ Weights: Liver weight was decreased in HDM by 40%, relative to control. This finding was driven mostly by a marked decrease in one animal euthanized *in extremis* (# 03M03).

Histopathology: Adequate Battery: No, nasal passages/turbinates not examined; Peer Review: No; Signed and Dated Pathology Report: Yes

HDM that died or were euthanized *in extremis* during the dosing period exhibited test article-related findings in liver, kidneys, spleen, adrenals, stomach, duodenum, small intestine, reproductive organs, and bone marrow (Sponsor's Table 8-1, below). In animals that survived until the end of the dosing period, there were no findings in LDM and MDM. One HDM exhibited findings in the liver, marrow, and thymus that were similar to those observed in early decedent HDM (Sponsor's Table 8-7, below).

TABLE 8-1
STUDY NO. S04007
E2007:A 13-Week Oral Toxicity Study in Male Rats (Additional Study)
SUMMARY OF HISTOPATHOLOGY DATA
- NON-NEOPLASTIC LESIONS MALE
- FOUND DEAD OR MORIBUND SACRIFICE

ORGAN AND FINDINGS		DOSE (mg/kg) --	0	60	100	300
		NO. OF ANIMALS EXAMINED --	0	0	0	5
Liver			(0)	(0)	(0)	(5)
Normal			0	0	0	4
Atrophy		2+	0	0	0	1
Necrosis, hepatocytes, centrilobular		2+	0	0	0	1
Kidneys			(0)	(0)	(0)	(5)
Normal			0	0	0	4
Focal fibrosis		1+	0	0	0	1
Spleen			(0)	(0)	(0)	(5)
Normal			0	0	0	1
Atrophy		1+	0	0	0	2
		2+	0	0	0	2
Adrenals			(0)	(0)	(0)	(5)
Normal			0	0	0	2
Cortical hypertrophy, bilateral		1+	0	0	0	3
Stomach			(0)	(0)	(0)	(5)
Normal			0	0	0	2
Erosion, glandular stomach		1+	0	0	0	3
Duodenum			(0)	(0)	(0)	(5)
Normal			0	0	0	4
Marked autolysis			0	0	0	1
Jejunum			(0)	(0)	(0)	(5)
Normal			0	0	0	3
Marked autolysis			0	0	0	2
Ileum			(0)	(0)	(0)	(5)
Normal			0	0	0	4
Marked autolysis			0	0	0	1
Cecum			(0)	(0)	(0)	(5)
Normal			0	0	0	4
Marked autolysis			0	0	0	1

Epididymides		(0)	(0)	(0)	(5)
Normal		0	0	0	1
Desquamated seminiferous epithelial cells, bilateral	1+	0	0	0	2
Decreased spermatozoa, bilateral	3+	0	0	0	1
Spermatic granuloma	1+	0	0	0	1
Seminal vesicles		(0)	(0)	(0)	(5)
Normal		0	0	0	3
Atrophy	1+	0	0	0	1
Marked autolysis		0	0	0	1
Coagulating glands		(0)	(0)	(0)	(5)
Normal		0	0	0	2
Atrophy	1+	0	0	0	2
Inflammatory cell infiltration	2+	0	0	0	1
Marked autolysis		0	0	0	1
Prostate		(0)	(0)	(0)	(5)
Normal		0	0	0	2
Acinar atrophy	1+	0	0	0	2
	2+	0	0	0	1
Inflammatory cell infiltration	1+	0	0	0	1
Urinary bladder		(0)	(0)	(0)	(5)
Normal		0	0	0	5
Testes		(0)	(0)	(0)	(5)
Normal		0	0	0	2
Hypocellularity, seminiferous epithelium, bilateral	1+	0	0	0	2
Atrophy, seminiferous tubules, bilateral	2+	0	0	0	1
Sternal marrow		(0)	(0)	(0)	(5)
Normal		0	0	0	1
Hypocellularity	1+	0	0	0	3
	2+	0	0	0	1
Femoral marrow		(0)	(0)	(0)	(5)
Normal		0	0	0	1
Hypocellularity	1+	0	0	0	3
	2+	0	0	0	1
Thymus		(0)	(0)	(0)	(5)
Lymphoid necrosis	2+	0	0	0	2
Atrophy	2+	0	0	0	3

GRADE ; 1+ : slight, 2+ : moderate, 3+ : marked

TABLE 8-7
STUDY NO. S04007
E2007:A 13-Week Oral Toxicity Study in Male Rats (Additional Study)
SUMMARY OF HISTOPATHOLOGY DATA
- NON-NEOPLASTIC LESIONS MALE
- TERMINAL SACRIFICE

ORGAN AND FINDINGS		DOSE (mg/kg) --	0	60	100	300
		NO. OF ANIMALS EXAMINED --	10	0	10	5
Liver			(10)	(0)	(10)	(5)
Normal			10	0	10	4
Atrophy	2+		0	0	0	1
Thymus			(10)	(0)	(10)	(5)
Normal			10	0	10	4
Lymphoid necrosis	2+		0	0	0	1
Sternal marrow			(10)	(0)	(10)	(5)
Normal			10	0	10	4
Hypocellularity	1+		0	0	0	1
Femoral marrow			(10)	(0)	(10)	(5)
Normal			10	0	10	4
Hypocellularity	1+		0	0	0	1

Toxicokinetics: Plasma levels of E2007 were similar between LD and MD animals on

Day 1 and Day 28 of the study. Plasma levels increased in a less-than-linear manner in relation to dose in all dose groups.

Table 4 Mean values of toxicokinetic parameters obtained from plasma levels of E2007 following repeated oral administration of E2007 for 13 weeks in male rats

Dose (mg/kg)		Cmax (ng/mL)	Tmax (h) median	Tmax (h) range	$AUC_{0\text{-}24h}$ (ng·h/mL)
60	Day 1	494.50 ± 135.64	3.0	1.0 - 4.0	5999.59 ± 3355.87
	Day 28	690.03 ± 206.47	1.5	1.0 - 2.0	7019.39 ± 3013.33
	Day 91	628.13 ± 195.89	0.5	0.5 - 0.5	3982.38 ± 1439.13
100	Day 1	525.49 ± 69.78	2.0	1.0 - 4.0	5752.74 ± 1583.66
	Day 28	682.04 ± 114.77	1.0	0.5 - 2.0	6643.02 ± 2699.49
	Day 91	628.25 ± 140.66	1.0	1.0 - 1.0	5709.60 ± 2634.62
300	Day 1	672.95 ± 176.64	14.0	2.0 - 24.0	10734.07 ± 1754.85
	Day 28 *	1807.40	4.5	1.0 - 8.0	31527.51

C_{max} and $AUC_{0\text{-}24h}$ values represent the mean ± S.D. of 4 animals (*: mean of 2 animals)
T_{max} values represent the median and range of 4 animals (*: mean of 2 animals)

Study title: E2007: A 26-Week Oral Toxicity Study in Rats

Study no.:	S02002
Study report location:	EDR
Conducting laboratory and location:	Eisai Co., Ltd; Gifu, Japan
Date of study initiation:	1/22/2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 11070303, Purity 99.6%

Key Study Findings

- **The MTD in this study was 10 mg/kg for females and ≥ 30 mg/kg for males. Two female rats dosed with 30 mg/kg died or were euthanized *in extremis*.**
- **The NOAEL in this study was 1 mg/kg for both males and females. Higher doses results in clinical signs such as abnormal gait and decreased activity.**
- **TK analysis was conducted, but plasma AUCs were not determined.**

Methods

Doses:	0, 1 (LD), 10 (MD), 30 (HD) mg/kg
Frequency of dosing:	Once daily for 26 weeks
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Sprague-Dawley (Crj:CD(SD)IGS) rats
Number/Sex/Group:	Man group = 10; TK group =4
Age:	8 weeks
Weight:	M= 249-272 g ; F= 170-187 g
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Dosing Solution Analysis: Dosing solutions were within ± 5% of the nominal concentration.

Mortality: One HDF was found dead on Day 7. This animal exhibited abnormal gait, decreased activity, prostration, and self-injury (bleeding, swelling, and/or severed digits) due to excessive grooming. The cause of death was determined to be anemia associated with the extensive self injury. One HDF was euthanized *in extremis* on Day 94 due to "*upper incisors completely fractured as a result of the CNS clinical signs*". This female exhibited hypothermia, piloerection, arched back, and BW loss.

Clinical Signs: In animals that survived until the end of the dosing period, the incidence of clinical signs (abnormal gait, decreased activity, prostration) decreased over time suggesting the development of tolerance.

Table Incidence of CNS clinical signs

Sex	Dose (mg/kg)	Clinical sign	No. of animals observed Week 1	4	8	12	26
Male	1	Abnormal gait	0	0	0	0	0
	10	Abnormal gait	5	2	0	0	0
	30	Abnormal gait	10	7	3	0	0
Female	1	Abnormal gait	0	0	0	0	0
		Decreased activity	0	0	0	0	0
		Prostration	0	0	0	0	0
	10	Abnormal gait	10	10	3	4	6
		Decreased activity	0	0	0	0	0
		Prostration	0	0	0	0	0
	30*	Abnormal gait	10	9	7	6	4
		Decreased activity	4	2	1	0	0
		Prostration	3	0	0	0	0

Group size (N=10), *: N=10 (Week 1), N=9 (Week 4, 8, 12), N=8 (Week 26)

Body Weights & Feed Consumption: There was no test article-related effect on BW in males. Beginning on Day 50 and lasting until the end of the dosing phase, a decrease in absolute BW of up to 11%, relative to control, was observed in MDF and HDF. There was no effect on food consumption in males or females.

Ophthalmoscopy: There were no test article-related effects observed when assessed on Day 178 of the study.

Hematology, Clinical Chemistry & Urinalysis: Blood was sampled on Day 182 for hematology and clinical chemistry assessments. There were no test article-related effects on hematology or clinical chemistry parameters. There was no dose related-effects observed when urinalysis was conducted on Day 178.

Gross Pathology: Alopecia was present in all dose groups (Male= 0/10, 1/10, 1/10, 1/10; Female= 0/10, 1/10, 2/10, 2/10; C, LD, MD, HD, respectively).

Organ Weights: Adrenal weight was increased in MDF (+31%) and HDF (+12%), relative to control.

Histopathology: Adequate Battery: No, tongue, nasal cavity/turbinates, rectum, cervix, Zymbal gland not assessed; Peer Review: No; Signed & Dated Pathology Report: Yes

Slight accumulation of foamy alveolar cells (MDM= 1/10, HDM= 2/10 and alveolitis (HDM=1/10) was observed (Sponsor's table, below).

TABLE B - 1
STUDY NO. S02002
E2007: A 26-Week Oral Toxicity Study in Rats
SUMMARY OF HISTOPATHOLOGY DATA
-ALL LESIONS MALE
- TERMINAL SACRIFICE

ORGAN AND FINDINGS		DOSE (mg/kg) --	0	1	10	30
		NO. OF ANIMALS EXAMINED --	10	2	3	10
Lung			(10)	(0)	(1)	(10)
Normal			10	0	0	7
Foamy cell accumulation, alveolar, focal	1+		0	0	1	2
Alveolitis	1+		0	0	0	1

Toxicokinetics: Plasma AUC was not calculated in this study. A marked sex-related difference in E2007 concentration was observed at 10 and 30 mg/kg with females exhibiting much higher plasma levels than males.

Table Toxicokinetic Summary

Dose (mg/kg)	Day	Male C_{1hr} (ng/mL)	Female C_{1hr} (ng/mL)
1	Day 1	113.89 ± 51.46	141.59 ± 61.15
	Day 28	92.15 ± 25.27	131.16 ± 50.39
	Day 179	103.63 ± 31.32	125.50 ± 46.66
10	Day 1	237.12 ± 26.55	510.6 ± 119.0
	Day 28	194.35 ± 63.98	761.6 ± 496.6
	Day 179	210.15 ± 24.08	936.5 ± 747.1
30	Day 1	337.83 ± 77.35	457.6 ± 182.2
	Day 28	506.52 ± 230.84	1373.4 ± 1201.2
	Day 179	591.04 ± 148.79	927.1 ± 567.7

Mean ± SD, N=4

Study title: E2007: A 26-Week Oral Toxicity Study in Male Rats

Study no.:	S05107
Study report location:	EDR
Conducting laboratory and location:	Eisai Co., Ltd; Gifu, Japan
Date of study initiation:	8/25/2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 13022002 and 14110902, Purity 100% and 99.6%, respectively.

Key Study Findings

- **The HD used in this study was considered the MTD based on results of the 13 week study.**
- **Abnormal gait was the main clinical sign observed in both dose groups. However, the incidence of this finding decreased over time in rats dosed with 60 mg/kg but not in rats dosed with 100 mg/kg.**
- **"Eye close reflex" was absent in one rat dosed with 100 mg/kg.**
- **Urine volume was increased in rats dosed with 100 mg/kg.**
- **The incidence of slight focal pancreatic acinar cell atrophy was increased in rats dosed with 100 mg/kg.**

Methods

Doses:	0, 60, 100 mg/kg
Frequency of dosing:	Once daily for 26 weeks
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Sprague-Dawley (Crl:CD(SD)) rat, male only
Number/Sex/Group:	Main group= 15; TK group= 5
Age:	8 weeks
Weight:	242.6-272.7 g
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Dosing Solution Analysis: Dosing formulations were within ± 5% of the nominal concentration.

Mortality & Clinical Signs: One LDM (#01M13) was euthanized *in extremis* on Day 10 after loss of BW, bradypnea, and hypothermia was observed. Corneal opacity, swelling/hemorrhage of forelimbs, prostration, and "accidental" gingival hemorrhage were also observed in this animal. Abnormal gait was the most common clinical sign in LDM and HDM. The incidence of this finding decreased over time and was not observed in LDM beyond Day 57 of the study but was observed in HDM until the end of the dosing period.

Body Weight & Food Consumption: Absolute BW was decreased in LDM and HDM at the end of the dosing phase by 6% and 13%, relative to control. There was no test article effect on food consumption.

Ophthalmoscopy: Opthalmoscopy was performed on Day 178 of the study. One HDM had loss of "eye close reflex."

Hematology & Clinical Chemistry: Blood for hematology and clinical chemistry assessment was collected on Day 182. There was no test article-related effect in either assessment.

Urinalysis: Urine volume was increased in HDM (C= 10.7 ml, HDM= 17.6 ml); osmolality was unaffected.

Gross Pathology & Organ Weights: There were no dose-dependent findings in the gross pathology assessment. Spleen weights were decreased by 17% in HDM, relative to control.

Histopathology: Adequate Battery: No, nasal cavity/turbinates and Zymbal gland not assessed; Peer Review: No; Signed and Dated Pathology Report: Yes

The incidence of slight focal pancreatic acinar cell atrophy was increased in HDM in relation to controls (Sponsor's table 2-2, below). The one moribund animal that was euthanized *in extremis* (01M13) exhibited gastric mucosal atrophy, lymphoid depletion, liver cell atrophy, atrophy of subcutaneous adipose tissue, muscle fiber atrophy, bone marrow hypocellularity, and testicular degeneration.

TABLE 2 - 2
STUDY NO. S05107
E2007:A 26-Week Oral Toxicity Study in Male Rats (An Additional Study)
SUMMARY OF HISTOPATHOLOGY DATA
- NON-NEOPLASTIC AND NEOPLASTIC AND PRE-NEOPLASTIC LESIONS MALE
- TERMINAL SACRIFICE

ORGAN AND FINDINGS		DOSE (mg/kg) --	0	60	100
		NO. OF ANIMALS EXAMINED --	15	14	15
Pancreas			(15)	(14)	(15)
Normal			11	12	10
Fibrosis, Langerhans islet		1+	3	1	2
Acinar cell atrophy, focal		1+	1	1	3

Toxicokinetics: Plasma AUC was not calculated in this study (Sponsor's Table, below).

Table Toxicokinetic Summary

Dose (mg/kg)	Day	C_{1hr} (ng/mL)
60	1	313.41
		39.25
	28	470.56
		141.74
	181	341.40
		67.63
100	1	475.75
		142.35
	28	991.71
		521.27
	181	733.56
		313.51

Mean (upper) and SD (lower) of 5 animals are presented.

6.2.3. Dog

Study title: E2007: A 7-day Oral Dose Range Toxicity Study in Dogs

Study no.:	TKB00008
Study report location:	EDR
Conducting laboratory and location:	Eisai Co., Ltd; Ibaraki, Japan
Date of study initiation:	9/21/2000
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	E2007, Lot 08066-007211, Purity unknown

Key Study Findings

- **Vomiting (≥ 1 mg/kg), abnormal gait (≥ 3 mg/kg), decreased activity (> 3 mg/kg), and prostration (> 3 mg/kg) were observed.**

Methods

Doses:	0, 1, 3, 10 mg/kg
Frequency of dosing:	Once daily for 7 days
Route of administration:	Oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Beagle dog
Number/Sex/Group:	1/ sex/group
Age:	19 months

Mortality & Clinical Signs: There were no deaths during the study. HD animals exhibited vomiting, abnormal gait, decreased activity, and prostration. According to the Sponsor, clinical signs in HD animals consisted of abnormal gait followed by vomiting, which lead to prostration and then eyes remained closed for up to one hour after administration. Normal activity resumed within 80 minutes after administration. Transient abnormal gait was observed approximately 30 minutes after dosing in MD animals and vomiting was observed in LD animals.

Body Weights, Food Consumption, Hematology, Clinical Chemistry, Gross Pathology & Histopathology: There was no effect of E2007 observed in this study.

Toxicokinetics: There was no sex-related difference in the PK parameters for E2007.

Table 6 Pharmacokinetic parameters

Theme: E2007 Study: A 7-day oral dose range toxicity study in dogs Species: Dog (Beagle)
Study No.: TKB00008 Sex: Male and Female Route: p.o.

Dose	Sex	Day	$t_{1/2}$ (hr)	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0\text{-}24hr}$ (ng·hr/mL)	$MRT_{0\text{-}24hr}$ (hr)
1 mg/kg	Male	1	6.2	45	1.0	202	4.9
		7	15.4	112	0.5	550	7.0
	Female	1	9.9	43	1.0	170	6.3
		7	20.1	75	1.0	337	6.8
3 mg/kg	Male	1	11.9	124	0.5	202	3.9
		7	15.3	65	0.5	188	5.0
	Female	1	7.4	124	0.5	333	4.4
		7	13.0	85	0.5	261	5.3
10 mg/kg	Male	1	12.0	226	0.5	705	5.7
		7	11.8	133	1.0	534	6.5
	Female	1	-	166	0.5	741	13.4
		7	20.6	131	0.5	512	6.6

-: no data

Study title: E2007: A 4-Week Oral Toxicity Study in Dogs

Study no.:	S00010
Study report location:	EDR
Conducting laboratory and location:	Eisai Co., Ltd.; Gifu, Japan
Date of study initiation:	10/26/2000
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 10092507, Purity 99.6%

Key Study Findings

- **The NOAEL in this study was 0.3 mg/kg.**
- **Although clinical signs were observed in all dose groups, abnormal gait was transient in animals dosed with 0.3 mg/kg E2007.**
- **Occult blood was detected in all 3 male dogs dosed with 10 mg/kg. There was no histopathology correlate.**

Methods

Doses:	0, 0.3 (LD), 1 (MD), 10 (HD) mg/kg
Frequency of dosing:	Once daily for 4 weeks
Route of administration:	Oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Beagle dog
Number/Sex/Group:	3
Age:	7 months
Weight:	M= 7.1-9.2 kg; F= 6.5-9.1 kg
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Dosing Solution Analysis: Dosing formulations were within ± 5% of the nominal concentration.

Mortality & Clinical Signs: There were no test article-related deaths during this study. Abnormal gait occurred in 2 LD animals on Day 1 and then 1 LD on Day 2, after which there were no findings of clinical signs in this dose group. In MD animals, abnormal gait, decreased activity, and prostration were observed from Day 1 to Day 12, after which there was no clinical signs observed in MD animals. All HD animals exhibited similar clinical signs as the MD animals, but the duration of the signs was greater (several hours after dosing) and these signs were observed during the entire dosing period.

Body Weights & Food Consumption: Absolute BW was decreased in HDM by 8%, relative to controls, at the end of the dosing period. There was no effect observed in females. There was no impact of E2007 on food consumption in female dogs during the dosing period. However, food consumption was decreased (~10%) in HDM beginning on Day 1 of the study.

Ophthalmoscopy: There were no test article-related findings in the ophthalmologic assessment on Day 26 of the study.

Hematology & Clinical Chemistry: Blood was sampled on Day 27 for hematology and clinical chemistry assessments. There were no test article-related effects.

Urinalysis: Urine was collected on Day 22 for assessment. Occult blood was detected in the urine of all 3 HDM but not in control males.

Gross Pathology & Organ Weights: There were no test article-related findings.

Histopathology: Adequate Battery: No, nasal cavity/turbinates were not assessed; Peer Review: No; Signed and Dated Pathology Report: Yes. There were no test article-related findings.

Toxicokinetics: Plasma levels of E2007 increased in a less-than-linear manner relative to dose. There was no sex-related difference in plasma concentrations except in HDF on Day 28 of dosing at which the plasma levels were 2.6-fold higher than in HDM.

Table 4 Mean values of pharmacokinetic parameters obtained from plasma levels of E2007 following repeated oral administration of E2007 for 4 weeks in dogs

Sex	Dose (mg/kg)	Day	C_{max} (ng/mL)		t_{max} (hr)		AUC_{0-24hr} (ng·hr/mL)	
Male	0.3	Day 1	49.27 ±	9.95	0.5	(0.5-0.5)	142.79 ±	65.57
		Day 7	41.52 ±	11.70	1	(0.5-1)	134.40 ±	63.70
		Day 28	57.82 ±	14.87	0.5	(0.5-0.5)	158.13 ±	58.84
	1	Day 1	89.02 ±	35.13	0.5	(0.5-0.5)	237.83 ±	80.37
		Day 7	83.45 ±	30.75	0.5	(0.5-1)	205.15 ±	71.24
		Day 28	75.67 ±	28.27	0.5	(0.5-1)	221.84 ±	83.75
	10	Day 1	212.26 ±	73.56	0.5	(0.5-0.5)	825.29 ±	273.26
		Day 7	246.60 ±	157.37	1	(0.5-2)	1322.16 ±	1093.40
		Day 28	303.83 ±	113.62	1	(0.5-1)	1222.54 ±	624.21
Female	0.3	Day 1	34.31 ±	8.55	0.5	(0.5-0.5)	87.55 ±	19.22
		Day 7	40.94 ±	7.47	0.5	(0.5-0.5)	94.97 ±	34.13
		Day 28	42.76 ±	1.48	0.5	(0.5-0.5)	98.00 ±	16.45
	1	Day 1	85.84 ±	20.94	0.5	(0.5-1)	365.80 ±	107.83
		Day 7	116.13 ±	21.37	0.5	(0.5-2)	513.94 ±	171.04
		Day 28	106.03 ±	9.86	0.5	(0.5-1)	343.40 ±	87.45
	10	Day 1	297.41 ±	75.20	0.5	(0.5-0.5)	959.98 ±	369.78
		Day 7	299.90 ±	46.60	0.5	(0.5-4)	1612.79 ±	1613.06
		Day 28*	485.02		2.25	(0.5,4)	3266.42	

C_{max} and AUC_{0-24hr} values represent the mean ±SD of 3 animals (* : n=2).

t_{max} values represent the medium and range of 3 animals (* : n=2).

Study title: E2007: A 13-Week Oral Toxicity Study in Dogs

Study no.:	S01009
Study report location:	EDR
Conducting laboratory and location:	Eisai Co., Ltd; Gifu, Japan
Date of study initiation:	5/31/2001
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 10092507, Purity 99.6%

Key Study Findings

- **Besides the clinical signs observed in animals dosed with ≥ 1 mg/kg, there were no test article-related adverse effects observed in this study.**
- **The NOAEL in this study was 0.1 mg/kg.**

Methods

Doses:	0, 0.1 (LD), 1 (MD), 10 (HD) mg/kg
Frequency of dosing:	Once daily for 13 weeks
Route of administration:	Oral by capsule
Dose volume:	0.5 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Beagle dog
Number/Sex/Group:	3
Age:	8 month
Weight:	M=9.4-10.1 kg; F= 7.4-9.3 kg
Deviation from study protocol:	There were marked deviations in this study a) Female # 01F02 and male #1017 had escaped from their cages on the morning of Day 52 and were cohabitating at the time they were discovered. The female was determined not to be pregnant. b) An unidentified foreign substance was found in the diet (Lot JAN29012A). The Sponsor states that "*this might little affect on integrity of study results*". The nature of the foreign substance was not specified. c) At necropsy, the following tissues for animals # 00F01 and 02F01 were preserved in the same vessel: Lacrimal gland, submaxillary lymph node, submaxillary glands, sublingual glands, parotid glands, adrenals, pituitary, thyroid, parathyroid, and ovaries. The Sponsor states that "*the above organs and tissues, excepted the lacrimal glands, from these two animals were difficult to identify the animal*". The Sponsor analyzed these tissues separately from the study tissues and there were no histopathology findings of concern. Therefore, this deviation is not expected to impact the validity of the study.

Dosing Solution Analysis: Dosing formulations were within ± 5% of the nominal concentration.

Mortality & Clinical Signs: There were no deaths in this study. Clinical signs were limited to sporadic vomiting and “muddy stool” in LD animals. MD animals exhibited abnormal gait beginning on Day 1 of the study. This clinical sign was observed sporadically in MD animals up until the end of the dosing period. Abnormal gait was observed in HD animals throughout the entire dosing period. The finding of abnormal gait lasted for up to 8 hours after dosing in MD and HD animals.

Body Weights & Food Consumption: Absolute BW was decreased in males (5%, 6%, and 9%; LD, MD, and HD, respectively) in a dose-dependent manner at the end of the dosing period. There was no dose-related effect on food consumption during the dosing period.

Ophthalmoscopy: Performed on Day 84, there were no test article-related effects detected in the ophthalmoscopic exam.

ECG: When assessed on Days 27 and 85 of the dosing period, there was no effect of the test article on heart rate, PR interval, QRS interval, or QT interval.

Hematology & Clinical Chemistry: Blood was sampled on Days 22 and 90 to assess hematology and clinical chemistry parameters. There were no test article-related effects.

Urinalysis: Urine was collected on Days 13, 23, 59, and 86 for analysis. There were no test article-related findings.

Gross Pathology & Organ Weights: There were no test article-related findings.

Histopathology: Adequate Battery: No, cervix and nasal cavity/ turbinates were not examined; Peer Review: No; Signed and Dated Pathology Report: Yes. There were no test article-related findings.

Toxicokinetics: There was no consistent sex-related difference in plasma concentration of E2007. Plasma levels of E2007 increased in a less-than-linear manner, relative to dose.

Table 4 Mean values of pharmacokinetic parameters obtained from plasma levels of E2007 following repeated oral administration of E2007 for 13 weeks in dogs

Dose (mg/kg)	Day	Male C_{max} (ng/mL)	Male t_{max} (hr)	Male $AUC_{0\text{-}24hr}$ (ng·hr/mL)	Female C_{max} (ng/mL)	Female t_{max} (hr)	Female $AUC_{0\text{-}24hr}$ (ng·hr/mL)
0.1	Day 1	5.87 ± 0.97	1 (0.5-1)	15.10 ± 6.96	9.14 ± 2.67	0.5 (0.25-1)	21.44 ± 11.39
	Day 28	7.70 ± 3.75	0.5 (0.25-1)	16.03 ± 9.05	9.10 ± 1.04	0.5 (0.5-1)	25.22 ± 5.55
	Day 91	8.96 ± 3.50	0.5 (0.5-0.5)	21.61 ± 9.74	13.51 ± 4.92	1 (0.5-1)	49.34 ± 15.38
1	Day 1	44.03 ± 31.48	0.5 (0.25-1)	203.28 ± 243.14	46.05 ± 8.69	1 (0.5-1)	175.95 ± 35.41
	Day 28	54.84 ± 24.40	1 (1-1)	293.43 ± 272.97	66.00 ± 19.02	1 (0.5-1)	234.85 ± 76.29
	Day 91	49.11 ± 26.75	0.5 (0.5-1)	281.41 ± 307.74	60.00 ± 21.94	1 (0.5-1)	264.35 ± 130.27
10	Day 1	83.89 ± 48.55	0.5 (0.5-4)	776.11 ± 573.97	92.77 ± 54.91	0.5 (0.5-1)	356.88 ± 192.20
	Day 28	110.18 ± 63.33	1 (0.5-1)	423.97 ± 267.54	139.03 ± 97.10	1 (0.25-1)	1032.40 ± 1256.40
	Day 91	148.83 ± 93.12	1 (1-2)	905.45 ± 500.67	122.85 ± 25.66	1 (1-2)	913.11 ± 400.93

C_{max} and $AUC_{0\text{-}24hr}$ values represent the mean ± SD of 3 animals.

t_{max} values represent the median and range of 3 animals.

6.2.4 Monkey

Study title: E2007: A 2-week Oral Repeated Dose Toxicity Study in Monkeys

Study no.: TKB01016
Study report location: EDR
Conducting laboratory and location: Eisai Co., Ltd.; Ibaraki, Japan
Date of study initiation: 11/19/2001
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: E2007, Lot 11070303, Purity unknown

Key Study Findings

- **Given the prostration, drowsiness, and mydriasis that occurred at 2 mg/kg, the HD was reduced to 1 mg/kg, at which ataxia was the main clinical sign.**
- **Food consumption was reduced by 40-100% of control in animals dosed with 2 mg/kg, possibly due to the protracted clinical signs observed at this dose.**
- **Although BW was not affected in this short term study, chronic dosing at 2 mg/kg would be predicted to have a marked effect on BW given the effect on food consumption in this study. Therefore, the MTD in this study is 1 mg/kg.**

Methods

Doses: 0, 0.5, 2 (reduced to 1 on Day 2 (F) & Day 4 (M)) mg/kg
Frequency of dosing: Once daily for 2 weeks
Route of administration: Oral gavage
Dose volume: 5 ml/kg
Formulation/Vehicle: 0.5% methylcellulose
Species/Strain: Cynomolgus monkey
Number/Sex/Group: 1/sex/group
Age: 31-53 months

Mortality & Clinical Signs: No test article-related deaths occurred during the study. Due to clinical signs in monkeys dosed with 2 mg/kg, the dose was reduced to 1 mg/kg on

Day 2 for the female and Day 4 for the male. Clinical signs at 2 mg/kg consisted of prostration, "sitting position", drowsiness, mydriasis (female only), decreased activity, and ataxia. These symptoms lasted for up to 8 hours after dosing. When reduced to 1 mg/kg, ataxia lasting for up to 4 hours was the sole clinical sign. Ataxia, which lasted between 1 to 4 hours after dosing, was the main clinical sign observed in monkeys dosed with 0.5 mg/kg, with sporadic decreased activity and drowsiness observed in the female.

Body Weights & Food Consumption: BW was not affected by the test article. Food consumption was decreased by 40-100% of control in monkeys dosed with 2 mg/kg E2007 (Sponsor's Table 3, below).

Table 3 Food consumption

E2007	Study: A 2-week oral repeated dose toxicity study in monkeys												
Study No.: TKB01016	Sex: Male and Female												
Group	Day (g)												
Animal No.	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7
Control													
M1	100	100	100	100	100	100	75	100	69	100	100	100	100
F1	100	100	100	100	100	100	85	100	100	100	100	100	100
E2007 (0.5 mg/kg)													
M2	100	100	100	100	100	100	95	100	96	100	100	100	100
F2	82	82	100	100	100	100	100	100	100	100	100	100	100
E2007 (2/1 mg/kg)													
M3	95	84	93	100	100	100	61	28	2	12	0	87	100
F3	100	100	100	100	100	100	87	10	40	33	68	72	100

The dose of 2 mg/kg was decreased to 1 mg/kg from Day 2 in the female and from Day 4 in the male.

Hematology & Clinical Chemistry: There were no obvious effects of E2007 on hematology and clinical chemistry parameters when assessed on Day 14 of the study.

Gross Pathology & Histopathology: There were no test article-related findings in the gross pathology assessment. Slight hepatocyte vacuolation and adrenal hemorrhage were observed in the HDF.

Toxicokinetics: There was no apparent difference in plasma levels between females and males exposed to the same dose level. Plasma levels increased roughly in a linear manner, relative to dose.

Dose (mg/kg)	Animal No.	Day	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0\text{-}24hr}$ (ng·hr/mL)	$AUC_{0\text{-}inf}$ (ng·hr/mL)
0.5	M2	1	118.12	2	1145.05	1257.31
		8	150.13	2	1524.39	-
		14	154.91	1	1581.02	-
0.5	F2	1	140.63	2	1336.77	1494.51
		8	185.15	2	1567.29	-
		14	193.32	2	1848.50	-

Dose* (mg/kg)	Animal No.	Day	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0\text{-}24hr}$ (ng·hr/mL)	$AUC_{0\text{-}inf}$ (ng·hr/mL)
2	M3	1	385.99	8	6689.02	8935.15
		4	873.24	4	13480.98	-
1	M3	8	393.61	2	4511.89	-
		14	389.66	2	4197.85	-
2	F3	1	544.06	2	5440.06	5832.32
		2	431.19	2	4055.95	-
1	F3	8	365.45	1	2822.63	-
		14	332.86	1	2821.45	-

-: not calculated

*: The dose level was reduced to 1 mg/kg on Day 2 in female and Day 4 in male.

Study title: E2007: A 4-Week Oral Toxicity Study in Monkeys

Study no.:	SBL47-47
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	1/11/2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 11070303, Purity 99.6%

Key Study Findings

- **The NOAEL in this study was 0.3 mg/kg in males and 0.1 mg/kg in females. At higher doses, thymic atrophy was observed.**
- **HD animals exhibited histopathology findings in the kidney that correlated with gross pathology findings.**
- **All HD animals exhibited chronic inflammation of the stomach; 4/6 were positive for H. pylori.**
- **A decrease in lymphocyte and basophil counts was observed in males and females dosed with 1 mg/kg.**
- **Clinical signs (ataxia, decreased activity, and "sitting position") were observed in monkeys dosed with ≥ 0.3 mg/kg.**

Methods

Doses:	0, 0.1 (LD), 0.3 (MD), 1 (HD) mg/kg
Frequency of dosing:	Once daily for 4 weeks
Route of administration:	Oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	3
Age:	3-6 years
Weight:	M= 3.64-5.29 kg; F= 2.63-3.26 kg
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Dosing Solution Analysis: Dosing formulations were ± 5% of the nominal concentration.

Mortality & Clinical Signs: There were no deaths during the dosing phase. Ataxia, decreased activity, and "sitting position" were the main clinical signs observed in HDM and HDF. Prostration was observed once during the dosing period in 1 HDF. Ataxia was observed in 1 MDF on the first day of dosing. Otherwise, there were no test article-related clinical signs in MD and LD animals.

Body Weights & Food Consumption: At the end of the dosing period, absolute BW was decreased by 17% in HDM, relative to controls. There was no effect on BW in females.

Ophthalmoscopy: When assessed on Day 23, there were no test article-related findings in the gross ophthalmologic examination, slit-lamp examination, or funduscopic examination.

ECG: When assessed on Day 28, there were no test article-related findings on heart rate, PR interval, QRS interval, QT interval, or QTc interval (method of correction not

specified).

Hematology & Clinical Chemistry: Blood was collected on Day 28 of the study for assessment of hematology and clinical chemistry parameters. Basophil (M= -23%, F= -80%) and lymphocyte (M= -41%, F= -54%) counts were decreased in HD animals relative to predosing values and control values on Day 28 (Sponsor's table, below). One HDM exhibited a 3.4-fold increase in ALT, relative to baseline values.

Table 4-1 Hematology in male cynomolgus monkeys

Group	Animal No.\Day	Baso. (10^3/mm^3) -11	Baso. (10^3/mm^3) 28	Lymph. (10^3/mm^3) -11	Lymph. (10^3/mm^3) 28
Control	1	0.03	0.10	4.16	4.70
	2	0.09	0.09	10.15	7.40
	3	0.08	0.16	6.22	7.82
	Mean	0.067	0.117	6.843	6.640
	±S.D.	0.032	0.038	3.043	1.693
E2007 0.1 (mg/kg/day)	7	0.10	0.07	8.18	6.21
	8	0.06	0.05	7.74	6.83
	9	0.15	0.09	9.20	8.43
	Mean	0.103	0.070	8.373	7.157
	±S.D.	0.045	0.020	0.749	1.145
E2007 0.3 (mg/kg/day)	13	0.23	0.16	9.56	8.15
	14	0.10	0.15	11.81	10.66
	15	0.10	0.07	7.92	7.08
	Mean	0.143	0.127	9.763	8.630
	±S.D.	0.075	0.049	1.953	1.838
E2007 1 (mg/kg/day)	19	0.03	0.02	5.68	3.47
	20	0.07	0.05	6.09	3.79
	21	0.04	0.04	6.39	3.54
	Mean	0.047	0.037	6.053	3.600
	±S.D.	0.021	0.015	0.356	0.168

Table 4-5 Hematology in female cynomolgus monkeys

Group	Animal No.\Day	Baso. (10^3/mm^3) -11	Baso. (10^3/mm^3) 28	Lymph. (10^3/mm^3) -11	Lymph. (10^3/mm^3) 28
Control	4	0.03	0.05	3.39	3.69
	5	0.05	0.04	7.83	6.15
	6	0.04	0.04	4.24	3.48
	Mean	0.040	0.043	5.153	4.440
	±S.D.	0.010	0.006	2.357	1.485
E2007 0.1 (mg/kg/day)	10	0.04	0.01	6.83	3.72
	11	0.07	0.07	6.77	5.09
	12	0.06	0.03	8.00	6.04
	Mean	0.057	0.037	7.200	4.950
	±S.D.	0.015	0.031	0.693	1.166
E2007 0.3 (mg/kg/day)	16	0.03	0.06	5.82	6.15
	17	0.05	0.05	7.63	5.51
	18	0.04	0.04	4.69	3.26
	Mean	0.040	0.050	6.047	4.973
	±S.D.	0.010	0.010	1.483	1.518
E2007 1 (mg/kg/day)	22	0.09	0.02	11.55	6.03
	23	0.15	0.01	7.50	3.27
	24	0.07	0.03	5.75	2.34
	Mean	0.103	0.020	8.267	3.880
	±S.D.	0.042	0.010	2.975	1.919

Notes) Baso.(%) : Basophilic leukocyte ratio
Mono. : Number of monocytes
Mono.(%) : Monocyte ratio
Lymph. : Number of lymphocytes
Lymph.(%) : Lymphocyte ratio
Neutro. : Number of neutrophilic leukocytes

Urinalysis: Urine was assessed on Day 26 of the dosing period. There were no test article-related effects.

Gross Pathology: 1 HDM and 1 HDF exhibited unilateral capsular adhesions in the kidney. There were histopathological correlates for these findings (see below).

Organ Weights: There were no test article-related findings.

Histopathology: Adequate Battery: No, nasal cavities/turbinates were not examined; Peer Review: No; Signed and Dated Pathology Report: Yes

All HD males (very slight to slight) and females (very slight) exhibited chronic inflammation in the fundus and pylorus of the stomach. Four of these animals were positive for *Helicobacter pylori,* which was assessed by immunohistochemistry. The animals that exhibited capsular adhesions of the kidney also exhibited slight renal cortical fibrosis (male) or thickening of the renal capsule (female).

Table 11-1 Histopathological findings in male cynomolgus monkeys

Findings	Group	Control							E2007							E2007							E2007						
	Dose(mg/kg)	0							0.1							0.3							1						
	Grade	−	±	+	2+	3+	P	NE	−	±	+	2+	3+	P	NE	−	±	+	2+	3+	P	NE	−	±	+	2+	3+	P	NE
Kidney																													
Cortical fibrosis,focal,unilateral		3	0	0	0	0			3	0	0	0	0			3	0	0	0	0			2	0	1	0	0		
Stomach(fundus,pylorus)																													
Chronic inflammation,mucosa,pylorus		3	0	0	0	0			3	0	0	0	0			3	0	0	0	0			0	2	1	0	0		
Thymus																													
Atrophy		3	0	0	0	0			3	0	0	0	0			3	0	0	0	0			0	3	0	0	0		

Table 11-5 Histopathological findings in female cynomolgus monkeys

Findings	Group	Control							E2007							E2007							E2007						
	Dose(mg/kg)	0							0.1							0.3							1						
	Grade	−	±	+	2+	3+	P	NE	−	±	+	2+	3+	P	NE	−	±	+	2+	3+	P	NE	−	±	+	2+	3+	P	NE
Kidney																													
Thickening,capsule,unilateral		3	0	0	0	0			3	0	0	0	0			3	0	0	0	0			2	0	1	0	0		
Stomach(fundus,pylorus)																													
Chronic inflammation,mucosa,pylorus		3	0	0	0	0			3	0	0	0	0			3	0	0	0	0			0	3	0	0	0		
Thymus																													
Atrophy		3	0	0	0	0			3	0	0	0	0			2	1	0	0	0			1	2	0	0	0		

Histopathological findings.

Grade
− : No abnormal changes
± : Very slight
+ : Slight
2+ : Moderate
3+ : Marked
P : Non-graded change
NE : Unexamined

Toxicokinetics: Plasma levels of E2007 increased linearly with dose and did not differ by sex.

Table 3 : Plasma concentrations (ng/mL) and TK parameters for E2007 on Day 1 of 4-week oral administration of E2007 to monkeys

Dose (mg/kg/day)	Sex	Animal No.	Time after administration (hr) 0.5	1	2	4	8	12	24	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-24h} (ng·hr/mL)	AUC_{0-inf} (ng·hr/mL)
0.1	Male	7	10.40	25.12	29.85	27.54	17.13	12.79	6.91	29.85	2	363.74	488.27
		8	15.05	25.59	23.88	22.07	10.27	7.00	3.62	25.59	1	247.55	305.18
		9	6.79	26.28	31.00	29.04	20.88	15.56	11.97	31.00	2	436.55	813.04
		Mean[1)]	10.75	25.66	28.24	26.22	16.09	11.78	7.50	28.81	2	349.28	535.50
		SD[1)]	4.14	0.58	3.82	3.67	5.38	4.37	4.21	2.85	(1-2)	95.33	257.20
	Female	10	27.42	41.02	35.75	30.26	15.40	8.71	3.25	41.02	1	339.66	374.33
		11	26.08	36.29	31.35	24.72	12.58	7.87	2.71	36.29	1	290.98	319.72
		12	2.71	12.70	29.69	31.17	17.50	8.86	2.71	31.17	4	306.07	330.16
		Mean[1)]	18.74	30.00	32.26	28.72	15.16	8.48	2.89	36.16	1	312.24	341.40
		SD[1)]	13.90	15.17	3.13	3.49	2.47	0.53	0.31	4.93	(1-4)	24.92	28.99
	Total	Mean[1)]	14.74	27.83	30.25	27.47	15.63	10.13	5.20	32.49	1.5	330.76	438.45
		SD[1)]	10.16	9.89	3.82	3.48	3.78	3.32	3.67	5.40	(1-4)	65.54	195.19
0.3	Male	13	83.00	90.40	76.20	74.39	41.02	28.79	13.90	90.40	1	924.57	1135.08
		14	43.27	64.27	74.61	76.50	46.87	34.33	16.88	76.50	4	974.65	1243.66
		15	33.59	73.56	68.28	82.11	62.63	42.21	22.34	82.11	4	1142.96	1504.46
		Mean[1)]	53.29	76.08	73.03	77.67	50.17	35.11	17.71	83.00	4	1014.06	1294.40
		SD[1)]	26.18	13.25	4.19	3.99	11.18	6.74	4.28	6.99	(1-4)	114.40	189.85
	Female	16	123.76	156.01	156.29	118.06	52.61	28.65	7.67	156.29	2	1253.16	1318.21
		17	63.52	67.92	96.60	91.76	46.87	29.72	11.18	96.60	2	995.20	1122.67
		18	88.58	79.25	77.51	68.07	40.65	29.36	19.11	88.58	0.5	936.34	1365.34
		Mean[1)]	91.95	101.06	110.13	92.63	46.71	29.24	12.65	113.82	2	1061.57	1268.74
		SD[1)]	30.26	47.92	41.10	25.01	5.98	0.54	5.86	37.00	(0.5-2)	168.51	128.68
	Total	Mean[1)]	72.62	88.57	91.58	85.15	48.44	32.18	15.18	98.41	2	1037.81	1281.57
		SD[1)]	33.00	34.29	33.10	17.99	8.24	5.35	5.36	29.19	(0.5-4)	131.42	145.73
1	Male	19	97.97	131.60	126.16	148.79	147.68	114.27	67.91	148.79	4	2695.64	4129.65
		20	49.18	102.65	138.27	140.26	189.17	201.67	141.16	201.67	12	3946.76	10689.54
		21	71.60	97.29	123.37	132.64	156.94	118.94	52.49	156.94	8	2585.96	3353.51
		Mean[1)]	72.92	110.51	129.27	140.56	164.60	144.96	87.19	169.13	8	3076.12	6057.57
		SD[1)]	24.42	18.46	7.92	8.08	21.78	49.17	47.37	28.47	(4-12)	755.99	4030.13
	Female	22	290.65	377.24	387.82	357.07	304.69	274.43	156.69	387.82	2	6435.54	10100.81
		23	110.30	140.34	158.61	186.20	133.38	78.64	19.96	186.20	4	2239.32	2408.92
		24	89.54	233.53	257.96	215.14	218.95	159.18	106.82	257.96	2	4042.44	6575.18
		Mean[1)]	163.50	250.37	268.13	252.80	219.01	170.75	94.49	277.33	2	4239.10	6361.64
		SD[1)]	110.61	119.34	114.94	91.45	85.66	98.41	69.19	102.20	(2-4)	2105.01	3850.39
	Total	Mean[1)]	118.21	180.44	198.70	196.68	191.80	157.86	90.84	223.23	4	3657.61	6209.60
		SD[1)]	87.14	108.17	105.33	84.56	63.34	70.99	53.19	89.52	(2-12)	1551.38	3529.13

[1)] : t_{max} values represent the median and range.

Study title: E2007: A 39-Week Oral Toxicity Study in Monkeys

Study no.:	SBL038-024
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10/25/2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, 14110902 and 16032801, Purity 99.6% and 99.7%, respectively.

Key Study Findings

- **By using a dose escalation scheme, the Sponsor was able to achieve dose levels of 8 mg/kg for up to 9 months. One death did occur (male) within 77 days of increasing the dose to 8 mg/kg.**
- **Clinical signs in animals dosed with 8 mg/kg included "coma", somnolence, sedation, and lateral recumbence.**
- **Except for ataxic gait, there were no other adverse effects observed in monkeys dosed with 1 mg/kg, for at least 9 months.**
- **One male dosed with 8 mg/kg exhibited increased protein in the urine (~4-fold over baseline), beginning at week 41. The same animal exhibited slight nephropathy at the end of the dosing period.**
- **Chronic inflammation of the stomach in animals dosed with 8 mg/kg was associated with H. pylori infection.**

Methods

Doses:	See chart below
Frequency of dosing:	Once daily for 39 weeks
Route of administration:	Oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	Main= 4; TK =2
Age:	3 to 7 years
Weight:	M= 4.8-6.1 kg; F= 2.2-3.6 kg
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study

Study Design: Dose escalation was employed in Groups 3 and 4 as described below.

Group	Treatment and Dose Level (mg/kg)		Number of animals	
			Male	Female
1	Control	0	4	4
2	E2007	1	4	4
3	E2007	1→2→4→8[a)]	2	2
4	E2007	1→2→4→8[b)]	2	2

[a)] Dose titration schedule; 1 mg/kg (Days 1 to 28), 2 mg/kg (Days 29 to 67), 4 mg/kg (Days 68 to 105), and then 8 mg/kg (Days 106 to 378)

[b)] Dose titration schedule; 1 mg/kg (Days 1 to 28), 2 mg/kg (Days 29 to 67), 4 mg/kg (Days 68 to 98), and then 8 mg/kg (Days 99 to 378)

1 control group and 3 test article groups

Group No.	Dose Level (mg/kg/day)	Dose Volume (mL/kg/day)	Concentration (mg/mL)	Number of Animals (Animal Numbers) Males	Females
1	Control	5	0	4 (1-4)	4 (5-8)
2	1	5	0.2	4 (9-12)	4 (13-16)
3	1 [a)] 2 [b)] 4 [c)] 8 [d)]	5	0.2 [a)] 0.4 [b)] 0.8 [c)] 1.6 [d)]	2 (17, 19)	2 (21, 23)
4	1 [a)] 2 [b)] 4 [e)] 8 [f)]	5	0.2 [a)] 0.4 [b)] 0.8 [e)] 1.6 [f)]	2 (18, 20)	2 (22, 24)

a) Weeks 1 to 4 of dosing
b) Weeks 5 to 10 of dosing (Days 29 to 67 of dosing)
c) Weeks 10 to 15 of dosing (Days 68 to 105 of dosing)
d) Weeks 16 to 54 of dosing (Days 106 to 378 of dosing)
e) Weeks 10 to 14 of dosing (Days 68 to 98 of dosing)
f) Weeks 15 to 54 of dosing (Days 99 to 378 of dosing)
In Group 3, 1 mg/kg was administered for 4 weeks. The dose level was progressively increased to 2, 4, and 8 mg/kg, which were then administered for 39, 38, and 273 days, respectively.
In Group 4, 1 mg/kg was administered for 4 weeks. The dose level was progressively increased to 2, 4, and 8 mg/kg, which were then administered for 39, 31, and 280 days, respectively.

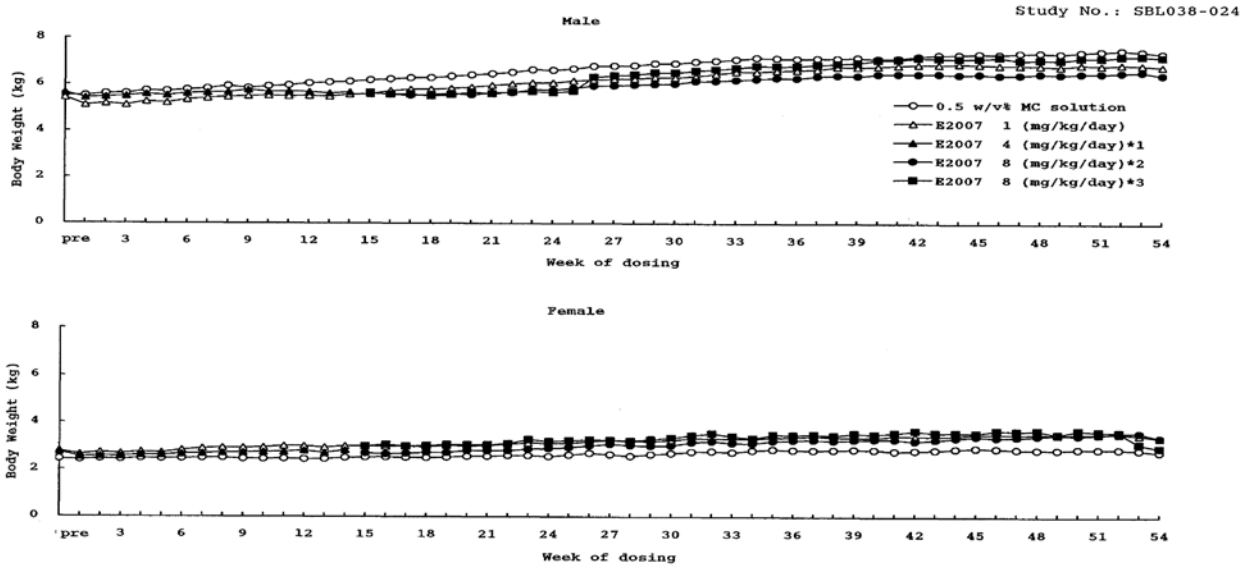
Mortality & Clinical Signs: One male (#18) dosed with 8 mg/kg was found dead on Day 176, which represents 76 days of dosing at 8 mg/kg. This male exhibited clinical signs such as ataxia, decreased activity, "sitting position" when dosed with 1 and 2 mg/kg. When exposed to higher doses, this animal exhibited sedation, somnolence, "coma", lateral recumbence, and decreased BW. Ataxic gait and sporadic decreased activity were the main clinical signs observed in monkeys dosed with 1 mg/kg (Group 2). Clinical signs in animals dosed with 1 mg/kg consisted of ataxic gait and sporadic decreased activity. Slight decrease in activity was observed along with ataxia and sporadic lateral recumbence and "sitting position" when the dose was raised to 2 mg/kg. At 4 mg/kg, moderate to severe decrease in activity, ataxia, "sitting position", sporadic somnolence, sedation, "prone position", and lateral recumbence were observed. At 8 mg/kg, ataxia, severe decreased activity, sedation, lateral recumbence, "sitting position", somnolence, and "coma" were observed (Sponsor's Table, below).

Major clinical signs during titration period (1 to 8 mg/kg)

Findings	Dose	1 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg
Ataxic gait		4 3	4 3	4 4	4 4
Decreased spontaneous activity		2 1	4 3	4 3	4 4
Sitting position		0 0	3 2	3 2	4 4
Lateral position		0 0	0 1	1 1	4 2
Prone position		0 0	0 0	0 1	1 1
Sedation		0 0	0 0	1 1	3 4
Somnolence		0 0	0 0	1 1	3 2
Coma		0 0	0 0	0 0	2 2

Number of animals (upper: male, lower: female) that showed the findings were presented.

Body Weights & Feed Consumption: Absolute BW was decreased by 8% in males dosed with 1 mg/kg/day and by 13% in males exposed to 8 mg/kg/day E2007, at the end of dosing (Sponsor's Figure, below). There was no consistent decrease in absolute BW in treated monkeys.



38

Figure 1 Changes in body weight in male cynomolgus monkeys

Notes) *1 : Weeks 1 to 4 of dosing 1 mg/kg/day, Weeks 5 to 10 of dosing 2 mg/kg/day, Weeks 10 to 14 of dosing 4 mg/kg/day
*2 : Week 15 of dosing 4 mg/kg/day, Weeks 16 to 54 of dosing 8 mg/kg/day (n=2)
*3 : Weeks 15 to 54 of dosing 8 mg/kg/day (n=2)

Ophthalmoscopy: Ophthalmology (Week 40 and 53) and electroretinography (Day 377) were performed. There were no test article-related findings.

ECG: When assessed on Days 285 and 376, there were no test article-related effects on heart rate, PR interval, QRS interval, and QT interval (method of correction not specified).

Hematology & Clinical Chemistry: Hematology and clinical chemistry parameters were assessed during Weeks 13, 41, and 54. There were no test article-related findings.

Urinalysis: Urinalysis was performed during Weeks 13, 41, and 54. 1/4 HDM (#17) exhibited elevated levels of protein in the urine during Weeks 41 and 54. 1/4 HDF (#23) exhibited elevated levels of protein in the urine during Weeks 13, 41 and 54. Although nephropathy was detected in the male, there were no histopathological correlates in the kidneys of the female (see below).

MALES

Group	Animal No.	Protein (mg/dL) Pre	13w	41w	54w
0.5 w/v% MC solution	1	7.0	0.9	1.3	5.3
	2	1.8	2.3	3.8	1.6
	3	3.4	5.3	4.7	1.3
	4	4.7	3.7	5.2	1.4
	Mean	4.23	3.05	3.75	2.40
	±S.D.	2.20	1.89	1.73	1.94
E2007 1 (mg/kg/day)	9	3.1	1.1	45.2	0.9
	10	1.3	2.3	1.1	1.4
	11	1.6	3.4	1.8	2.0
	12	3.5	3.1	3.1	0.3
	Mean	2.38	2.48	12.80	1.15
	±S.D.	1.09	1.03	21.62	0.72
E2007 8 (mg/kg/day)#	17	4.0	4.4	7.2	16.5
	18	0.9	7.2		
	19	2.0	3.0	1.1	0.2
	20	2.3	2.7		
	Mean	2.30	4.33	4.15	8.35
	±S.D.	1.28	2.05		

FEMALES

Group	Animal No.	Protein (mg/dL) Pre	13w	41w	54w
0.5 w/v% MC solution	5	3.3	4.8	3.1	7.0
	6	9.7	4.5	4.1	3.0
	7	4.6	4.7	3.9	18.6
	8	4.6	14.7	3.6	1.4
	Mean	5.55	7.18	3.68	7.50
	±S.D.	2.83	5.02	0.43	7.77
E2007 1 (mg/kg/day)	13	4.9	5.6	4.0	2.9
	14	7.2	3.5	6.1	10.5
	15	7.2	6.7	7.5	4.7
	16	3.3	4.2	3.5	3.2
	Mean	5.65	5.00	5.28	5.33
	±S.D.	1.91	1.43	1.86	3.54
E2007 8 (mg/kg/day)#	21	8.9	7.2	24.5	5.2
	22	8.1	1.9		
	23	3.6	20.6	55.4	95.0
	24	4.7	13.1		
	Mean	6.33	10.70	39.95	50.10
	±S.D.	2.57	8.03		

Gross Pathology & Organ Weights: There were no dose-related findings.

Histopathology: Adequate Battery: No, nasal cavities/ turbinates not examined; Peer Review: Yes; Signed and Dated Pathology Report: Yes

Slight thymic atrophy (0/4 CM, 1/4 HDM), chronic inflammation of the stomach mucosa (0/4 CM, 2/4 HDM, 1/4 LDF, 1/4 HDF) and slight nephropathy (0/4CM, 1/4 HDM) were observed. The renal findings were in the same male that exhibited an increase in protein in the urine (#17). The chronic inflammation in the stomach was associated with H. pylori infection. The expression of Ki67, TUNEL staining, thymine dimers, p53, and MSH2 were assessed in the skin due to the potential of E2007 to be photo-reactive (Study report # CK-168). There was no dose-related effect on the expression of these biomarkers. However, it is important to mention that animals were not directly exposed to UV light in this study.

Toxicokinetics: Plasma levels of E2007 increased in a less-than-linear manner, relative to dose.

Sex	Day	Dose (mg/kg/day)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)
Male	1	1	197.0 ± 90.7	8.00 (2.00 - 24.00)	3463.8 ± 1361.5	4850.9 ± N.C.
	29	1	398.1 ± 120.5	4.00 (2.00 - 4.00)	5416.5 ± 1624.9	
		2	389.0 ± 113.7	4.00 (2.00 - 4.00)	6438.3 ± 1741.1	
	68	1	390.6 ± 108.1	4.00 (2.00 - 4.00)	5444.1 ± 1716.5	
		4	625.8 ± 173.8	8.00 (2.00 - 12.00)	11104.1 ± 4315.4	
	99	8	801.2 ± N.C.	3.00 (2.00 - 4.00)	11952.3 ± N.C.	
	106	8	834.7 ± N.C.	4.00 (4.00 - 4.00)	14864.8 ± N.C.	
	378	1	415.6 ± 88.2	2.00 (1.00 - 4.00)	6286.8 ± 1619.6	
		8	844.5 ± 321.4	4.00 (2.00 - 4.00)	13141.1 ± 4654.9	
Female	1	1	240.4 ± 86.5	6.00 (2.00 - 8.00)	4030.1 ± 1273.8	6204.0 ± 1271.4
	29	1	343.0 ± 120.8	4.00 (2.00 - 4.00)	4117.9 ± 1155.8	
		2	456.4 ± 256.7	4.00 (2.00 - 4.00)	5770.3 ± 2840.5	
	68	1	333.8 ± 111.0	3.00 (2.00 - 4.00)	4016.5 ± 1007.0	
		4	649.2 ± 145.3	4.00 (2.00 - 4.00)	8865.7 ± 2083.9	
	99	8	872.0 ± N.C.	3.00 (2.00 - 4.00)	13515.9 ± N.C.	
	106	8	582.3 ± N.C.	3.00 (2.00 - 4.00)	9216.3 ± N.C.	
	378	1	435.4 ± 153.9	2.00 (1.00 - 2.00)	5821.5 ± 2542.8	
		8	808.5 ± 257.8	2.00 (2.00 - 2.00)	9549.3 ± 2615.4	

C_{max}, AUC_{0-24h}, and AUC_{0-inf} values represent the mean ± SD , t_{max} values represent the median and range.
N.C.: Not calculated

Study title: E2007: A 52-week Oral Toxicity Study in Monkeys

Study no.:	SBL-47-61
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6/26/2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 11070303, Purity 99.6%

Key Study Findings

- **The NOAEL in this study was 0.1 mg/kg. Ataxic gait was observed at higher doses.**

Methods

Doses:	0.1 (LD), 0.3 (MD), 0.6 (HD) mg/kg
Frequency of dosing:	Once daily for 52 weeks
Route of administration:	Oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	4
Age:	3 to 5 years
Weight:	M= 3.21-4.99 kg; F= 2.26-2.97 kg
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Dosing Solution Analysis: Formulations were within ± 5% of their respective nominal concentrations.

Mortality & Clinical Signs: There were no test article-related deaths in this study. There were no test article-related clinical signs in LD animals. Ataxic gait was frequently observed in one MDM and sporadically in other MD animals. All HDM and HDF exhibited ataxic gait for up to 3-5 hours after dosing.

Body Weights & Food Consumption: There were no test article-related effects on absolute BW, relative to control, or food consumption.

Ophthalmoscopy: There were no test article-related findings in the gross ophthalmologic, slit-lamp, or funduscopic examinations when performed during Week 51 of the study.

ECG: When assessed during Week 52 of the study, there were no test article-related findings in heart rate, PR Interval, QRS interval, QT interval, or QTc interval (method of correction not provided).

Hematology & Clinical Chemistry: Blood was collected for hematology and clinical chemistry assessment during Weeks 13 and 52 of the study. There were no test article-related effects observed.

Urinalysis: There were no test article-related findings when urinalysis was performed during Weeks 13 or 52.

Gross Pathology & Organ Weights: There were no test article-related findings.

Histopathology: Adequate Battery: No, nasal cavities/turbinates not examined; Peer Review: No; Signed and Dated Pathology Report: Yes.

Chronic inflammation of the stomach associated with H. pylori infection was observed in all dose groups (M= 1, 1, 1, 2; F= 2, 4, 2, 1; C, LD, MD, HD, respectively). There were no test article-related findings.

Toxicokinetics: The T_{max} for E2007 was between 1 and 4 hours after dosing (Sponsor's table, below).

Summary Table 1 Pharmacokinetic parameters (mean ± SD) of E2007 on Days 1, 91 and 364

Dose (mg/kg/day)	Sex	Day	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ ($AUC_{0\text{-}inf}$) * (ng·hr/mL)
0.1	Male	1	25.91 ± 2.33	291.76 ± 57.96 (363.38 ± 98.36)
		91	32.93 ± 8.23	347.49 ± 86.74
		364	43.42 ± 6.74	446.90 ± 93.71
	Female	1	35.30 ± 8.80	347.21 ± 44.46 (411.32 ± 31.89)
		91	46.01 ± 5.20	459.53 ± 74.80
		364	41.10 ± 3.17	429.02 ± 16.37
0.3	Male	1	71.71 ± 10.27	1044.28 ± 168.40 (1839.76 ± 799.67)
		91	113.24 ± 41.44	1510.95 ± 568.62
		364	171.15 ± 75.84	2431.45 ± 1614.49
	Female	1	112.10 ± 48.42	1250.95 ± 372.33 (1618.75 ± 495.80)
		91	115.77 ± 27.49	1592.92 ± 506.05
		364	123.10 ± 21.28	1493.42 ± 427.74
0.6	Male	1	112.81 ± 33.54	1508.07 ± 275.85 (2959.52 ± 2501.95)
		91	210.86 ± 47.77	2514.39 ± 1080.89
		364	235.02 ± 51.88	2777.50 ± 1190.38
	Female	1	150.22 ± 40.99	1986.29 ± 659.88 (2781.54 ± 1379.11)
		91	169.33 ± 48.21	2185.25 ± 727.18
		364	244.19 ± 30.71	3072.93 ± 1093.33

*: Values inside the parentheses on Day 1 represent $AUC_{0\text{-}inf}$ extrapolated.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

7.1.1

Study title: E2007 and (b) (4) Preliminary Reverse Mutation Assay in Bacteria

Study no.:	S00604
Study report location:	EDR
Conducting laboratory and location:	Eisai Co, Ltd.; Gifu, Japan
Date of study initiation:	4/24/2000
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	E2007, Lot 05995-99Z281, purity unknown (b) (4) Lot 08213-99Z063-2, purity unknown

Key Study Findings

- **E2007 & (b) (4) were negative in a preliminary bacterial reverse mutation assay. (b) (4) is another AMPA receptor antagonist (b) (4)**

Methods

Strains:	TA100 and TA98
Concentrations of test article:	0,156, 313, 625, 1250, 2500, 5000 µg/plate
Negative control/ Vehicle:	DMSO, concentration not provided
Positive control:	None
Incubation & sampling time:	Test article were incubated in the presence or absence of rat S9 hepatic fraction.

Results and Study Validity: When incubated in the presence or absence of rat hepatic S9, E2007 and (b) (4) showed no mutagenic effect on TA100 and TA98 strains.

Test articles	Dose (µg/plate)	No. of revertants per plate TA100 -S9	TA100 +S9	TA98 -S9	TA98 +S9
Negative control	0	122 122 111	132 128 117	17 20 28	38 34 38
	(Mean)	(118)	(126)	(22)	(37)
ER-155055	156	126 P	123	25 P	29
	313	116 P	129	18 P	37
	625	143 P	120 P	17 P	25 P
	1250	99 P	139 P	18 P	34 P
	2500	115 P	135 P	20 P	35 P
	5000	103 P	145 P	15 P	33 P
(b) (4)					

P : Precipitation

7.1.2.

Study title: E2007: Reverse Mutation Assay in Bacteria

Study no.:	S00612
Study report location:	EDR
Conducting laboratory and location:	Eisai Co., Ltd; Gifu, Japan
Date of study initiation:	10/13/2000
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 10091905, Purity 99.5%

Key Study Findings

- **E2007 was not genotoxic in the bacterial reverse mutation assay.**

Methods

Strains:	S. typhimurium TA100, TA1535, TA98, TA1537 & E. coli WP2 uvrA(PKM101)
Concentrations in definitive study:	0, 313, 625, 1250, 2500, 5000 µg/plate
Basis of concentration selection:	A range-finding test using 156 to 5000 µg/plate of E2007 was performed. See below for details.
Negative control:	DMSO, final concentration in assay not stated.
Positive control:	A) Absence of Rat Hepatic S9: TA100, TA98, WP2: 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF2) TA1535: Sodium azide (SA) TA1537: 9-aminoacridine HCL (9AA) B) Presence of Rat Hepatic S9: All strains: 2-aminoanthracene (2AA)
Formulation/Vehicle:	DMSO, final concentration in assay not stated.
Incubation & sampling time:	Bacterial cultures were preincubated for 20 minutes at 37°C before plating. Three plates per concentration level were prepared. Plates were incubated for 48 hours at 37°C before reading.

Study Validity & Results

In the dose range-finding study, precipitate was observed at all concentrations (≥156 µg/plate) in the absence of metabolic activation and at concentrations >625 µg/plate in the presence of metabolic activation (Sponsor's Table 1, below). Precipitation of the test article was also observed in all dose levels in the absence of S9 and at most of the doses in the presence of S9 in the main study. Although it does not seem that the Sponsor attempted to solve the precipitation of the test article, the Sponsor does not state that the precipitation interfered with scoring and did not result in a toxicity that limited the evaluation of the assay. Therefore, according to "ICH S2A (R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use, June 2012", the issue of precipitated test article does not invalidate this assay. There was no

concentration-related decrease in the number of revertants observed in strains TA100, TA1535, or TA98. However, the number of revertants in the strains TA1537 and WP2 was generally decreased, relative to the negative control, at all concentrations of E2007 in the range-finding study; however, this decrease did not occur in a concentration-related manner. This finding was not recapitulated in the main study. Overall, the concentration range used in the main study appeared to be appropriate. There was no concentration-related increase in the number of revertants in any of the strains tested in the range-finding or main studies, thus demonstrating that E2007 is not genotoxic in the bacterial reverse mutation assay. In this study, the Sponsor used an appropriate concentration range, a full panel of Salmonella and E.coli strains, adequate positive controls, and acceptable incubation and sampling methods. Therefore, this study is valid.

Table 1 Summary of Range-finding Test

		No. of revertants (mean ± S.D. for 3 plates)				
Without metabolic activation						
	Dose (μg/plate)	TA100	TA1535	TA98	TA1537	WP2 *uvrA* (pKM101)
Control	0	111 ± 10.8	11 ± 1.5	17 ± 3.0	9 ± 5.6	120 ± 3.8
E2007	156	111 ± 4.6 P	12 ± 5.1 P	14 ± 1.5 P	6 ± 0.6 P	98 ± 14.0 P
	313	107 ± 12.1 P	10 ± 2.9 P	21 ± 4.6 P	8 ± 0.6 P	82 ± 3.2 P
	625	108 ± 6.0 P	11 ± 2.3 P	20 ± 3.0 P	8 ± 1.2 P	96 ± 7.2 P
	1250	98 ± 11.7 P	10 ± 1.5 P	22 ± 3.0 P	6 ± 1.5 P	92 ± 5.0 P
	2500	110 ± 7.2 P	11 ± 5.5 P	20 ± 2.9 P	6 ± 1.7 P	108 ± 13.6 P
	5000	107 ± 7.6 P	9 ± 1.5 P	19 ± 1.7 P	5 ± 1.5 P	101 ± 6.7 P
AF2	0.005	NT	NT	NT	NT	1013 ± 23.9
	0.01	457 ± 66.7	NT	NT	NT	NT
	0.1	NT	NT	694 ± 28.6	NT	NT
9AA	80	NT	NT	NT	429 ± 132.7	NT
SA	0.5	NT	477 ± 41.7	NT	NT	NT

With metabolic activation

	Dose (μg/plate)	TA100	TA1535	TA98	TA1537	WP2 *uvrA* (pKM101)
Control	0	111 ± 8.4	10 ± 3.6	34 ± 2.1	13 ± 1.5	145 ± 8.4
E2007	156	118 ± 18.7	11 ± 2.6	34 ± 10.5	9 ± 1.0	134 ± 24.8
	313	116 ± 9.2	13 ± 2.1	26 ± 6.8	7 ± 3.1	164 ± 15.6
	625	116 ± 5.3	12 ± 3.1	33 ± 8.5	9 ± 2.9	142 ± 11.8
	1250	119 ± 14.0 [P]	10 ± 5.6 [P]	30 ± 2.1 [P]	10 ± 7.5 [P]	130 ± 20.0 [P]
	2500	126 ± 3.8 [P]	11 ± 6.4 [P]	27 ± 4.2 [P]	5 ± 2.6 [P]	140 ± 8.7 [P]
	5000	116 ± 15.3 [P]	10 ± 3.0 [P]	25 ± 4.0 [P]	11 ± 3.1 [P]	134 ± 2.0 [P]
2AA	0.5	NT	NT	561 ± 14.2	NT	NT
	1	1288 ± 202.2	NT	NT	NT	NT
	2	NT	259 ± 3.5	NT	248 ± 4.4	1481 ± 23.5

S.D.: Standard deviation, NT: Not tested, [P]: Precipitation,
AF2: 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, 9AA: 9-aminoacridine hydrochloride,
SA: sodium azide, 2AA: 2-aminoanthracene.

Table 2 Summary of Main Test

		No. of revertants (mean ± S.D. for 3 plates)				
Without metabolic activation						
	Dose (μg/plate)	TA100	TA1535	TA98	TA1537	WP2 *uvrA* (pKM101)
Control	0	116 ± 8.1	9 ± 1.7	23 ± 6.1	9 ± 2.5	116 ± 11.2
E2007	313	106 ± 5.5 [P]	10 ± 1.5 [P]	16 ± 1.7 [P]	7 ± 1.5 [P]	93 ± 16.7 [P]
	625	116 ± 12.4 [P]	7 ± 3.1 [P]	15 ± 2.9 [P]	11 ± 0.6 [P]	95 ± 5.7 [P]
	1250	108 ± 9.0 [P]	11 ± 4.6 [P]	16 ± 4.2 [P]	13 ± 2.0 [P]	113 ± 10.6 [P]
	2500	113 ± 6.8 [P]	7 ± 1.5 [P]	13 ± 1.2 [P]	8 ± 1.7 [P]	111 ± 9.0 [P]
	5000	114 ± 7.5 [P]	8 ± 1.7 [P]	14 ± 2.1 [P]	7 ± 1.2 [P]	94 ± 6.7 [P]
AF2	0.005	NT	NT	NT	NT	1022 ± 57.8
	0.01	479 ± 6.7	NT	NT	NT	NT
	0.1	NT	NT	743 ± 45.0	NT	NT
9AA	80	NT	NT	NT	365 ± 34.1	NT
SA	0.5	NT	502 ± 29.7	NT	NT	NT
With metabolic activation						
	Dose (μg/plate)	TA100	TA1535	TA98	TA1537	WP2 *uvrA* (pKM101)
Control	0	126 ± 18.0	15 ± 0.6	21 ± 5.0	7 ± 1.5	143 ± 9.5
E2007	313	128 ± 2.6	11 ± 5.7	32 ± 5.9	11 ± 3.1	151 ± 2.0
	625	124 ± 17.0	10 ± 4.2	25 ± 3.1	9 ± 1.0	142 ± 9.5
	1250	124 ± 3.8 [P]	8 ± 0.6 [P]	30 ± 8.7 [P]	9 ± 5.5 [P]	150 ± 7.2 [P]
	2500	121 ± 15.0 [P]	7 ± 2.0 [P]	25 ± 8.5 [P]	10 ± 2.5 [P]	151 ± 18.9 [P]
	5000	134 ± 10.0 [P]	8 ± 1.5 [P]	25 ± 9.0 [P]	6 ± 3.6 [P]	133 ± 13.2 [P]
2AA	0.5	NT	NT	552 ± 37.0	NT	NT
	1	1576 ± 60.5	NT	NT	NT	NT
	2	NT	247 ± 35.9	NT	199 ± 9.6	1532 ± 90.9

S.D.: Standard deviation, NT: Not tested, [P]: Precipitation,
AF2: 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, 9AA: 9-aminoacridine hydrochloride,
SA: sodium azide, 2AA: 2-aminoanthracene.

7.1.3

Study title: Mutagenicity Study of (b) (4) with the Bacterial Reverse Mutation Assay

Study no.:	12546
Study report location:	EDR (4/11/12 submission)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/7/2007
GLP compliance:	No GLP compliance statement provided
QA statement:	QA statement provided
Drug, lot #, and % purity:	Impurity VI: (b) (4) Lot 17YP0201, Purity 101%

Key Study Findings

- **Impurity VI was genotoxic in the bacterial reverse mutation assay, with an increase in the number of revertants observed in TA100, TA98, and WP2uvrA.**

Methods

Strains:	S. typhimurium TA100, TA1535, TA98, TA1537 & E. coli WP2 uvrA
Concentrations in definitive study:	See below
Positive control:	In the presence or absence of rat hepatic S9 fraction, see table below.
Vehicle & Negative control	DMSO, concentration not disclosed
Incubation & sampling time:	Bacterial cultures were preincubated for 20 minutes at 37°C before plating. Plates were incubated for 48 hours at 37°C before reading.

(2) Positive controls

Strain	Without S9(μg/plate)		With S9(μg/plate)	
TA100	AF-2	(0.01)	B[a]P	(5.0)
TA1535	NaN_3	(0.5)	2AA	(2.0)
WP2 *uvrA*	AF-2	(0.01)	2AA	(10.0)
TA98	AF-2	(0.1)	B[a]P	(5.0)
TA1537	ICR-191	(1.0)	B[a]P	(5.0)

AF-2= 2-(2-furayl)-3-(5-nitro-2-furyl)acrylamide; NaN_3= sodium azide; ICR-191= 2-methoxy-6-chloro-9-[3-(2-chloroethyl)aminopropylamino]acridine; 2AA= 2-amino Anthracene; B[a]P= Benzo[a]pyrene

Study Results

The number of revertants in the absence of S9 fraction was increased by at least 2-fold, relative to control, in TA100 at ≥ 1250 μg/plate, in WP2uvrA at ≥ 625 μg/plate and in TA98 at 2500 μg/plate. In the presence of S9 fraction, the number of revertants was increased by at least 2-fold, relative to control, in TA100 at 2500 μg/plate, in WP2uvrA at ≥ 625 μg/plate and in TA98 at ≥ 1250 μg/plate. 5000 μg/plate was considered toxic to all strains, in the presence and absence of S9 fraction.

Table of Main Test Results

Name of test substance [redacted] (b) (4)

No.12546

A term of test	November 13, 2007 - November 16, 2007					
With or without S9mix	Dose of test substance (μg/plate)	Number of revertant colonies/plate				
		Base-pair substitution type			Frame-shift type	
		TA100	TA1535	WP2*uvrA*	TA98	TA1537
−S9mix	Solvent Control (DMSO)	93 94 (94)	12 17 (15)	22 18 (20)	20 18 (19)	18 11 (15)
	156	126 96 (111)	12 10 (11)	NT	21 16 (19)	13 14 (14)
	313	89 111 (100)	6 9 (8)	31 20 (26)	24 16 (20)	14 13 (14)
	625	115 141 (128)	11 7 (9)	52 51 (52)	20 27 (24)	8 6 (7)
	1250	194 185 (190)	8 8 (8)	102 83 (93)	37 27 (32)	17 13 (15)
	2500	290 287 (289)	11 7 (9)	173 180 (177)	63 57 (60)	12 9 (11)
	5000	0* 0*(0)*	6* 2*(4)*	180 145 (163)	32* 33*(33)*	9* 7*(8)*
+S9mix	Solvent Control (DMSO)	125 102 (114)	8 10 (9)	19 20 (20)	20 28 (24)	26 22 (24)
	78	NT	NT	30 23 (27)	NT	NT
	156	113 95 (104)	10 12 (11)	29 18 (24)	24 28 (26)	28 26 (27)
	313	109 92 (101)	11 6 (9)	36 50 (43)	33 33 (33)	32 22 (27)
	625	145 147 (146)	11 10 (11)	70 60 (65)	35 28 (32)	38 20 (29)
	1250	155 185 (170)	10 9 (10)	123 101 (112)	41 51 (46)	32 32 (32)
	2500	253 256 (255)	7 4 (6)	170 166 (168)	46 55 (51)	24 16 (20)
	5000	0* 0*(0)*	4* 7*(6)*	130 135 (133)	26* 19*(23)*	7* 3*(5)*
Positive control not requiring S9mix	Name	AF-2	NaN_3	AF-2	AF-2	ICR-191
	Dose (μg/plate)	0.01	0.5	0.01	0.1	1.0
	Number of colonies/plate	569 521 (545)	549 551 (550)	138 119 (129)	611 572 (592)	2415 2125 (2270)
Positive control requiring S9mix	Name	B[a]P	2AA	2AA	B[a]P	B[a]P
	Dose (μg/plate)	5.0	2.0	10.0	5.0	5.0
	Number of colonies/plate	856 767 (812)	304 298 (301)	307 291 (299)	217 206 (212)	84 99 (92)

AF-2 : 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
NaN_3 : Sodium azide
ICR-191 : 2-Methoxy-6-chloro-9-[3-(2-chloroethyl)aminopropylamino]acridine·2HCl
2AA : 2-Aminoanthracene
B[a]P : Benzo[a]pyrene

Notes
* : The growth inhibition of the tested bacterium by the test substance was observed.
NT : Not tested
The average number of colonies of two plates at each concentration is shown in the ( ).

7.2 *In Vitro* Assays in Mammalian Cells

Study title: E2007: Mouse Lymphoma TK Assay

Study no.:	S00613
Study report location:	EDR
Conducting laboratory and location:	Eisai Co., Ltd.; Gifu, Japan
Date of study initiation:	10/20/2000
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 10091905, Purity 99.5%

Key Study Findings

- **E2007 was not genotoxic in the mouse lymphoma *tk* assay.**

Methods

Cell line:	Mouse lymphoma L5178Y $TK^{+/-}$ cells
Concentrations in definitive study:	See below
Basis of concentration selection:	Precipitate was observed at ≥ 100 µg/ml and was, therefore, chosen as the highest dose in the cytotoxicity and main studies.
Negative control & Vehicle:	1% DMSO in 3 hour incubation study; 0.5% DMSO in 24 hour incubation study
Positive control:	In absence of rat hepatic S9: methyl methanesulfonate (MMS) In presence of rat hepatic S9: Cyclophosphamide monohydrate (CP)
Incubation & sampling time:	In the 3- and 24-hour incubation study, cells were incubated in suspension with the test article at 37°C and then plated. Plating efficiency was determined after a 2-day incubation period. The number of large and small colonies was determined in this study.

Study Design

Method	S9 mix	Compound	Treatment concentrations (µg/mL)
Short treatment method for 3 hours	with S9 mix	Control E2007 CP	0 12.5, 25, 50, 100 2
	without S9 mix	Control E2007 MMS	0 12.5, 25, 50, 100 20
Continuous treatment method for 24 hours	without S9 mix	Control E2007 MMS	0 10, 20, 40, 50, 60, 70, 80 5

Study Validity and Results

Precipitation was observed in both the 3- and 24-hour treatment studies at concentrations ≥ 100 µg/ml. A 49% reduction in cell survival was observed at 100 µg/ml after 3 hours of incubation with the test article in the presence of S9 and at 25 µg/ml

after 24 hours of incubation with the test article in the absence of S9 (Sponsor's Table 1, below). Cell survival was reduced by 17% after a 3-hour incubation with test article in the absence of S9 fraction (Sponsor's Table 1, below). Since the plating method was applied in this study, the appropriate global evaluation factor (GEF) to be applied is 90 [4]. The mutation frequency for all concentration levels and incubation conditions did not exceed the GEF-adjusted control values (Sponsor's Table 2). Therefore, E2007 was not genotoxic in this assay. The positive controls (CP and MMS) markedly increased the mutation frequency under all incubation conditions (Sponsor's Table 2).

Table 1 Raw Counts and Relative Survival for Cytotoxicity Test

Short treatment method for 3 hours with S9 mix

Compound	Concentration (μg/mL)	Cell counts ($\times 10^5$cells/mL)	PW (Day 0)	PE0 (%)	%RS (Day 0)
Control	0	11.14	80	112	100
E2007	3.13	11.06	70	82	73
	6.25	11.83	65	71	67
	12.5	11.40	64	69	63
	25	11.71	70	82	77
	50	11.46	63	67	62
	100[P]	11.01	58	58	51
	200[P]	NM	NM	NM	NM

Short treatment method for 3 hours without S9 mix

Compound	Concentration (μg/mL)	Cell counts ($\times 10^5$cells/mL)	PW (Day 0)	PE0 (%)	%RS (Day 0)
Control	0	11.40	73	89	100
E2007	3.13	12.22	67	75	90
	6.25	11.59	77	101	115
	12.5	10.41	79	108	111
	25	11.13	70	82	90
	50	10.06	74	92	91
	100[P]	9.159	74	92	83
	200[P]	NM	NM	NM	NM

Continuous treatment method for 24 hours without S9 mix

Compound	Concentration (μg/mL)	Cell counts ($\times 10^5$cells/mL)	PW (Day 0)	PE0 (%)	%RS (Day 0)
Control	0	9.556	73	89	100
E2007	3.13	8.687	72	87	89
	6.25	8.063	75	95	90
	12.5	6.626	80	112	87
	25	4.442	76	98	51
	50	2.042	79	108	26
	100[P]	0.143	NM	NM	NM
	200[P]	NM	NM	NM	NM

Cell counts = Post-treatment cell concentration.
PW = Positive wells (wells with colonies)/96 wells/plate.
PE0 = Plating efficiency (Day 0); %RS = % Relative survival.
[P] = Precipitate; NM = Not measured.

Table 2 Summary of Mutagenicity Test

Short treatment method for 3 hours with S9 mix

Compound	Concentration (μg/mL)	%RS (Day 0)	RTG	MF ($\times 10^{-6}$cells)	% of SC
Control	0	100	100	143	27
E2007	12.5	97	90	110	27
	25	72	90	100	22
	50	86	76	113	20
	100[P]	69	67	135	21
CP	2	29	19	1266	33

Short treatment method for 3 hours without S9 mix

Compound	Concentration (μg/mL)	%RS (Day 0)	RTG	MF ($\times 10^{-6}$cells)	% of SC
Control	0	100	100	83	22
E2007	12.5	70	88	92	30
	25	89	84	109	23
	50	87	90	100	21
	100[P]	53	61	114	25
MMS	20	64	48	924	33

Continuous treatment method for 24 hours without S9 mix

Compound	Concentration (μg/mL)	%RS (Day 0)	RTG	MF ($\times 10^{-6}$cells)	% of SC
Control	0	100	100	95	20
E2007	10	78	91	85	18
	20	66	71	70	24
	40	35	36	85	21
	50	37	23	102	15
	60	30	24	103	18
	70^{P}	18	17	99	21
	80^{P}	NM	NM	NM	NM
MMS	5	64	70	477	28

%RS = % Relative survival; RTG = Relative total growth; MF = Mutant frequency.
% of SC = % of small colony; CP = Cyclophosphamide monohydrate.
MMS = Methyl methanesulfonate; ^{P} = Precipitate; NM = Not measured.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: E2007: Micronucleus Assay in Rats Following Oral Administration

Study no: S01620
Study report location: EDR
Conducting laboratory and location: Eisai Co., Ltd.; Gifu, Japan
Date of study initiation: 11/15/2001
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: E2007, Lot 10092507, Purity 99.6%

Key Study Findings

- **E2007 was not genotoxic in the *in vivo* micronucleus assay performed in rats dosed with up to 2000 mg/kg.**

Methods

Doses in definitive study: See below
Frequency & Route of dosing: Single dose by oral gavage; animals were euthanized either 24 or 48 hours after dosing.
Dose volume: 20 ml/kg for vehicle & E2007; 10 mg/kg for CP
Formulation/Vehicle: 0.5% methylcellulose
Species/Strain: Sprague-Dawley Rat (Crj:CD(SD)IGS)
Number/Sex/Group: 5 males/group
Basis of dose selection: In Study TKB00005, abnormal clinical signs, but no deaths, were observed at 1000 mg/kg. Therefore, the limit dose of 2000 mg/kg was selected as the high dose.
Negative control: 0.5% methylcellulose
Positive control: Cyclophosphamide (10 mg/kg)

Study Design

Dose Group (mg/kg)		Concentration (%)	Sampling Time (hours)	Number of Male Animals	Animal Number
Control[a]		0	24	5	001-005
			48	5	031-035
E2007[b]	100	0.5	24	5	006-010
			48	5	036-040
	300	1.5	24	5	011-015
			48	5	041-045
	1000	5	24	5	016-020
			48	5	046-050
	2000	10	24	5	021-025
			48	5	051-055
CP[c]	10	0.1	24	5	026-030

[a]Negative control (vehicle), [b]Test article, [c]Positive control article.

Study Validity & Results

There were no deaths in any of the E2007 dose groups, but abnormal gait, decreased activity, and mydriasis were observed in all E2007 dose groups at one hour after dosing. At 24 hours after dosing, decreased activity and abnormal gait were observed in rats dosed with ≥ 1000 mg/kg; similar clinical signs were limited to 1/5 and 2/5 animals in the 1000 and 2000 mg/kg dose groups, 48 hours after dosing. Body weights, relative to the predosing values, were decreased by 3.5%, 7.2%, and 8.8% at 24 hours after dosing in rats dosed with 300, 1000, or 2000 mg/kg, respectively, and 2.5% and 9.0% at 48 hours after dosing in rats dosed with 1000 and 2000 mg/kg, respectively. There was no dose-related increase in the number of micronucleated PCEs at 24 or 48 hours after dosing with E2007. The positive control did increase the number of micronucleated PCEs. Overall, E2007 was not genotoxic in this study.

Table 4 Micronucleus Observation of Male Rats

Sampling time: 24 hours

Compound	Animal No.	No. of MNPCE (/2000 PCE)	MNPCE (%)	No. of PCE (/200 E)	PCE (%)
Control	001	3	0.15	116	58.0
	002	2	0.10	104	52.0
	003	8	0.40	112	56.0
	004	0	0.00	131	65.5
	005	4	0.20	99	49.5
	Mean		0.17		56.2 #
E2007	006	5	0.25	117	58.5
100 mg/kg	007	2	0.10	124	62.0
	008	1	0.05	157	78.5
	009	4	0.20	116	58.0
	010	4	0.20	134	67.0
	Mean		0.16		64.8
E2007	011	3	0.15	114	57.0
300 mg/kg	012	2	0.10	134	67.0
	013	2	0.10	87	43.5
	014	4	0.20	103	51.5
	015	4	0.20	148	74.0
	Mean		0.15		58.6
E2007	016	1	0.05	28	14.0
1000 mg/kg	017	0	0.00	54	27.0
	018	2	0.10	137	68.5
	019	6	0.30	115	57.5
	020	1	0.05	143	71.5
	Mean		0.10		47.7
E2007	021	1	0.05	58	29.0
2000 mg/kg	022	2	0.10	43	21.5
	023	3	0.15	80	40.0
	024	4	0.20	88	44.0
	025	1	0.05	35	17.5
	Mean		0.11		30.4 *
CP	026	34	1.70	74	37.0
10 mg/kg	027	36	1.80	116	58.0
	028	32	1.60	111	55.5
	029	14	0.70	86	43.0
	030	24	1.20	114	57.0
	Mean		1.40		50.1

Sampling time: 48 hours

Compound	Animal No.	No. of MNPCE (/2000 PCE)	MNPCE (%)	No. of PCE (/200 E)	PCE (%)
Control	031	4	0.20	129	64.5
	032	4	0.20	127	63.5
	033	6	0.30	103	51.5
	034	4	0.20	108	54.0
	035	4	0.20	134	67.0
	Mean		0.22		60.1
E2007	036	0	0.00	114	57.0
100 mg/kg	037	4	0.20	104	52.0
	038	2	0.10	132	66.0
	039	5	0.25	111	55.5
	040	2	0.10	150	75.0
	Mean		0.13		61.1
E2007	041	0	0.00	66	33.0
300 mg/kg	042	2	0.10	123	61.5
	043	3	0.15	143	71.5
	044	3	0.15	106	53.0
	045	2	0.10	135	67.5
	Mean		0.10		57.3
E2007	046	3	0.15	110	55.0
1000 mg/kg	047	2	0.10	93	46.5
	048	3	0.15	103	51.5
	049	4	0.20	161	80.5
	050	2	0.10	107	53.5
	Mean		0.14		57.4
E2007	051	2	0.10	140	70.0
2000 mg/kg	052	2	0.10	63	31.5
	053	1	0.05	107	53.5
	054	1	0.05	104	52.0
	055	2	0.10	91	45.5
	Mean		0.08		50.5

MNPCE = micronucleated polychromatic erythrocytes; PCE = polychromatic erythrocytes.
E = erythrocytes.
CP = cyclophosphamide.
Significant difference compared to control, *P<0.05 (Steel's test, two-sided).
Significant trend, #P<0.05 (Jonckheere's test, one-sided).

8 Carcinogenicity

8.1 Mouse

Study title: E2007: A 24-Month Oral Carcinogenicity Study in mice

Study no.:	B-4955
Study report location:	EDR
Conducting laboratory:	(b) (4)
Date of study initiation:	3/5/2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, 13022002, Purity 100%
ExecCAC concurrence:	No. The ExecCAC communicated the following to the Sponsor in the response to the SPA submitted on 11/6/2003: *"The Committee did not concur with the doses proposed for both male and female mice. This decision was based on the observation that deaths occurred in males and females at doses used in the 13-week study. The 4-week study was considered inadequate to support dose-selection because of the short duration of the study. The Committee recommended that the sponsor conduct a 13-week study (to include histopathology and toxicokinetic evaluation) using lower doses in order to identify an MTD for the 2-year study."*

Key Study Findings

- **There was no evidence in this study to suggest that E2007 is carcinogenic.**
- **Due to excessive mortality, dosing was stopped at Week 87 and 85 in males receiving 10 and 30 mg/kg, respectively, and on Week 92 in females dosed with 30 mg/kg. Dosing for remaining females was stopped between Weeks 101 and 103.**
- **The increased mortality rate observed at ≥ 3 mg/kg was associated with self-injury secondary to excessive grooming.**
- **The major cause of death in males was trauma-related urogenital tract lesion. Bladder distension and uroschesis were observed in many of the males exhibiting urogenital tract lesions.**
- **The HD was excessive, as evidenced by extensive mortality in HDM and HDF. However, approximately 50% of the animals in each of the lower dose groups survived to 18 months of dosing.**

Methods

Doses:	0, 1 (LD), 3 (MD1), 10 (MD2), 30 (HD) mg/kg/day
Frequency of dosing:	Once daily; dosing duration varied, see table below
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose

Basis of dose selection:	Death secondary to skin excoriation resulting from excessive grooming occurred in mice dosed with 60 mg/kg for 4 weeks (Study B5121). The next lowest dose was 30 mg/kg in this study. Deaths were observed in mice dosed with > 100 mg/kg (the lowest dose) in the 13-week study (Study B4954). Based on these studies, the MTD was considered to be 30 mg/kg and was chosen as the HD for this study.
Species/Strain:	ICR Mice (Crlj:CD-1(ICR)) ; (b) (4)
Number/Sex/Group:	60/sex/group
Age:	6 weeks at dosing initiation
Animal housing:	Individual housing
Paradigm for dietary restriction:	Food and water *ad libitum*
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	10/sex/group for TK assessment.
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Dosing Solution Analysis: Dosing formulations were within ± 5% of the nominal concentration.

Study Design: Due to mortality in the higher dose groups, the duration of dosing varied by dose group, but all dose groups were euthanized during either Week 103 or 104 (see sponsor's table, below).

Dosing period and study period in each group

Dose (mg/kg/day)	Sex	Dosing Period (week)	Study Period (week)
0 (Control)	Male	104	104
	Female	103	103
1	Male	104	104
	Female	103	103
3	Male	104	104
	Female	101	103
10	Male	87	104
	Female	101	103
30	Male	85	104
	Female	92	103

Mortality: Due to excessive mortality, dosing was discontinued in MD2 and HD males after Week 87 and 85, respectively. Dosing was discontinued for the same reason in MD1, MD2, and HD females after Week 101, 101, and 92, respectively. Survival rate at the end of the study was <20% in MD2M, HDM, and HDF (Sponsor's text tables 1 and 2, below).

Text Table 1. Summary of mortality and survival rates

Sex	Male					Female				
Dose (mg/kg)	0	1	3	10	30	0	1	3	10	30
No. of animals used	60	60	60	60	60	60	60	60	60	60
Week of administration										
52	2 [a)]	5	2	13	25	3	1	3	9	6
80	19	23	22	34	47	18	14	23	26	35
90	23	29	33	46	51	30	23	30	33	42
103	37	44	42	51	55	46	39	46	45	49
104	37	44	43	51	55	/	/	/	/	/
Number of survivors	23	16	17	9	5	14	21	14	15	11
Survival rate (%)	38.3$	26.7	28.3	15.0*	8.3*	23.3$	35.0	23.3	25.0	18.3

a): Cumulative number of animals that died (including those sacrificed as moribund).
$: p<0.05 (significant trend of decreasing survival rate, Tarone test)
*: p<0.05 (significantly different from the control group, log-rank test)
/: Not applicable

Text Table 2. Summary of number of survivors and survival rates in Weeks 80 and 90

Sex	Male					Female				
Dose (mg/kg)	0	1	3	10	30	0	1	3	10	30
Week 80	68.3 (41/60)	61.7 (37/60)	63.3 (38/60)	43.3 (26/60)	21.7 (13/60)	70.0 (42/60)	76.7 (46/60)	61.7 (37/60)	56.7 (34/60)	41.7 (25/60)
Week 90	61.7 (37/60)	51.7 (31/60)	45.0 (27/60)	23.3 (14/60)	15.0 (9/60)	50.0 (30/60)	61.7 (37/60)	50.0 (30/60)	45.0 (27/60)	30.0 (18/60)

Number in parentheses: Numerator is the number of animals alive in the given week and denominator is the total number of animals at the initiation of the study.

The main causes of death and euthanasia *in extremis* are provided in Sponsor's Text Table 3, below. The high rate of trauma-related urogenital tract lesion in males is consistent with what was observed in studies of shorter duration and was associated with urinary obstruction in this study and in previous studies. In females, the cause of death was mostly due to trauma-related skin lesions, similar to what was observed in previous studies of shorter duration.

Text Table 3. Summary of presumptive cause of death and moribund sacrifice

Sex	Male					Female				
Dose (mg/kg/day)	0	1	3	10	30	0	1	3	10	30
No. of animals used	60	60	60	60	60	60	60	60	60	60
No. of deaths	37	44	43	51	55	46	39	46	45	49
Neoplastic lesion	5	14	6	3	2	25	23	20	15	13
Non-neoplastic lesion	32	30	37	48	53	21	16	26	30	36
Trauma-related skin lesions with anemia or bacterial infection	8	6	4	8	13	3	7	11	15	15
Trauma-related urogenital tract lesion	10	12	24	38	34	0	0	0	1	0

Number in the table indicates the number of animals.

Clinical Signs: Abnormal gait was observed in all MD2 and HD animals, but incidence and duration decreased over time suggesting the development of tolerance to E2007 (Sponsor's text table 4). A dose-dependent increase in wounding (MD2 and HD) was consistent with what was observed in studies of shorter duration in mice.

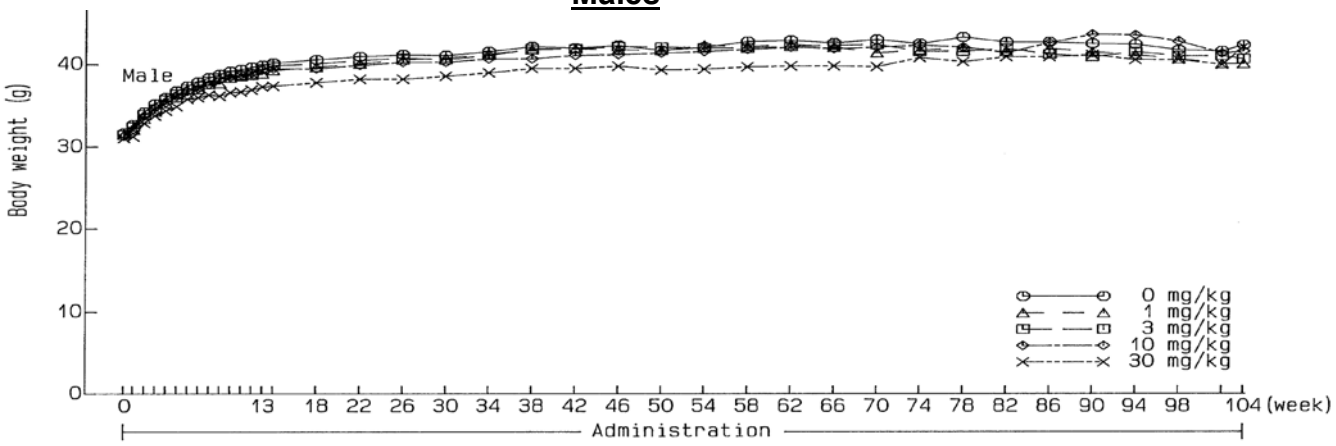
Text Table 4. Summary of major clinical signs

Sex	Male					Female				
Dose (mg/kg/day)	0	1	3	10	30	0	1	3	10	30
No. of animals used	60	60	60	60	60	60	60	60	60	60
Abnormal gait	0	0	0	60	60	0	0	0	60	60
Excoriation	21	17	20	17	24	13	13	16	26	21
Loss, limbs/digit/ skin/muscle	0	0	0	3	8	1	2	2	6	11
Induration, intercarpal joint	0	0	0	3	4	0	0	2	7	4
Wound, penis	7	5	13	13	16	/	/	/	/	/
Distention, abdomen	6	4	7	20	15	7	12	9	4	3

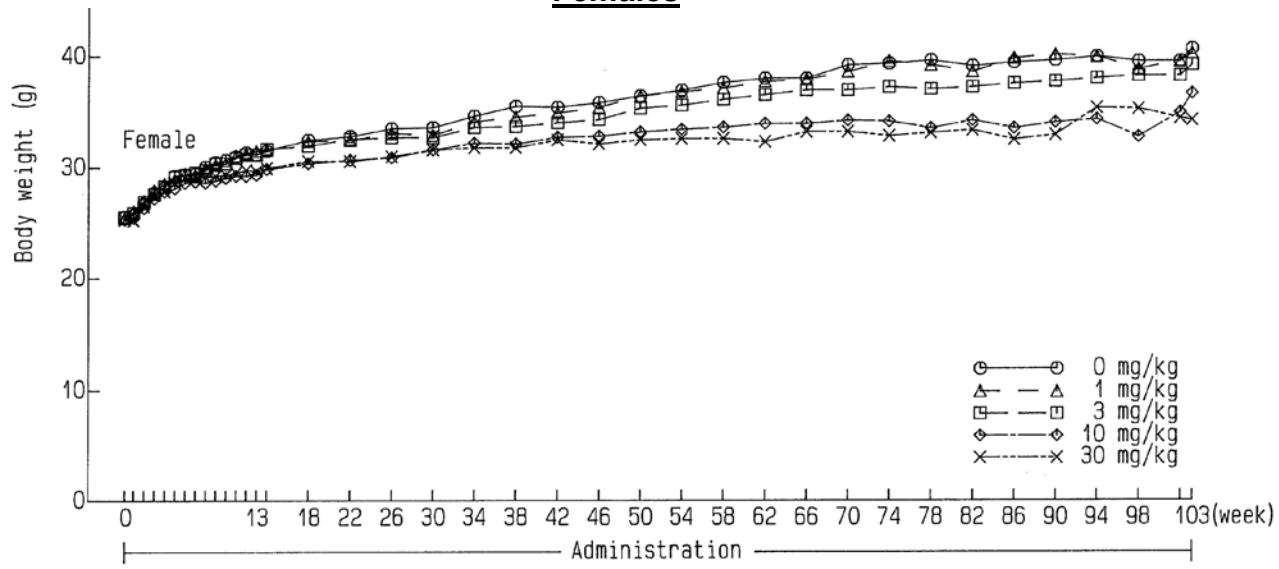
Number in the table indicates the total number of animals with respective findings.
/: Not applicable

Body Weights & Food Consumption: Absolute BW was decreased, relative to controls, from Weeks 13 to 72 in HDM (max -8%) and from Weeks 13 to 103 in MD2F (max -17%) and HDF (max -19%; Sponsor's figures below). Food consumption was increased in MD2M (max +23%) and HDM (max +32%) from Weeks 22 to 98 of dosing. There was no consistent test article-related effect on food consumption in females.

Males



Females



Hematology: Blood samples were collected on the day of euthanasia for hematology assessment. There were no dose-related findings.

Gross Pathology: Induration and loss of limbs in MD2M, HDM, MD1F, MD2F, and HDF were secondary to the excessive grooming (see Sponsor's Text table 6). Although there was a high background level of bladder distention and uroschesis (15 CM), this observation increased in a dose-dependent manner in males only; uroschesis was limited in female mice. The incidence of penis wounding was increased in males dosed with ≥ 3 mg/kg.

Text Table 6. Summary of gross lesions associated with self-trauma

Sex	Male					Female				
Dose (mg/kg/day)	0	1	3	10	30	0	1	3	10	30
No. of animals used	60	60	60	60	60	60	60	60	60	60
Limb lesions										
Induration	0	0	0	3	4	1	0	2	6	4
Loss	0	0	0	1	4	0	1	2	4	5
Penis										
Induration	0	0	2	1	5	/	/	/	/	/
Wound	4	3	8	8	11	/	/	/	/	/
Kidney										
Large	5	3	4	5	10	1	0	2	0	0
Dilatation, pelvic	4	2	7	9	10	0	1	1	3	0
Urinary bladder										
Distention	15	22	33	36	40	1	1	1	2	1
Thymus										
Small	0	0	2	3	6	0	0	1	0	1

Number in the table indicates the total number of animals with respective lesions.
/: Not applicable

Histopathology: Peer Review: Yes; Signed and Dated Pathology Report: Yes

Neoplastic: The incidence of tumors in this study was not test article-related (Sponsor's Table 8-1, below). The ExecCAC agreed that perampanel was not carcinogenic in mice (See Appendix). Although, according to the statistical reviewer, there was a trend for osteoma (p=0.0346; see statistical review) in MD1F (1/60, 1.66%) and MD2F (2/60, 3.3%), the maximum incidence for this finding in the control animal database referenced by the Sponsor in this study report (Giknis MLA and Clifford CB, 2005) is 3.1%. Therefore, the incidence of osteoma in this study was similar to spontaneous rates and is not of toxicological concern. Additionally, when combined with osteosarcoma, the incidence is no longer dose-related. The members of the ExecCAC concurred that the finding of osteoma in female mice was not drug-related.

Non Neoplastic: With the exception of splenic atrophy in males, all non neoplastic findings that increased in a dose-dependent manner were also observed in control animals (Sponsor's text Table 8, below). Keratitis (slight to mild) of the eye increased in a dose-dependent manner in all female dose groups; this finding did occur in males but not in a dose-dependent manner. Self-inflicted wounds secondary to the excessive grooming that occurred in these animals manifested as an increase in the incidence, relative to control, of ulceration of the skin in all female dose groups and ulceration of the penis in all male dose groups. Increased incidence of inflammation of the prostate and seminal vesicles was observed in MD2M and HDM. Increased incidence of dilation of the renal pelvis was observed at ≥ 3 mg/kg; uroschesis and/or bladder distension

were also detected in many of the animals exhibiting dilation of the renal pelvis.

Table 8-1 E2007 : A 24-month oral carcinogenicity study in mice
Histopathological findings - tumor data
Kill type : All

Organs / Findings	Sex:	M	M	M	M	M	F	F	F	F	F
	Dose(mg/kg):	0	1	3	10	30	0	1	3	10	30
	Number:	60	60	60	60	60	60	60	60	60	60
Adrenal											
Number examined		60	59	60	60	58	60	60	60	59	59
ADENOMA,SUBCAPSULAR CELL		0	0	0	0	0	0	0	0	1	0
ADENOMA,CORTICAL CELL		0	1	0	1	0	0	0	0	0	0
PHEOCHROMOCYTOMA		0	0	0	1	0	0	2	2	0	0
CARCINOMA,SUBCAPSULAR CELL		0	0	0	0	0	1	0	0	0	0
PHEOCHROMOCYTOMA,MALIGNANT		0	0	0	0	0	0	1	0	0	0
Bone+Bone marrow,femoral											
Number examined		60	60	60	60	58	60	60	60	59	59
OSTEOMA		0	0	0	0	0	0	0	0	1	0
Cerebrum											
Number examined		60	60	60	60	58	60	60	60	59	59
ASTROCYTOMA,MALIGNANT		0	1	0	0	0	0	0	0	0	0
MENINGIOMA,MALIGNANT		0	1	0	0	0	0	0	0	0	0
Ear											
Number examined		1	1	1	0	1	1	1	1	0	0
CARCINOMA,SQUAMOUS CELL		0	0	0	0	0	0	1	0	0	0
FIBROSARCOMA		0	0	0	0	1	0	0	0	0	0
Gallbladder											
Number examined		47	45	38	42	29	44	44	41	46	43
PAPILLOMA		2	1	0	0	1	0	1	0	0	0
Harderian gland											
Number examined		60	60	60	60	58	60	60	60	59	59
ADENOMA		6	6	7	1	0	4	3	0	1	2
Hemolymphoreticular(all sites)											
Number examined		60	60	60	60	58	60	60	60	59	59
LYMPHOMA,MALIGNANT		2	3	0	0	0	16	8	8	8	5*
SARCOMA,HISTIOCYTIC		2	4	4	1	0	2	6	2	4	1
Intestine,duodenum											
Number examined		57	56	57	56	51	58	56	60	56	58
ADENOMA		0	0	0	0	0	0	0	1	0	0
Intestine,ileum											
Number examined		57	58	55	59	55	58	57	60	57	58
ADENOCARCINOMA		1	0	0	0	0	0	0	0	0	0
Intestine,jejunum											
Number examined		56	57	54	51	56	57	59	59	56	55
ADENOMA		1	0	0	0	0	0	0	1	0	0
Kidney											
Number examined		60	60	60	60	58	60	60	60	59	59
NEPHROBLASTOMA		0	0	0	1	0	0	0	0	0	0
Liver											
Number examined		60	60	60	60	58	60	60	60	59	59
ADENOMA,HEPATOCELLULAR		13	16	12	15	8	3	6	0	5	5
HEMANGIOMA		4	2	0	1	1	1	0	1	0	0
CARCINOMA,HEPATOCELLULAR		4	5	2	1	1	1	0	0	1	0
HEMANGIOSARCOMA		3	3	3	0	0	4	1	5	1	1
Lung(bronchus)											
Number examined		60	60	60	60	58	60	60	60	59	59
ADENOMA,BRONCHIOLO-ALVEOLAR		5	7	5	6	4	6	11	9	4	3
CARCINOMA,BRONCHIOLO-ALVEOLAR		7	6	6	3	1	4	5	6	3	5

* : p<0.01 Significantly difference from the control group in Fisher's exact test.

Organs / Findings	Sex:	M	M	M	M	M	F	F	F	F	F
	Dose(mg/kg):	0	1	3	10	30	0	1	3	10	30
	Number:	60	60	60	60	60	60	60	60	60	60
Mammary gland											
Number examined		-	-	-	-	-	60	59	60	59	59
ADENOCARCINOMA		-	-	-	-	-	5	2	1	3	2
ADENOACANTHOMA,MALIGNANT		-	-	-	-	-	0	1	2	1	0
Ovary											
Number examined		-	-	-	-	-	60	60	60	58	59
CYSTADENOMA		-	-	-	-	-	0	1	1	0	1
LEIOMYOMA		-	-	-	-	-	0	0	0	1	0
LUTEOMA		-	-	-	-	-	1	0	0	0	0
SERTOLI CELL TUMOR		-	-	-	-	-	0	0	0	1	0
SEX CORD STROMAL TUMOR,MIXED		-	-	-	-	-	1	0	0	0	0
LEIOMYOSARCOMA		-	-	-	-	-	0	0	1	0	1
Pancreas											
Number examined		60	60	60	60	58	60	60	60	59	59
ADENOMA,ISLET CELL		1	0	0	0	0	0	0	0	0	0
Parathyroid											
Number examined		51	51	49	55	51	56	53	59	57	48
ADENOMA		0	0	0	0	0	0	1	0	0	0
Pituitary											
Number examined		59	60	59	60	58	60	60	60	59	59
ADENOMA,PARS DISTALIS		0	0	0	1	0	1	2	1	2	3
ADENOMA,PARS INTERMEDIA		0	0	0	0	0	1	1	1	0	1
CARCINOMA,ANTERIOR		0	1	0	0	0	0	0	0	0	0
Rib											
Number examined		0	0	0	0	0	0	0	0	1	0
OSTEOMA		0	0	0	0	0	0	0	0	1	0
Seminal vesicle											
Number examined		60	60	60	60	58	-	-	-	-	-
ADENOMA		0	2	1	0	0	-	-	-	-	-
Skeletal system(all sites)											
Number examined		60	60	60	60	58	60	60	60	59	59
OSTEOSARCOMA		0	2	0	0	0	0	2	0	0	0
Skin											
Number examined		60	60	60	60	58	60	60	60	59	59
KERATOACANTHOMA		0	0	0	0	0	0	0	0	1	0
CARCINOMA,SQUAMOUS CELL		0	0	1	0	0	1	0	0	0	0
FIBROSARCOMA		0	0	0	0	0	1	0	0	0	0
HEMANGIOSARCOMA		0	0	0	1	0	0	0	0	0	0
LEIOMYOSARCOMA		0	0	0	0	0	1	0	1	0	0
LIPOSARCOMA		0	0	0	0	0	0	3	1	0	1
RHABDOMYOSARCOMA		0	0	0	0	0	0	0	1	0	0
Spinal cord											
Number examined		60	60	60	60	58	60	60	60	59	59
ASTROCYTOMA		0	0	0	1	0	0	0	0	0	0
Spleen											
Number examined		60	60	60	60	58	59	60	60	59	59
HEMANGIOMA		1	0	0	0	0	0	1	0	0	0
HEMANGIOSARCOMA		0	0	0	0	0	1	0	0	0	1
Stomach											
Number examined		60	59	60	60	58	60	60	60	59	59
PAPILLOMA		0	0	0	0	0	0	1	1	1	1
CARCINOMA,SQUAMOUS CELL		0	0	0	0	0	0	2	0	0	0

Organs / Findings	Sex:	M	M	M	M	M	F	F	F	F	F
	Dose(mg/kg):	0	1	3	10	30	0	1	3	10	30
	Number:	60	60	60	60	60	60	60	60	60	60
Tail											
Number examined		0	2	2	2	2	0	1	0	1	2
HEMANGIOMA		0	0	0	1	0	0	0	0	0	0
Testis											
Number examined		60	60	60	60	58	-	-	-	-	-
ADENOMA,RETE TESTIS		0$	0	0	0	1	-	-	-	-	-
LEYDIG CELL TUMOR		0	1	1	0	0	-	-	-	-	-
SEMINOMA		1	0	0	0	0	-	-	-	-	-
Thyroid											
Number examined		58	60	60	60	58	60	59	60	59	59
ADENOMA,FOLLICULAR CELL		1	0	0	0	0	0	0	0	0	0
CARCINOMA,FOLLICULAR CELL		0	1	0	0	0	0	0	0	0	0
Urinary bladder											
Number examined		59	57	56	59	57	58	60	60	59	59
PAPILLOMA		0	0	1	0	0	0	0	0	0	0
Uterus											
Number examined		-	-	-	-	-	60	60	60	59	59
ADENOMA,ENDOMETRIAL		-	-	-	-	-	0$	0	1	0	2
HEMANGIOMA		-	-	-	-	-	0	0	1	0	0
LEIOMYOMA		-	-	-	-	-	2	1	2	1	0
POLYP,ENDOMETRIAL STROMAL		-	-	-	-	-	7	2	6	7	3
SCHWANNOMA		-	-	-	-	-	0	1	0	0	0
CARCINOMA,ENDOMETRIAL		-	-	-	-	-	1	0	0	2	0
HEMANGIOSARCOMA		-	-	-	-	-	2	1	1	2	0
LEIOMYOSARCOMA		-	-	-	-	-	1	1	2	1	3
SARCOMA,ENDOMETRIAL STROMAL		-	-	-	-	-	5	3	5	7	5
Vagina											
Number examined		-	-	-	-	-	60	60	60	59	59
POLYP,VAGINAL STROMAL		-	-	-	-	-	0	1	0	0	0
SARCOMA,VAGINAL STROMAL		-	-	-	-	-	0	1	0	0	0
Vertebra											
Number examined		0	1	0	0	0	0	0	1	0	0
OSTEOMA		0	0	0	0	0	0	0	1	0	0

- : Not applicable
No significantly difference from the control group in Fisher's exact test.
$: p<0.025 Significantly difference from the control group in pooled(fatal + incidental) tumors in Peto's positive trend test of all groups.

Text Table 8. Summary of major non-neoplastic lesions

Sex	Male					Female				
Dose (mg/kg/day)	0	1	3	10	30	0	1	3	10	30
No. of animals used	60	60	60	60	60	60	60	60	60	60
Eye	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(59)	(60)
Keratitis	8	9	4	6	8	6	8	10	11	17
Skin	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
Ulcer	16	13	17	15	12	6	8	11	13	13
Forelimb		(1)		(3)	(5)			(2)	(7)	(5)
Cell infiltration, inflammatory	/	1	/	1	2	/	/	2	5	4
Ulcer	/	0	/	2	3	/	/	2	3	2
Penis	(20)	(18)	(27)	(27)	(37)					
Ulcer	10	14	22	22	30	/	/	/	/	/
Prostate	(60)	(60)	(60)	(60)	(60)					
Cell infiltration, inflammatory	11	10	12	18	19	/	/	/	/	/
Seminal vesicle	(60)	(60)	(60)	(60)	(60)					
Cell infiltration, inflammatory	7	11	5	15	14	/	/	/	/	/
Kidney	(60)	(60)	(60)	(60)	(60)					
Dilatation, pelvic	11	11	16	28	26	1	5	2	4	0
Dilatation, tubular	1	3	6	3	8	2	2	4	5	2
Urinary bladder	(59)	(57)	(56)	(59)	(59)	(58)	(60)	(60)	(60)	(60)
Mesenchymal lesion	0	1	0	3	6	1	0	1	0	0
Thymus	(51)	(54)	(48)	(45)	(51)	(58)	(57)	(57)	(56)	(56)
Atrophy (severe)	4	6	5	14	12	2	4	6	3	4
Spleen	(60)	(60)	(60)	(60)	(60)	(59)	(60)	(60)	(60)	(60)
Atrophy	0	4	2	6	11	2	0	0	3	9
Stomach	(60)	(59)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
Erosion, glandular stomach	7	9	12	12	14	12	12	14	15	10

Number in the table indicates the number of animals with respective lesions.
Number of parentheses indicated the number of animals examined.
/: Not applicable

Toxicokinetics: Plasma levels at 30 minutes after dosing increased in a less-than dose-proportional manner (Sponsor's table, below).

Text Table 5. The $C_{0\ 5h}$ values for E2007 in Weeks 13 and 26

Dose (mg/kg)	Week	Male $C_{0\ 5hr}$ (ng/mL)	Female $C_{0\ 5hr}$ (ng/mL)
1	13	101.34 ± 12.21	145.80 ± 81.17
	26	135.73 ± 52.59	252.25 ± 64.38
3	13	289.08 ± 41.92	485.72 ± 138.24
	26	397.19 ± 367.23	477.97 ± 132.36
10	13	774.78 ± 215.69	991.43 ± 173.85
	26	760.43 ± 203.76	1108.03 ± 120.12
30	13	1186.54 ± 79.00	1507.32 ± 126.88
	26	1371.88 ± 211.94	1879.27 ± 351.51

Mean ± SD of 4 animals are presented.

8.2 Rat

Study title: E2007: An Oral Carcinogenicity Study in Rats

Study no.:	S04063
Study report location:	EDR
Conducting laboratory:	Eisai Co., Ltd.; Gifu, Japan
Date of study initiation:	8/6/2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lots 13022002 & 14110902, Purity 100% & 99.6%, respectively.
ExecCAC concurrence:	No. The ExecCAC communicated the following to the Sponsor in the response to the SPA submitted on 11/6/2003: *"The Committee concurred with the doses selected by the sponsor for female rats based on the body weight effect (~10% decrease in body weight compared to control) observed at the end of the 26-week study. The Committee did not concur on the doses selected for male rats due to the lack of dose-limiting toxicities in the 4-week, 13-week, and 26-week studies in males. (The Committee did not consider the moribund sacrifice in one male at 100 mg/kg in the 4-week study to be drug-related). The Committee recommended that the sponsor conduct a 13-week study (to include histopathology and toxicokinetic evaluation) in male rats using higher doses in order to identify an MTD for the 2-year study."*

Key Study Findings

- **There was no evidence in this study to suggest that E2007 is carcinogenic.**
- **Abnormal gait, decreased activity, and prostration/ lateral recumbence were the most common clinical signs observed during the dosing period. Convulsions occurred at a markedly higher incidence in low dose animals than in other dose groups.**
- **The incidence of ovarian cysts was increased in females dosed with ≥ 10 mg/kg.**
- **The incidences of pleuritis and epicarditis were increased in all male dose groups but not in a dose-dependent manner.**
- **Since dosing was performed at the MTD in males (100 mg/kg) and at a level which decreased BW by more than 10% in females in the 13-week study (30 mg/kg) and a sufficient number of animals survived in all dose groups at 2 years, this study is considered to be adequate.**

Methods

Doses:	M= 0, 10, 30, 100 mg/kg; F= 0, 3, 10, 30 mg/kg
Frequency of dosing:	Once daily for 104 weeks
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Basis of dose selection:	In Study #S04007 (13-week repeat dose, males only), the MTD in male rats was determined to be 100 mg/kg due to deaths at 300 mg/kg. The HD in females (30 mg/kg) was determined based on decreased BW at the end of the study (-11%, relative to control) in the 26-week study (#S02002). The ExecCAC concurred with the dose selection for females but not males.
Species/Strain:	Sprague-Dawley rat (Crj:CD(SD)ISG)
Number/Sex/Group:	Main group= 60; TK group=5
Age:	6 weeks at dosing initiation
Animal housing:	Single housing in steel cage; 12/12 light cycle
Paradigm for dietary restriction:	Water and food *ad libitum*
Dual control employed:	No
Interim sacrifice:	No
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Dosing Solution Analysis: Dosing formulations were within ± 5% of the nominal concentration.

Mortality: Survival rate in males dosed with E2007 was lower than in control males; a similar finding was not observed in females (Sponsor's text table 1, below). Mortality was not excessive in any dose group and the survival rate was > 50% at the end of the study (104 weeks). There was no test article-related trend for non-neoplastic or neoplastic lesions as the cause of mortality (Sponsor's text table 2, below). Accidental death was increased in a test article-related manner in all male dose groups and in MDF and HDF. Pituitary tumors were the most frequent neoplasia-related cause of death.

Text Table 1. Summary of mortality and survival rates

Sex	Male				Female			
Dose (mg/kg)	0	10	30	100	0	3	10	30
No. of animals used	60	60	60	60	60	60	60	60
Week of administration								
26	0[a)]	0	2	2	1	0	1	3
52	0	1	3	2	3	1	1	10
78	3	5	7	5	10	5	5	14
Terminal	12	21	19	23	21	16	18	21
Number of survivors	48	39	41	37	39	44	42	39
Survival rate (%)	80	65	68	62*	65	73	70	65

a): Cumulative number of animals that died (including those sacrificed as moribund).
*: $p<0.05$ (significantly different from the control group, log-rank test)

Text Table 2. Cause of death/moribundity

Sex	Male				Female			
Dose (mg/kg)	Control	10	30	100	Control	3	10	30
No. of animals used	60	60	60	60	60	60	60	60
No. of death/moribundity	12	21	19	23	21	16	18	21
Neoplastic lesion	8	16	10	9	18	13	13	12
Non-neoplastic lesion	4	1	2	6	1	1	0	0
Accidental*	0	4	4	7	2	2	4	7
Unclear	0	0	3	1	0	0	1	2

*: possibly due to gavage error

Clinical Signs: Abnormal gait, decreased activity, and prostration/ lateral recumbence were the most common clinical signs observed during the dosing period (Sponsor's text table 3, below). The incidence of decreased activity was highest during the first week of dosing in all dose groups. The incidence of prostration/ lateral recumbence was highest during the first week of dosing in HDM, MDF, and HDF. The number of animals exhibiting convulsions at any time during the study was highest in LD animals (Males= 4, 13, 10, 7; Females= 4, 16, 4, 1; C, LD, MD, HD, respectively). The total number of days on which convulsions were observed exhibited an inverted U-shaped dose response in both sexes (Males= 11/729, 71/729, 71/729, 28/729; Females= 13/730, 112/730, 28/730, 1/730; C, LD, MD, HD, respectively). The lower incidence of convulsions at the HD, relative to lower dose groups, may reflect the anti-convulsant activity of E2007. It is unclear why the incidence of convulsion was markedly increased in LDM, MDM, and LDF. The first observation of convulsions was not evident until well into the dosing period in these groups (LDM= Day 99, MDM= Day 169, Day 215).

Text Table 3. Incidence of CNS clinical signs

Sex	Dose (mg/kg)	Clinical sign	Week						
			1	4	12	26	52	78	104
Male	10	Abnormal gait	3	0	0	0	8	5	39
		Decreased activity	0	0	0	0	0	2	5
		Prostration/Lateral position	0	0	0	0	0	0	7
	30	Abnormal gait	47	7	5	5	44	28	44
		Decreased activity	37	3	2	0	0	2	5
		Prostration/Lateral position	0	2	0	0	0	0	2
	100	Abnormal gait	62	35	29	33	97	62	62
		Decreased activity	97	13	3	0	0	5	5
		Prostration/Lateral position	18	5	2	2	0	0	3
Female	3	Abnormal gait	35	0	0	0	2	5	34
		Decreased activity	18	0	0	0	0	0	5
		Prostration/Lateral position	0	0	0	0	0	0	2
	10	Abnormal gait	48	25	12	15	42	27	74
		Decreased activity	100	3	0	0	0	2	2
		Prostration/Lateral position	2	0	0	0	0	0	0
	30	Abnormal gait	33	68	18	24	92	74	74
		Decreased activity	100	5	2	2	0	0	5
		Prostration/Lateral position	28	3	2	2	0	0	3

Numbers in the table showed % (observed/survival animal)

Body Weights & Food Consumption: Absolute BW, relative to control, was decreased in MDM, HDM, and all female dose groups during the dosing period (Sponsor's text table 4, below). There was no consistent test article-related effect on food consumption.

Text Table 4. Summary of body weight changes

Sex	Male				Female			
Dose (mg/kg)	Control	10	30	100	Control	3	10	30
Day 1	189.2 g	+0	+1	+1	132.3g	-0	-0	+1
Day 183	507.7 g	-2	-7	-14	269.3 g	-7	-9	-12
Day 239	532.8 g	-2	-8	-16	276.2 g	-8	-11	-14
Day 253	537.3 g	-2	-7	-16	278.4 g	-9	-11	-14
Day 351	583.4 g	-1	-7	-14	292.2 g	-8	-11	-15
Day 365	585.5 g	-1	-7	-14	293.6 g	-8	-11	-14
Day 547	596.3 g	-2	-8	-11	291.1 g	-6	-7	-9
Day 728	535.8 g	-2	-6	-7	272.0 g	-5	-7	-3

Values of the controls are group means. For treated groups, percent differences from controls are shown.

Hematology & Blood Chemistry: Blood was collected on Day 244 of the study for the assessment of hematology and blood chemistry parameters. There were no test article-related findings.

Gross Pathology: A dose-dependent increase in lung distension was observed in MDM, HDM, and all female dose groups (Sponsor's table, below); there was no consistent histopathological correlate for this finding. Ovarian cysts occurred in a dose-dependent manner at all doses. Other observations were increased tail crust in MDM and HDM, thoracic cavity adhesions in all male groups, and thickening of the foot pad in all female dose groups.

SUMMARY OF GROSS PATHOLOGY DATA
- TERMINAL SACRIFICE , FOUND DEAD , MORIBUND SACRIFICE MALE

ORGAN AND FINDINGS	DOSE (mg/kg) -- / NO. OF ANIMALS EXAMINED --	0 / 60	10 / 60	30 / 60	100 / 60
Lung		(60)	(60)	(60)	(60)
Distension		0	0	2	3
Prostate		(60)	(60)	(60)	(60)
Edema		0	0	1	3
Tail		(60)	(60)	(60)	(60)
Crust		10	8	21	19
Thoracic cavity		(60)	(60)	(60)	(60)
Normal		59	56	58	55
Adhesion		0	2	2	4

SUMMARY OF GROSS PATHOLOGY DATA
- TERMINAL SACRIFICE , FOUND DEAD , MORIBUND SACRIFICE FEMALE

ORGAN AND FINDINGS	DOSE (mg/kg) -- / NO. OF ANIMALS EXAMINED --	0 / 60	3 / 60	10 / 60	30 / 60
Lung		(60)	(60)	(60)	(60)
Distension		0	1	3	4
Ovaries		(60)	(60)	(60)	(60)
Cyst		3	4	8	12
Limb		(60)	(60)	(60)	(60)
Hard thickening, foot pad		0	4	4	4

Histopathology: Peer Review: Yes; Signed and Dated Pathology Report: Yes

Neoplastic: There were no test article-related neoplastic findings (Sponsor's tables 2-1; 2-7). The ExecCAC agreed that perampanel was not carcinogenic in mice (See Appendix).

TABLE 2 - 1
STUDY NO. S04063
E2007: An Oral Carcinogenicity Study in Rats
SUMMARY OF HISTOPATHOLOGY DATA
- NEOPLASTIC LESIONS MALE
- TERMINAL SACRIFICE , FOUND DEAD , MORIBUND SACRIFICE

ORGAN AND FINDINGS	DOSE (mg/kg) -- / NO. OF ANIMALS EXAMINED --	0 / 60	10 / 60	30 / 60	100 / 60
Liver		(60)	(60)	(60)	(60)
Hepatocellular carcinoma		1	2	0	1
Hepatocellular adenoma		1	1	0	0
Cholangioma		0	0	0	1
Kidneys		(60)	(60)	(60)	(60)
Adenoma		1	0	0	1
Heart		(60)	(60)	(60)	(60)
Malignant mesothelioma		0	0	1	0
Malignant schwannoma		0	1	0	0
Lung		(60)	(60)	(60)	(60)
Carcinoma, bronchiolo-alveolar		1	0	0	0
Pleura		(0)	(0)	(0)	(1)
Malignant mesothelioma		0	0	0	1
Mesenteric lymph node		(60)	(60)	(59)	(60)
Hemangiosarcoma		1	0	0	0
Hematopoietic and lymphatic organs		(1)	(1)	(1)	(2)
Histiocytic sarcoma		1	0	1	2
Malignant lymphoma		0	1	0	0
Adrenals		(60)	(60)	(60)	(60)
Malignant pheochromocytoma		4	8	2	2
Pheochromocytoma		13	8	11	9
Cortical adenoma		0	1	0	0
Pituitary		(58)	(60)	(59)	(60)
Adenocarcinoma, pars distalis		4	5	2	6
Adenoma, pars distalis		27	29	29	16
Adenoma, pars intermedia		2	0	0	0
Thyroids		(60)	(60)	(60)	(60)
C-cell carcinoma		1	0	0	0
Follicular cell adenoma		1	1	0	1
C-cell adenoma		4	3	2	2
Parathyroids		(55)	(59)	(58)	(58)
Adenoma		0	0	0	1
Testes		(60)	(60)	(60)	(60)
Interstitial cell adenoma		2	1	0	4
Pancreas		(60)	(60)	(60)	(60)
Islet-cell carcinoma		2	3	2	4
Islet-cell adenoma		4	6	6	3
Stomach		(60)	(60)	(60)	(60)
Leiomyosarcoma		0	1	0	0

Duodenum	(60)	(60)	(60)	(60)
Leiomyosarcoma	0	0	0	1
Cecum	(60)	(60)	(60)	(60)
Hemangioma	1	0	0	0
Brain	(60)	(60)	(60)	(60)
Glioma	1	0	0	2
Granular cell tumor	0	0	1	1
Spinal cord	(60)	(60)	(60)	(60)
Glioma	0	1	0	0
Mammary gland	(60)	(58)	(60)	(56)
Adenoma	0	0	0	1
Fibroadenoma	1	0	0	0
Skin	(60)	(60)	(60)	(60)
Basal cell carcinoma	0	1	0	0
Squamous cell papilloma	1	1	3	0
Sebaceous cell adenoma	0	2	0	0
Keratoacanthoma	1	3	0	5
Subcutis	(6)	(6)	(5)	(3)
Fibrosarcoma	1	0	0	0
Liposarcoma	0	1	0	0
Malignant Schwannoma	0	0	1	0
Fibroma	2	4	3	1
Lipoma	2	1	0	0
Eyes	(60)	(60)	(60)	(60)
Malignant schwannoma	0	1	0	0
Zymbal glands	(0)	(1)	(0)	(0)
Carcinoma	0	1	0	0
Limb	(27)	(25)	(14)	(4)
Rhabdomyosarcoma	0	0	1	0
Bone	(1)	(0)	(0)	(0)
Osteosarcoma	1	0	0	0

GRADE ; 1+ : slight, 2+ : moderate, 3+ : marked

TABLE 2 - 7
STUDY NO. S04063
E2007: An Oral Carcinogenicity Study in Rats
SUMMARY OF HISTOPATHOLOGY DATA
- NEOPLASTIC LESIONS FEMALE
- TERMINAL SACRIFICE , FOUND DEAD , MORIBUND SACRIFICE

ORGAN AND FINDINGS	DOSE (mg/kg) -- / NO. OF ANIMALS EXAMINED --	0 60	3 60	10 60	30 60
Liver		(60)	(60)	(60)	(60)
Hepatocellular carcinoma		0	0	0	1
Hepatocellular adenoma		1	0	1	1
Kidneys		(60)	(60)	(60)	(60)
Liposarcoma		1	0	0	0
Spleen		(60)	(60)	(60)	(60)
Fibrosarcoma		0	0	0	1
Hemangioma		0	0	0	1
Lung		(60)	(60)	(60)	(60)
Paraganglioma		0	0	0	1
Thymus		(57)	(53)	(56)	(58)
Thymoma		0	0	1	0
Hematopoietic and lymphatic organs		(1)	(1)	(2)	(3)
Histiocytic sarcoma		1	1	2	2
Malignant lymphoma		0	0	0	1
Adrenals		(60)	(60)	(60)	(60)
Malignant pheochromocytoma		2	2	0	0
Cortical carcinoma		1	0	0	0
Pheochromocytoma		1	2	2	3
Cortical adenoma		1	0	0	0
Pituitary		(60)	(60)	(60)	(60)
Adenocarcinoma, pars distalis		12	6	5	7
Adenoma, pars distalis		23	24	28	10
Thyroids		(60)	(60)	(60)	(60)
C-cell carcinoma		0	0	1	0
C-cell adenoma		2	2	2	0
Parathyroids		(56)	(58)	(59)	(57)
Adenoma		0	0	1	0
Ovaries		(60)	(60)	(60)	(60)
Sertoli's cell tumor		0	1	0	0
Uterus		(60)	(60)	(60)	(60)
Endometrial stromal sarcoma		3	1	0	0
Leiomyosarcoma		1	0	0	2
Hemangiosarcoma		0	0	0	1
Endometrial stromal polyp		3	3	4	3
Leiomyoma		1	0	0	0
Vagina		(60)	(60)	(60)	(60)
Squamous cell papilloma		0	0	1	0
Urinary bladder		(60)	(60)	(60)	(60)
Transitional cell carcinoma		1	0	0	0

Pancreas	(60)	(60)	(60)	(60)
Islet-cell carcinoma	1	0	0	0
Islet-cell adenoma	1	0	0	0
Jejunum	(60)	(60)	(60)	(60)
Leiomyosarcoma	0	1	0	0
Cecum	(60)	(60)	(60)	(60)
Leiomyosarcoma	0	1	1	0
Hamartoma, malignant	0	1	0	0
Brain	(60)	(60)	(60)	(60)
Meningeal sarcoma	0	0	0	1
Glioma	0	1	0	0
Mammary gland	(60)	(60)	(60)	(60)
Adenocarcinoma	10	4	4	5
Carcinosarcoma	0	0	0	1
Adenoma	2	3	0	3
Mammary gland	(60)	(60)	(60)	(60)
Fibroadenoma	20	18	14	11
Skin	(60)	(60)	(60)	(60)
Squamous cell carcinoma	0	0	0	1
Squamous cell papilloma	0	0	1	0
Basal cell tumor	0	0	0	1
Subcutis	(2)	(2)	(4)	(3)
Fibrosarcoma	1	1	1	0
Lipoma	0	1	1	0
Preputial/Clitoral glands	(59)	(60)	(59)	(58)
Squamous cell papilloma	0	0	1	0
Zymbal glands	(1)	(1)	(0)	(0)
Carcinoma	1	1	0	0
Diaphragm	(0)	(1)	(0)	(1)
Lipoma	0	1	0	0
Other peripheral nerve	(0)	(0)	(1)	(0)
Schwannoma	0	0	1	0
Bone	(0)	(0)	(0)	(1)
Osteosarcoma	0	0	0	1

GRADE ; 1+ : slight, 2+ : moderate, 3+ : marked

Non Neoplastic: Epicarditis was observed in all male dose groups but not in control animals; the incidence of this finding was not strictly dose-dependent (Sponsor's tables, below). Inflammation of the prostate was increased in a dose-dependent manner in MDM and HDM. The incidence of focal epidermal hyperplasia was observed in MDM and HDM. Although this finding was associated with the "tail crust" observed in some males, it was not observed in all males exhibiting "tail crust" in the gross pathology assessment. The number of females with ovarian cysts was increased in MDF and HDF.

SUMMARY OF HISTOPATHOLOGY DATA
- NON-NEOPLASTIC LESIONS MALE
- TERMINAL SACRIFICE , FOUND DEAD , MORIBUND SACRIFICE

ORGAN AND FINDINGS		DOSE (mg/kg) -- / NO. OF ANIMALS EXAMINED --	0 / 60	10 / 60	30 / 60	100 / 60
Heart			(60)	(60)	(60)	(60)
Epicarditis	1+		0	1	0	0
	2+		0	1	1	2
	3+		0	1	0	2
Lung			(60)	(60)	(60)	(60)
Pleuritis	1+		0	1	0	0
	2+		0	1	0	3
	3+		0	1	1	1
Prostate			(60)	(60)	(60)	(60)
Inflammation	1+		4	0	2	5
	2+		4	3	5	4
	3+		0	0	2	5
Tail			(13)	(8)	(22)	(20)
Focal epidermal hyperplasia, reactive	1+		6	5	9	13

SUMMARY OF HISTOPATHOLOGY DATA
- NON-NEOPLASTIC LESIONS FEMALE
- TERMINAL SACRIFICE , FOUND DEAD , MORIBUND SACRIFICE

ORGAN AND FINDINGS		DOSE (mg/kg) -- / NO. OF ANIMALS EXAMINED --	0 / 60	3 / 60	10 / 60	30 / 60
Ovaries			(60)	(60)	(60)	(60)
Cyst	1+		8	4	7	10
	2+		1	0	4	5

Toxicokinetics: Plasma levels at 30 minutes after dosing increased in a less-than dose-proportional manner. Plasma levels in females were slightly higher than in males at comparable dose levels. Similar plasma levels were achieved at the HD in males and females.

Text Table 5 Toxicokinetic Summary

Dose (mg/kg)	Week	Male C_{1hr} (ng/mL)	Female C_{1hr} (ng/mL)
3	13	-	437.67 ± 123.28
	26	-	376.65 ± 93.70
10	13	481.81 ± 433.43	737.47 ± 286.11
	26	525.88 ± 599.02	768.21 ± 443.77
30	13	685.95 ± 275.29	1067.20 ± 380.09
	26	671.72 ± 264.78	1195.32 ± 409.42
100	13	1188.02 ± 887.94	-
	26	1152.70 ± 388.45	-

Mean ± SD of 5 animals are presented.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: E2007: An Oral Fertility Study in Rats

Study no.:	S01011
Study report location:	EDR
Conducting laboratory and location:	Eisai Co. Ltd.; Gifu, Japan
Date of study initiation:	8/20/2001
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 10092507, Purity 99.6%

Key Study Findings

- **Fertility was not affected in rats exposed to doses of up to 30 mg/kg E2007.**
- **Prolonged and irregular estrous cycles were observed at 30 mg/kg.**
- **Clinical signs were prolonged and of increased severity in males and females dosed with 30 mg/kg E2007.**

Methods

Doses:	0, 1, 10, 30 mg/kg
Frequency of dosing:	Once daily; males and females were dosed for the 14 days prior to mating and during the mating period (GD 0-6 for females).
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Sprague-Dawley (Crj:CD(SD)IGS) rat; 9 weeks old
Number/Sex/Group:	20/sex/group
Deviation from study protocol:	There were no deviations that compromised the validity of the study.

Dosing Solution Analysis: Dosing formulations were within ± 5% of the nominal concentration.

Mortality & Clinical Signs: There were no test article-related deaths during the study. Abnormal gait, decreased activity, prostration, and increased grooming were observed in HDM, MDF, and HDF. One HDM and three HDF exhibited prostration and decreased activity that lasted until the next dosing. Piloerection and bradypnea was observed in HDF, while emaciation was observed in one HDM.

Body Weight & Food Consumption: Absolute BW was decreased in HDF and HDM (-11% to -12%, relative to control) beginning on Day 3 of dosing and lasting until the end of the mating period. BW gain was reduced, relative to control, in MDM (-40%), HDM (-70%), MDF (-57%), and HDF (-55%) during the pre-mating period. BW was not affected at 1 mg/kg. Food consumption was decreased, relative to control, by 22% in HDM, 13-19% in MDF, 20-35% in HDF.

Necropsy: One HDM exhibited small testes (bilateral). There were no test article-related findings in females or in LDM or MDM.

Fertility Parameters: A majority of HDF (12/20) exhibited consecutive diestrus that was 5 days or longer; 0/20 control females, LDF and MDF exhibited this finding (Sponsor's tables, below). There was no test article-related effect on the copulation index, fertility index, the number of days of copulation, the number of corpora lutea, the number of implantations, the number of live embryos, the number of resorptions, or the number of post implantation losses.

Table 9 Estrous cycles

Theme : E2007	Study : Fertility Study				Species (Strain) : Rat
Study No. : S01011	Generation : F0				Route : p.o.
	Group No.	00	01	02	03
	Dose (mg/kg)	E2007 0	E2007 1	E2007 10	E2007 30
No. of animals		20	20	20	20
Estrous cycle length (days)#1	Mean±S.D.	4.0 ± 0.0	4.2 ± 0.6	4.4 ± 1.3	4.9 ± 1.9#2
No. of animals with abnormal estrous cycle (%) 6 days and over		0 (0.0)	2 (10.0)	1 (5.0)	1 (5.0)
No. of animals with consecutive estrus (%) 3 days and over		0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)
No. of animals with consecutive diestrus (%) 5 days and over		0 (0.0)**w	0 (0.0)	0 (0.0)	12 (60.0)**f

Significant difference compared to Group 00, * P ≤ 0.05 , ** P ≤ 0.01 , f: Fishers Exact
Significant trend, *P≤0.05, ** P≤0.01, w : Cochran-Armitage
#1: Not analyzed by Dunnett test
#2: n=10

Table 10 Mating and fertility

Theme : E2007	Study : Fertility Study				Species (Strain) : Rat
Study No. : S01011	Generation : F0				Route : p.o.
	Group No.	00	01	02	03
	Dose (mg/kg)	E2007 0	E2007 1	E2007 10	E2007 30
Male fertility					
No. of males					
Mated		20	20	20	20
Copulated		20	20	20	19
Impregnated		20	20	19	18
Copulation index	(%)	100.0	100.0	100.0	95.0
Fertility index	(%)	100.0	100.0	95.0	94.7
Female fertility					
No. of females					
Mated		20	20	20	20
Copulated		20	20	20	19
Pregnant		20	20	19	18
Copulation index	(%)	100.0	100.0	100.0	95.0
Fertility index	(%)	100.0	100.0	95.0	94.7
Days of copulation	Mean±S.D.	2.1 ± 1.1	1.8 ± 1.0	2.5 ± 1.2	2.9 ± 1.7

Copulation index : (No. of copulated animals / No. of mated animals) × 100
Fertility index : (No. of impregnated or pregnant animals / No. of copulated animals) × 100
Significant difference compared to Group 00, * P ≤ 0.05 , ** P ≤ 0.01

Table 11 Cesarean section

Theme : E2007	Study : Fertility Study	Species(Strain) : Rat
Study No. : S01011	Generation : F0	Route : p.o.

	Group No.	00 E2007	01 E2007	02 E2007	03 E2007
	Dose (mg/kg)	0	1	10	30
No. of dams		20	20	19	18
No. of corpora lutea	Total	303	312	278	271
	Mean±S.D.	15.2 ± 2.0	15.6 ± 1.5	14.6 ± 1.8	15.1 ± 2.3
No. of implantations	Total	282	297	260	252
	Mean±S.D.	14.1 ± 3.5	14.9 ± 1.9	13.7 ± 2.1	14.0 ± 3.5
Preimplantation losses	Mean %	7.6	4.7	6.5	8.0
No. of live embryos	Total	267	285	251	238
	Mean±S.D.	13.4 ± 3.8	14.3 ± 1.8	13.2 ± 2.1	13.2 ± 3.3
No. of resorptions and dead embryos	Total	15	12	9	14
	Mean±S.D.	0.8 ± 1.4	0.6 ± 0.7	0.5 ± 0.7	0.8 ± 0.9
Postimplantation losses	Mean %	9.8	4.0	3.4	5.2
No. of dams with all resorptions	Total	1	0	0	0
	(%)	(5.0)	(0.0)	(0.0)	(0.0)

Preimplantation losses = (No. of corpora lutea - No. of implantations) / No. of corpora lutea × 100
Postimplantation losses = (No. of implantations - No. of live embryos) / No. of implantations × 100
Significant difference compared to Group 00, * $P \leq 0.05$, ** $P \leq 0.01$

9.2. Embryonic Fetal Development

9.2.1 Rat

Study title: E2007: Dose Range Toxicity Study in Pregnant Rats

Study no.:	200420p
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6/19/2001
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	E2007, Lot 10092507, Purity 99.6%

Key Study Findings

- **Dam BW was decreased in all dose groups.**
- **The number of implantation losses, the post implantation loss rate, and fetal BW were all decreased at ≥ 30 mg/kg.**

Methods

Doses:	0, 10, 30, 60 mg/kg
Frequency of dosing:	Once daily for 12 days (GD 6-17)
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Sprague-Dawley (Crj:CD(SD) IGS) rat, pregnant
Number/Sex/Group:	7/group

Dosing Solution Analysis: Dosing formulations were within ± 5% of the nominal concentration.

Mortality & Clinical Signs: There was only one early death in this study (HDF #04456 died on GD 19). There were no extraordinary clinical signs observed in this dam preceding death. Abnormal gait, decreased activity, and increased grooming were observed in all dose groups. Prostration was also observed in MDF and HDF.

Body Weight & Feed Consumption: Absolute BW was decreased, relative to control, by 7.5% in LDF, 22.2% in MDF, and 22.8% in HDF on GD 16. Food consumption was decreased, relative to control, by 19.2% in LDF and 38.5% in MDF and HDF on GD 16.

Necropsy: There were no test article-related findings in the dams.

Cesarean Section and Offspring Findings: There were no fetuses with external abnormalities in any of the dose groups. An assessment for visceral and skeletal abnormalities was not performed in this study. The number of implantation losses (1.1, 1.1, 2.3, 3.7; C, LD, MD, HD, respectively) and post-implantation loss rate (13.5%, 7.1%, 16.5%, 24.3%; C, LD, MD, HD, respectively) were increased in a dose-dependent manner in MDF and HDF. Fetal BW was decreased, relative to control, at the MD (21-24%) and HD (21-23%).

Study title: E2007: Oral Embryo-Fetal Development Study in Rats

Study no.:	200420
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/24/2001
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 10092507, Purity 99.6%

Key Study Findings

- **The NOAEL in this study is <1 mg/kg. Diverticulum of the intestine was observed in fetuses of all E2007 dose groups (≥ 1 mg/kg) and the incidence increased in a dose-dependent manner.**
- **Post-implantation losses and early resorptions were elevated in animals dosed with ≥ 3 mg/kg E2007.**
- **Dams dosed with ≥ 3 mg/kg exhibited decreased activity, prostration, and increased grooming.**
- **BW gain and food consumption were decreased in dams dosed with ≥ 3 mg/kg.**

Methods

Doses:	0, 1, 3, 10 mg/kg
Frequency of dosing:	Once daily for 12 days (GD 6-17); dams were euthanized on GD 20.
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Sprague Dawley (Crj:CD(SD)IGS) rat, pregnant
Number/Sex/Group:	20
Deviation from study protocol:	There were no deviations that compromised the validity of the study.

Dosing Solution Analysis: Dosing formulations were within ± 5% of the nominal concentration.

Mortality & Clinical Signs: There were no test article-related deaths in this study. Abnormal gait (≥ 1 mg/kg), decreased activity (≥ 3 mg/kg), prostration (≥ 3 mg/kg), and increased grooming (10 mg/kg) were observed during the dosing period. The incidence of the clinical signs increased with dose. Swelling of limbs secondary to excessive grooming was observed in 2 HDF; there were no skin excoriations reported in this study.

Body Weight & Food Consumption: BW gain was decreased, relative to control, in MDF (-39%) and HDF (-49%) during the dosing period (GD 6-17) but not during the predose (GD 0-6) or the post dose periods (GD 17-20). A similar effect was observed on food consumption, which was decreased by 22 to 26%, relative to control, from GD 8 to 18.

Necropsy: There were no test article-related findings in the gross pathology assessment.

Cesarean Section Data: The number of post-implantation losses (0.6, 0.9, 1.1, 1.1; C,

LD, MD, HD, respectively) and early resorptions (12, 16, 20, 20; C, LD, MD, HD, respectively) were increased in MDF and HDF (Sponsor's table, below).

Table 6-1. Observation of fetuses from dams in embryo-fetal development study of E2007 by oral administration

Group	Control	E2007		
mg/kg	0	1	3	10
Number of dams	20	20	19	19
Number of corpora lutea				
Total	317	321	321	328
Mean ± S.D. per dam	15.9 ± 2.1	16.1 ± 3.5	16.9 ± 2.4	17.3 ± 1.7
Number of implantation sites				
Total	292	293	289	301
Mean ± S.D. per dam	14.6 ± 2.9	14.7 ± 4.1	15.2 ± 3.4	15.8 ± 2.2
Implantation rate				
Mean % ± S.D. per dam[a)]	91.2 ± 13.3	89.2 ± 13.3	89.0 ± 13.0	91.6 ± 8.4
Number of post-implantation losses				
Total	12	17	20	20
Mean ± S.D. per dam	0.6 ± 0.9	0.9 ± 0.8	1.1 ± 0.9	1.1 ± 1.2
Implantation scars	0	0	0	0
Early resorptions	12	16	20	20
Late resorptions	0	1	0	0
Macerated fetuses	0	0	0	0
Dead fetuses	0	0	0	0
Post-implantation loss rate				
Mean % ± S.D. per dam[b)]	4.6 ± 8.9	6.6 ± 7.9	7.8 ± 6.7	6.7 ± 7.4
Number of live fetuses				
Total	280	276	269	281
Mean ± S.D. per dam	14.0 ± 3.3	13.8 ± 4.0	14.2 ± 3.7	14.8 ± 2.3
Sex ratio (Mean ± S.D. per dam[c)])	0.54 ± 0.17	0.57 ± 0.21	0.46 ± 0.12	0.42 ± 0.11
Mean fetal body weight (g)				
Male (Mean ± S.D. per dam)	3.97 ± 0.22	3.93 ± 0.29	3.97 ± 0.25	3.90 ± 0.21
Female (Mean ± S.D. per dam)	3.70 ± 0.18	3.69 ± 0.24 (18)	3.75 ± 0.24	3.72 ± 0.23

a): (Number of implantation sites/number of corpora lutea) × 100.
b): (Number of post-implantation losses/number of implantation sites) × 100.
c): Number of males/(number of males + number of females).
Figures in parentheses indicate number of dams.

Offspring: Diverticulum of the intestine was increased in a dose-dependent manner in all groups exposed to E2007 (Sponsor's Table, below); there were no other perampanel-related abnormalities. Only one fetus per litter exhibited this finding and the number of litters affected increased in a dose dependent manner (0, 1, 2, 3; C, LD, MD, HD, respectively; Reviewer's table, below). The incidence of this finding in a relevant historical control was not provided in this study report.

Table 7. Visceral examination of fetuses in embryo-fetal development study of E2007 by oral administration

Group	Control	E2007		
mg/kg	0	1	3	10
Number of dams	20	20	19	19
Number of fetuses examined	137	133	128	137
Abnormalities				
Number of fetuses with abnormalities	7	6	10	10
Mean % ± S.D.	4.7 ± 6.6	4.7 ± 9.3	8.4 ± 14.9	7.4 ± 10.3
Diverticulum of intestine	0	1	2	3
Mean % ± S.D.	0.0 ± 0.0	0.6 ± 2.8	1.5 ± 4.5	2.3 ± 5.5

Dose (mg/kg)	Dam #	Fetus #	Abnormalities
0	None	None	None
1	F02259	F0015	**Diverticulum of intestine**, no other findings
3	F03354	M013	**Diverticulum of intestine**, no other findings
	F03365	F016	**Diverticulum of intestine**, no other findings
10	F04457	M002	**Diverticulum of intestine**, no other findings
	F04463	M014	**Diverticulum of intestine**, no other findings
	F04465	F005	**Diverticulum of intestine**, no other findings

Reviewer's Table: Diverticulum of the intestine in pups of dams dosed with perampanel during organogenesis.

9.2.2. Rabbit

Study title: E2007: Dose Range Toxicity Study in Pregnant Rabbits

Study no.:	250520p
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	2/27/2001
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	E2007, Lot 10092507, Purity 99.6%

Key Study Findings

- **The MTD in this study was 10 mg/kg. Deaths occurred at higher doses.**
- **Fetuses were unavailable for assessment from does dosed with ≥ 30 mg/kg.**
- **Does dosed with 10 mg/kg exhibited decreased number of corpora lutea, implantation sites, implantation rate, and live fetuses.**

Methods

Doses:	0, 10, 30, 60 mg/kg
Frequency of dosing:	Once daily for 13 days (GD 6-18), animals were euthanized on GD 28
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	New Zealand white rabbits Kbl:NZW
Number/Sex/Group:	7

Dosing Solution Analysis: Dosing solutions were within ± 5% of the nominal concentration.

Mortality & Clinical Signs: All HDF died during the dosing phase (One on GD 9, two on GD 10, two on GD 11, two on GD 12). Two MDF died during the dosing period (one on GD 15 and one on GD 25). Spontaneous abortion was observed in one MDF on GD 26. Abnormal gait (≥ 10 mg/kg), prostration (≥ 30 mg/kg), decreased activity (≥ 30 mg/kg), and increased grooming (60 mg/kg) were observed during the dosing period.

Body Weight & Food Consumption: Absolute BW was decreased, relative to control, in LDF (-11% on GD 18), MDF (-31% on GD 18), and HDF (- 11% on GD 12). Food consumption was decreased, relative to control, at the end of the dosing period in LDF (-68%), MDF (-98%), and HDF (-98%) on GD 12.

Necropsy: The lung was dark red in color in 1/2 MDF and 7/7 HDF that died before the end of the dosing period.

Cesarean Section Data and External Observation of Offspring: There were no test article-related abnormalities observed in fetuses from LDF. There were no fetuses available for assessment from the MD and HD group. The number of corpora lutea, number of implantation sites, implantation rate, and the number of live fetuses were decreased in a dose-dependent manner (Sponsor's Table, below). The post-implantation loss rate was 100% in MDF.

Table 6-1. Observation of fetuses from dams in embryo-fetal development study of E2007 by oral administration (preliminary study)

Group	Control	E2007					
mg/kg	0	10		30		60	
Number of dams	7	7		4		7	
Number of corpora lutea							
Total	75	68		29		73	
Mean ± S.D. per dam	10.7 ± 2.9	9.7 ± 1.5		7.3 ± 1.5		10.4 ± 2.8	
Number of implantation sites							
Total	67	53		22		51	
Mean ± S.D. per dam	9.6 ± 2.6	7.6 ± 2.4		5.5 ± 3.0		7.3 ± 4.5	
Implantation rate							
Mean % ± S.D. per dam[a)]	89.6 ± 10.5	77.0 ± 18.4		72.2 ± 29.4		66.8 ± 26.4	
Number of post-implantation losses							
Total	4	7		2		−	
Mean ± S.D. per dam	0.6 ± 0.8	1.2 ± 1.2	(6)	2.0	(1)	−	
Implantation scars	0	0		2		−	
Early resorptions	4	4		0		−	
Late resorptions	0	3		0		−	
Macerated fetuses	0	0		0		−	
Dead fetuses	0	0		0		−	
Post-implantation loss rate							
Mean % ± S.D. per dam[b)]	7.8 ± 12.4	14.7 ± 13.7	(6)	100.0	(1)	−	
Number of live fetuses							
Total	63	39		0		−	
Mean ± S.D. per dam	9.0 ± 3.2	6.5 ± 2.5	(6)	0.0	(1)	−	
Sex ratio (Mean ± S.D. per dam[c)])	0.48 ± 0.13	0.43 ± 0.12	(6)	−		−	
Mean fetal body weight (g)							
Male (Mean ± S.D. per dam)	35.2 ± 4.2	34.0 ± 7.9	(6)	−		−	
Female (Mean ± S.D. per dam)	34.3 ± 3.7	34.4 ± 8.1	(6)	−		−	

a): (Number of implantation sites/number of corpora lutea) × 100.
b): (Number of post-implantation losses/number of implantation sites) × 100.
c): Number of males/(number of males + number of females).
Figures in parentheses indicate number of dams.

Study title: E2007: Oral Embryo-Fetal Development Study in Rabbits

Study no.:	250520
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/24/2001
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 10092507, Purity 99.6%

Key Study Findings

- **The NOAEL in this study was 3 mg/kg. The number of implantation sites, implantation rate, and the number of live fetuses were decreased at 10 mg/kg.**
- **There were no test article-related developmental abnormalities observed in this study.**
- **Spontaneous abortion occurred in 3/20 does dosed with 10 mg/kg.**
- **BW gain was decreased by 50% in does dosed with 3 mg/kg. BW loss was observed in does dosed with 10 mg/kg.**

Methods

Doses:	0, 1, 3, 10 mg/kg
Frequency of dosing:	Once daily for 13 days (GD 6-18)
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	New Zealand white rabbit Kbl:NZW
Number/Sex/Group:	20
Deviation from study protocol:	There were no deviations that compromised the validity of the study.

Dosing Solution Analysis: Dosing solutions were within ± 5% of the nominal concentration.

Mortality & Clinical Signs: There were no deaths in any of the dose groups. Abnormal gait, decreased activity, and prostration were observed in HDF. One HDF aborted spontaneously on GD 26, while two others did so on GD 27.

Body Weight & Food Consumption: Absolute BW was decreased, relative to control, in HDF (-10 %) at the end of the dosing period. BW gain was decreased, relative to control, in MDF by 50% during the dosing phase while BW loss was observed in HDF during the same period. Food consumption was decreased, relative to controls, during the dosing period by 24% in MDF and 60% in HDF.

Necropsy: There were no test article-related findings.

Offspring: There were no test article-related or dose-dependent abnormalities observed in this study.

Cesarean Section Data: The number of implantation sites, implantation rate, and the number of live fetuses were decreased in HDF (Sponsor's table, below).

Table 6-1. Observation of fetuses from dams in embryo-fetal development study of E2007 by oral administration

Group	Control	E2007		
mg/kg	0	1	3	10
Number of dams	19	18	18	17
Number of corpora lutea				
Total	189	173	185	158
Mean ± S.D. per dam	9.9 ± 1.5	9.6 ± 2.7	10.3 ± 2.5	9.3 ± 2.5
Number of implantation sites				
Total	172	148	166	128
Mean ± S.D. per dam	9.1 ± 1.9	8.2 ± 3.3	9.2 ± 3.2	7.5 ± 3.0
Implantation rate				
Mean % ± S.D. per dam[a)]	90.8 ± 11.7	82.9 ± 19.2	87.0 ± 19.0	78.6 ± 21.1
Number of post-implantation losses				
Total	9	7	15	11
Mean ± S.D. per dam	0.5 ± 0.7	0.4 ± 0.6	0.8 ± 1.5	0.8 ± 1.1 (14)
Implantation scars	0	0	0	0
Early resorptions	5	4	2	9
Late resorptions	2	2	4	2
Macerated fetuses	2	1	6	0
Dead fetuses	0	0	3	0
Post-implantation loss rate				
Mean % ± S.D. per dam[b)]	5.6 ± 8.2	4.9 ± 8.4	10.4 ± 16.9	10.1 ± 12.8 (14)
Number of live fetuses				
Total	163	141	151	96
Mean ± S.D. per dam	8.6 ± 2.0	7.8 ± 3.2	8.4 ± 3.3	6.9 ± 2.9 (14)
Sex ratio (Mean ± S.D. per dam[c)])	0.46 ± 0.12	0.45 ± 0.16	0.51 ± 0.24	0.51 ± 0.15 (14)
Mean fetal body weight (g)				
Male (Mean ± S.D. per dam)	33.6 ± 3.4	35.1 ± 6.9	32.8 ± 5.8 (17)	34.1 ± 4.9 (14)
Female (Mean ± S.D. per dam)	32.4 ± 3.8	34.5 ± 6.2	31.8 ± 6.2 (17)	33.6 ± 4.7 (14)

a): (Number of implantation sites/number of corpora lutea) × 100.
b): (Number of post-implantation losses/number of implantation sites) × 100.
c): Number of males/(number of males + number of females).
Figures in parentheses indicate number of dams.

Study title: E2007: An Oral TK Study in Pregnant Rabbits

Study no.:	091027
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8/20/2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 14110902, Purity 99.6%

Key Study Findings

- **Plasma concentrations of E2007 were measured in pregnant does dosed with 1, 3, 10 mg/kg E2007.**

Methods

Doses:	1, 3, 10 mg/kg
Frequency of dosing:	Once daily for 13 days (GD 6-18)
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	New Zealand white rabbit (Kbl:NZW)
Number/Sex/Group:	5 pregnant females/group
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Mortality & Clinical Signs: There were no deaths in this study. One HDF (not pregnant) exhibited abnormal gait, prostration, and decreased activity beginning on Day 11.

Body Weight and Necropsy: There was no effect of the test article on BW. There were no test article-related findings during the necropsy.

Toxicokinetics: One LD animal exhibited exceptionally high levels of E2007 on GD 18.

Text Table 1 Mean values of toxicokinetic parameters of E2007

Group	Dose (mg/kg)	Sampling time point	Toxicokinetic parameters		
			C_{max} (ng/mL)	T_{max}(median) (h)	AUC_{0-24h} (ng•h/mL)
1	1	GD 6	4.45 ± 2.63	1.0	22.13 ± 14.14
		GD 18	25.19 ± 30.42	0.5	198.01 ± 331.39
2	3	GD 6	10.38 ± 5.15	1.0	55.16 ± 17.60
		GD 18	12.89 ± 2.42	1.0	65.63 ± 10.76
3	10	GD 6	34.40 ± 13.58	2.0	214.04 ± 60.74
		GD 18	51.98 ± 27.50	2.0	416.48 ± 344.79

+/- Standard deviation

9.3 Prenatal and Postnatal Development

Study title: E2007: An Oral Dose Range Toxicity Study of Effects on Pre- and Postnatal Development Including Maternal Functions in Rats

Study no.:	300326p
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8/21/2006
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	E2007, Lot 14110902, Purity 99.6%

Key Study Findings

- **There were no test article-related effects on pre- and postnatal development observed in the pups born to dams dosed up to 10 mg/kg.**
- **Maternal BW gain was decreased in dams dosed with ≥ 3 mg/kg.**

Methods

Doses:	0, 1, 3, 10 mg/kg
Frequency of dosing:	Once daily from GD 6 to PND 6
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 % methylcellulose
Species/Strain:	Crl: CD (SD) rat
Number/Sex/Group:	8
Study design:	Dams were allowed to deliver F1 pups which were euthanized on PND 7.

F_0 Dams:

Mortality & Clinical Signs: There were no deaths in this study. Abnormal gait (≥ 1 mg/kg), decreased activity (≥ 3 mg/kg), and prostration (≥ 3 mg/kg) were observed in the F_0 dams during the dosing period.

Body Weight & Food Consumption: Absolute BW and BW gain were decreased, relative to controls, in HDF by 6-12% and 31.3%, respectively, during the dosing period. Food consumption was decreased, relative to control, in MDF and HDF by 12-26% during the dosing period.

Delivery, Lactation & Necropsy: Delivery and lactation were normal in all dose groups. There was no test article-related effect on gestation index, the number of live offspring at birth, sex ratio, the number of stillbirths, the birth index, viability index, or number of external abnormalities.

F_1 Generation: There was no test article-related mortality, clinical signs, effects on absolute BW, or observations in the gross necropsy of pups.

Study title: E2007: An Oral Toxicity Study of Effects on Pre- and Postnatal Development, Including Maternal Functions, in Rats

Study no.:	300326
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	12/15/2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 14110902, Purity 99.6%

Key Study Findings

- **The NOAEL in this study was 1 mg/kg. Incidence of stillborn pups was increased at higher doses.**
- **Auditory function and auditory reflex were not assessed in this study.**
- **Clinical signs and BW effects observed in dams dosed with ≥ 3 mg/kg were consistent with those observed in previous studies.**
- **The incidence of stillbirths was increased and the birth index and viability index were decreased in dams dosed with ≥ 3 mg/kg.**
- **Vaginal opening and preputial separation were delayed in pups born to dams dosed with 10 mg/kg.**
- **There were no test article related effects on motor activity, learning and memory, or reproductive function in F_1 pups in this study.**

Methods

Doses:	0, 1, 3, 10 mg/kg
Frequency of dosing:	Once daily from GD 6 to PND 20
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Crl: CD (SD) rat
Number/Sex/Group:	20
Study design:	Dams were dosed from GD 6 to PND 20 and were euthanized when pups were weaned. Litters were adjusted to 4/sex on PND 4. Pups were followed for developmental milestones. Open field activity was tested on PND 28. Multiple T-maze was performed 6-7 weeks after birth. One pup from each litter was euthanized on PND 56 and necropsied. Reproductive function was assessed 10 weeks after birth and F_2 embryos were examined on GD 13.
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Dosing Solutions: Dosing solutions were within ± 5% of the nominal concentration.

F_0 Dams:

Mortality & Clinical Signs: There were no deaths in this study. Abnormal gait (≥ 1 mg/kg), decreased activity (≥ 3 mg/kg), and prostration (≥ 3 mg/kg) were observed in

the F_0 dams during the dosing period. An entire litter from a MDF (F03363; 9 stillbirths, 5 live births that were hypothermic on PND 1 and died on PND 2) and a HDF (F04462; 2 live births that died on PND 1) died during the study.

Body Weight & Food Consumption: Absolute BW was decreased, relative to control, in MDF (-4%) and HDF (-14%) during pregnancy and lactation. BW gain was also decreased during the same time period in these groups (MDF= -13%; HDF= -26%, relative to control). The decreases in BW and BW gain were associated with decreased food consumption during pregnancy and lactation (MDF= -11%, HDF= -53%, relative to control).

Delivery, Lactation & Necropsy: One HDF (F04452) had "prolonged parturition" (duration unknown); the entire litter was stillborn. Faulty nest building was observed in 1 MDF and 1 HDF. There were no test article-related necropsy findings in the dams euthanized at weaning.

F_1 Generation:

Mortality & Clinical Signs: The number of stillbirths was increased in a dose-dependent manner in litters born to MDF and HDF (Sponsor's Table, below). The number of live offspring at birth, birth index, and viability index were decreased in the HD group.

Table 12 **Observation of offspring (F_1)**

Study No. 300326	Code: E2007	Study: PPN study in pregnant rats		
Species: Rat	Strain: Crl:CD(SD)	Route: Oral	Sex: Female	
Group	Control	E2007		
mg/kg	0	1	3	10
Number of dams	18	20	19	20
Gestation length (days)				
Mean ± S.D. per dam	22.1 ± 0.5	21.9 ± 0.3	22.1 ± 0.3	22.4 ± 0.5
Number of implantation scars				
Total	250	294	268	280
Mean ± S.D. per dam	13.9 ± 3.3	14.7 ± 2.0	14.1 ± 1.9	14.0 ± 1.6
Gestation index (%) [a]	100.0	100.0	100.0	95.0
Number of live offspring at birth				
Total	229	273	238	213
Mean ± S.D. per dam	12.7 ± 2.9	13.7 ± 2.4	12.5 ± 3.0	10.7 ± 4.2
Sex ratio [b]				
Mean ± S.D. per dam	0.48 ± 0.14	0.58 ± 0.11 *	0.50 ± 0.19	0.46 ± 0.15 (19)
Number of stillbirths				
Total	0	0	14	30
Mean ± S.D. per dam	0.0 ± 0.0 ##	0.0 ± 0.0	0.7 ± 2.1 *	1.5 ± 2.8 *
Birth index [c]				
Mean% ± S.D. per dam	92.4 ± 9.6	92.7 ± 9.1	89.0 ± 17.5	76.9 ± 30.1
Viability index [d]				
Mean% ± S.D. per dam	98.1 ± 3.2	99.3 ± 2.1	92.5 ± 22.9	86.8 ± 27.3 (19)
Weaning index [e]				
Mean% ± S.D. per dam	97.2 ± 5.3	98.8 ± 3.8	99.3 ± 2.9	98.6 ± 5.9 (18)
Number of external abnormalities [f]	0	0	0	0
Mean% ± S.D. per dam	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0 (19)

a): (Number of dams with live offspring/number of pregnant dams)×100.
b): Number of male offspring/(number of male offspring + number of female offspring)
c): (Number of live offspring at birth/number of implantation scars)×100.
d): (Number of live offspring 4 days after birth/number of live offspring at birth)×100.
e): (Number of live offspring 21 days after birth/number of live offspring after culling)×100.
f): Number of external abnormalities in live offspring at birth.
Figures in parentheses indicate number of dams.
Significantly different by dose response analysis (##: p<0.01 by Jonckheere's test).
Significantly different from the control group (*: p<0.05 by Steel's test).

Body Weight: Absolute BW was decreased in pups born to HDF (birth to weaning: -14 to - 20%; weaning to end of study: M= -11 to -12%; F= -7 to -10%).

Developmental Milestones: Vaginal opening was delayed in HDF pups (Day 36: C= 75% vs. HD= 47%; Day 37: C= 94% vs. HD= 69%). However, all females in each dose

group exhibited vaginal opening by Day 39. Preputial separation was also delayed in HDM pups (Day 43: C= 92% vs. HD= 67%; Day 44: C= 100% vs. HD= 83%). All pups in the HD exhibited preputial separation by Day 52.

Neurological Assessment: There were no test article-related effects on righting reflex at Day 7, negative geotaxis at Day 14, air righting reflex at Day 17, or on corneal and pinna reflex at Day 17. There were no test article-related effects on motor activity when assessed in the open field test 4 weeks after birth. Performance in the multiple T-maze was not affected in a dose-dependent manner when assessed 6 to 7 weeks after birth. Auditory function was not assessed in this study.

Necropsy: There were no test article-related findings in the gross necropsy performed on PND 56.

Reproduction: There was no test article-related effect on copulation index, the number of days until copulation after pairing, the number of pregnant females, BW and BW gain during pregnancy, number of corpora lutea, number of implantation site, implantation rate, number of pre- or post-implantation losses, or the number of live embryos.

10 Special Toxicology Studies

10.1 Juvenile Toxicology Studies

10.1.1 Rat

Study Title: E2007: A Dose Range-Finding Oral Toxicity Study in the Juvenile Rat

Study no.:	901162
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8/16/2006
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	E2007, Lot 14110902, 99.6%

Key Study Findings

- **The MTD in this study was 3 mg/kg.**
- **The NOAEL in this study was <1.5 mg/kg. At all doses tested, adverse clinical signs were observed.**

Methods

Doses:	Design of study is given below
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% (w/v) methylcellulose
Species/Strain:	Sprague-Dawley [Crl:CD(SD)] rats

Study Design: Rat pups were given a daily dose of E2007 from postnatal day (PND) 7 to PND 11 or for 3 weeks beginning on PND 7 (Sponsor's Tables, below). Initiation of dosing on PND 7 is considered appropriate for a juvenile toxicity study in rats.

Table 1 Subacute Phase I

Group No. Identification	Dose Level (mg/kg)	Dosing Period	No. of Litters	No. of Pups	
				Males	Females
1 Vehicle Control	0	Days 7-11 *pp*	1	4	4
2 E2007	100	Day 7 *pp*	1	4	4
3 E2007	10	Days 8-11 *pp*	1	4	4
4 E2007	30	Days 8 *pp*	1	4	4
5 E2007	3	Days 9 and 10 *pp*	1	4	4

Table 2 Subacute Phase II

Group No. Identification	Dose Level (mg/kg)	Dosing Period	No. of Litters	No. of Pups	
				Males	Females
1 Vehicle Control	0	Days 7-11 *pp*	1	4	4
2 E2007	1	Days 7-11 *pp*	1	4	4
3 E2007	3	Days 7-11 *pp*	1	4	4
4 E2007	6	Days 7-11 *pp*	1	4	4
5 E2007	2	Days 9 and 10 *pp*	1	4	4

Table 3 Subchronic Phase

Group No Identification	Dose Level (mg/kg)	Dosing Period	Number of Animals					
			Main Study Phase			Toxicokinetic Phase**		
			No of Litters.	No. of Pups		No of Litters	No. of Pups	
				♂	♀		♂	♀
1 Vehicle Control	0	Day 7 *pp*	2	8	8	-	-	-
2 E2007	1.5	Day 7 *pp*	2	8	8	16	60	60
3 E2007	3	Day 7 *pp*	2	8	8	16	60	60
4 E2007	4.5	Day 7 *pp*	2	8	8	16	60	60
5 E2007*	3/4.5	Day 7 *pp*	2	8	8	16	60	60
Additional Toxicokinetic Phase:								
6 E2007***	3	Day 7 *pp*	NA	NA	NA	NA	45	45
7 E2007***	4.5	Day 7 *pp*	NA	NA	NA	NA	45	45
8 E2007***	6	Day 7 *pp*	NA	NA	NA	NA	45	45

* The dose level for Group 5 was increased from 3 mg/kg to 4.5 mg/kg on Day 14 *pp*.

** Groups 2 to 5 Toxicokinetic Phase included the dosing of 4 additional pups/sex/group as spares.

*** Groups 6 to 8 were dosed on a single occasion (Day 10, 14 or 17 *pp*) and a blood sample was taken for additional TK evaluation.

Analysis of Dosing Formulations: All dosing solutions were within 10% of the nominal concentration.

Mortality: Mortality was observed in groups dosed with > 3 mg/kg E2007 (100% at 100 mg/kg, 100% at 30 mg/kg, 75% at 10 mg/kg, 87% at 6 mg/kg, 37% at 4.5 mg/kg, 12.5% when animals were started at 4.5 mg/kg and then reduced to 3 mg/kg). Given these results, the MTD for this study, as identified in the subchronic phase, is 3 mg/kg.

Clinical Signs: Test article-related clinical signs (lying on side, decreased respiration, excessive scratching, head shaking, and incoordination) were observed in all dose groups of the subchronic study (Sponsor's Table). Due to the severe clinical signs observed at 4.5 mg/kg, the dose was lowered to 3 mg/kg on Day 10.

Table 2 Incidence of Clinical Observations

Subchronic Phase - Main Subgroup
F1 Generation

Group 1 - Vehicle Control
Group 2 - E2007 1.5 mg/kg
Group 3 - E2007 3 mg/kg
Group 4 - E2007 4.5 mg/kg
Group 5 - E2007 3/4.5# mg/kg

	Number of Animals Exhibiting Clinical Observations										
	Males					Sex	Females				
Observations	1	2	3	4	5	Group	1	2	3	4	5
Number of animals per group	8	8	8	8	8		8	8	8	8	8
Activity, decreased	1	1	8	8	8		.	.	8	8	8
Cold to touch	1	1	1	4	.		.	.	.	1	.
Dehydrated, suspected	1	.	.	.	.		.	.	.	.	.
Empty stomach suspected	1	.	1	4	1		.	.	.	1	.
Lying on side	.	8	8	8	8		.	8	8	8	8
Respiratory rate, decreased	.	5	8	8	8		.	8	8	8	8
Uncoordinated	.	8	7	5	8		.	8	8	5	7
Excessive scratching	.	7	7	.	7		.	8	8	.	7
Head shaking	.	7	5	.	7		.	8	7	.	7
Skin, pallor	1	1	.	2	1		.	.	.	.	.
Skin, papule, ventral thoracic	.	.	1	.	.		.	.	.	.	.
Tail, tattoo injury	.	.	.	.	.		.	.	1	.	.
Thin	1	.	1	.	.		.	.	3	1	1

The group 5 dose level was increased on day 14 post partum

Body Weights and Food Consumption: There were no dose-related effects on BW in Subacute Phase I. BW gain between Day 7 and Day 11 in rats dosed with 3 mg/kg was 57% of vehicle control in Subacute Phase II. In the subchronic phase of the study, BW gain was initially depressed in the 3 mg/kg dose group by 16%, relative to control, but beginning on Day 10 and continuing until the end of the study, there were no differences in any dose group in BW gain, relative to control. Food consumption was slightly lower, compared to control, in all dose groups in the subchronic study between Day 21 and Day 24.

Gross Pathology: There were no test article-related findings in the subacute or subchronic studies.

Histopathology: Adequate Battery: No, only adrenal, brain, eye, heart, kidney, liver, lung, lymph node, spleen, thymus, and uterus were assessed in the subchronic study. There were no dose-related findings.

Toxicokinetics: TK assessment (Sponsor's table, below) was performed only during the subchronic study. Plasma levels of E2007 were higher in pups before weaning (< PND21) than in weaned pups (> PND 21). There were no sex-related differences in plasma concentrations of E2007.

Table 13 Toxicokinetic Summary

Dose (mg/kg)	Day (*post partum*)	Male		Female	
		C_{max} (ng/mL)	AUC_{024h} (ng·h/mL)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)
1.5	7	270	3110	195	2741
	14	244	3736	347	5471
	21	158	1290	220	1754
	28	195	870	143	920
3	7	421	5178	302	4738
	14	652	8128	643	8768
	21	355	3109	324	3210
	28	352	2331	382	2664
4.5	7	635	10080	501	9043
3/4.5	7	408	7202	405	6561
	14	1127	14775	827	13075
	21	313	2229	341	3062
	28	307	2313	-	-

Study Title: E2007: A 12-Week Oral Gavage Toxicity Study in the Juvenile Rat Followed by a 4-Week Recovery Period

Study no.:	901163
Study report location:	EDR
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	11/15/2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 14110902, 99.9%

Key Study Findings

- **Due to clinical signs (e.g. uncoordination and excessive grooming) observed at every dose level, the NOAEL in this study is < 1 mg/kg.**
- **Crown-to-rump measurements and absolute BW were decreased in rats given a dose of E2007 that was titrated from 3 mg/kg to 30 mg/kg (HD). This decrease persisted at the end of the recovery period. Bone density was not assessed.**
- **Vaginal opening and preputial separation were delayed in HD animals, relative to vehicle controls.**
- **Decreased hind limb grip strength was observed at Week 5 and Week 11 but not at the end of the recovery period in animals dosed with ≥ 3 mg/kg.**
- **Hindlimb foot splay was decreased, relative to controls, in all dose groups throughout the dosing period and at the end of the recovery period.**
- **MDF and HDF exhibited an increased error rate in Path B of the Cincinnati water maze during the dosing phase. This finding was present at the end of the recovery phase, but the magnitude of effect was small at both doses.**
- **Adrenal, thyroid, heart, and kidney weights were decreased in MD and HD animals. However, there was no histopathology correlate to these findings.**
- **Except in a few HD animals, test article-related histopathology findings were limited. In 1 HDM, seminiferous tubule atrophy and epididymal aspermia were observed at the end of the dosing phase. Hyperplasias of the squamous epithelium of the stomach and of the urinary bladder transitional cells were observed in two separate HDFs.**
- **Females exhibited higher plasma levels than males at most sampling time points.**
- **Post weaning plasma levels of E2007 were similar to those observed in adult rats dosed at the same levels used in this study. Pre-weaning plasma levels of E2007 were 2 to 3.5-fold higher than those observed in adults.**

Methods

Doses:	See Sponsor's Table, below
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Sprague-Dawley (Crl:CD[SD]) rat
Number/Sex/Group:	See Table below
Age:	Dosing was initiated at PND 7
Weight:	12-20 g at dosing initiation
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Study Design: The dose range employed in this study was based upon the results of the dose range-finding study performed in juvenile rats (Study 901162). In the dose range-finding study, the MTD was determined to be 3 mg/kg, with higher doses resulting in marked mortality. In order to investigate a dose higher than 3 mg/kg, the Sponsor included a dose group in which the dose was titrated from 3 to 10 to 30 mg/kg over the course of 48 days (Group 4).

Text Table 3 Study Design

Phase I

Group No. ID	Dose Level (mg/kg)	No. of Litters	Main Study Subgroup (A)		Neurobehavioral/ Recovery Subgroup (B)		Reproductive Subgroup (C)		Toxicokinetic Subgroup on Days 63 & 90 *pp* (D)	
			M	F	M	F	M	F	M	F
1/ Control	0	15	15	15	15	15	15	15	4	4
2/ E2007	1	15	15	15	15	15	15	15	10	10
3/ E2007	3	15	15	15	15	15	15	15	10	10
4/ E2007	3→10→30[a]	15	15	15	15	15	15	15	10	10

M = Male, F = Female, *pp* = *post partum*

a = Dose ramping schedule: 3 mg/kg (Days 7 to 27 *pp*), 10 mg/kg (Days 28 to 55 *pp*), 30 mg/kg (Days 56 *pp* to terminal necropsy).

One pup/sex/litter was assigned to each of Subgroups A, B, C and D or was designated as dosed spares (*i.e.*, 1/sex/litter to A, B, and C, 10/sex/litter for D – with only 4/sex/litter for D control group)

Phase II

Group No. ID	Dose Level (mg/kg)	No. of Litters	Toxicokinetic Subgroup on Day 7 or 14 *pp* (E)		No. of Litters	Toxicokinetic Subgroup on Day 35 *pp* (F)	
			M	F		M	F
1/ Control	0	1	4[c]	4[c]	1	4	4
2/ E2007	1	5	20[c]	20[c]	5	20	20
3/ E2007	3	5	20[c]	20[c]	5	20	20
4/ E2007	3→10[b]	5	20[d]	20[d]	5	20	20

M = Male, F = Female, *pp* =*post partum*

b = Dose ramping schedule: 3 mg/kg (Days 7 to 27 *pp*), 10 mg/kg (Days 28 to 35 *pp*

c = Plasma samples were collected on Day 7 *pp*

d = Plasma samples were collected on Day 14 *pp*

Dosing Formulation Analysis: Dosing solutions were within 6% of the nominal concentration.

Mortality: Litter # 166 (vehicle control) was euthanized due to signs of cannibalism. Two LDM were found dead (Dam #266/ Pup #4- gavage accident; Dam #255/ Pup #2- no abnormal findings on Day 20 and Day 14, respectively). On postnatal day 8-10, two MDF (Dam #357/ Pup #8-cannibalism; Dam # 366/ Pup #6- missing) and one MDM (Dam #361/ Pup #4-missing) were either found dead or missing. Two HDM (Dam #458/ Pup #2- no abnormal findings; Dam #469/ Pup #4-missing) and two HDF (Dam #456/ Pup #7- no abnormal findings; Dam #456/ Pup #8- missing) were either found dead or missing between PND 8-9.

Clinical Signs: In suckling pups, the most prominent clinical signs were decreased activity (PND-7-19), incoordination (PND 9-20), lateral recumbence (PND 7-19), excessive grooming (PND 16-18), and excessive scratching in pups (beginning on PND 12) dosed with 3 mg/kg (Sponsor's Table 2, below). After weaning, the main clinical signs observed in all dose groups were changes in activity (decreased or increased), incoordination, excessive grooming, excessive licking, excessive scratching, and partial palpebral closure (Sponsor's Table 4). The intensity and incidence of these clinical signs increased in a dose-dependent manner. The Sponsor states that clinical signs lasted for several hours but were not observed just prior to administration of the next dose.

Table 2 Incidence of Clinical Observations (Cage Side Observations)

F1 Generation - Pre-Weaning
Males

Group 1 - Vehicle Control
Group 2 - E2007 1 mg/kg
Group 3 - E2007 3 mg/kg
Group 4 - E2007 3[d]/10[e]/30[f] mg/kg

		Day Post Partum													
Observation	Group	7	8	9	10	11	12	13	14	15	16	17	18	19	20
		L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)
Activity Decreased	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	2	4 (16)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	3	12 (48)	16 (64)	16 (62)	16 (63)	16 (59)	16 (60)	15 (59)	16 (63)	15 (59)	15 (58)	14 (51)	9 (33)	2(2)	0 (0)
	4	12 (48)	16 (63)	16 (61)	16 (62)	16 (62)	16 (57)	16 (62)	14 (54)	16 (62)	15 (57)	15 (53)	10 (39)	4 (15)	0 (0)
Uncoordinated	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (8)	3 (6)	4 (13)	2 (4)	0 (0)	0 (0)
	3	0 (0)	0 (0)	3 (4)	0 (0)	5 (6)	4 (4)	3 (4)	4 (5)	6 (15)	5 (12)	7 (15)	10 (25)	6 (23)	2 (8)
	4	0 (0)	0 (0)	2 (2)	7 (9)	5 (6)	5 (9)	3 (4)	6 (17)	1 (1)	4 (7)	10 (16)	4 (13)	5 (13)	5 (17)
Lying on Side	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	2	4 (16)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	3	12 (48)	16 (64)	16 (62)	15 (59)	16 (58)	12 (44)	10 (37)	3 (11)	2 (7)	2 (8)	1 (4)	0 (0)	2 (2)	0 (0)
	4	12 (48)	15 (59)	16 (61)	16 (58)	14 (51)	15 (49)	12 (46)	4 (11)	0 (0)	3 (9)	0 (0)	0 (0)	0 (0)	0 (0)

		Day Post Partum													
Observation	Group	7	8	9	10	11	12	13	14	15	16	17	18	19	20
		L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)
Excessive Grooming	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (1)	1 (1)	0 (0)	0 (0)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (4)	3 (6)	0 (0)	0 (0)
	4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Excessive Scratching	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	1 (4)	2 (5)	2 (2)	1 (1)
	4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (4)	2 (5)	2 (8)	1 (1)	3 (6)

L = Litters affected
P = Pups affected

Table 2 Incidence of Clinical Observations (Cage Side Observations)

F1 Generation - Pre-Weaning
Females

Group 1 - Vehicle Control
Group 2 - E2007 1 mg/kg
Group 3 - E2007 3 mg/kg
Group 4 - E2007 3[d]/10[e]/30[f] mg/kg

		Day Post Partum													
Observation	Group	7	8	9	10	11	12	13	14	15	16	17	18	19	20
		L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)
Activity Decreased	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	2	4 (16)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	3	12 (48)	16 (63)	16 (60)	16 (62)	16 (58)	16 (59)	15 (58)	16 (62)	15 (58)	15 (56)	14 (50)	9 (35)	0 (0)	0 (0)
	4	12 (48)	16 (63)	16 (62)	16 (62)	16 (59)	16 (57)	16 (61)	14 (54)	16 (62)	15 (56)	15 (53)	10 (40)	4 (16)	0 (0)
Uncoordinated	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	2	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	3 (10)	3 (5)	6 (16)	1 (4)	0 (0)	0 (0)
	3	0 (0)	0 (0)	2 (2)	1 (1)	2 (3)	3 (4)	1 (1)	6 (7)	7 (13)	7 (14)	8 (15)	8 (23)	6 (23)	3 (10)
	4	0 (0)	0 (0)	0 (0)	3 (5)	3 (4)	3 (7)	5 (5)	7 (18)	2 (2)	4 (8)	8 (14)	4 (11)	6 (18)	4 (14)
Lying on Side	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	2	4 (16)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	3	12 (48)	16 (63)	16 (60)	16 (59)	16 (58)	12 (45)	10 (37)	4 (12)	2 (7)	2 (8)	1 (4)	1 (2)	0 (0)	0 (0)
	4	12 (48)	15 (60)	16 (62)	16 (60)	14 (50)	15 (53)	12 (44)	3 (9)	0 (0)	2 (8)	0 (0)	0 (0)	0 (0)	0 (0)

		Day Post Partum													
Observation	Group	7	8	9	10	11	12	13	14	15	16	17	18	19	20
		L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)	L (P)
Excessive Grooming	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	2 (3)	1 (4)	0 (0)	0 (0)
	4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Excessive Scratching	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	1 (4)	1 (4)	1 (2)	2 (5)
	4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	2 (2)	0 (0)	0 (0)	1 (4)	2 (5)	2 (8)	2 (5)	2 (4)

L = Litters affected
P = Pups affected

d Dosed Day 7 to 27 Post Partum

e Dosed Day 28 to 55 Post Partum

f Dosed Day 56 Post Partum until termination

Text Table 4 Incidence of Clinical Signs (Post Weaning)

Observation:	Sub-group	Group 1 0 mg/kg		Group 2 1 mg/kg		Group 3 3 mg/kg		Group 4 3/10/30 mg/kg					
		♂	♀	♂	♀	♂	♀	♂			♀		
	Dose	0	0	1	1	3	3	3*	10*	30*	3*	10*	30*
No. of animals assessed/day	A	15	15	15	15	15	15	15	15	15	15	15	15
	B	15	15	15	15	15	15	15	15	15	15	15	15
Activity decreased	A	-	-	4	3	12	10	7	15	8	1	14	7
	B	-	-	4	1	13	13	6	15	8	3	13	7
Activity increased	A	-	-	4	1	4	6	0	1	0	0	3	4
	B	-	-	5	5	5	9	0	1	2	0	3	6
Uncoordinated	A	-	-	9	13	15	15	15	15	15	15	15	15
	B	-	-	12	13	15	15	15	15	15	15	15	15
Excessive grooming	A	-	-	12	13	15	15	5	15	15	5	15	15
	B	-	-	12	13	15	15	11	15	15	3	15	14
Excessive licking	A	-	-	1	4	10	9	0	11	5	0	12	8
	B	-	-	2	8	11	9	4	12	10	3	13	8
Excessive scratching	A	-	-	15	15	15	15	10	15	15	12	15	15
	B	-	-	15	15	15	15	9	14	15	8	15	15
Eye partially closed, left	A	-	-	2	1	14	9	5	14	6	7	15	10
	B	-	-	2	-	12	14	7	13	8	11	15	6
Eye partially closed, right	A	-	-	2	1	14	9	5	14	6	7	15	10
	B	-	-	2	-	12	14	7	13	8	11	15	6

* 3 mg/kg: *pp* 7-27, 10 mg/kg: *pp* 28-55, 30mg/kg: *pp* 56 to euthanasia

Body Weights and Food Consumption: Absolute BW in rats dosed with 3 mg/kg was decreased by 15-18% at weaning, relative to control. This decrease (16-22%, relative to control) in absolute BW persisted in HD rats to the end of the dosing period (Sponsor's Figures 1-4, below) and throughout the recovery period (~24-34%, relative to control). These findings are consistent with the decrease in food consumption observed in MD and HD animals during the course of the study.

Figure 1 **Group Mean Body Weights - F_1 Generation Adults - Subgroup A - Males**

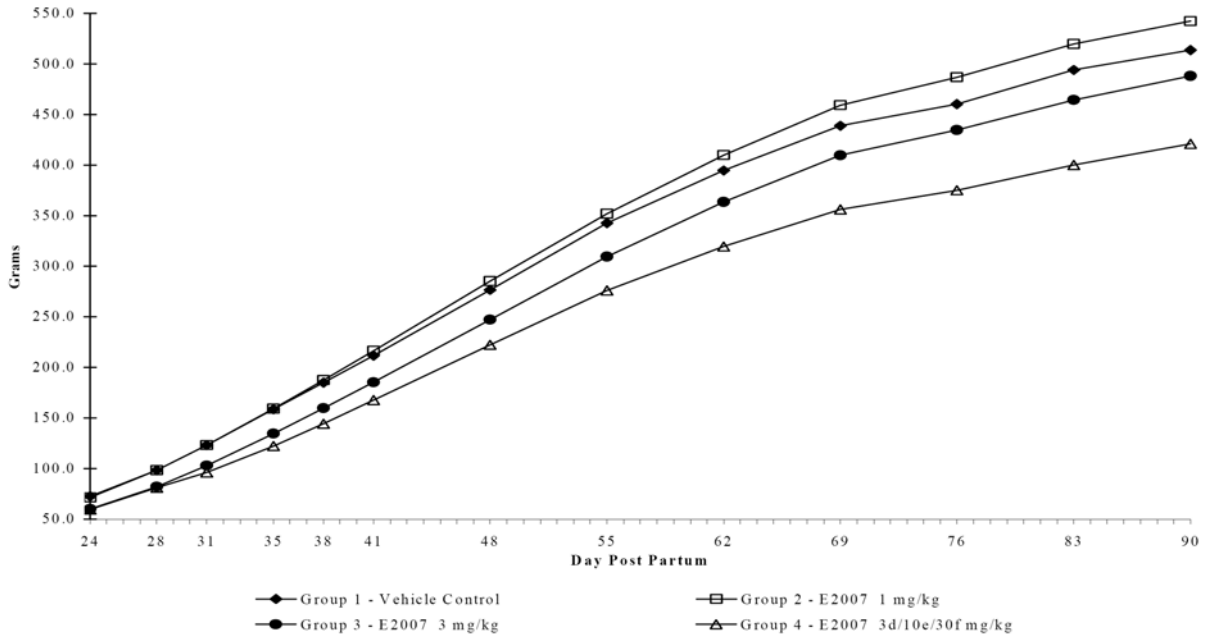


Figure 2 **Group Mean Body Weights - F_1 Generation Adults - Subgroup A - Females**

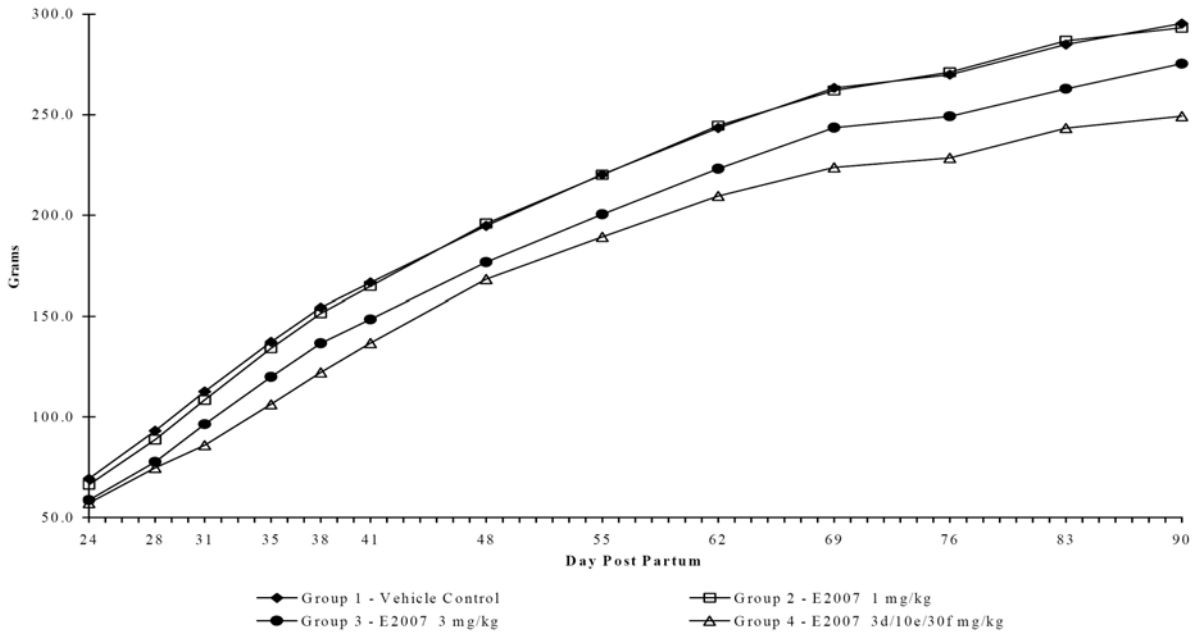


Figure 3 **Group Mean Body Weights - F_1 Generation Adults - Subgroup B - Males**

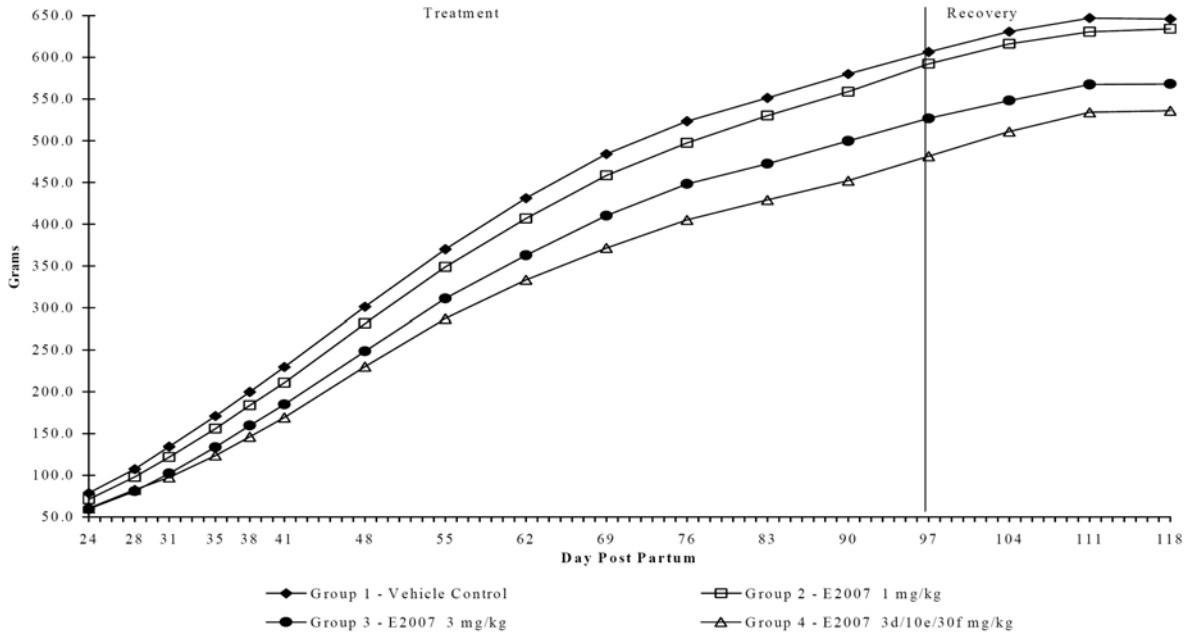
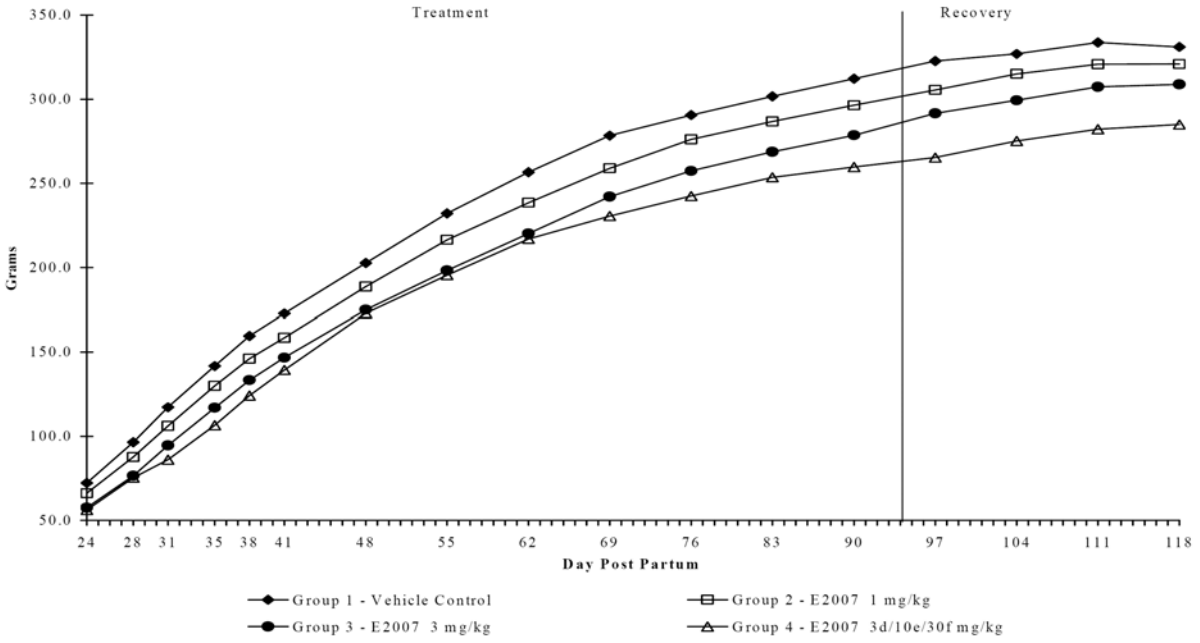


Figure 4 **Group Mean Body Weights - F_1 Generation Adults - Subgroup B - Females**



Growth and Developmental Landmarks: Crown-to-rump length was decreased in animals dosed with 3 mg/kg, on PND 17 (-4%) and PND 21 (-8%). Post-weaning, the lower crown-to rump length persisted in the MD (approximately -6%) and HD (approximately -8%) animals throughout the dosing period and to the end of the recovery period in HD animals (-6%).

Preputial Separation: Preputial separation was delayed by 2.3-3.5 days in HDM.

Vaginal Opening: Vaginal opening in HDF was delayed by 4.2-6.4 days.

Ophthalmoscopy: Opthalmoscopy assessment was performed on PND 84-86 for Subgroup A and B and an additional assessment was performed on PND 115-123 in Subgroup B. There were no test article-related findings.

Behavioral Assessment: Behavioral assessment was performed during Weeks 5, 11, and 16. Measures of motor activity, behavior, coordination, body temperature, and sensory-motor function were included in the Sponsor's observational assessment.

a) Observational Assessment: Dosing with perampanel did not cause abnormal alterations in body position, clinical signs, ease of removal from home cage, vocalization, palpebral closure, arousal, grooming, defecation, urination, olfactory response, lacrimation, pupil size, salivation, body tone, respiratory rate, corneal reflex, pinna reflex, toe pinch, tail pinch, visual placing, auricular startle, body temperature, or air righting.

A dose-dependent decrease in hindlimb grip strength was observed in MDM, MDF, HDM, and HDF animals at Week 5 and in MDF and HDF at Week 11 (Sponsor's Table, below). There was no observed effect on hindlimb grip strength at the end of the recovery period. Hindlimb splay was affected throughout the dosing period and into the recovery period. When assessed during Week 5 and Week 11, hindlimb splay was decreased in all male and female dose groups. This decrease persisted during the recovery period (week 16). The Sponsor attributed these findings to the fact that treated animals were smaller than controls. However, LD animals, in which limb splay was also affected, did not exhibit a consistent difference in size or BW, relative to control animals, during the study.

Table 14 Group Mean Functional Observational Battery

Subgroup B - Males: Week 5 of Dosing

	Group 1 Vehicle Control		Group 2 E2007 1 mg/kg		Group 3 E2007 3 mg/kg		Group 4 E2007 3[d]/10[e]/30[f] mg/kg	
Category	No. 15	% 100.0	No. 15	% 100.0	No. 15	% 100.0	No. 15	% 100.0
Forelimb								
Grip Strength (g)								
Mean	546.1		504.5		475.9		499.5	
SD	57.1		75.5		81.4		90.9	
Hindlimb								
Grip Strength (g)								
Mean	342.8		314.4		294.9B		288.7C	
SD	29.8		48.0		37.7		37.0	
Hindlimb Splay (cm)								
Mean	8.13		5.65C		5.54C		5.53C	
SD	1.46		1.43		1.38		1.67	

Significantly different from control group (group 1) value: * - P≤0.05 ** - P≤0.01 *** - P≤0.001 (Fisher)
A - P≤0.05 B - P≤0.01 C - P≤0.001 (Dunnett)
D - P≤0.05 E - P≤0.01 F - P≤0.001 (Dunn)

Subgroup B - Females: Week 5 of Dosing

	Group 1 Vehicle Control		Group 2 E2007 1 mg/kg		Group 3 E2007 3 mg/kg		Group 4 E2007 3[d]/10[e]/30[f] mg/kg	
Category	No. 15	% 100.0	No. 15	% 100.0	No. 15	% 100.0	No. 15	% 100.0
Forelimb								
Grip Strength (g)								
Mean	517.5		518.5		464.7		470.7	
SD	68.2		82.4		63.5		65.2	
Hindlimb								
Grip Strength (g)								
Mean	319.8		302.7		275.9 A		268.9 B	
SD	42.2		62.0		28.5		26.4	
Hindlimb Splay (cm)								
Mean	5.94		5.18		5.01		4.91	
SD	1.60		1.37		1.18		1.24	

Significantly different from control group (group 1) value: * - P≤0.05 ** - P≤0.01 *** - P≤0.001 (Fisher)
A - P≤0.05 B - P≤0.01 C - P≤0.001 (Dunnett)
D - P≤0.05 E - P≤0.01 F - P≤0.001 (Dunn)

Subgroup B - Males: Week 11 of Dosing

	Group 1 Vehicle Control		Group 2 E2007 1 mg/kg		Group 3 E2007 3 mg/kg		Group 4 E2007 3[d]/10[e]/30[f] mg/kg	
Category	No. 15	% 100.0	No. 15	% 100.0	No. 15	% 100.0	No. 15	% 100.0
Hindlimb								
Grip Strength (g)								
Mean	781.9		729.9		696.5		673.4	
SD	110.2		118.0		113.1		124.3	
Hindlimb Splay (cm)								
Mean	9.43		7.52 A		7.81		7.43 A	
SD	1.80		1.88		2.36		1.75	

Subgroup B - Females: Week 11 of Dosing

	Group 1 Vehicle Control		Group 2 E2007 1 mg/kg		Group 3 E2007 3 mg/kg		Group 4 E2007 3[d]/10[e]/30[f] mg/kg	
Category	No. 15	% 100.0	No. 15	% 100.0	No. 15	% 100.0	No. 15	% 100.0
Hindlimb								
Grip Strength (g)								
Mean	657.1		595.0		550.5 B		545.3 C	
SD	79.1		91.0		81.2		61.6	
Hindlimb Splay (cm)								
Mean	6.85		6.00		6.23		5.96	
SD	1.97		1.96		1.68		2.06	

Subgroup B - Males: Week 16 - End of Recovery

	Group 1 Vehicle Control		Group 2 E2007 1 mg/kg		Group 3 E2007 3 mg/kg		Group 4 E2007 3[d]/10[e]/30[f] mg/kg	
Category	No. 15	% 100.0	No. 15	% 100.0	No. 15	% 100.0	No. 15	% 100.0
Hindlimb Splay (cm)								
Mean	9.83		8.49		7.93		7.24 A	
SD	2.13		2.67		2.60		1.94	

Subgroup B - Females: Week 16 - End of Recovery

Category	Group 1 Vehicle Control No.	Group 1 Vehicle Control %	Group 2 E2007 1 mg/kg No.	Group 2 E2007 1 mg/kg %	Group 3 E2007 3 mg/kg No.	Group 3 E2007 3 mg/kg %	Group 4 E2007 3[d]/10[e]/30[f] mg/kg No.	Group 4 E2007 3[d]/10[e]/30[f] mg/kg %
	15	100.0	15	100.0	15	100.0	15	100.0
Hindlimb Splay (cm)								
Mean	7.13		6.49		6.71		5.83	
SD	2.02		2.11		2.02		2.25	

b) Motor Activity: There was no test article-related effect on motor activity when assessed at Weeks 5, 11, or 16.

c) Auditory Startle: There was no test article-related effect on motor activity when assessed at Weeks 5, 11, or 16.

d) Cincinnati Water Maze: Water maze testing was performed during Week 10 of the study while animals were still being dosed. A consistent increase in the number of errors was observed in MDF and HDF when performing Path B, a more difficult task than Path A in the Cincinnati water maze (See Sponsor's Table 19, below). Although there was a slight increase in the number of errors in female rats when Path B of the water maze was performed at the end of the recovery period, the magnitude of effect was not as great as was observed during week 10 (See Table 19, below).

Table 19 Group Mean Cincinnati Water Maze Performance - Errors

Subgroup A - Main
Week 10 to 11 of Dosing
Path B - Females

Group 1 - Vehicle Control
Group 2 - E2007 1 mg/kg
Group 3 - E2007 3 mg/kg
Group 4 - E2007 3[d]/10[e]/30[f] mg/kg

Group	Summary Information	Trial Number 1	2	3	4	5	6
1	Mean	12.5	8.0	5.5	1.4	1.3	0.5
	SD	7.7	9.0	8.5	3.1	3.9	1.6
	N	15	15	15	15	15	15
2	Mean	19.1	9.1	4.9	0.5	1.7	1.2
	SD	8.1	8.7	6.5	1.6	4.9	3.9
	N	15	15	15	15	15	15
3	Mean	18.0	9.7	6.8	3.1	2.7	1.6
	SD	9.9	7.5	6.8	5.2	7.4	6.2
	N	15	15	15	15	15	15
4	Mean	23.4 E	12.9	6.7	4.6	4.6	2.9
	SD	11.1	8.8	9.3	9.1	8.3	10.0
	N	15	15	15	15	15	15

Significantly different from control group (group 1) value: D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table 19 Group Mean Cincinnati Water Maze Performance - Errors

Subgroup B - Recovery
Week 17 of Dosing
Path B - Females

Group 1 - Vehicle Control
Group 2 - E2007 1 mg/kg
Group 3 - E2007 3 mg/kg
Group 4 - E2007 3[d]/10[e]/30[f] mg/kg

Group	Summary Information	Trial Number 1	2	3	4	5	6
1	Mean	11.0	2.7	2.4	0.7	0.1	0.2
	SD	8.7	3.5	3.2	1.9	0.4	0.6
	N	15	15	15	15	15	15
2	Mean	11.7	3.9	1.3	0.3	0.1	0.3
	SD	6.6	5.0	2.2	0.6	0.3	0.8
	N	15	15	15	15	15	15
3	Mean	13.1	4.9	5.1	0.6	0.3	0.0
	SD	8.1	6.9	10.2	1.8	0.6	0.0
	N	15	15	15	15	15	15
4	Mean	14.3	6.0	4.7	1.3	0.3	0.3
	SD	11.1	7.9	6.5	2.8	1.0	0.6
	N	15	15	15	15	15	15

Significantly different from control group (group 1) value: D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

F_1 Reproductive Performance: Reproductive performance was assessed beginning with cohabitation on PND 86. There were no test article-related effects on the number of days in estrus, the number of estrous cycles or the average cycle length, the number of days to mating, the mating index, fertility index, conception rate, number of corpora lutea, implantation sites, or live embryos.

Hematology and Clinical Chemistry: There were no test article-related findings.

Gross Pathology: There was no effect of the test article on brain length or width.

Urinalysis: An increase in sodium and chloride levels in the urine of MDM, HDM, MDF, and HDF was observed at the end of the dosing period but not at the end of the recovery period (Sponsor's table, below). Chloride was also elevated in the urine of LDF. As discussed below, there were no test article-related findings in the histopathology assessment of the kidneys at the end of the dosing period.

Table 22 Group Mean Urinalysis

F1 Generation - Adults
Subgroup A - Males

Group 1 - Vehicle Control
Group 2 - E2007 1 mg/kg
Group 3 - E2007 3 mg/kg
Group 4 - E2007 3[d]/10[e]/30[f] mg/kg

		Electrolytes		
Group	Summary Information	NA mmol/L	K mmol/L	CL mmol/L
1	Mean	80.5	237.251	92.6
	SD	46.6	99.150	70.6
	N	10	10	10
2	Mean	66.3	249.447	79.5
	SD	38.1	49.783	46.1
	N	10	10	10
3	Mean	98.7	290.423	131.3
	SD	33.8	75.723	48.6
	N	10	10	10
4	Mean	147.7 B	309.812	186.4 B
	SD	42.4	61.369	42.8
	N	10	10	10

Significantly different from control group (group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

F1 Generation - Adults
Subgroup A - Females

Group 1 - Vehicle Control
Group 2 - E2007 1 mg/kg
Group 3 - E2007 3 mg/kg
Group 4 - E2007 3[d]/10[e]/30[f] mg/kg

		Electrolytes		
Group	Summary Information	NA mmol/L	K mmol/L	CL mmol/L
1	Mean	65.7	207.715	66.8
	SD	26.7	49.494	33.4
	N	10	10	10
2	Mean	79.5	223.915	108.9 A
	SD	16.3	60.868	30.6
	N	10	10	10
3	Mean	92.5 A	232.334	115.8 A
	SD	23.5	77.633	46.5
	N	10	10	10
4	Mean	101.3 B	183.739	125.2 B
	SD	29.0	41.673	40.1
	N	10	10	10

Significantly different from control group (group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Organ Weights: In rats euthanized at the end of the dosing phase, a decrease in adrenal (C= 67 mg, HD= 57 mg) and thyroid (C= 27.7 mg, MD= 23.3 mg, HD= 23.3 mg) weight was observed in males. There was no difference in the weight of these organs in males at the end of the recovery period. Heart weight was decreased in HDF (C=1.13 g, 0.96 g) at the end of the dosing period and in MDF and HDF at the end of the recovery period (C=1.2 g, MDF= 1.08 g, HDF= 1.08 g). Kidney weights were also decreased in females, relative to control at the end of the dosing phase (C=1.96 g, MDF= 1.77 g,

HDF= 1.69 g) and at the end of the recovery period (C=2.03g, MDF= 1.788, HDF= 1.766 g).

Bone Density Assessment**:** Femur and tibia length were 3% shorter in HD, relative to controls. This finding persisted into the recovery phase of the study. Bone density was not assessed.

Histopathology: Adequate Battery: No, nasal turbinates/cavity and rectum not examined; Peer Review: Yes; Signed and Dated Pathologist's Report: Yes

Overall, there were limited test article-related findings in the histopathology assessment (Sponsor's table, below). At the end of the dosing period (Subgroup A), there was a finding, in one HDM (#4007), of bilateral atrophy of the seminiferous tubules of the testes and bilateral aspermia in the epididymis. Slight vacuolation of the adrenal cortex was observed in 1 CM, 2 MDM, and 2 HDM. In female rats, the only findings of interest were squamous cell hyperplasia of the stomach in 1 HDF and hyperplasia of the urinary bladder and kidney transitional cells in another HDF.

F1 Generation - Adults
Phase I - Subgroup - A - Main Study
MALE

DOSE GROUP		**1**	**2**	**3**	**4**
NUMBER OF ANIMALS EXAMINED		**10**	**10**	**10**	**10**
ADRENAL	EXAMIN:	10	10	10	10
- Vacuolation: cortical		1	-	2	2
DOSE GROUP		**1**	**2**	**3**	**4**
NUMBER OF ANIMALS EXAMINED		**10**	**10**	**10**	**10**
EPIDIDYMIS	EXAMIN:	10	10	10	10
- Oligo/aspermia		-	-	-	1
- Granuloma: spermatic		-	-	-	1
TESTIS	EXAMIN:	10	10	10	10
- Atrophy: seminiferous epithelium		-	-	-	1

F1 Generation - Adults
Phase I - Subgroup - A - Main Study
FEMALE

DOSE GROUP		1	2	3	4
NUMBER OF ANIMALS EXAMINED		10	10	10	10
STOMACH	EXAMIN:	10	10	10	10
- Hyperplasia: squamous mucosa		-	-	-	1
URINARY BLADDER	EXAMIN:	9	10	10	10
- Inflammation		-	-	-	1
- Hyperplasia: transitional cell		-	-	-	1

Neuropathology: The brain was assessed from animals at the end of the dosing and recovery phases. The brain was sectioned at 6 levels (olfactory bulb, forebrain (through septum), center of the cerebrum (through the hypothalamus), midbrain, cerebellum/pons, and mid-cerebellum (medulla oblongata). In addition, the retina, optic nerve, spinal cord (cervical, thoracic, and lumbar), sciatic nerve, trigeminal ganglion, and lumbar DRG were sampled and examined. There were no test article-related findings.

Toxicokinetics: Females exhibited higher plasma levels than males at most sampling time points (C_{max} up to 1.8-fold and AUC_{0-24hr} up to 2-fold; Sponsor's Table, below). LD rats exhibited plasma levels that were 2 to 3.5-fold higher than in adult animals given the same dose. Due to the design of the titration phase and the TK sampling scheme, direct comparison of plasma levels in juvenile animals dosed with 10 mg/kg could not be compared to the levels observed in adult animals. HD rats in the juvenile study exhibited plasma levels that were similar to those observed in adult animals given the same dose.

Text Table 2 Toxicokinetic Summary

Dose (mg/kg)	*pp*	Male			Female		
		C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
1	Day 7	171.73	3	2179.81	189.03	3	2009.02
	Day 35	257.98	1	563.66	316.56	1	1127.49
	Day 63	182.55	1	738.50	331.01	1	1583.54
	Day 90	162.88	1	869.05	305.04	1	1619.78
3	Day 7	418.97	3	6062.48	429.36	8	6409.32
	Day 35	412.06	1	2104.68	657.70	1	1946.14
	Day 63	339.98	1	1450.72	574.39	1	2677.69
	Day 90	340.54	1	1675.90	589.09	1	3017.73
3[a]/10[b]/30[c]	Day 14	662.74	8	9786.66	812.44	1	10449.86
	Day 35	1130.63	1	4295.77	1007.24	1	5679.14
	Day 63	597.51	1	5376.36	1056.25	1	8696.77
	Day 90	597.34	1	4729.57	1046.01	1	8841.50

a = Dosed from Days 7 to 27 *pp*
b = Dosed from Days 28 to 55 *pp*
c = Dosed from Day 56 *pp* until termination
Lower limit of quantification: 0.30 ng/mL

TK Data from 13-Week Study Conducted in Adult Rats (#S01008)

Report Title: E2007: A 13-Week Oral Toxicity Study in Rats Test Article: Perampanel

Species/Strain: Rats/Sprague Dawley | Duration of Dosing: 13 weeks | Study No.: S01008
Initial Age: 8 weeks | Duration of Post-dose: Not applicable | Location in CTD: 4.2.3.2.6
Date of First Dose: June 13, 2001 | Vehicle/Formulation: 0.5% MC solution | Testing Facility: Eisai
Special Feature: None | Methods of Administration: Oral by gavage | GLP Compliance: Yes
No Observed Adverse-Effect Level: 10 (M), 1(F) mg/kg

Daily Dose (mg/kg)	0 (Control)		1		10		30	
Number of Animals:	M:10	F: 10	M:10	F: 10	M:10	F: 10	M:10	F: 10[*]
Toxicokinetics:								
Cmax (ng/mL):								
Day 1	NA	NA	150.00	201.03	471.81	611.2	413.16	877.4
Day 28	NA	NA	168.20	226.31	540.55	1010.0	548.58	1241.3
Day 85	NA	NA	167.28	255.64	460.98	902.7	501.96	1137.9
AUC $_{(0\text{-}24h)}$ (ng·hr/mL):								
Day 1	NA	NA	473.65	851.55	3125.49	3866.7	4100.80	11107.5
Day 28	NA	NA	557.93	834.15	3278.53	4079.2	3837.80	8488.6
Day 85	NA	NA	631.80	998.50	3243.16	4318.9	5638.33	8454.1
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight (%[a])	457.3 g	253.6 g	+2.0	-1.2	-3.5	-8.0*	-7.7**	-8.9**
Food Consumption	21.0 g	14.0 g	-1.4	0	0	0	0	0
Clinical Observations								
Number examined	10	10	10	10	10	10	10	10
Abnormal gait	0	0	0	0	8	10	10	10
Decreased activity	0	0	0	0	0	4	3	10
Prostration	0	0	0	0	0	0	0	4
Mydriasis	0	0	0	0	0	5	2	2

10.1.2 Dog

Study Title: E2007: An Oral Dose-Range-Finding Toxicity Study in Juvenile Dogs

Study no.:	901978
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7/14/2009
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	E2007, Lot 16091902, 100%

Key Study Findings

- **The MTD in the repeat dose subchronic phase of this study was 7.5 mg/kg. Euthanasia *in extremis* was required in higher dose groups.**
- **Due to test article-related clinical signs, the NOAEL was <1 mg/kg.**
- **Dosing commenced at PND 42.**

Methods

Doses:	See sponsor's table below
Frequency of dosing:	Once daily; dosing from PND 42-72.
Route of administration:	Oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	0.5% (w/v) methylcellulose
Species/Strain:	Beagle dog, (b) (4)
Number/Sex/Group:	See below for study design
Age:	Age at dosing initiation was PND 42
Weight:	1.9-2.7 kg

Study Design: Dosing commenced at PND 42.

Group No. Identification	Dose Level (mg/kg/day)	Dose Conc. (mg/mL)	Dose Volume (mL/kg)	No. of Litters	Number of Pups	
					Male	Female
Acute Phase I (single dose)						
1 E2007	10	2	5	1	1	1
2 E2007	20	4	5		1	1
3 E2007	40	8	5		1	1
Subchronic Phase II (repeat dose – 28 days)						
1 E2007**	7.5	1.5	5	1	2	2
2 E2007**	10	2	5	1	2	2
3 E2007**+	5→10	1, 2	5	1	3	1
4 E2007**	1	0.2	5	1	1	3

\+ Ramping dose, dose increased on Study Day 11 (Day 55 *p p*).

** These litters contained 4 dosed pups and one or two undosed pups kept for comparative observation of clinical signs and body weight. The data from the two undosed pups per litter are not reported. Administrations in Subchronic Phase II were performed by the following order; Group 2 → Group 3 → Group 4 → Group 1.

Mortality: In the acute phase study, 1 HDF and 1 HDM were euthanized due to extreme clinical signs (labored breathing, tremors, prostration, excessive scratching/ chewing). In the subchronic study, 1 male (#203) and 1 female (#252) dosed with 10 mg/kg were euthanized due to severe clinical signs (up to 7 hours of ataxic gait, falling, uncoordination and tremors). Due to these findings, the MTD in the subchronic study is

considered to be 7.5 mg/kg.

Clinical Signs: In the acute phase of the study, pups dosed with 10 mg/kg exhibited uncoordination, prostration, abnormal gait, and loss of consciousness for up to 6 hours after dosing. In addition to these signs, pups dosed with 20 mg/kg exhibited vocalization, trembling, and excessive chewing. As described previously, pups dosed with 40 mg/kg exhibited excessive clinical signs that resulted in euthanasia *in extremis* of one male and one female.

In the subchronic phase of the study, test article-related clinical signs were observed in pups dosed with ≥1 mg/kg E2007 (Sponsor's Tables, below). Severe clinical signs in the 10 mg/kg resulted in euthanasia *in extremis* of one male and one female pup. Due to the severe signs at 10 mg/kg, a dose group was added to the study in which the dose was titrated from 5 mg/kg to 10 mg/kg. However, the dose titration did not result in marked changes in the type and intensity of clinical signs observed during the study.

Table 2 Summary Incidence of Recurring Clinical Observations

Subchronic Phase ll - Males
Overall Incidence Days 1 to 28 Post Dosing

Observation	Group 1 E2007 7.5 mg/kg	Group 2 E2007 10 mg/kg	Group 3 E2007 5→10 mg/kg	Group 4 E2007 1 mg/kg
Number of animals per group	2	2	3	1
Body Position				
1 Completely flattened, limbs spread out	.	2	.	.
2 Lying down on ventral surface	.	2	.	.
3 Lying on side, limbs extended off floor	.	.	.	.
4 Lying on side or curled up	2	1	3	.
5 Sitting or standing	2	2	3	1
Tremors: (Involuntary trembling motions of body, head or limbs)				
H **Head**				
2 Slight	1	.	2	.
4 Moderate	.	1	.	.
6 Severe	.	.	.	.
B **Body**				
2 Slight	1	2	3	.
4 Moderate	1	1	.	.
6 Severe	.	.	.	.
L **Limb(s)**				
2 Slight	1	.	3	.
4 Moderate	1	.	.	.
6 Severe	.	.	.	.

Subchronic Phase ll - Males
Overall Incidence Days 1 to 28 Post Dosing

Observation		Group 1 E2007 7.5 mg/kg	Group 2 E2007 10 mg/kg	Group 3 E2007 5→10 mg/kg	Group 4 E2007 1 mg/kg
Bizarre/Stereotypic Behavior					
D	Spatial disorientation and/or walking or stumbling into object				
2	Slight	2	2	3	1
4	Moderate	2	2	3	.
6	Severe	.	2	3	.
Vocalization:					
W	Whining				
2	Occasionally	2	2	3	1
4	Intermittently	2	1	1	.
6	Continuously	.	.	.	.
Y	Yelping				
2	Occasionally	1	1	3	.
4	Intermittently	2	1	.	.
6	Continuously	.	.	1	1
Bk	Barking				
2	Occasionally	1	.	.	.
4	Intermittently	1	.	.	.
6	Continuously	1	.	.	.

Subchronic Phase ll - Males
Overall Incidence Days 1 to 28 Post Dosing

Observation		Group 1 E2007 7.5 mg/kg	Group 2 E2007 10 mg/kg	Group 3 E2007 5→10 mg/kg	Group 4 E2007 1 mg/kg
Ataxic Gait: (Sway, rock, lurch, excessively)					
2	Slight	2	2	3	1
4	Moderate	2	2	3	.
6	Severe	.	2	3	.
F	Falls over	2	2	3	1

Subchronic Phase ll - Females
Overall Incidence Days 1 to 28 Post Dosing

Observation		Group 1 E2007 7.5 mg/kg	Group 2 E2007 10 mg/kg	Group 3 E2007 5→10 mg/kg	Group 4 E2007 1 mg/kg
Number of animals per group		2	2	1	3
Body Position					
1	Completely flattened, limbs spread out	.	1	.	.
2	Lying down on ventral surface	.	2	.	.
3	Lying on side, limbs extended off floor	.	.	.	.
4	Lying on side or curled up	2	2	.	.
5	Sitting or standing	2	2	1	3
Tremors: (Involuntary trembling motions of body, head or limbs)					
H	**Head**				
2	Slight	.	1	1	.
4	Moderate	.	.	.	.
6	Severe	.	.	.	.
B	**Body**				
2	Slight	1	2	1	.
4	Moderate	.	1	.	.
6	Severe	.	.	.	.
L	**Limb(s)**				
2	Slight	.	1	1	.
4	Moderate	.	.	.	.
6	Severe	.	.	.	.

Subchronic Phase II - Females
Overall Incidence Days 1 to 28 Post Dosing

Observation		Group 1 E2007 7.5 mg/kg	Group 2 E2007 10 mg/kg	Group 3 E2007 5→10 mg/kg	Group 4 E2007 1 mg/kg
Bizarre/Stereotypic Behavior					
D	Spatial disorientation and/or walking or stumbling into object				
2	Slight	2	2	1	3
4	Moderate	2	2	1	.
6	Severe	.	1	1	.
Vocalization:					
W	Whining				
2	Occasionally	2	2	1	3
4	Intermittently	1	1	.	.
6	Continuously	.	.	1	.
Y	Yelping				
2	Occasionally	2	1	1	1
4	Intermittently	1	1	1	.
6	Continuously	1	.	.	1
Bk	Barking				
2	Occasionally	2	.	.	.
4	Intermittently	1	.	.	.
6	Continuously	.	.	.	.

Subchronic Phase II - Females
Overall Incidence Days 1 to 28 Post Dosing

Observation		Group 1 E2007 7.5 mg/kg	Group 2 E2007 10 mg/kg	Group 3 E2007 5→10 mg/kg	Group 4 E2007 1 mg/kg
Ataxic Gait: (Sway, rock, lurch, excessively)					
2	Slight	2	2	1	3
4	Moderate	2	2	1	.
6	Severe	.	2	1	.
F	Falls over	2	2	1	3

Body Weights and Food Consumption: In the subchronic phase of this study, absolute BW was 10% higher in females and 27% higher in males dosed with 1 mg/kg, relative to other dose groups. There was no vehicle control in this study, making it difficult to determine if a test article-related effect existed in pups dosed with 1 mg/kg. There were no clear effects of E2007 on food consumption.

Hematology and Clinical Chemistry: Due to the absence of a vehicle control group, it is difficult to determine if there was a test article-related effect on hematology or clinical chemistry parameters. However, none of the hematology or clinical chemistry parameters were altered in a dose-dependent manner in the subchronic phase.

Gross Pathology: Intestinal thickening was observed in the animals that were euthanized *in extremis*. There were no other test article-related findings in the subchronic phase.

Organ Weights: The absence of a vehicle control in the subchronic phase prevented attribution of any findings to the test article. However, the brain weights observed in male pups dosed with 7.5 mg/kg and 10 mg/kg were 16% and 8% lower than the brain weight of animals in the 1 mg/kg group. This difference in brain weight was not observed in female pups.

Histopathology: Adequate Battery: No, nasal cavities and turbinates were not examined. There were no test article-related findings evident.

Toxicokinetics: Toxicokinetic parameters were determined at the initiation of the dosing phase and at the termination of the study (Sponsor's table, below).

Study No.

Table 2.1 Toxicokinetic Parameters of E2007 in Juvenile Beagle Dog Plasma Following Oral Gavage of E2007

Study Day 1 (Post Partum Day 45) - Males

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
1	7.5	102	1.00	131	1120	17.5	149
		103	1.00	71.7	315	9.56	41.9
		Mean	1.00	101	717	13.5	95.6

Study Day 1 (Post Partum Day 45) - Females

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
1	7.5	152	3.00	114	859	15.2	114
		153	1.00	105	607	13.9	80.9
		Mean	2.00	109	733	14.6	97.7

Study Day 28 (Post Partum Day 72) - Males

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
1	7.5	102	1.00	82.3	589	11.0	78.6
		103	1.00	176	833	23.5	111
		Mean	1.00	129	711	17.2	94.9

Study Day 28 (Post Partum Day 72) - Females

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
1	7.5	152	1.00	129	653	17.3	87.0
		153	1.00	151	1183	20.2	158
		Mean	1.00	140	918	18.7	122

Table 2.2 Toxicokinetic Parameters of E2007 in Juvenile Beagle Dog Plasma Following Oral Gavage of E2007

Study Day 1 (Post Partum Day 42) - Males

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
2	10	202	1.00	81.5	1274	8.15	127
		203	8.00	246	3052	24.6	305
		Mean	4.50	164	2163	16.4	216

Study Day 1 (Post Partum Day 42) - Females

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
2	10	252	8.00	409	5734	40.9	573
		253	3.00	99.0	846	9.90	84.6
		Mean	5.50	254	3290	25.4	329

Study Day 4 (Post Partum Day 45) - Male

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
2	10	202	1.00	171	1334	17.1	133

Study Day 4 (Post Partum Day 45) - Female

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
2	10	253	8.00	200	2897	20.0	290

Study No. 9

Table 2.3 Toxicokinetic Parameters of E2007 in Juvenile Beagle Dog Plasma Following Oral Gavage of E2007

Study Day 1 (Post Partum Day 44) - Males

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
3	5	302	1.00	97.2	869	19.4	174
		303	1.00	54.0	198	10.8	39.5
		304	1.00	58.0	427	11.6	85.4
		Mean [a]	1.00	69.7	498	13.9	99.6
		SD		23.9	341	4.77	68.2

Study Day 1 (Post Partum Day 44) - Female

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
3	5	352	1.00	104	442	20.8	88.4

Study Day 12 (Post Partum Day 55) - Males

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
3	10	302	1.00	216	1032	21.6	103
		303	1.00	152	674	15.2	67.4
		304	1.00	188	1342	18.8	134
		Mean [a]	1.00	185	1016	18.5	102
		SD		32.1	334	3.21	33.4

Study Day 12 (Post Partum Day 55) - Female

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
3	10	352	1.00	184	891	18.4	89.1

a Median value reported for Tmax.

Study No.

Table 2.3 Toxicokinetic Parameters of E2007 in Juvenile Beagle Dog Plasma Following Oral Gavage of E2007

Study Day 28 (Post Partum Day 71) - Males

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
3	10	302	1.00	400	1776	40.0	178
		303	1.00	209	883	20.9	88.3
		304	1.00	214	2085	21.4	208
		Mean [a]	1.00	274	1581	27.4	158
		SD		108	624	10.8	62.4

Study Day 28 (Post Partum Day 71) - Female

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
3	10	352	1.00	137	509	13.7	50.9

a Median value reported for Tmax.

Table 2.4 Toxicokinetic Parameters of E2007 in Juvenile Beagle Dog Plasma Following Oral Gavage of E2007

Study Day 1 (Post Partum Day 43) - Male

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
4	1	401	1.00	38.3	108	38.3	108

Study Day 1 (Post Partum Day 43) - Females

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
4	1	451	1.00	74.9	196	74.9	196
		452	1.00	57.7	159	57.7	159
		453	1.00	84.9	235	84.9	235
		Mean [a]	1.00	72.5	197	72.5	197
		SD		13.7	38.0	13.7	38.0

Study Day 28 (Post Partum Day 70) - Male

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
4	1	401	1.00	44.7	131	44.7	131

Study Day 28 (Post Partum Day 70) - Females

Group No.	Dose Level (mg/kg)	Animal No.	Tmax (h)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Cmax/ Dose	AUC(0-24h)/ Dose
4	1	451	1.00	48.7	141	48.7	141
		452	1.00	41.5	132	41.5	132
		453	1.00	29.3	132	29.3	132
		Mean [a]	1.00	39.8	135	39.8	135
		SD		9.83	5.51	9.83	5.51

a Median value reported for Tmax.

Study Title: E2007: A 33-week oral gavage toxicity study in the juvenile dog followed by a 4-week recovery period

Study no.:	901979
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	12/14/2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 16091902, 100%

Key Study Findings:

- **Dosing was initiated in this study on PND 42.**
- **Due to clinical signs (e.g. abnormal gait, altered activity, excessive scratching, tremors, and uncoordination) observed at every dose level, the NOAEL was < 1 mg/kg.**
- **Circling, head shaking, and weakness were observed in dogs dosed with ≥ 5 mg/kg E2007.**
- **One MDM exhibited sustained convulsions beginning two days into the recovery period and was euthanized *in extremis*.**
- **Reproductive hormones were not assessed in this study.**
- **Dilation of the cerebral ventricles was observed in 1 HDM and 1 HDF.**
- **Prostatitis was observed in all MDM and HDM.**
- **Post-weaning plasma levels of E2007 in this study were similar to those observed in adult dogs administered E2007 for 13 weeks. Pre-weaning levels were 1.7 to 2.4 fold higher than those observed in adults. There was no sex-related difference in TK parameters in this study.**

Methods

Doses:	See Sponsor's Table, below
Frequency & Route of dosing:	Once daily, oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	0.5% (w/v) methylcellulose
Species/Strain:	Beagle dogs, (b) (4)
Number/Sex/Group:	See below.
Age:	Pregnant dogs were received 3-4 weeks before parturition.
Weight:	Pups were 1.4-3.3 kg at initiation of dosing.
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Study Design: Dosing was initiated on postnatal (PND) 42 and continued through week 39.

Group	Dose Level (mg/kg)	Dose Conc. (mg/mL)	Number of Litters	Number of Animals			
				Main Study Phase		Recovery Phase	
				♂	♀	♂	♀
1/ Control	0	0	4	4	4	4	4
2/ E2007	1	0.2	4	4	4	4	4
3/ E2007	5	1.0	4	4	4	4	4
4/ E2007	5→10*	1.0→2.0	4	4	4	4	4

*The timing of ramping was 15 days after the start of treatment (Day 56 *pp*).

Dosing Formulation Analysis: All formulations were within 10% of the nominal concentration.

Mortality: Although there were some early deaths during the study, a few were considered to be unrelated to the test article. For example, one vehicle control (#101) died under anesthesia during the ERG assessment on Day 271. One HDM was euthanized due to "deteriorating condition" on Day 221. Necropsy of this animal (#405) determined the presence of a GI obstruction (piece of a towel). Neither of these early deaths were considered test article-related. However, one MDM was euthanized *in extremis* on Day 274. Two days after dosing cessation, this animal (#304) exhibited sustained convulsions (see below for further information regarding clinical signs in animal #304).

Clinical Signs: Animal # 304 (MDM) exhibited head tilt, lack of coordination, and circling during the dosing period, and limited forelimb and hindlimb usage on Day 135.

Clinical signs that lasted for up to 4 hours after dosing were observed in all E2007 dose groups. Incidence and severity of the clinical signs, detailed in the Sponsor's Table below, were dose-related. Abnormal gait, altered activity, excessive scratching, tremors, uncoordination were observed in all dose groups of both genders. All male dose groups, MDF, and HDF exhibited circling and head shaking. Weakness was observed in MDM, HDM, and HDF.

Table 1 Incidence of Clinical Observations

Males

Group 1 - Control
Group 2 - Low dose 1 mg/kg
Group 3 - Middle dose 5 mg/kg
Group 4 - High dose 5→10 mg/kg

	Group			
Clinical Sign\Site	1	2	3	4
Number of animals per group	8	8	8	8
Abdominal Firm Inter Structure	.	.	.	1
Abnormal Gait	1	8	8	8
Activity Decreased	.	5	8	8
Activity Increased	.	2	2	3
Backbone Prominent	.	.	.	1
Breathing Shallow	.	.	1	.
Broken Toe Nail\Forepaw Left	1	.	.	2
Broken Toe Nail\Forepaw Right	1	.	.	1
Chewing Action	.	.	.	2
Circling	.	2	3	7
Cold to Touch	.	.	1	.
Convulsions Sustained	.	.	1	.
Coprophagia	1	2	3	5
Dehydrated Suspected	.	.	1	1
Excessive Grooming	1	.	2	5
Excessive Licking	1	.	.	7
Excessive Scratching	.	4	8	8
Head Shaking	.	1	4	8
Headtilt	.	.	1	.
Tremors	1	6	8	8
Uncoordinated	1	8	8	8
Vocalization Decreased	.	.	.	1
Vocalization Increased	.	1	3	5
Weak	.	.	1	2

Table 1 Incidence of Clinical Observations

Females

Group 1 - Control
Group 2 - Low dose 1 mg/kg
Group 3 - Middle dose 5 mg/kg
Group 4 - High dose 5→10 mg/kg

	Group			
Clinical Sign\Site	1	2	3	4
Number of animals per group	8	8	8	8
Abnormal Gait	2	8	8	8
Activity Decreased	1	4	8	8
Activity Increased	.	1	4	6
Backbone Prominent	.	.	.	1
Broken Toe Nail\Forepaw Left	.	.	1	.
Broken Toe Nail\Forepaw Right	.	1	.	.
Broken Toe Nail\Hindpaw Right	.	1	.	.
Chewing Action	.	.	.	1
Circling	1	.	1	6
Coprophagia	2	2	2	3
Excessive Grooming	.	1	1	5
Excessive Licking	.	.	.	7
Excessive Scratching	.	2	8	8
Head Shaking	.	.	5	6
Tremors	.	3	7	8
Uncoordinated	1	8	8	8
Weak	.	.	.	1

Body Weights and Food Consumption: There were no test article-related effects.

Growth: Height and length were not affected by E2007 during the dosing period or at the end of the recovery period.

Ophthalmoscopy: Animals were subjected to funduscopic and slit lamp examination by a board certified veterinary ophthalmologist during Weeks 10/11, 20/21, 32/33, and during the recovery period. In addition to the ophthalmoscopic examination, an electroretinogram was performed on each animal during Weeks 32/33 of the study. There were no test article-related findings on either assessment.

Developmental Landmarks: Developmental landmarks such as eye opening and teeth eruption were not recorded in this study due to the fact that dosing began on PND 42.

Behavioral Assessment:

Functional Observational Battery and Neurological Examination: An observational battery was performed on all animals prior to daily dosing during study Week 10, 20, 32 and during the recovery period. The FOB included assessments of motor activity, behavioral changes, coordination, and sensory-motor function. There were no test article-related findings on these parameters. Learning and memory was not assessed.

Hematology, Clinical Chemistry and Urinalysis: Hematology, clinical chemistry, and urinalysis parameters were assessed during Week 13 and Week 32/33, and at the end of the recovery period. There were no test article-related effects on any of these assessments.

Bone Density Assessment: Dual energy X-ray absorptiometry (DXA) was used to assess bone mineral density (lumbar spine, femur, and whole body), bone mineral content, and bone area during the pretreatment period, Week 13, and Week 32/33. There were no test article-related effects observed on any of these parameters.

Brain Measurements: There were no test article-related effects on cerebrum length and width and cerebellum width at the end of the dosing period and at the end of the recovery period.

Reproductive Assessment: Reproductive hormones were not measured in this study.

Gross Pathology: Dilated cerebral ventricles were observed in 1 HDM and 1 HDF at the end of the dosing phase.

Organ Weights: There were no test article-related effects on organ weights (adrenal, brain, heart, kidney, liver, ovary, spleen, testis, thymus, thyroid/parathyroid).

Histopathology: Adequate Battery: No, nasal cavity/turbinates and tongue not examined; Peer Review: Yes; Signed and Dated Report: Yes

All tissues were examined with H&E staining. In addition, brain sections (forebrain, midbrain, cerebellum, medulla oblongata, caudate putamen, cerebral cortex, piriform cortex, thalamus/hypothalamus, hippocampus, leptomeninges) were also processed for TUNEL staining.

Slight cerebral ventricle dilation (observed in 1 HDM and 1 HDF) and prostatitis in all MDM (3/4) and HDM (4/4) were observed. Neither finding is mentioned by the study Pathologist to be test article-related. There were no test article-related microscopic findings in brain. The HDM that exhibited sustained convulsions at the beginning of the recovery period (#304) exhibited moderate renal tubule necrosis, moderate liver congestion, moderate lung congestion with alveolar and perivascular edema, marked autolysis of the gall bladder, brain hemorrhage, and decreased pancreatic zymogen granules.

TABLE 1 7
STUDY NO. 901979
E2007: A 33 Week Oral Gavage Toxicity Study in the Juvenile Dog Followed by a 4 Week Recovery Period
SUMMARY OF HISTOPATHOLOGY DATA
ALL LESIONS MALE
TERMINAL SACRIFICE

ORGAN AND FINDINGS	DOSE (mg/kg) / NO. OF ANIMALS EXAMINED	0 / 3	1 / 4	5 / 4	10 / 3
Brain		(3)	(4)	(4)	(3)
Normal		3	4	4	2
Ventricular dilatation	1+	0	0	0	1

TABLE 1 15
STUDY NO. 901979
E2007: A 33 Week Oral Gavage Toxicity Study in the Juvenile Dog Followed by a 4 Week Recovery Period
SUMMARY OF HISTOPATHOLOGY DATA
ALL LESIONS FEMALE
TERMINAL SACRIFICE

ORGAN AND FINDINGS	DOSE (mg/kg) / NO. OF ANIMALS EXAMINED	0 / 4	1 / 4	5 / 4	10 / 4
Brain		(4)	(4)	(4)	(4)
Normal		4	4	4	3
Ventricular dilatation	1+	0	0	0	1

TABLE 2 5
STUDY NO. 901979
E2007: A 33 Week Oral Gavage Toxicity Study in the Juvenile Dog Followed by a 4 Week Recovery Period
SUMMARY OF HISTOPATHOLOGY DATA
ALL LESIONS MALE
RECOVERY SACRIFICE

ORGAN AND FINDINGS	DOSE (mg/kg) / NO. OF ANIMALS EXAMINED	0 / 4	1 / 4	5 / 3	10 / 4
Prostate		(4)	(4)	(3)	(4)
Normal		2	3	0	0
Prostatitis	1+	1	1	1	3
	2+	1	0	2	1

Toxicokinetics: TK parameters were determined for all dose groups at weeks 1, 4, 20, and 33 of the study (Sponsor's tables, below). Post weaning plasma levels in HD animals ($AUC_{0\text{-}24hr}$) were similar to those observed in adult dogs administered comparable doses of E2007 in a 13-week study (Study S01009). Pre-weaning plasma levels in LD animals were 1.7 to 2.4-fold higher than in adult animals dosed with 1 mg/kg E2007.

Table Toxicokinetic Summary

Dose (mg/kg)	Timing	Male C_{max} (ng/mL)	Male $AUC_{(0\text{-}24h)}$ (ng·h/mL)	Female C_{max} (ng/mL)	Female $AUC_{(0\text{-}24h)}$ (ng·h/mL)
1	Week1	98.8	681	78.6	442
		37.3	326	24.0	319
	Week 4	92.1	420	74.0	300
		47.4	296	27.8	208
	Week 20	68.9	472	47.1	390
		56.7	359	36.8	355
	Week 33	54.9	448	47.7	334
		32.4	267	40.2	339
5	Week1	146	1168	166	1826
		65.0	626	50.8	1752
	Week 4	142	699	188	1483
		59.0	225	90.1	1382
	Week 20	118	731	185	1362
		39.4	414	114	804
	Week 33	101	672	187	881
		49.8	273	129	460
5→10*	Week1	125	1088	126	775
		49.4	1108	16.6	267
	Week 2	198	2054	149	913
		111	1784	59.5	518
	Week 20	181	1295	123	1021
		56.5	674	26.2	392
	Week 33	127	1084	84.2	860
		53.7	745	32.6	651

Mean (upper) and SD (lower) of 4 animals are presented.
* The timing of ramping was 15 days after the start of treatment (Week 2).

13-Week Study Conducted in Adult Dogs (Study #S01009)

2.6.7.7.I Repeated-Dose Toxicity

Report Title: E2007: A 13-Week Oral Toxicity Study in Dogs Test Article: Perampanel

Species/Strain: Dog/Beagle | Duration of Dosing: 13 weeks | Study No.: S01009
Initial Age: 8 months | Duration of Post-dose: Not applicable | Location in CTD: 4.2.3.2.12
Date of First Dose: June 20, 2001 | Vehicle/Formulation: 0.5% MC solution | Testing Facility: Eisai
Special Feature: None | Methods of Administration: Oral by gavage | GLP Compliance: Yes
No Observed Adverse-Effect Level: 1 (M), 10(F) mg/kg

Daily Dose (mg/kg)	0 (Control)		0.1		1		10	
Number of Animals:	M:3	F: 3	M:3	F: 3	M:3	F: 3	M:3	F: 3
Toxicokinetics:								
Cmax (ng/mL):								
Day 1	NA	NA	5.87	9.14	44.03	46.05	83.89	92.77
Day 28	NA	NA	7.70	9.10	54.84	66.00	110.18	139.03
Day 91	NA	NA	8.96	13.51	49.11	60.00	148.83	122.85
$AUC_{(0\text{-}24h)}$ (ng·hr/mL):								
Day 1	NA	NA	15.10	21.44	203.28	175.95	776.11	356.88
Day 28	NA	NA	16.03	25.22	293.43	234.85	423.97	1032.40
Day 91	NA	NA	21.61	49.34	281.41	264.35	905.45	913.11

10.2. Phototoxicity

10.2.1 *In vitro* Studies

1) Study F06003- "E2007: Phototoxicity test using BALB/3T3 cells"

Neutral red uptake was assessed in BALB/3T3 cells pretreated with E2007 for 60 minutes and then irradiated with UVA (2.5 mW/cm^2) for 50 minutes. E2007 was determined to be phototoxic with an LD_{50} of 390 ng/ml in the presence of UVA irradiation (230 ng/ml), which is similar to the positive control, chlorpromazine.

Table 2 Results of the main test in BALB/3T3 cells treated with E2007

Concentration (μg/mL)	OD_{540} Data from each well 1	2	3	4	Average ± S.D.	(net OD[a])	Relative survival (%)	IC_{50} (μg/mL)
Non-irradiation								
Blank	0.019	0.013	0.015	0.013	0.015 ± 0.003	(0.000)	0.0	
DMSO 1 vol%	0.457	0.442	0.414	0.409	0.431 ± 0.023	(0.416)	100.0	
3.9	0.433	0.422	0.465	0.432	0.438 ± 0.019	(0.423)	101.7	> 500
7.8	0.423	0.446	0.429	0.428	0.432 ± 0.010	(0.417)	100.2	
16	0.435	0.482	0.445	0.481	0.461 ± 0.024	(0.446)	107.2	
31 [b,c]	0.436	0.433	0.447	0.424	0.435 ± 0.009	(0.420)	101.0	
63 [b,c]	0.450	0.431	0.387	0.401	0.417 ± 0.029	(0.402)	96.6	
130 [b,d]	0.423	0.418	0.408	0.418	0.417 ± 0.006	(0.402)	96.6	
250 [b,d]	0.398	0.414	0.442	0.351	0.401 ± 0.038	(0.386)	92.8	
500 [b,d]	0.405	0.380	0.417	0.422	0.406 ± 0.019	(0.391)	94.0	
Irradiation								
Blank	0.019	0.022	0.019	0.022	0.021 ± 0.002	(0.000)	0.0	
DMSO 1 vol%	0.391	0.376	0.375	0.360	0.376 ± 0.013	(0.355)	100.0	
0.11	0.321	0.351	0.340	0.343	0.339 ± 0.013	(0.318)	89.6	0.39
0.22	0.225	0.267	0.303	0.289	0.271 ± 0.034	(0.250)	70.4	
0.44	0.094	0.158	0.230	0.229	0.178 ± 0.065	(0.157)	44.2	
0.88	0.028	0.046	0.058	0.063	0.049 ± 0.016	(0.028)	7.9	
1.8	0.022	0.022	0.020	0.022	0.022 ± 0.001	(0.001)	0.3	
3.5	0.029	0.028	0.026	0.024	0.027 ± 0.002	(0.006)	1.7	
7.0	0.034	0.023	0.026	0.023	0.027 ± 0.005	(0.006)	1.7	
14	0.024	0.028	0.023	0.023	0.025 ± 0.002	(0.004)	1.1	
PIF								> 1282

PIF: photo irritation factor = IC_{50} value of non-irradiation/IC_{50} value of irradiation
DMSO: dimethyl sulfoxide
a): Average OD_{540} of each group - Average OD_{540} of blank
b): Precipitation was observed during and after the treatment period.
c): Precipitation was dissolved into medium during the incubation period.
d): Precipitation was observed after the fixation but not after the extraction.

10.2.2. Genotoxicity

Study title: Photomutagenicity in a Salmonella typhimurium reverse mutation assay with E2007

Study no.:	1060501
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/22/2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 14110902, Purity 99.6%

Key Study Findings

- **E2007 is negative in the photomutagenicity assay.**

Methods

Strains:	TA100, TA1537, TA98, TA102. These strains were chosen due to the ability to tolerate UV irradiation.
Concentrations in definitive study:	Pre-experiment (without UV): 3, 10, 33, 100, 333, 1000, 2500, 5000 µg/plate Experiment I: 10, 33, 100, 333, 1000, 2500, 5000 µg/plate Experiment II: 33, 100, 333, 1000, 2500, 5000 µg/plate
Negative control and formulation:	DMSO
Positive control:	Without Irradiation: Sodium azide (TA100), 4-nitro-o-phenylene-diamine (TA1537, TA98), methyl methane sulfonate (TA102) With Irradiation: 8-methoxypsoralen (TA102)
Incubation & sampling time:	Bacterial suspensions were incubated with the test article and then irradiated until the intended UV dose was delivered (see sponsor's table below). Suspensions were then plated and incubated at 37°C for 48 hours in the dark before quantification.

Methods and Study Validity: The following doses of UV irradiation were used in this study. An adequate concentration range was tested and the positive controls resulted in the expected increase in revertants. Therefore, the study is valid.

Bacterial Strains	Dose Range		
	UVA (mJ/cm^2)	UVB (mJ/cm^2)	UVB (mJ/cm^2)
		Exp. I	Exp. II
TA 1537	58.5	2.76	2.25
TA 98	21	1.0	0.81
TA 100	5	0.23	0.19
TA 102	81	3.7	3.1

Results: E2007 did not increase the number of revertants in the presence or absence of UV irradiation. Positive controls did result in an increase in the number of revertants. Overall, E2007 was negative in the photomutagenicity assay.

12.1 Pre-Experiment Without Irradiation

Study Name: 1060501
Experiment: 1060501 VV Plate
Assay Conditions:

Study Code: (b) (4) 1060501
Date Plated: 22/11/2006
Date Counted: 27/11/2006

Metabolic Activation	Test Group	Dose Level (µg/plate)	Revertant Colony Counts (Mean ±SD)			
			TA 1537	TA 98	TA 100	TA 102
Without Irradiation	DMSO		9 ± 3	25 ± 4	106 ± 16	383 ± 26
	Untreated		8 ± 1	28 ± 1	115 ± 10	384 ± 9
	E2007	3 µg	9 ± 3	22 ± 6	125 ± 3	394 ± 1
		10 µg	9 ± 1	23 ± 5	123 ± 10	368 ± 12
		33 µg	7 ± 2	24 ± 4	127 ± 8	362 ± 22
		100 µg	8 ± 2	23 ± 7	118 ± 22	363 ± 16
		333 µg	7 ± 4 P M	18 ± 3 P M	87 ± 8 P M	349 ± 9 P M
		1000 µg	6 ± 2 M P	17 ± 3 P M	90 ± 3 P M	295 ± 18 P M
		2500 µg	4 ± 1 P M	13 ± 3 P M	83 ± 8 P M	309 ± 17 P M
		5000 µg	5 ± 2 P M	15 ± 3 P M	88 ± 10 P M	312 ± 27 P M
	4-NOPD	10 µg		416 ± 50		
	4-NOPD	50 µg	94 ± 21			
	NaN3	10 µg			1692 ± 242	
	MMS	3 µL				3003 ± 211

Key to Positive Controls		Key to Plate Postfix Codes	
NaN3	sodium azide	P	Precipitate
MMS	methyl methane sulfonate	M	Manual count
4-NOPD	4-nitro-o-phenylene-diamine		

12.2 Experiment I

Study Name: 1060501
Experiment: 1060501HV1 Plate
Assay Conditions:

Study Code: (b) (4) 1060501
Date Plated: 28/11/2006
Date Counted: 01/12/2006

Metabolic Activation	Test Group	Dose Level (µg/plate)	Revertant Colony Counts (Mean ±SD)			
			TA 1537	TA 98	TA 100	TA 102
Without Irradiation	DMSO		9 ± 2	28 ± 2	120 ± 23	474 ± 12
	Untreated		10 ± 6	33 ± 3	127 ± 9	403 ± 122
	E2007	0				
	4-NOPD	10 µg		463 ± 31		
	4-NOPD	50 µg	91 ± 5			
	NaN3	10 µg			2132 ± 87	
	MMS	3 µL				3602 ± 485
With Irradiation	DMSO		22 ± 6	50 ± 3	207 ± 30	699 ± 6
	Untreated		21 ± 3	66 ± 10	204 ± 16	764 ± 45
	E2007	10 µg	20 ± 3	44 ± 5	199 ± 13	706 ± 5
		33 µg	25 ± 3	70 ± 17	243 ± 21	728 ± 64
		100 µg	30 ± 12	48 ± 8	210 ± 21	709 ± 17
		333 µg	20 ± 1	45 ± 10	231 ± 42	778 ± 33
		1000 µg	27 ± 7 P	47 ± 3 P M	379 ± 91 P	739 ± 62 P
		2500 µg	22 ± 4 P M	48 ± 7 P M	201 ± 13 P M	741 ± 237 P M
		5000 µg	18 ± 2 P M	47 ± 4 P M	184 ± 9 P M	494 ± 15 P M
	8-MOP	125 µg				2595 ± 256

Key to Positive Controls		Key to Plate Postfix Codes	
NaN3	sodium azide	P	Precipitate
MMS	methyl methane sulfonate	M	Manual count
8-MOP	8-Methoxypsoralen		
4-NOPD	4-nitro-o-phenylene-diamine		

12.3 Experiment II

Study Name: 1060501
Experiment: 1060501 HV2 Pre
Assay Conditions:

Study Code: (b) (4)1060501
Date Plated: 04/12/2006
Date Counted: 07/12/2006

Metabolic Activation	Test Group	Dose Level (µg/plate)	Revertant Colony Counts (Mean ±SD)			
			TA 1537	TA 98	TA 100	TA 102
Without Irradiation	DMSO		6 ± 1	35 ± 7	111 ± 14	375 ± 16
	Untreated		8 ± 2	44 ± 8	115 ± 19	415 ± 16
	E2007	0				
	4-NOPD	10 µg		441 ± 24		
	4-NOPD	50 µg	129 ± 12			
	NaN3	10 µg			1791 ± 80	
	MMS	3 µL				1366 ± 97
With Irradiation	DMSO		12 ± 2	40 ± 12	134 ± 4	446 ± 13
	Untreated		8 ± 4	39 ± 7	163 ± 6	396 ± 41
	E2007	33 µg	8 ± 2	34 ± 2	164 ± 21	454 ± 36
		100 µg	11 ± 4	35 ± 8	146 ± 8	483 ± 60
		333 µg	13 ± 4	31 ± 6	133 ± 10	445 ± 18
		1000 µg	12 ± 3 [P]	28 ± 5 [P]	128 ± 8 [P]	421 ± 15 [P]
		2500 µg	4 ± 2 [P M]	24 ± 9 [P M]	104 ± 11 [P M]	273 ± 25 [P M]
		5000 µg	5 ± 2 [P M]	18 ± 6 [P M]	118 ± 22 [P M]	259 ± 27 [P M]
	8-MOP	125 µg				1699 ± 333

Key to Positive Controls

NaN3	sodium azide
MMS	methyl methane sulfonate
8-MOP	8-Methoxypsoralen
4-NOPD	4-nitro-o-phenylene-diamine

Key to Plate Postfix Codes

P	Precipitate
M	Manual count

Study title: Chromosome aberration test *in vitro*: Photomutagenicity in Chinese hamster V79 cells with E2007

Study no.:	1060502
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/29/2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 14110902, Purity 99.6%

Key Study Findings

- **E2007 is a photo-clastogen in the presence of UV irradiation.**

Methods

Cell line:	V79 Chinese hamster cells
Concentrations in definitive study:	See below
Negative and Formulation control:	DMSO
Positive control:	With irradiation: 8-methoxypsoralene; Without irradiation: Ethylmethane sulfonate
Incubation & sampling time:	See sponsor's table below

Methods and Study Validity: Incubation and irradiation conditions are provided below. The positive controls resulted in the expected increase in clastogenicity and the concentration range used in the main study was considered to be adequate (high concentrations of 17.6 and 19.8 µg/ml resulted in precipitation).

	With irradiation		Without irradiation
	Exp. IA	Exp. IB	Exp. IA and IB
Pre-incubation of the cells with the test item	30 min	30 min	30 min
Intensity of irradiation (UVA)	0.3 mW/cm^2	0.3 mW/cm^2	0 mW/cm^2
Dosage UVA/UVB [mJ/cm^2]	125/4.2	125/6.3	0/0
Total exposure period	3 hrs	3 hrs	3 hrs
Recovery	15 hrs	15 hrs	15 hrs
Preparation interval	18 hrs	18 hrs	18 hrs

Results: Cells incubated with E2007 exhibited an increase in the number of aberrant cells in the presence of UV irradiation (Sponsor's Table, below). The increase occurred at concentrations at which the mitotic index was not affected and no precipitation of test article was observed. Therefore, E2007 is considered to be a photo-clastogen.

Without Irradiation

Table 3: Summary of results of the chromosome aberration study with E2007

Exp.	Preparation interval	Test Item concentration in µg/mL	Polyploid cells in %	Cell number in % of control	Mitotic index in % of control	Aberrant cells in % Incl. gaps	Aberrant cells in % Excl. gaps*	Exchanges
Exposure period 3 hrs without irradiation								
IA	18 hrs	Negative control[1]	1.2	n.t.	61.6	1.0	1.0	0.5
		Solvent control[2]	1.9	100.0	100.0	3.5	2.0	0.0
		Positive contro[3]	2.4	n.t.	144.8	10.5	**9.0**[S]	1.5
		4.4	1.7	90.5	73.1	1.5	1.5	0.0
		8.8	2.4	118.6	76.0	2.0	1.0	0.0
		17.6[P]	2.4	119.7	101.5	4.0	2.5	0.0
IB	18 hrs	Negative control[1]	2.3	n.t.	101.5	3.0	2.0	0.5
		Solvent control[2]	2.4	100.0	100.0	1.5	1.0	0.0
		Positive control[3]	1.8	n.t.	113.3	10.0	**8.5**[S]	3.5
		4.4	1.8	89.1	119.7	1.0	1.0	0.0
		8.8	2.7	81.9	113.9	3.0	3.0	0.0
		11.0	2.0	90.3	98.8	4.5	**4.5**[S]	0.0
		13.2	1.8	87.7	112.0	2.5	2.5	0.5
		15.4	2.0	73.2	122.0	1.5	1.5	0.5
		17.6	2.4	87.6	120.8	2.5	2.0	0.5
		19.8[P]	3.9	87.9	122.8	2.0	2.0	0.5

* Inclusive cells carrying exchanges
n.t. Not tested
P Precipitation occurred
S Aberration frequency statistically significant higher than corresponding control values
1 Culture medium
2 DMSO 0.5 % (v/v)
3 EMS 800 µg/mL

With Irradiation

Table 3 cont.: Summary of results of the chromosomal aberration study with E2007

Exp.	Preparation interval	Test Item concentration in µg/mL	Polyploid cells in %	Cell number in % of control	Mitotic index in % of control	Aberrant cells in % Incl. gaps	Excl. gaps*	Exchanges
Exposure period 3 hrs with irradiation dose UVA/UVB 125/4.2 mJ/cm²								
IA	18 hrs	Negative control[1]	2.5	n.t.	128.4	3.0	1.5	0.0
		Solvent control[2]	1.7	100.0	100.0	3.0	3.0	0.0
		Positive control[3]	1.9	n.t.	73.8	34.5	**33.5**[S]	20.5
		4.4	2.2	83.8	129.4	5.5	5.0	1.0
		8.8	1.7	124.9	139.3	5.0	4.5	2.0
		17.6[P#]	1.7	89.3	104.3	9.8	**8.8**[S]	2.0
Exposure period 3 hrs with irradiation dose UVA/UVB 125/6.3 mJ/cm²								
IB	18 hrs	Negative control[1]	2.8	n.t.	77.3	4.5	4.0	1.5
		Solvent control[2]	2.9	100.0	100.0	3.0	2.5	0.5
		Positive control[3]	2.4	n.t.	97.0	26.5	**26.5**[S]	11.5
		4.4	2.6	99.6	91.3	2.5	1.5	0.0
		8.8	3.3	134.7	82.0	6.0	**6.0**[S]	3.0
		11.0	2.7	106.2	99.7	6.5	**6.0**[S]	2.0
		13.2	2.1	106.6	92.7	6.0	5.5	1.5
		15.4[#]	2.9	90.7	99.1	12.8	**12.3**[S]	4.5
		17.6[#]	2.2	111.9	98.0	7.3	**7.0**[S]	3.3
		19.8[P#]	2.9	81.5	78.5	13.8	**12.5**[S]	5.5

* Inclusive cells carrying exchanges
[#] Evaluation of 200 metaphase plates per culture
n.t. Not tested
[P] Precipitation occurred
[S] Aberration frequency statistically significant higher than corresponding control values
[1] Culture medium
[2] DMSO 0.5 % (v/v)
[3] 8-methoxypsoralene 0.25 µg/mL

10.2.3. Repeat Dose Toxicity

Study title: 13-week oral range finding study of W2007 in hairless mice, with or without simulated sunlight

Study no.:	LFA00036
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/2/2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 14110902, Purity 100.1%

Key Study Findings

- **The MTD in this study is 30 mg/kg. Deaths occurred at higher doses.**
- **There was no phototoxicity evident in this study.**

Methods

Doses:	0, 3, 10, 30, 60 mg/kg
Frequency of dosing:	Once daily for 13 weeks
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Crl:SKH1-hr hairless mouse
Number/Sex/Group:	6
Age:	5 weeks
Weight:	M= 25.3-32.1 g; F= 22.4-26.9 g
Unique study design:	Animals were exposed to UV irradiation for up to 5 days/week, see tables below.
Deviation from study protocol:	Deviations were minor and did not affect the validity of the study.

Study Design: Animals were dosed once daily as detailed below and were exposed to UV irradiation up to 5 times per week for a total weekly dose of 600 RBU (400 RBU approximates 1 minimal erythema dose (MED) in previously untanned human skin).

5.4.1. Groups, Assigned Mouse Numbers, Formulation Information and UVR Exposure Information

Group	Descriptor	Dosage (mg/kg)	Formulation Concentration (mg/mL)	Administration Volume (mL/kg)	Assigned Mouse Numbers	
					Male	Female
1	Untreated	NA	NA	NA	4528 - 4533	4600 - 4605
2	Vehicle	0	0	10	4534 - 4539	4606- 4611
3	Test Article	3	0.3	10	4540 - 4545	4612 - 4617
4	Test Article	10	1.0	10	4546 - 4551	4618 - 4623
5	Test Article	30	3.0	10	4552 - 4557	4624 - 4629
6	Test Article	60	6.0	10	4558 - 4563	4630 - 4635
7	Untreated	NA	NA	NA	4564 - 4569	4636 - 4641
8	Vehicle	0	0	10	4570 - 4575	4642 - 4647
9	Test Article	3	0.3	10	4576 - 4581	4648 - 4653
10	Test Article	10	1.0	10	4582 - 4587	4654 - 4659
11	Test Article	30	3.0	10	4588 - 4593	4660 - 4665
12	Test Article	60	6.0	10	4594 - 4599	4666 - 4671

The test article was considered 100% active/pure for the purpose of dosage calculations.
NA - Not applicable

5.4.2. Formulation Administration Regimen for Days of UVR Exposure

Group	Administration and UVR Exposure Mondays, Wednesday, Fridays		Administration and UVR Exposure Tuesdays, Thursdays		RBU Per Week
	Formulation Pre-UVR	UVR (RBU)	UVR (RBU)	Formulation Post-UVR	
1	No	NA	NA	No	0
2 through 6	Yes	NA	NA	Yes	0
7	No	120	120	No	600
8 through 12	Yes	120	120	Yes	600

Group 1: Neither formulation administration nor UVR exposure.
Groups 2 through 6: Formulation administration only.
Group 7: UVR exposure only.
Groups 8 through 12: Both formulation administration and UVR exposure.
Abbreviations:
UVR: Ultraviolet Radiation
RBU: Robertson-Berger Units (a measure of effectiveness for UVR; 400 RBU approximates one minimal erythema dose in previously untanned human skin).
NA: Not applicable

Dosing Solution Analysis: Dosing formulations were within ± 5% of the nominal concentration.

Mortality & Clinical Signs: 1 HDF (4597) and 1 HDM (4667) were euthanized *in extremis* on Day 1 of the study. The clinical signs in these animals consisted of hyperactivity to touch, ataxia, circling, low carriage, lost righting reflex, and splayed limbs. In animals that survived until the end of the dosing period, the most common clinical signs were excessive grooming (≥ 3 mg/kg), ataxia (≥ 3 mg/kg), and hyperactivity (F ≥ 3 mg/kg; M ≥ 10 mg/kg).

Body Weights & Feed Consumption: Absolute BW was decreased by 9-10 %, relative to control, between Day 8 and Day 22 of the study in mice dosed with ≥ 30 mg/kg. These differences were not present at the end of the dosing period in mice not exposed to UV but did persist until the end of the dosing period in HDM exposed to UV.

Skin Reaction Observations: There were no test article-related increases in wrinkles or erythema in mice exposed to UV. There was no test article-related increase in skin thickness.

Toxicokinetics: Plasma concentrations were measured one hour after dosing and the only TK parameter calculated in this study was plasma concentration one hour after dosing C_{1hr} (Sponsor's test table 2, below).

Text Table 2 Mean values of plasma concentrations of E2007

Group	Dosage (mg/kg)	UVR exposure	Mean of plasma concentration (ng/mL)	
			Male	Female
1	N/A	N/A	B.Q.L.	B.Q.L.
2	0	N/A	0.44	B.Q.L.
3	3	N/A	487.84	662.53
4	10	N/A	1361.52	1485.57
5	30	N/A	2111.03	1828.20
6	60	N/A	2229.95	2718.12
7	N/A	A	B.Q.L.	0.42
8	0	A	2.15	2.09
9	3	A	597.19	650.00
10	10	A	1231.66	2125.51
11	30	A	2269.22	2273.33
12	60	A	2496.93	2602.64

N/A: Not applicable
A: Applicable
UVR: Ultraviolet radiation
B.Q.L.: Below the quantifiable limit < 0.30 ng/mL

10.2.4. Immunotoxicity

Study title: Topical photoallergy test of E2007 in albino hairless guinea pigs

Study no.:	LFA00042
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	1/16/2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E2007, Lot 14110902, Purity 100.1%

Key Study Findings

- **There was no evidence of primary irritancy, phototoxicity, contact hypersensitivity, or photoallergy when guinea pigs were co-exposed topically to E2007 and UV irradiation.**

Methods

Doses:	See sponsor's study design tables below.
Frequency of dosing:	Test articles were applied for 2 hours under occlusion and then wiped clean. Four doses were tested simultaneously on each animal (1 dose level per test site).
Route of administration:	Topical
Dose volume:	0.3 ml
Formulation/Vehicle:	Aloe Vera cream (b) (4)
Species/Strain:	Crl:IAF(HA)-hr hairless guinea pig, male
Number/Sex/Group:	5/group
Age:	8 weeks
Weight:	437-546 g
Unique study design:	Photoallergy study: Four injections of Freund's complete adjuvant occurred during the induction phase. Phototoxicity and Photoallergy studies: 2.25 minimal erythema doses (MED) of UV (900 RBU) were delivered on days 1, 3, 5, 8, 10, and 12 during Photoallergy induction and once on day 22 for photoallergy challenge.
Deviation from study protocol:	There were no deviations that compromised the validity of the study.

Study Design: E2007 was assessed for primary irritancy, contact hypersensitivity and photoallergy as described below.

Positive Controls

Comparator Article Information						
Identification - Phototoxicity Phase: 8-Methoxypsoralen (8-MOP) Identification - Photoallergy Phase: 3,3′,4′,5′-Tetrachlorosalicylanilide (TCSA)						
Name	Description	Lot Number	Supplier	Date Received	Storage	Expiration Date
8-MOP	Off-white powder	035K1267	(b) (4)	03 SEP 06	RT, PL	MAR 07
TCSA	White powder	A009656801		02 NOV 04	RT, PL	NOV 08

Overall Study Design

Group	Purpose for Inclusion[a]	Primary Irritancy or Phototoxicity		Contact Hypersensitivity or Photoallergy Induction		Contact Hypersensitivity or Photoallergy Challenge	
		Formulation Administration	UVR Exposure	Formulation Administration	UVR Exposure	Formulation Administration	UVR Exposure
1	Primary Irritancy	Yes	None	N/A	N/A	N/A	N/A
2 & 3	Phototoxicity	Yes	Yes	N/A	N/A	N/A	N/A
4 & 5	Contact Hypersensitivity	N/A	N/A	Yes	None	Yes	None
6 & 7	Photoallergy	N/A	N/A	Yes	Yes	Yes	Yes

a. The primary irritancy study phase included test article evaluation only. The phototoxicity phase included test article and comparator article (8-MOP) evaluations. The contact hypersensitivity and photoallergy study phase included evaluations of the test article and comparator article (TCSA).

N/A - Not applicable

Dosing Group Assignments

Group (Animal Numbers)	Primary Irritancy or Phototoxicity		Contact Hypersensitivity or Photoallergy Induction		Contact Hypersensitivity or Photoallergy Challenge	
	Formulation Administration (mg/mL)	UVR Exposure	Formulation Administration (mg/mL)	UVR Exposure	Formulation Administration (mg/mL)	UVR Exposure
1 (19751-19755)	E2007 (0, 1, 10 and 100)	None	N/A	N/A	N/A	N/A
2 (19756-19760)	E2007 (0, 10 and 100)	Yes	N/A	N/A	N/A	N/A
3 (19761-19765)	8-MOP (0.01, 0.03 and 0.1)	Yes	N/A	N/A	N/A	N/A
4 (19766-19770)	N/A	N/A	E2007 (100)	None	E2007 (0, 10 and 100)	None
5 (19771-19775)	N/A	N/A	TCSA (30)	None	TCSA (0, 10 and 30)	None
6 (19776-19780)	N/A	N/A	E2007 (100)	Yes	E2007 (0, 10 and 100)	Yes
7 (19781-19785)	N/A	N/A	TCSA (30)	Yes	TCSA (0, 10 and 30)	Yes

N/A = Not applicable

Primary Irritancy Studies: When dosed with 0, 1, 10, or 100 mg/ml E2007, there was no dose-related evidence of irritancy.

Phototoxicity Studies: When dosed with 0, 10, or 100 mg/ml E2007, there was no dose-related erythema, skin flaking, or edema observed after exposure to UV. Exposure to the positive control (8-MOP) and UV irradiation resulted in such severe erythema and edema that the animals were euthanized on or before Day 3 of the study.

Contact Hypersensitivity/ Photoallergy Studies: There were no skin reactions indicative of contact hypersensitivity or photoallergy in any of the guinea pigs administered E2007. Guinea pigs exposed to TCSA, the positive control, exhibited erythema, edema, and flaking before the challenge and in response to the challenge on Day 22.

11 Integrated Summary and Safety Evaluation

Perampanel (E2007; ER-155055-90) is a noncompetitive AMPA receptor (AMPAR) antagonist that has been developed by Eisai to treat partial-onset seizures with or without secondarily-generalized seizures in patients with epilepsy aged 12 years or older. *In vitro* studies demonstrated that perampanel and several of its metabolites (M1, M3, M4, M5 and M7), of which only the parent compound circulates in human plasma at levels greater than 10% of the total drug-related exposure, were potent inhibitors of AMPAR-mediated ion flux in rat cortical neurons. Binding studies described in the NDA and in the peer-reviewed literature demonstrate that perampanel is a noncompetitive antagonist of the AMPAR [3], a receptor for the excitatory neurotransmitter, glutamate. Possibly due to its activity towards AMPAR, perampanel exhibited the ability to abrogate seizures in several animal models of epilepsy (i.e. AMPA-induced, audiogenic, electroshock, PTZ-induced, corneal kindling, amygdala kindling); perampanel showed no antiepileptic activity in the genetic model of absence epilepsy in the rat (GAERS). The results of these primary pharmacology studies suggest that perampanel may be useful as an antiepileptic medication in humans.

Moderate oral bioavailability was exhibited in rats (~47%) and dogs (~49%) with higher bioavailability exhibited in monkeys (~74%). These species were used in a majority of the nonclinical studies submitted to support NDA 202-834. Perampanel plasma protein binding was 90 to 94% in monkeys and mice, respectively. Perampanel distributed widely and rapidly throughout the body, especially to the mammary tissue, adrenal gland, liver, kidney, ovary, fetuses, and milk; it is mainly eliminated in feces in rats. Extended residence time was observed in the liver (6 weeks in rat; at least 7 days in monkey), kidney (21 days in rat, at least 7 days in monkey), eye (106 weeks, pigmented rat only; at least 7 days in monkey), skin (12 weeks, pigmented rat only; at least 7 days in monkey), and aorta (106 weeks, rat but not monkey). The extended residence time in the liver of rats was mainly due to covalent binding, as a majority of the compound was not extractible with methanol or trichloroacetic acid. In kidney, most of the perampanel could be extracted with methanol suggesting that the extended residence time in the kidney was not due to a covalent interaction. Given that the residence time of perampanel was higher in the eyes of pigmented rats when compared to albino rats and the fact that most of the binding was associated with pigmented areas of the eyes (e.g. iris, retina) it is probable, although there is no explicit evidence of this in the NDA, that perampanel interacted with melanin in the eye, a phenomenon known to occur with xenobiotics such as polyaromatic hydrocarbons [5]. There was no evidence of ocular toxicity or retinal damage in any of the nonclinical studies submitted to support this NDA. Therefore, while perampanel does have an extended residence time in the eye, it does not seem to be of toxicological consequence.

The extended residence time of perampanel in the aorta (at least 106 weeks) after a single oral dose of perampanel (1 mg/kg or 6 mg/m^2) is unusual and is mainly due to a covalent interaction between perampanel and a component of the aorta, possibly elastin, since perampanel could be liberated from the aorta by treatment with the proteolytic enzymes elastase or pronase. When assessed by light microscopy, there were no findings of cardiovascular toxicity or histopathological abnormalities observed in the vasculature in any of the general toxicology studies conducted with perampanel. It is important to mention that distribution studies generally do not sample other regions of

the arterial vasculature, such as the aortic arch, coronary artery, femoral artery, or cerebral arteries. Therefore, the extent of the covalent binding of perampanel through the entire arterial vasculature as well as at other sites where elastin is common, is currently unknown. The Sponsor has demonstrated that residence time of perampanel in the venous vasculature is short (< 24 hours in rat), suggesting that the extended binding may be limited to only the arteries. Accumulation of xenobiotics and therapeutics in the aorta has been previously documented, with some of these compounds being cardiovascular toxicants [6-11]. For example, rofecoxib (Vioxx), a COX-2 inhibitor withdrawn from the market due to adverse cardiovascular findings, is also known to bind covalently with both rat and human aorta [6-8]. Ten days after oral dosing of rats with rofecoxib, Oitate et al [6] demonstrated that the only anatomical regions in which radiolabeled rofecoxib could be detected were the aorta and the interspinal ligaments. The retention of rofecoxib in the aorta was determined to be due to a covalent interaction based on the ability to liberate the radiolabeled compound from the aorta with elastase, similar to what was observed for perampanel. Although there was no evidence of perampanel-related damage in the vasculature of rats when assessed by light microscopy, it is possible that the ultra structure of the arterial vasculature may be affected by the covalent binding of perampanel. Specifically, in rats dosed with rofecoxib, transmission electron microscopy demonstrated disruption and swelling of the elastic lamellae of the aorta, decreased numbers of smooth muscle cells, and abnormal deposition of collagen fibers. Given that covalent binding of rofecoxib in the aorta was associated with these ultrastructural changes, as detected by electron microscopy, it is possible that other compounds that bind to the aorta covalently, such as perampanel, may induce similar findings [7]. Since there was no ultrastructural assessment of the aorta in perampanel-exposed rats, it is unknown if similar findings are present. Given that rofecoxib was associated with a marked occurrence of cardiovascular adverse events detected during the marketing of this compound, the covalent binding of perampanel to the aorta is of some concern. It is important to be clear, however, that covalent binding of rofecoxib to the aorta has never been definitively shown to be the mechanism of the cardiovascular findings associated with this drug. However, given the coincidence of covalent binding in the aorta and adverse cardiovascular events that occurred with rofecoxib, the finding of a similar molecular action with perampanel (i.e. covalent binding of the aorta) does increase the concern with this compound. However, in the absence of frank cardiovascular toxicity in the nonclinical studies conducted with perampanel, the finding of covalent binding of perampanel to the aorta is not a reason to advise against the approval of FYCOMPA. It is possible that post market monitoring for similar findings to those observed in patients exhibiting rofecoxib-induced cardiovascular toxicity may demonstrate the presence or absence of a similar finding in patients exposed to perampanel; this, of course, would be a decision reserved for the clinical team to make. However, additional nonclinical studies into the binding of perampanel to the aorta may be helpful in understanding the magnitude of the risk posed by this compound. For example, ultrastructural analysis of the aorta of rats exposed to perampanel, similar to the methods used in Oitate et al [7], could provide additional information regarding the histopathological consequences of the covalent binding of perampanel to the aorta. Additionally, studies performed with human aorta, similar to Oitate et al [8], would provide information on the ability of

perampanel to bind covalently to human arteries. Therefore, it is recommended that the Sponsor perform a study, as a post marketing requirement, similar to the one described in Oitate et al [8] in which the ability of perampanel to bind covalently to the human aorta is assessed. Ultrastructural assessment of the aorta from rats exposed to perampanel, as described in [7], would be useful but would not be necessary if covalent binding to the human aorta could not be demonstrated.

Single and repeat-dose toxicology studies to support the approval of FYCOMPA were performed in mouse, rat, dog, and monkey; the pivotal chronic studies were performed in rat and monkey. Since there are no metabolites of perampanel that circulate in humans at levels which are >10% of the total drug-related exposure, there was no need to test the safety of specific metabolites of perampanel in animals. The design of the chronic pivotal nonclinical studies was sufficient, with high doses that represented the MTD in rats (F= 10 mg/kg; M= 100 mg/kg) and monkeys (8 mg/kg). A complete battery of reproductive and developmental toxicity studies was performed in rats and rabbits, as described in ICH S5(R2) [12]. Adequate carcinogenicity studies, which demonstrated that perampanel is not carcinogenic, were performed in rat and mouse. A complete battery of adequate genetic toxicology studies, consistent with "Option 1" described in ICH S2(R1) [13], demonstrated that perampanel was not a genotoxicant. In addition, adequately designed and executed juvenile toxicology studies were performed in rat and dog. Overall, the nonclinical studies provided to support the approval of FYCOMPA are consistent with current regulatory guidance, as stated in ICH M3(R2) [14].

The main test article-related finding in the nonclinical studies was the occurrence of clinical signs. In general, the clinical signs, suggested both a sedative-like effect (e.g. abnormal gait/ ataxia, decreased activity, prostration) and the induction of stereotypy. Stereotypy manifested as excessive grooming in adult mice and rats, self mutilation in adult mice, excessive grooming in juvenile rats, and excessive scratching in juvenile dogs. In addition, delayed-onset of convulsions was observed in rats after long-term dosing with perampanel (> 6 months). Body excoriations and self mutilation of the genitals (e.g. prolapse of the penis) were observed in every study conducted with mice. The genital mutilation, especially in males, was of such severity that it resulted in urine retention in some animals. The excoriations observed in these studies resulted in the development of infections that caused death or euthanasia *in extremis* in some cases. The excoriations and self mutilation were related to excessive grooming. The human relevance of the finding of excessive grooming in mice dosed with perampanel is unknown. However, sterotypies, such as excessive grooming, in rodents have been used as models of obsessive behavior [15]. The delayed-onset of convulsions in rats was only observed in the 2-year study and only in the low dose group. There was no evidence of convulsions at the higher doses, possibly reflecting an anticonvulsive effect; the incidence of convulsions in the low dose group is marked and convincing. The mechanism of this delayed onset and the relevance to humans are unknown. However, this finding suggests that long term, sub-therapeutic doses of perampanel may increase the risk of convulsions. Specifically, the plasma level of perampanel associated with rats dosed with the lowest dose in the 2-year study, 10 mg/kg, was $AUC_{0\text{-}24hr}$ = 3780 ng*hr/ml. Similar plasma levels were observed in humans dosed with 2 to 4 mg of perampanel (Study E2007-E044-002).

The Sponsor has identified seven specified and 15 unspecified impurities that may occur during the manufacture of the drug substance. With the exception of the first GMP batch of perampanel (Lot # 10092507), none of the GMP batches have contained impurities that exceed the identification threshold of 0.10%. The Sponsor states that Impurity # VI (b) (4) was found to be genotoxic by DEREK analysis and a bacterial reverse mutation assay (page 20 of Section 3.2.S.3.2: "Impurities"); however, the results of both assessments were not provided in the initial submission of the application. Copies of these analyses were requested from the Sponsor and were received on April 11, 2012. Given the spontaneous hydrolysis of (b) (4) in aqueous solutions to (b) (4) (Impurity #VII; (b) (4) the Sponsor states that both Impurity # VI and Impurity # VII can be assessed via (b) (4) and hence controlled as (b) (4) rather than mass (i.e. µg) of each compound. Since Impurity #VI is a genotoxicant, this compound should be present at levels which result in a dose of no more than 1.5 µg/day, in a chronic dosing regimen in humans. The specification for (b) (4) in the drug product is set at (b) (4) which is equivalent to (b) (4) In a dose of 12 mg FYCOMPA, (b) (4) controlled at (b) (4) would result in a daily dose of (b) (4) µg/ day, which is consistent with the daily intake limit of 1.5 µg/day for a genotoxic compound. The levels of (b) (4) detected in all GMP batches of perampanel were (b) (4) ppm, suggesting that actual exposure to Impurity # VI would be equal to (b) (4) µg/day in a daily 12-mg dose of FYCOMPA.

In the 4/11/2012 submission to the NDA, the Sponsor provided the results of a DEREK analysis of all of the specified and unspecified impurities and a study report for a bacterial reverse mutation (Ames) assay for Impurity #VI (reviewed in Section 7 of this review). DEREK analysis of the specified and unspecified impurities identified no structural alerts for genotoxicity for any of the compounds tested, which is not consistent with page 20 of Section 3.2.S.3.2 in which the Sponsor states that "*As a result of the DEREK (Deductive Estimation of Risk from Existing Knowledge software) assessment (in silico assessment), there were no genotoxic impurities with the exception of* (b) (4) It is unclear why the Sponsor has stated in Section 3.2.S.3.2 of the initial submission that Impurity VI is genotoxic by DEREK analysis when the DEREK assessment clearly does not support this statement. The Ames study performed on this impurity does, however, demonstrate that it is genotoxic (see review of this study in Section 7 of this review). Although none of the specified or unspecified impurities were found to be genotoxic via a DEREK analysis performed by the Sponsor, the *in silico* assessment did identify a structural alert for skin sensitization for a theoretical impurity, (b) (4) which has not been detected in the drug substance at levels (b) (4) ppm (Study Report W-20110327). For some unknown reason, the Sponsor has interpreted the finding of skin sensitization to mean that (b) (4) is a genotoxicant. In Study Report W-20110327 entitled "*Retrospective analysis of* (b) (4) *as genotoxic impurity in E2007 drug substance from GMP 12th to GMP 25* " the Sponsor states "(b) (4) *is a potentially genotoxic as per in silico prediction using the informational database (DEREK; in silico prediction)*". However, as was the case for Impurity #VI, the DEREK assessment provided in the 4/11/2012 submission does not support this conclusion.

There was no evidence that perampanel was genotoxic or carcinogenic under standard testing conditions. However, a phototoxicity battery did demonstrate that perampanel was a clastogen, but not a mutagen, in the presence of UV irradiation. This finding should be reported in the labeling for FYCOMPA as described in "Guidance for Industry: Photosafety Testing" [16]. In addition, Impurity #VI, which spontaneously degrades to Impurity VII, was demonstrated to be a mutagen in the Ames assay. This finding is consistent with that of a peer-reviewed study which assessed, in the Ames assay, the mutagenicity of (b) (4) containing compounds [17]. Interestingly, computational toxicology assays, performed by both the Sponsor and by the CDER computational toxicology group, were unable to predict the mutagenic potential of Impurity #VI or its degradation product, Impurity #VII. The inability to predict the mutagenicity of this impurity was attributed to the presence of a (b) (4) in the structure; there was an insufficient database for this type of compound (see Appendix). Since Impurity #VI is a genotoxic impurity, as determined in the Ames assay, it is controlled in the final drug product at a concentration that would result in a dose of 1.5 µg/ day, an acceptable specification for chronic dosing in humans [18]. In the two-year bioassays conducted in rat and mouse, there was no evidence to suggest that perampanel is carcinogenic. The two studies were considered to be negative; the Executive CAC concurred with this conclusion (see Appendix for Executive CAC minutes). Doses up to 12 times (mouse), 81 times (male rat), and 24 times (female rat) the maximum recommended human dose (MRHD), on a mg/m^2 basis, were tested in the carcinogenicity studies.

The reproductive and developmental toxicity battery was performed in rat (fertility, embryo-fetal development [EFD], and pre/postnatal development) and rabbit (embryo-fetal development). The finding of teratogenicity in the rat study, specifically diverticulum of the intestine in all dose groups, (b) (4) should be included in the revised labeling. Since the finding of diverticulum of the intestine was observed in all dose groups in the rat EFD study, there was no NOAEL determined for the developmental toxicity of perampanel. The lowest dose in the rat EFD study was 1 mg/kg or 6 mg/m^2. On a dose per body surface basis, the lowest dose at which diverticulum of the intestine occurred in rats was 4.9 times the lowest (2 mg; 1.2 mg/m^2) and 0.8 times the highest (12 mg; 7.4 mg/m^2) clinical doses of FYCOMPA. Since these effects were observed at a range of doses that included the clinical dose, when normalized to dose per body surface area, there is no safety margin for this finding. The finding of diverticulum of the intestine in fetuses and the potential risk to humans should be communicated in the label for FYCOMPA. The finding of teratogenicity is not uncommon with antiepileptic medications. Therefore, although the finding of diverticulum of the intestine is of enough concern to warrant reporting in the label for FYCOMPA, this finding would not preclude the approval of FYCOMPA. Additional effects on reproduction and development were observed in the fertility and the pre-/ post-natal (PPN) development studies performed in rat. An increase in early resorptions and stillborn pups was noted in litters of dams exposed to >1 mg/kg perampanel. At doses of 30 mg/kg perampanel, prolonged and irregular estrous cycles were observed in female rats, but this alteration in estrous cycle did not impact the reproductive potential of the dams dosed at this level. The nature of the perturbation of the estrous cycle is unknown because the Sponsor did not assess

hormone levels in these studies. However, there is an emerging understanding of the role of AMPA receptors in controlling the activity of neurons that release gonadotropin-releasing hormone [19].

The Sponsor assessed the toxicity of perampanel in juvenile animals (rat and dog) in order to support the safe use of FYCOMPA in pediatric populations. With the exception of the initiation of dosing in dogs (see below), the design of the juvenile studies was consistent with accepted principles of juvenile toxicology testing [20]. Specifically, daily dosing was initiated in rat pups on postnatal day (PND) 7 and continued for 12 weeks until PND 90, followed by a 4-week recovery period. Daily dosing in dogs began on PND 42 and continued for 33 weeks, through postnatal Week 39. The duration of dosing in rats was slightly longer than usual but is not expected to affect the validity of the study. Although dosing in the dog study was initiated much later (PND 42) than what is suggested (PND 5; [20]), the period of juvenile development was adequately covered in the rat study. Therefore, the rat study is sufficient to support the safety of perampanel in pediatric populations. It is important to state that even though dosing was initiated in the dog study later than what is recommended; the overall design of the study included the expected elements of a well-designed juvenile toxicology study.

The main test article-related finding in the juvenile toxicology studies was the adverse clinical signs observed at all doses tested in both juvenile rats and dogs. In juvenile rats, decreased activity, prostration, uncoordination, and excessive grooming were the clinical signs observed at each dose level (NOEL < 1 mg/kg); these clinical signs were similar to those observed in adult rats, albeit at lower doses. Specifically, in adult rats dosed with perampanel for 13 weeks (Study S01008), the test article-related clinical signs observed at 10 or 30 mg/kg were abnormal gait, decreased activity and prostration; excessive grooming was observed in male rats dosed with 300 mg/kg for 13-weeks (Study S04007) and in the 26-week study (Study S02002) at 30 mg/kg. There were no clinical signs observed in adult rats dosed with 1 mg/kg for 13-weeks (Study S01008) or 26-weeks (Study S02002). Although the clinical signs were associated with higher levels of perampanel in juvenile rats at PND 7, relative to adults, (juvenile rats @ PND 7: $AUC_{0\text{-}24hr}$ at 1 mg/kg= 2179 (M) and 2009 (F) ng*h/ml; adult rats $AUC_{0\text{-}24hr}$ at 1 mg/kg= 631 (M) and 998 (F) ng*h/ml), the levels of perampanel in rats from the 1 mg/kg dose group in the juvenile rat study were similar at PND 35, PND 63, and PND 90 to those observed in adult rats dosed with 1 mg/kg. The clinical signs (decreased activity, uncoordination, prostration, excessive grooming, excessive licking, excessive scratching) observed in rats during the pre-weaning period persisted in all dose groups of the juvenile toxicology study during the post weaning period, a phase of the study at which perampanel levels in the rats dosed with 1 mg/kg are similar to those observed in adults dosed with 1 mg/kg perampanel. The persistence into the post weaning period of these clinical signs in juvenile rats at exposure levels that do not result in similar clinical signs in animals dosed only during adulthood (Study S01008, S04007 and S02002) suggests that juvenile rats are more susceptible to the development of the sedative-like clinical signs and stereotypies associated with perampanel exposure. A similar finding of juvenile susceptibility to stereotypy existed in dogs. Juvenile dogs exhibited abnormal gait, altered activity, excessive scratching, tremors, and uncoordination at doses ≥ 1 mg/kg; plasma levels of perampanel in juvenile dogs ranged from an $AUC_{0\text{-}24hr}$ = 334 to 681 ng*hr/ml. Abnormal gait was the only clinical sign observed in adult dogs dosed up

to 10 mg/kg for 13 weeks (Study S01009), a dose which resulted in perampanel plasma levels of $AUC_{0\text{-}24hr}$ = 905-913 ng*hr/ml.

Female juvenile rats dosed with ≥ 3 mg/kg perampanel exhibited an increase in the number of errors in Path B of the Cincinnati water maze. This finding was robust when the water maze was performed during the dosing phase of the study and was still present, albeit to a minor extent, when assessed at the end of the recovery phase. Since perampanel is an AMPA receptor antagonist, it is not surprising that an adverse effect on learning and memory was documented in the juvenile rat study. Disruption of AMPA receptor function by genetic deletion of the AMPA receptor subunit GluR1 is known to result in disruption of spatial memory [21, 22]. It is interesting that this finding was only observed in female rats dosed with perampanel. Although plasma levels of perampanel were generally higher in females, it is unlikely that the sex-related difference in TK contributed to this finding. For example, when assessed on Day 63, plasma $AUC_{0\text{-}24hr}$ in HD males was twice as high as in MD females, a group exhibiting an increased error rate in the water maze. The findings in the Cincinnati water maze should be included in the label of FYCOMPA, as they appear to be test article-related.

Overall, the toxicities observed in the nonclinical general toxicology, reproductive and developmental toxicology, and the carcinogenicity studies of perampanel are not of such severity or type that these findings would prevent the approval of FYCOMPA. When performed on a dose per body surface area (mg/m^2) basis, it is clear that the NOAELs for many of the toxicology studies (i.e., general toxicology, fertility, EFD, Pre/Postnatal study (PPN), and juvenile) are within the range of the proposed clinical doses (Reviewer's Summary Table, below). However, the main finding in the repeat-dose general toxicology studies (i.e. clinical signs) is a manifestation of the pharmacological activity of perampanel and is reversible upon dosing cessation. There is no evidence that perampanel poses a cancer risk, as there was no finding of carcinogenicity at doses of up to 81 times and 12 times the MRHD in rat and mice, respectively. The findings in the EFD and juvenile toxicology studies were of the most concern. Specifically, perampanel was a teratogen in rats and there was no NOAEL observed for this finding. The dose levels at which diverticulum of the intestine was observed were similar to the proposed clinical doses, on a mg/m^2 basis. The teratogenic risk of perampanel should be disclosed in the label for FYCOMPA. The finding of cognitive dysfunction in the Cincinnati water maze performed as a part of the juvenile rat toxicology study is consistent with perampanel's ability to antagonize the activity of the AMPAR, a receptor known to be important for learning and memory [22]. Although the NOAEL for the rat juvenile toxicology study is provided below as < 1 mg/kg, there was a NOEL for the finding of cognitive dysfunction in female rats (1 mg/kg). However, this NOEL is well within the range of clinical doses and should be included in the labeling of FYCOMPA. Although not fully reversed at the end of a recovery period, the severity of the cognitive dysfunction observed in female rats was markedly reduced relative to the severity of the finding during the active dosing period. In general, the adverse effects observed in the nonclinical studies are monitorable and mainly reversible, with the exception of the teratogenic and cognitive dysfunction findings. Therefore, it is concluded that the results of the nonclinical safety studies are not of sufficient concern to advise against the approval of FYCOMPA.

Toxicity	Species	NOAEL (mg/kg)	NOAEL (mg/m^2)	Safety Margin (based on BSA at MRHD)
Repeat Dose (4-week, dose range) Clinical Signs (abnormal gait, decreased activity), excoriations & self mutilation (genital trauma)	Mouse	3	9	1.2
Repeat Dose (13-week, pivotal) Clinical Signs (vomiting, abnormal gait, decreased activity)	Dog	0.1	2	0.3
Chronic (26-week, pivotal) Clinical Signs (abnormal gait, decreased activity)	Rat	1	6	0.8
Chronic (52-week, pivotal) Clinical Signs (ataxia, somnolence, sedation)	Monkey	0.1	1.2	0.2
Carcinogenicity No test article-related tumors. Convulsions at LD (10 mg/kg).	Mouse	> 30	> 90	> 12
	Rat	> 100 (M) > 30 (F)	> 600 (M) > 180 (F)	> 81 > 24
Reproductive Tox---Fertility Prolonged/ irregular estrous	Rat	10	60	8.1
Reproductive Tox---EFD Rat: Diverticulum of the intestine, resorptions, implantation losses	Rat	< 1	< 6	< 0.8
Rabbit: Decreased implantations, decreased # of live fetuses, spontaneous abortion	Rabbit	3	36	4.9
Reproductive Tox---PPN Stillborn, clinical signs, delayed sexual development	Rat	1	6	0.8
Juvenile Tox Rat: Clinical signs (uncoordination, excessive grooming), delayed sexual maturation, cognitive dysfunction (F, only)	Rat	< 1	< 6	< 0.4
Dog: Clinical signs (abnormal gait, tremors, uncoordination, circling, head shaking)	Dog	< 1	< 20	< 1.3

Reviewer's Summary Table: No Observed Adverse Effect Levels (NOAEL) for Pivotal Studies and Safety Margins Based on the Maximum Recommended Human Dose (MRHD). The MRHD of FYCOMPA (12 mg) is equal to 7.4 mg/m^2 based on body surface area of a 60 kg human and 15 mg/m^2 for a 20 kg child (used for dose comparison of juvenile study). The k_m values used for dose normalization were as follows: Adult human (37), child (25 for 20 kg child), rat (6), dog (20), mouse (3), rabbit (12) and monkey (12). The adverse effects listed for each study were considered to be related to the test article and were observed at doses higher than the NOAEL. A "< "denotes that adverse effects were observed at the lowest dose tested in the study. A ">" denotes that no adverse effects were observed at any of the dose levels used in the study.

12 References and Appendix

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(b) (4)

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APPENDIX:

To: Christopher Toscano
cc: Lois Freed
From: CDER/OPS/OTR/DDSR: The CDER Computational Toxicology Group
Re: NDA 202834
Date: March 29, 2012

Six chemicals were evaluated by the CDER computational toxicology group for genetic toxicity endpoints using three (quantitative) structure-activity relationship [(Q)SAR] computational toxicology software programs[1]. The results of the predictions from all software programs used at each endpoint were weighted equally and the analysis was optimized for sensitivity (minimizing false negatives) to reach the overall conclusions.

Genetic Toxicity for Predicting the ICH S2 Battery for Impurity VII: (b) (4)

Software	*Salmonella* Mutagenicity
Derek Nexus	NSA
Leadscope	NC
MC4PC	NC
Overall Prediction	**NC**

[1] Derek Nexus 2.0, Leadscope Model Applier 1.3.3-3, and MC4PC 2.4.0.7

[2] + = positive; – = negative; Eqv = equivocal; NSA = no structural alerts are identified by Derek Nexus (Derek Nexus cannot differentiate between a negative call and the inability to make a call because of no coverage); NC = test chemical features are not adequately represented in the model training data set, leading to a no call; N/A = no available model

To: Christopher Toscano
cc: Lois Freed
From: CDER/OPS/OTR/DDSR: The CDER Computational Toxicology Group
Re: NDA 202834
Date: May 09, 2012

(b) (4) was evaluated by the CDER computational toxicology group for *Salmonella* mutagenicity using three (quantitative) structure-activity relationship [(Q)SAR] computational toxicology software programs[1]. The results of the predictions from all software programs used were weighted equally and the analysis was optimized for sensitivity (minimizing false negatives) to reach the overall conclusion.

Predicting *Salmonella* Mutagenicity for (b) (4)

(b) (4)

Software	*Salmonella* Mutagenicity
Derek Nexus	NSA
Leadscope	NC
MC4PC	NC
Overall Prediction	**NC**

No prediction could be made for the *Salmonella* mutagenicity of (b) (4) because its chemical features were not adequately represented in the model training data sets.

This report has been reviewed and approved by CDER/OPS/OTR/DDSR.

[1] Derek Nexus 2.0.2, Leadscope Model Applier 1.3.3-3, and MC4PC 2.4.1.2

[2] + = positive; – = negative; Eqv = equivocal; NSA = no structural alerts are identified by Derek Nexus (Derek Nexus cannot differentiate between a negative call and the inability to make a call because of no coverage); NC = test chemical features are not adequately represented in the model training data set, leading to a no call; N/A = no available model

2 Pages Have Been Withheld as a Duplicate Copy of The "Executive CAC" dated July 3, 2012 which is located in The Other Review Section of this NDA Approval Package.

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/s/

CHRISTOPHER D TOSCANO
08/22/2012

LOIS M FREED
08/22/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202834 **Applicant: Eisai, Inc.** **Stamp Date: 12/22/11**

Drug Name: FYCOMPA (perampanel or E2007) tablets **NDA Type: 505(b)(1)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The nonclinical sections of the submission (2.4, 2.6 and 4) are present.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		Bookmarks and hyperlinks in the electronic study reports seem to be functional.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?		X	The Pathology report in the mouse carcinogenicity study report (B-4955) contains handwritten English and Japanese comments in the margin of the report. The Sponsor should submit an amended report which incorporates this information into the body of the report.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		The Sponsor states that signed and dated Pathology Reports are not available for the following non-GLP study reports: #TKB00006 (4-day rat study), #TKB00008 (7-day dog study), #TKB01016 (2-week monkey study).
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	N/A	N/A	Not applicable. See comment #6.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		Animals were dosed via the oral route in all pivotal nonclinical studies. The proposed clinical formulation is tablet for oral dosing.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		GLP and QA statements are provided for all pivotal studies.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X	The ExeCAC did not concur with the doses of (b) (4) mg/kg in the proposed mouse carcinogenicity study (IND 68368; 12/18/2003) and recommended an additional 13-week mouse study be performed to determine appropriate doses for the carcinogenicity study. A study report for the recommended 13-week study was not included in the NDA. The Sponsor has included in the NDA a study report for a mouse carcinogenicity study, conducted using the doses with which the ExecCAC did not concur.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		X	The *Indications and Usage* section of the *Highlights* section of the label does not mention the pharmacologic class as advised in "*Guidance for Industry and Review Staff Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information*; October 2009".
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		The impurity levels in GMP batch #11-GMP batch #25 are (b) (4) and are, therefore, below the qualification threshold of 0.15%.
11	Has the applicant addressed any abuse potential issues in the submission?	X		To be addressed by CSS.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	N/A	N/A	Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___YES_____

Draft Comments to the Sponsor for the 74-day letter:

- *The Indications and Usage section of the Highlights section of the label does not mention the pharmacologic class as advised in "Guidance for Industry and Review Staff Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information; October 2009". You should amend the draft labeling accordingly.*
- *The Pathology report for study B-4955 (mouse carcinogenicity study) contains handwritten amendments in the margins of the report. We recommend that you submit an amended copy of this report in which you have incorporated these amendments into the body of study report.*

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/s/

CHRISTOPHER D TOSCANO
01/10/2012

LOIS M FREED
01/10/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202834 **Applicant: Eisai, Inc.** **Stamp Date: 5/25/11**

Drug Name: FYCOMPA (perampanel or E2007) tablets **NDA Type: 505(b)(1)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The nonclinical sections of the submission (2.4, 2.6 and 4) are present.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		Bookmarks and hyperlinks in the electronic study reports seem to be functional.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?		X	A) Study B04002 has several lines that contain, what appears to be, missing words that were replaced with two bullet points (e.g. page 9). This should be corrected in all relevant sections of this report. B) Pages 21 through 209 of Study #S05107 (26-week rat study) are missing from the study report. These pages should be submitted for review. C) The completeness of the steady state AUC table on page 13 of the Toxicology Tabulated Summary (2.6.7.) should be confirmed.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?		X	A) Signed and dated Pathology Reports are not provided for the following study numbers: #TKB00007 (single dose dog study), #B-4954 (13-week mouse study), #TKB00006 (4-day rat study), #S04007 (13-week male rat study), #TKB00008 (7-day dog study), #TKB01016 (2-week monkey study), #SBL-47-47 (4-week monkey study), #B-4955 (mouse carcinogenicity study). The Sponsor should submit these signed and dated reports, if they are available. Without a signed and dated Pathology Report, these data are considered to be incomplete as per the FDA Final Rule published in the Federal Register on September 4, 1987. B) Individual line listings of fetal observations are not provided in the pivotal embryo-fetal development

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
				studies (#200420, #250520, #250526). These study reports cannot be reviewed until the Sponsor provides this information.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	N/A	N/A	Not applicable. See comment #6.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		Animals were dosed via the oral route in all pivotal nonclinical studies. The proposed clinical formulation is tablet for oral dosing.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?		X	Although all pivotal, nonclinical studies in this submission include both a valid and signed Quality Assurance Statement and Good Laboratory Practice Statement, many studies are missing a signed Pathology Report which is considered a violation of GLP (see question #4).
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X	A) The Sponsor was informed during the EOP2 meeting held on 12/5/2007 that a rodent and nonrodent juvenile toxicology study would be required. A pivotal nonrodent juvenile toxicology study was not submitted in the NDA. B) The CAC did not concur with the doses of (b) (4) mg/kg in the proposed mouse carcinogenicity study (IND 68368; 12/18/2003) and recommended an additional 13-week mouse study be performed to determine appropriate doses for the carcinogenicity study. A study report for the recommended 13-week study was not included in the NDA. The Sponsor has included in the NDA a study report for a mouse carcinogenicity study in which the doses that the CAC did not concur with were utilized.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative		X	The Highlights and Section 1. (Indications and Usage) of the label do not include a discussion of the pharmacologic class as recommended in "*Guidance for Industry and Review Staff*

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
	serum/plasma levels) and in accordance with 201.57?			*Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information*."
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		The impurity levels in GMP batch #11- GMP batch #25 are (b) (4) and are, therefore, below the qualification threshold of 0.15%.
11	Has the applicant addressed any abuse potential issues in the submission?	X		To be addressed by CSS.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	N/A	N/A	Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___NO_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Individual line listings of fetal observations are not provided in the pivotal embryo-fetal development studies (2000420, 250520, 250526). Also, the line listings for the pivotal 6-month rat study are not provided (pages 21 to 209 of study # S05107). These pivotal studies can not be independently reviewed without this information. Comments to the Sponsor are provided below.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments to the Sponsor in the 74-day letter:

- Study B04002 has several lines that contain, what appears to be, missing words that were replaced with two bullet points (e.g. page 9). This should be corrected in all relevant sections of this report.
- Pages 21 through 209 of Study #S05107 are missing from the study report. These pages should be submitted for review.
- The completeness of the steady state AUC table on page 13 of the Toxicology Tabulated Summary (2.6.7.) should be confirmed.
- Signed and dated Pathology Reports are not provided for the following study numbers: #TKB00007, #B-4954, #TKB00006, #S04007, #TKB00008, #TKB01016, #SBL-47-47, #B-4955. Signed and dated reports should be submitted, if they are available. Without a signed and dated Pathology Report, these data are considered to be incomplete as per the FDA Final Rule published in the Federal Register on September 4, 1987.
- You have not provided the individual line listings for fetal observations in the pivotal embryo-fetal development studies (#200420, #250520, #250526). These line listings should be submitted to allow for review of the embryo-fetal studies.
- We acknowledge that you have conducted a juvenile toxicology study in rodents. However, during the End-of-Phase 2 meeting conducted on 12/5/2007, you were informed that a juvenile toxicology study in a nonrodent species would be required. You should provide an update on the progress of the nonrodent juvenile toxicology study.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

- We acknowledge that the Carcinogenicity Assessment Committee did not concur with the dose levels you have used in the mouse carcinogenicity study included in your application. The adequacy of this study will be determined during the review cycle; it is possible that additional studies may be required if this study is determined to be inadequate.

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/s/

CHRISTOPHER D TOSCANO
07/14/2011

LOIS M FREED
07/15/2011