Drug, lot #, and % purity: L-000900612, lot #'s L-000900612-003E015, [redacted] ure by HPLC

Methods:

Doses: 0, 50, 200, and 600 mg/kg/day

Species/strain: Sprague-Dawley rats:CD®(SD)IGS BR

Number/sex/dose (main study): 44 (except for the 200 mg/kg/day male group which had 43)

Route, formulation, volume, and infusion rate: Oral gavage, dissolved in 80% PEG400, dosing volume of 2.5 ml/kg

Satellite groups used for toxicokinetics or recovery: No separate rats were used for TK blood sampling. Blood samples were taken from 3-4 rats/sex/dose/time point (each rats bled no more than twice) that were assigned to the main study.

Age: 5 days old

Weight: 6.1-15.2 g for females; 8.1-15.9 g for males

Treatment duration: PND 5 to 52-54

Frequency of dosing: Once a day

Sampling times for TK study: 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose in PNW 7 from 3-4 rats/sex/dose/time point

Observation and Times:

Clinical signs: Daily for mortality and physical signs from PND 4 to 55; daily for mortality and twice per week for physical signs from PNW 9 to termination.

Body weights: Daily from PND 5 to 34; twice per week from PNW 6 to 8; once per week from PNW 9 to termination.

Developmental signs: Presence of vaginal opening for all females on PND 28 and every other day thereafter until either opening observed or PND 38; preputial separation for all males on PND 38 and every other day until either separation observed or PND 54

Ophthalmoscopy: Control and high dose animals only in PNW 7

Hematology: PNW 7 or 8

Serum biochemistry: PNW 7 or 8

Behavioral assessments: Passive avoidance test for learning, short-term retention, and long-term retentions in PNW 9 (PND 61-63) and one week later; Auditory startle habituation test to assess sensorimotor reflexes and habituation to redundant, nonsignificant stimili in PNW 11 (PND 71 to 72); Open field motor test to evaluate the general activity levels in PNW 10 (PND 64 to 66) between the first and second session of passive avoidance test.

Reproductive assessment: Eleven to 14 pairs of rats/dose were mated during PNW 11 to assess the mating, fertility, and fecundity indices, pre, peri- and post-implantation loss, resorption, and liver fetuses/pregnant female.

Gross pathology: PND 52-54.

Organ weights: PND 52-54 on adrenals, liver, brain, pituitary, heart, prostate, ovaries, spleen, kidneys, testes, thymus, thyroid

Histopathology: PND 52-54; Control, high dose, and found-dead/moribund animals only on adrenals, aorta, bone (femur, tibia, and femorotibial joint), bone marrow (in bone section), brain (including cerebral cortex, subcortical white matter, basal ganglia, hippocampus, thalamus, cerebellum, and medulla oblongata), cervix,

epididymides, esophagus, eye, Harderian gland, heart, kidneys, lymph nodes (mesenteric and cervical), large intestine (colon and cecum), liver, lung, mammary gland, optical nerve, ovaries, pancreas, parathyroids, peripheral nerve (sciatic), Peyer's patches, pituitary, prostate, salivary gland (submandibular/sublingual), seminal vesicles, small intestine (duodenum, jejunum, and ileum), skeletal muscle (quadriceps), skin (from inguinal mammary region), spinal cord (cervical), spleen, stomach (glandular and nonglandular portions), testis, thymus, thyroids, trachea, urinary bladder, uterus, vagina

Results:

Mortality: Most of the deaths occurred before PND 14 and the cause of demise was not determined. The deaths in the high dose groups occurred during the PNW 1 and 2. Those that happened after PNW 2 were caused by incubation error. The mortality rate, cause of death, and time of death did not show any dose relationship. Deaths were unlikely caused by the drug toxicity.

	Male				Female			
Doses (mg/kg/day)	**0**	**50**	**200**	**600**	**0**	**50**	**200**	**600**
# animals/group	44	44	43	44	44	44	44	44
# rats died/sacrificed	4	1	2	4	2	0	2	4
PNW of death	2,2,3,5	4	1,7	2,3,3,3	5,7	0	1,2	1,2,2,3
Cause of death	N,N,P,C	U	U, A	N, I, I, I	C, A	-	N, N	N, N, N, I

A = Died post anesthesia
I = Intubation accident
U = Undetermined
C = Clinical sign
N = Not examined since prior to PND 14
P = Partially cannibalized

Clinical signs: No effect.

Body weights: No effect.

Developmental signs: No effect.

Ophthalmoscopy: No effect was claimed. No actual and verifiable data were included in the report.

Hematology: No effect.

Serum biochemistry: No effect.

Behavioral assessments: No effect.

Reproductive assessments: No effect.

Gross pathology: No effect.

Organ weights: No effect.

Histopathology: The incidence rate for increased inflammation and nonglandular mucosal vacuolation in the stomach were increased with increasing doses of L-000900612. In addition, the mean severity score for nonglandular mucosal vacuolation was also increased in a dose-dependent manner. No other dose-related increase in the incidence rate of histopathological findings was observed. Irritation to the stomach glandular mucosa was seen in the adult rats dosed with L-000900612. Similar irritation effect was also seen in the nasopharyngeal mucosa in adult rats at the same doses, which was believed to be caused by the aspiration of drug formulation into the nasopharyngeal tract. The results suggested that age of the rats did not alter the toxicity profile of L-000900612.

	Male				Female			
Doses (mg/kg/day)	**0**	**50**	**200**	**600**	**0**	**50**	**200**	**600**
Number examined	14	14	13	14	14	14	14	14
Stomach –								
Increased inflammation								
% animal affected	0	0	7.1	42.9	0	0	0	21.4
Mean severity	0.00	0.00	1.00	1.33	0.00	0.00	0.00	1.00
Nonglandular mucosal vacuoloation								
% animal affected	0	0	15.4	35.7	0	0	7.1	7.1
Mean severity	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
The severity scores are: 1 = very slight; 2 = slight, 3 = moderate; 4 = marked; 5 = severe								

Toxicokinetics: There was no sex difference in the systemic exposures to L-000900612 or its metabolite, L-001277512. Systemic exposures, in general, increased with increasing doses between the mid and high dose groups. Absorption and glucuronidation to L-001277512 were rapid in all doses and in both sexes with the maximum plasma concentrations occurring at 0.5 hours postdose. Plasma drug elimination was generally biphasic and rapid at mid and high doses with the mean trough concentrations less than 3% of their respective C_{max} values. The terminal elimination was slow (between 12 to 24 hours).

		Male			Female		
Dose (mg/kg/day)		**50**	**200**	**600**	**50**	**200**	**600**
L-000-900612	**T_{max}** (hr)	0.5	0.5	0.5	0.5	0.5	0.5
	C_{max} (µM)	18.2 ± 6.60	16.3 ± 5.84	39.2 ± 14.1	27.2 ± 5.18	57.5 ± 24.1	61.1 ± 23.4
	AUC_{0-24h} (µM-hr)	23.9 ± 3.19	33.3 ± 4.77	67.4 ± 9.70	33.1 ± 1.81	60.8 ± 12.5	90.5 ± 18.5
L-00-1277512	**T_{max}** (hr)	0.5	0.5	0.5	0.5	0.5	0.5
	C_{max} (µM)	29.9 ± 8.25	33.7 ± 7.84	38.4 ± 14.1	26.0 ± 4.43	45.1 ± 14.6	33.5 ± 8.54
	AUC_{0-24h} (µM-hr)	59.3 ± 4.47	93.4 ± 8.52	137 ± 15.8	49.4 ± 6.04	92.4 ± 10.6	99.1 ± 9.73

Study title: L-000900612: Oral range-finding and toxicokinetic study in juvenile rats.

Key study findings: The effects of L-000900612 on the clinical signs, body weight gain, hematology, and serum biochemistry parameters were evaluated in sixteen 5-day old rats/sex/dose that were administered orally with 0, 150, 300, 450, and 600 mg/kg/day L-000900612 from PND 5 to PND 56-58. Eighteen deaths were observed in the treated groups without apparent dose-relationship. In addition, a least a half of the deaths in the 450 and 600 mg/kg/day groups occurred in pups from the same litter, suggesting that they were likely due to inadequate maternal care rather than drug toxicity. No other parameter was affected. Toxicokinetic data indicated that saturation of absorption occurred at 450 mg/kg/day dose. NOAEL for the study was 600 mg/kg/day which was selected as the high dose in the definitive study in juvenile rats.

Study no.: TT #05-7305

Volume: \\Cdsesub1\evsprod\NDA022145\0000\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42354-juv\tt057305\tt057305.pdf

Conducting laboratory and location: Merck Research Laboratories, West Point, PA

Date of study initiation: 6/24/2005

GLP compliance: Yes

QA report: yes (X) no ( )

Drug, lot #, and % purity: L-000900612, lot #'s L-000900612-003E014, L-000900612-003E017, and L-000900612-003E015; ——— pure by HPLC

Methods:

Doses: 0, 150, 300, 450, and 600 mg/kg/day

Species/strain: Sprague-Dawley rats/——CD®(SD)IGS BR

Number/sex/dose (main study): 16 (from 4 litters, 4 pups/sex)

Route, formulation, volume, and infusion rate: Oral gavage, dissolved in 80% PEG400, dosing volume of 2.5 ml/kg

Satellite groups used for toxicokinetics or recovery: No separate rats were used for TK blood sampling. Blood samples were taken from 3-4 rats/sex/dose/time point (each rats bled no more than twice) that were assigned to the main study.

Age: 5 days old

Weight: 7.6-14.7 g for females; 6.4-16.3 g for males

Treatment duration: PND 5 to PND 56, 57, or 58

Frequency of dosing: Once a day

Sampling times for TK study: 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose in postnatal week 7 from 3-4 rats/sex/dose/time point

Observation and Times:

Clinical signs: Daily for mortality and physical signs.

Body weights: Daily from PND 5 to 21; twice per week thereafter.

Hematology: PNW 8

Serum biochemistry: PNW 8

Toxicokinetic: Blood samples collected from 3-4 rats/sex/dose in PNW 9 at 0.5, 1, 2, 4, 8, 12, and 24 hours postdose.

Results:

Mortality: Most of the deaths occurred before PNW 2. There was no clear dose-relationship for mortality. Deaths were unlikely caused by the drug toxicity. Three out of six deaths in the 450 and 600 mg/kg/day groups were from the same litter and were likely due to inadequate maternal care.

	Male				Female			
Doses (mg/kg/day)	**150**	**300**	**450**	**600**	**150**	**300**	**450**	**600**
# animals/group	16	16	16	16	16	16	16	16
# of litters	4	4	4	4	4	4	4	4
# rats died/sacrificed	3	1	3	3	1	1	3	3
PNW of death	1,2,6	2	2,2,2	3,4,4	1	8	2,2,8	2,4,4
# litters affected	3	2	2	2	1	1	3	2

Clinical signs: No effect.

Body weights: No effect.

Hematology: No effect.

Serum biochemistry: No effect.

Toxicokinetics: There was no sex difference in the systemic exposure to L-000900612. Saturation of absorption was reached at 450 mg/kg/day. Absorption was rapid in all dose groups and in both sexes with the maximum plasma concentrations occurring in ≤ 2 hours postdose. Plasma drug elimination was generally biphasic and rapid at mid and high dose with the mean trough concentrations less than 3% of their respective C_{max} values. The terminal elimination was slow (between 12 to 24 hours).

	Male				Female			
Dose (mg/kg/day)	**50**	**300**	**450**	**600**	**50**	**300**	**450**	**600**
T_{max} (hr)	0.5	1.0	2.0	1.0	0.5	1.0	0.5	1.0
C_{max} (μM)	8.54	22.0	24.0	33.1	28.5	29.2	20.9	43.9
$AUC_{0\text{-}24h}$ (μM-hr)	17.8	43.2	64.5	55.0	34.9	67.0	45.5	79.0

2.6.6.7 Local tolerance

Study title: Local lymph node assay in mice (LLNA)

Key study findings: The allergenic potential of L-000900612 was evaluated in a murine local lymph node assay. Concentrations of 10, 100, and 1000 mg/ml of L-000900612 were administered to the murine ears. A test was considered positive if the stimulation index (SI), which was calculated by dividing the mean BrdU-containing cells of each treatment group by the mean BrdU-containing cells of the vehicle control group, was greater than 3.0 and/or statistically significant increases in SIs were observed. It was found that a stimulation index of 11.0 was determined for the positive control, 25% hexylcinnamaldehyde, while the three concentrations of L-000900612 produced SIs ranged from 0.69 to 1.10. Thus, L-000900612 was not considered a dermal sensitizer in mice.

Study no.: TT #04-5541

Volume: *\\Cdsesub1\evsprod\NDA022145\0000\m4\42-stud-rep\423-tox\4236-loc-tol\tt055541\tt055541.pdf*

Conducting laboratory and location: [redacted]

Date of study initiation: 10/20/2004

GLP compliance: Yes

QA reports: yes ( ) no (X)

Drug, lot #, and % purity: L-000900612, lot # L-000900612Y

Formulation/vehicle: Dissolved in N,N-dimethylformamide (DMF)

Methods:

Doses: 25 μl/ear/animal of 0 (DMF), 10, 25, or 50% L-000900612 dissolved in DMF, or 25% hexylcinnamaldehyde (HCA; positive control)

Study design: Five female CBA/JHsd mice/dose received 25 μl of controls (DMF and HCA) or L-000900612 (10, 25, and 50%) topically on dorsum of each ear for 3 consecutive days. The animals were sacrificed 24 hours after the last application and an intravenous injection of 5-bromo-2'-deoxy-uridine (BrdU; 100 mg/kg) was performed before sacrifice. Body weight gain and clinical signs were monitored. Single cell suspensions from the draining auricular lymph nodes were prepared. A stimulation index (SI) was calculated by dividing the mean number of BrdU-containing cells of each treatment group by the mean BrdU-containing cells of the vehicle control group. The test was considered positive of local lymph node assay if there were statistically significant increases in cell proliferation in the test group as compared to the vehicle control and/or SIs were greater than 3.0

Results: No clinical sign was observed for any of the groups. In addition, there was no statistically significant increase in the mean body gain as compared to the control. The

positive control (25% HCA) produced a mean SI of 6.6 while the mean SIs for the three L-000900612 concentrations ranged from 0.8 to 1.2. No statistically significant increases in SIs as compared to the controls were observed. Therefore, the test was valid and L-000900612 was not considered a dermal sensitizer in mice.

Study title: L-000900612-003E: Local lymph node assay (LLNA) in mice
Key study findings: The allergenic potential of L-000900612 was evaluated in a murine local lymph node assay. Concentrations of 10, 100, and 1000 mg/ml of L-000900612 were administered to the murine ears. A test was considered positive if the stimulation index (SI), which was calculated by dividing the mean radioactivity (dpm) of each group by the mean dpm of the vehicle control group, was greater than 3.0 and/or statistically significant increases in SIs were observed. It was found that a stimulation index of 11.0 was determined for the positive control, 25% hexylcinnamaldehyde while the three concentrations of L-000900612 produced SIs ranged from 0.69 to 1.10. Thus, L-000900612 was not considered a dermal sensitizer in mice.
Study no.: TT #04-5545
Volume: *\\Cdsesub1\evsprod\NDA022145\0000\m4\42-stud-rep\423-tox\4236-loc-tol\tt045545\tt045545.pdf*
Conducting laboratory and location: [redacted]
Date of study initiation: 11/3/2004
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: L-000900612, lot # L-000900612-003E, [redacted] by HPLC
Formulation/vehicle: Dissolved in N,N-dimethylformamide (DMF)
Methods
Doses: 25 µl/ear/animal of 0 (DMF), 10, 100, or 1000 mg/ml L-000900612 dissolved in DMF, 25% hexylcinnamaldehyde (HCA; positive control), or 0 (4:1 mixture of acetone:olive oil; AOO; positive control vehicle)
Study design: Six female CBA/JHsd mice/dose received 25 µl of controls (DMF, HCA, and AOO) or L-000900612 (1-100%) topically on dorsum of each ear for 3 consecutive days. The animals were sacrificed 24 hours after the last application and an intravenous injection of 20 µCi of [^{3}H]-thymidine was performed before sacrifice. Body weight gain and clinical signs were monitored. Single cell suspensions from the draining auricular lymph nodes were prepared. A stimulation index (SI) was calculated by dividing the mean radioactivity (dpm) of each group by the mean dpm of the vehicle control group. The test was considered positive if there were statistically significant increases in cell proliferation in the test group as compared to the vehicle control and/or SIs were greater than 3.0
Results: No clinical sign was observed for any of the groups. In addition, there was no statistically significant increase in the mean body gain as compared to the control. The positive control (25% HCA) produced a mean SI of 11.10 while the mean SIs for the three L-000900612 concentrations ranged from 0.69 to 1.10. No statistically significant increases in SIs as compared to the controls were observed. Therefore, the test was valid and L-000900612 was not considered a dermal sensitizer in mice.

Study title: L-000900612-003E: Acute dermal irritation study in rabbits
Key study findings: The dermal irritation potential of L-000900612 was evaluated in male New Zealand White rabbits. 0.5 g of L-000900612 was applied to the dermal skin of the rabbits for 4 hours before the evaluation for erythema, edema, and other dermal effects. No dermal effect was observed in any of the rabbits. Thus, L-000900612 was not considered a dermal irritant under the test conditions.
Study no.: TT #04-5546
Volume: *\\Cdsesub1\evsprod\NDA022145\0000\m4\42-stud-rep\423-tox\4236-loc-tol\tt045546\tt045546.pdf*
Conducting laboratory and location: [redacted]
Date of study initiation: 10/4/2004
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: L-000900612, lot # L-000900612-003E, [redacted] by HPLC
Formulation/vehicle: Water
Methods
Doses: 0.5 g
Study design: 0.5 g of L-000900612 dissolved in 0.4 ml of deionized water to form a thick paste was applied to an area of approximately 6 cm^2 on the dorsal skin (fur shaved off) of 3 male New Zealand White rabbits for 4 hours. The area was allowed to be free of test article for an hour before the evaluation for erythema, edema, and other evidence of dermal effects and scored according to the Draize Scale. Additional evaluations were also performed at 24, 48, and 72 hours after removal of the test article. The adjacent areas of untreated skin were used for comparison. Body weight gain and clinical signs were also monitored.
Results: No treatment effects were observed on body weight gain and clinical signs. In addition, no dermal irritation was observed during the study. Therefore, the L-000900612 was not considered a skin irritant in rabbits.

Study title: Primary dermal irritation/corrosion in rabbits
Key study findings: The dermal irritation potential of L-000900612 was evaluated in male New Zealand White rabbits. 0.5 g of L-000900612 was applied to the dermal skin of the rabbits for 4 hours before the evaluation for erythema, edema, and other dermal effects. No dermal effect was observed in any of the rabbits. Thus, L-000900612 was not considered a dermal irritant under the test conditions.
Study no.: TT #04-5550
Volume: *\\Cdsesub1\evsprod\NDA022145\0000\m4\42-stud-rep\423-tox\4236-loc-tol\tt045550\tt045550.pdf*
Conducting laboratory and location: [redacted]
Date of study initiation: 9/24/2004
GLP compliance: Yes
QA reports: yes ( ) no (X)
Drug, lot #, and % purity: L-000900612, lot # L-000900612-00Y
Formulation/vehicle: Water
Methods

Doses: 0.5 g
Study design: 0.5 g of L-000900612 dissolved in 0.4 ml of deionized water to form a thick paste was applied to an area of approximately 6 cm^2 on the dorsal skin (fur shaved off) of 1 male and 2 female New Zealand White rabbits for 4 hours. The area was allowed to be free of test article for an hour before the evaluation for erythema, edema, and other evidence of dermal effects and scored according to the Draize Scale. Additional evaluations were also performed at 24, 48, and 72 hours after removal of the test article. The adjacent areas of untreated skin were used for comparison. Body weight gain and clinical signs were also monitored.
Results: No treatment effects were observed on body weight gain and clinical signs. In addition, no dermal irritation was observed during the study. Therefore, the L-000900612 was not considered a skin irritant in rabbits.

Study title: Bovine corneal opacity and permeability assay
Key study findings: The ocular irritation potential of L-000900612 was evaluated using BCOP. 0.75 ml of 20% L-000900612 incubated with bovine cornea for 4 hours in 32°C before its effect on the opacity and permeability of cornea was evaluated. The *in vitro* score suggested that L-000900612 was severely irritating to bovine cornea.
Study no.: TT #04-5510
Volume: *\\Cdsesub1\evsprod\NDA022145\0000\m4\42-stud-rep\423-tox\4236-loc-tol\tt055510\tt055510.pdf*
Conducting laboratory and location: [redacted]
Date of study initiation: 11/30/2004
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: L-000900612, lot # L-000900612-003E015, [redacted]% by HPLC
Formulation/vehicle: Deionized water
Methods
Doses: 25 mg/ml L-000900612
Study design: Freshly isolated bovine cornea was incubated with 0.75 ml of 20% L-000900612 for 4 hours at 32°C. Opacity was measured through cornea using an [redacted] opacitometer. After the measurement of opacity, dye permeability was also measured. A positive (20% imidazole) and a negative (deionized water) controls were included. An *in vitro* score of 0-25 is considered mild irritant, 25.1 to 55, moderate irritant, and 55.1 and above severe irritant.
Results: The *in vitro* score for L-000900612 was 126.3 and that for the positive control 91.0. Based on the score, L-000900612 was considered a severe irritant to the cornea. However, it was suspected that some residual L-000900612 may have remained on the corneas to cause a high opacity score. Another test was performed in another testing facility.

Study title: Bovine corneal opacity and permeability test (BCOP)
Key study findings: The ocular irritation potential of L-000900612 was evaluated using BCOP. This test was performed previously in [redacted] and indicated that L-000900612 was severely irritating to bovine cornea. 0.75 ml of 20%

L-000900612 incubated with bovine cornea for 4 hours in 32°C before its effect on the opacity and permeability of cornea was assessed. The *in vitro* score suggested that L-000900612 was not irritating to bovine cornea. This result contradicted that from similar study done in [redacted], which found L-000900612 to be severely irritating to bovine cornea.

Study no.: TT #04-5551

Volume: \\Cdsesub1\evsprod\NDA022145\0000\m4\42-stud-rep\423-tox\4236-loc-tol\tt045551\tt045551.pdf

Conducting laboratory and location: [redacted]

Date of study initiation: 9/24/2004

GLP compliance: Yes

QA reports: yes ( ) no (X)

Drug, lot #, and % purity: L-000900612, lot # L-000900612-00Y

Formulation/vehicle: Water

Methods

Doses: 20% L-000900612 in Minimum Essential Medium (MEM)

Study design: Freshly isolated bovine cornea was incubated with 0.75 ml of 20% L-000900612 for 4 hours at 32°C. Opacity was measured through cornea suing an [redacted] opacitometer. After the measurement of opacity, dye permeability was also measured. An *in vitro* score of 0-25 is considered mild irritant, 25.1 to 55, moderate irritant, and 55.1 and above severe irritant.

Results: The corrected mean opacity score for L-000900612 was 1.3 and opacity density (permeability) score was 0.018. The combined *in vitro* score was calculated as 1.57 indicating that L-000900612 was a very mild corneal irritant.

Study title: Skin irritation test (SIT) using the [redacted]™ skin model with optional IL-1α

Key study findings: The dermal irritation potential of L-000900612 was evaluated using the [redacted] Skin Model (using human skin epithelial layer) with optional IL-1α. 25 mg of L-000900612 were used per culture and cell viability determined. L-000900612 was found not to affect the cell viability and considered not dermal irritant.

Study no.: TT #04-5509

Volume: \\Cdsesub1\evsprod\NDA022145\0000\m4\42-stud-rep\423-tox\4236-loc-tol\tt055509\tt055509.pdf

Conducting laboratory and location: [redacted]

Date of study initiation: 11/3/2004

GLP compliance: Yes

QA reports: yes (X) no ( )

Drug, lot #, and % purity: L-000900612, lot # L-000900612-003E015, [redacted] by HPLC

Formulation/vehicle: Deionized water

Methods

Doses: 25 mg L-000900612

Study design: Triplicate [redacted] cultures were treated with negative control (sterile water), 25 mg L-000900612, or positive control (1% Triton® X-100). The treatment time for L-000900612 was 25 minutes and for the positive control was 4 or 8 hours. Cell viability was determined using MTT assay.

Results: It was found that the positive control, 1% Triton® X-100, reduced cell survival rate (25-83%) at exposure-time dependent manner. L-000900612 did not affect the cell viability and consider not a dermal irritant by this assay.

2.6.6.8 Special toxicology studies

Study title: MK-0518: Single-dose oral phototoxicity study in female mice
Key study findings: The phototoxic potential of MK-0518 was evaluated in female CD-1 mice. Six mice/group were administered a single oral dose of vehicle (water), 1000, 1500, or 2000 mg/kg/day L-000900612 or 80 mg/kg chlorpromazine (positive control) and exposed to 15 minutes of UVB light and 4 hours of UVA and visible light. In addition, negative controls were included in which dosed mice (2000 mg/kg and positive control groups) were kept in the dark when the rest of the groups were exposed to UVA and visible light. The effect on body weights, clinical signs, and degree of erythema, sloughing, and necrosis of the ears were monitored. It was found that at 2000 mg/kg, MK-0518 caused transient decreased activity. In addition to decreased activity, the mice that received positive control exhibited sternal recumbency, bradypnea, and ptosis for two days. Exposure to light caused moderate to severe erythema of the ears in mice treated with positive control throughout the observation period. No such effect was observed in any of the MK-0518 groups indicating that MK-0518 was not phototoxic.
Study no.: TT #06-2519
Volume: *\\Cdsesub1\evsprod\NDA022145\0000\m4\42-stud-rep\423-tox\4237-other-tox-stud\42377-other\tt062519\tt062519.pdf*
Conducting laboratory and location: Merck Research Laboratories, West Point, PA
Date of study initiation: 3/24/2007
GLP compliance: yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: MK-0518, lot # L-000900612-003E023. [redacted] by LCAP
Formulation/vehicle: Dissolved in 0.5% (w/v) methylcellulose in deionized water
Methods

Doses: 0, 1000, 1500, 2000 (not exposed to uv & visible light), and 2000 mg/kg MK-0518; 80 and 80 (not exposed to uv & visible light) mg/kg chlorpromazine (positive control)

Study design: Six female CD-1 mice/group received a single oral dose of vehicle (water), MK-0518 (1000-2000 mg/kg), or chlorpromazine (80 mg/kg). Approximately 2 hours postdose, all but one group that received 2000 mg/kg MK-0518 and one group that received the positive control, were exposed to UVB light (~ 280-320 nm) for 5 minutes and UVA light (~300-400 nm) and visible light (~400-900 nm) for 4 hours. The two groups that were not exposed to the uv and visible light were placed in the dark during the 4-hour exposure period to serve as negative controls. The animals were observed for 7 days, body weights measured pretest and on day 7, and sacrificed on day 7. Signs of phototoxicity were recorded by observing for degree of erythema, sloughing, and/or necrosis of the ears.

Results: All animals survived to the scheduled sacrifice. No effect on body weights was detected. However, decreased activity was observed in 2 out of 6 animals exposed 2000 mg/kg and uv and visible light in day 1. Majority to all of the animals in the positive control groups (both exposed and not exposed groups) exhibited decreased activity, sternal recumbency, bradypnea, and ptosis during the first two days. These clinical signs disappeared starting on day 3. In addition, the positive control animals that were exposed to uv and visible light had moderate to marked erythema of the ears throughout the 7-day observation period. Thus, the study was considered valid and L-000900612 was not phototoxic under the test conditions.

Study title: L-000900612: Hemolytic assay
Key study findings: Hemolytic potential of L-000900612 (20 and 40 mg/ml in 0.9% saline solution) was evaluated using washed red blood cells and whole blood isolated from rats, dogs, and humans. It was found that L-000900612 did not cause hemolysis under the condition tested.
Study no.: TT #06-4903 & #06-4905
Volume: *\\Cdsesub1\evsprod\NDA022145\0000\m4\42-stud-rep\423-tox\4237-other-tox-stud\42377-other\tt064903* & *\\Cdsesub1\evsprod\NDA022145\0000\m4\42-stud-rep\423-tox\4237-other-tox-stud\42377-other\tt064905\tt064905.pdf*
Conducting laboratory and location: Merck Research Laboratories, West Point, PA
Date of study initiation: 2/15/2006
GLP compliance: no
QA reports: yes ( ) no (X)

2.6.6.9 Discussion and Conclusions

The safety profile of L-000900612, also known as MK-0518 and raltegravir, has been extensively characterized in rats, mice, rabbits, and dogs. The absorption, distribution, metabolism, and excretion (ADME) profiles of raltegravir in these species are similar to that in humans which made them appropriate animal models for the nonclinical safety evaluation. The toxicological, genotoxic, allergenic, immunologic, and reproductive toxicological potentials as well as raltegravir's effects on cardiovascular, neurological, respiratory, gastrointestinal, renal, and other systems were evaluated. The assessment of carcinogenic potential for raltegravir is ongoing in rats and mice. The dosing phase is expected to end at the 4th quarter of 2007. All of the pivotal toxicology studies employed adequate range of doses that were administered via clinical route of administration (oral) and produced sufficient systemic exposures and safety margins over that at clinical dose of 400 mg BID. Raltegravir was found to readily cross blood-brain and blood-placental barriers and was secreted in milk. Doses used in a myriad of general toxicology studies ranged from 5 to 1000 mg/kg/day. The highest doses investigated following chronic oral administration of raltegravir were 360 mg/kg/day in dogs (12 month administration) and 600 mg/kg/day in rats (26 weeks administration). The exposures at these doses were 5- and 3-fold over that at the clinical dose of 400 mg BID, respectively. At these doses, raltegravir was found to be well tolerated and produced few or no adverse effect at doses

studied. One notable exception was the irritation to the mucosal surfaces raltegravir came in contact with.

Rodents seemed to be more sensitive to the irritability to mucosal surfaces by raltegravir than dogs and rabbits. This irritation was dose- and duration-related but was independent of age. Raltegravir at doses ≥ 120 mg/kg/day caused dose-related increases in salivation (probably because of poor palatability), the incidence of glandular mucosal degeneration and erosion in stomach, and the incidence and severity of inflammation in nose and nasopharynx (presumably due to aspiration of drug formulation during drug administration) in adult rats. In addition, decreased food consumption, decreased body weight, and mortality were also associated with raltegravir at dose of 600 mg/kg/day. Similar irritation to mucosal surfaces was also observed in young rats (5-56 days old) that were administered similar doses of raltegravir. The only difference in the manifestation of stomach irritation was that nonglandular mucosa instead of glandular mucosa was affected in the young rats. No additional toxicities were noted in juvenile rats indicating that juvenile rats were not more sensitive to drug effects than adult rats. In mice, the mucosal irritation was manifested as the dose-related increases in the incidences of gastrointestinal bloating (with corresponding glandular mucosal multifocal erosion in stomach) and deaths at doses ≥ 500 mg/kg/day. Males were more sensitive to the irritation than female mice. Irritation to mucosal surfaces is dose-limiting (mortality in rats and mice and >10% reduction in body weight gain in rats). It is independent of formulation. While the vehicle used in dogs, rabbits, and mice was 0.5% methylcellulose and 80% PEG 400 in rats, this type of toxicity was seen in rats and mice only. In addition, the toxicity was likely related the local (at stomach, nose, or nasopharynx) concentration of raltegravir rather than the systemic exposure. Dogs had highest and longest systemic exposure to raltegravir, however, no adverse effect was observed.

The no-adverse-effect level (NOAEL) is 50 mg/kg/day (0.25-fold of the exposure in humans at 800 mg/day) in mice, 30 mg/kg/day (0.9-fold of the exposure in humans at 800 mg/day) in rats, >360 mg/kg/day (5-fold of the exposure in humans at 800 mg/kg/day) in dogs, and for >1000 mg/kg/day (3.7-fold of the human exposure at 800 mg/kg/day) in pregnant rabbits.

The genotoxic potential of raltegravir was investigated in three *in vitro* and one *in vivo* genotoxicity assays. It was found not to be mutagenic or clastogenic with and without metabolic activation. The carcinogenic potential of raltegravir is being evaluated in two-year carcinogenicity studies in rats and mice. Dosing is still ongoing in the two studies and will be completed during 4th quarter of 2007. The doses selected for rats were 0, 50, 150, and 300 mg/kg/day in males and 0, 50, 300, and 600 mg/kg/day in females. The high doses were selected as the maximum tolerated dose and the maximum feasible dose, respectively. The doses selected for mice were 0, 50, 100, and 250 mg/kg/day in males and 0, 50, 250, and 400 mg/kg/day in females. The high doses were the maximum tolerated doses based on data from the 13-week toxicity study.

Male and female fertility were assessed either by direct oral dosing to young (5-56 days old) and adult rats or by exposure *in utero* and via breast milk. The results indicated that fertility was not affected at doses as high as 600 mg/kg (about 3-times human exposure) in rats. *In utero* exposure to raltegravir did not adversely affect embryo and fetal survival, weight, and external, skeletal, and visceral development in rabbits at doses up to 1000 mg/kg/day (4-fold human exposure at 800 mg/day). Fetal plasma drug

concentrations were about 2% of those in maternal plasma at 1 and 24 hours postdose, respectively. However, an increased incidence of supernumerary ribs in rat fetuses exposed *in utero* to 600 mg/kg/day (3-fold human exposure at 800 mg/day) raltegravir was observed. Mean drug concentrations in rat fetal plasma were approximately 1.5- to 2.5-fold greater than those in maternal plasma at 1 and 24 hours postdose, respectively. Based on the skeletal finding in rats, raltegravir will be classified under "Pregnancy Category C" and is not recommended for use during pregnancy unless necessary. It was also secreted into rat milk. Mean drug concentration in milk at 2 hours postdose was approximately 3-fold that in maternal plasma. Exposure to this drug *in utero* or in milk did not affect pup delivery or neonatal development in rats. The second generations exhibited normal behavior and postnatal development, growth, sexual maturity, and fertility. Young rats had similar sensitive to raltegravir as adult rats. The same type of mucosal surface irritability was observed in 5-56 day-old rats administered the same dose range as adults. The No-adverse-effect level (NOAEL) for reproductive toxicity is 1000 mg/kg/day for rabbits (3.7-fold human exposure at 800 mg/day) and 300 mg/kg/day for rats (2.2-fold human exposure at 800 mg/day).

The safety of raltegravir was also investigated in a variety of *in vitro* and local tolerance studies. It was not a dermal sensitizer in the mouse local lymph node assay or a skin irritant in *in vivo* rabbit dermal irritation model or *in vitro* Skin Model. It was not phototoxic in female rats or hemolytic *in vitro* to blood cells isolated from rats, dogs, and humans. The irritation potential to bovine cornea was tested in two different testing laboratories and the results were equivocal. It was classified as a severe irritant in the *in vitro* bovine corneal opacity and permeability test with an *in vitro* score higher than that for the positive control, imidazol. However, it was not considered a bovine corneal irritant in the same test performed in another lab. Since it caused irritation to mucosal surfaces, it's not unexpected that it may be irritating to cornea.

The toxicity of intravenous administration of raltegravir was investigated in dogs and female rats. MK-0518, the monopotassium salt, was used. Mortality was associated with single intravenous doses ≥ 200 mg/kg/day in female rats. Treatment-related clinical signs including recumbency, gasping, labored breathing, and decreased activity usually preceded deaths which occurred within 8 minutes postdose. Mortality was also observed in a male dog that was intended to have received 400 mg/kg MK-0518 intravenously. Treatment-related mortality occurred after 358 mg/kg was administered and was believed to be associated with cardiac arrhythmia caused by the high amount of potassium in MK-0518 rather than the direct effect of the MK-0518 molecule. Increases in aspartate aminotransferase (both sexes), alanine aminotransferase (male only), and alkaline phosphatase (male only) levels without the corresponding histopathological findings in liver were associated with 100 mg/kg dose. At the same dose, treatment-related interstitial inflammation of kidney cortex was seen in the female dog. These effects were likely associated with the systemic toxicity of raltegravir if the administration of raltegravir was not limited by the solubility and formulation. Since raltegravir will be administered orally in humans and no plan for the development for any intravenous formulation is proposed by the sponsor

In conclusion, except for the irritation to mucosal surfaces observed in rodents, raltegravir has a clean safety profile in animals at multiples of exposure in humans.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The results of the nonclinical pharmacology/toxicology studies submitted by the sponsor adequately support the approval of raltegravir.

Unresolved toxicology issues (if any): None

Recommendations: None

Suggested labeling:
Please see the executive summary for the language to be used on the proposed label.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX I

Executive CAC
Date of Meeting: Nov. 1, 2005

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Joseph Contrera, Ph.D., OPS, Member
Paul Brown, Ph.D., DDDDP, Alternate Member
Lois Freed, Ph.D., DNP, Alternate Member
James Farrelly, Ph.D., Team Leader
Ita Yuen, Ph.D., Presenting Reviewer

Author of Draft: Ita Yuen

The following information reflects a brief summary of the Committee discussion and its recommendations.

IND # 69,928
Drug Name: L-000900612
Sponsor: Merck & Co., Inc.,
Sumneytown Pike, P.O. Box 4, BLA-20,
West Point, PA 19486

Background:

L-000900612 is an HIV integrase inhibitor which is a new class of compound for the treatment of HIV-1 infection. Integrase is one of 3 HIV-1 enzymes required for viral replication and catalyzes the insertion of the HIV-1 DNA into the genome of the host cell. Integration is required for stable maintenance of the viral genome as well as efficient viral gene expression. Integrase inhibitors block the insertion of HIV-1 DNA into the host genome.
L-000900612 is not genotoxic as found by the ICH recommended genotoxicity assays. It is moderately bound to the mouse plasma proteins (~70% bound). The major metabolite in bile after oral administration to mice is a phenolic glucuronide derivative of the parent compound, M2, which accounted for an average of 95.6% and 62% of radioactivity recovered in bile of mice and rats, respectively. Two other minor metabolites, M1 (glucose conjugate of the parent compound) and M3 (an acetyl hydrazine derivative), were also present in rats and accounted for less than 1% of the dose.
It was noted by the reviewer that the study reports used to support the proposed protocols for the 2-year carcinogenicity studies contained minimal information. For example, descriptions of statistical methodology and histopathology evaluation and individual line listings for several parameters (including clinical signs and gross pathology) were not included.

Mouse Carcinogenicity Study Protocol and Dose Selection

The proposed doses of 50, 200 and 400 mg/kg/day were based on the results of a three-month oral (gavage) dose range-finding study in mice. The results of the 13-week range finding study indicated that L-000900612 in 0.5% methylcellulose was very irritating to the gastrointestinal tract of mice. At doses of 1000 mg/kg/day and above, L-000900612 caused clinical signs consistent with gastrointestinal bloating and a high mortality rate (33-60%). Three deaths were associated with a 500 mg/kg/day dose in males, but not in females. The clinical signs at this dose correlated with necropsy finding of mucosal reddening in the glandular stomach (individual animal data not included) and histopathological observations of erosion of the glandular stomach and ulcerative esophagitis. In addition, after 13 weeks of dosing at 500 mg/kg/day, the body weight gain for the males and females was 58 and 71% of that for the control. Thus, the 500 mg/kg/day dose probably exceeds the maximum tolerated dose (MTD) in males but is close to the MTD in females. At the proposed high dose of 400 mg/kg/day, the AUC value will be about 1.1-1.7-fold of the anticipated clinical exposure.

Rat Carcinogenicity Study Protocol and Dose Selection

The proposed doses of 0, 0, 50, 250, & 400 mg/kg/day in males and 0, 0, 50, 250, & 600 mg/kg/day in females were based on the results of a 26-week oral (gavage) toxicity study. Rats were administered single daily doses of 0, 30, 120 or 600 mg/kg L-000900612 in an 80% PEG400 formulation. The 600 mg/kg/day dose is a maximum feasible dose (MFD). At this dose, there were 3 deaths in addition to a 14% reduction in body weight gain in males as compared to the control. The MTD was probably exceeded for the males. One death (out of 20 animals/sex/dose) was seen in the female rats receiving this dosage without any other dose-limiting toxicity. A dose-related increase in the incidences of very slight stomach nonglandular mucosal degeneration and erosion was seen in both males and females. Similar stomach histopathological findings were seen in a 5-week study in the same species. However, both the severity and incidence rate did not change with additional weeks of treatment. Thus, it is unclear if the MTD was reached in the females. Since 600 mg/kg/day dose is the MFD, it is the proposed high dose for the carcinogenicity study in females. The proposed high dose of 400 mg/kg/day in males and 600 mg/kg/day in females should achieve exposure 2.7- and 3.2-fold of the anticipated clinical exposure.

Executive CAC Recommendations and Conclusions:

Adequate details regarding methodology used in the conduct of the studies or proposed for the 2-year studies were not provided for either species. No descriptions of statistical methodology and histopathology evaluation were included. The Committee, in providing feedback on the sponsor's dose selection, made the assumption that the 2-year carcinogenicity studies in mouse and rat will be conducted using a feeding regimen similar to that in the studies used to support dose selection (i.e., ad libitum). If that is not the case, then additional range-finding studies using dietary restriction would been

needed in order for the Committee to provide concurrence on dose selection.

Mouse Carcinogenicity Study Protocol and Dose Selection

The Committee recommended doses of 0, 0, 50, 100, and 250 mg/kg/day for males, based on the deaths observed in males at 500 mg/kg/day in the 13-week range-finding study. The Committee concurred with the sponsor's proposed doses for females (0, 0, 50, 200, and 400 mg/kg/day), based on clinical signs and deaths observed in females at doses ≥500 mg/kg/day and ≥1000 mg/kg/day, respectively, in the 13-week range-finding study.

Rat Carcinogenicity Study Protocol and Dose Selection

The Committee recommended doses of 0, 0, 50, 150, and 300 mg/kg/day for males, based on the deaths observed in males at 600 mg/kg in the 26-week toxicity study. The Committee concurred with the sponsor's proposed doses for females, based on maximum feasible dose.

For both the mouse and rat carcinogenicity studies, the sponsor should contact the division if a change in dose or early termination of one or more groups is being considered.

In addition, it is unclear from the 2-year study protocols for both rats and mice which dosing group will be evaluated histologically. However, if the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

(a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups
(b) for statistically significant or otherwise remarkable findings in the high dose group, the sponsor will need to look at the affected tissues in all of the dose groups.
(c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,
(d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

David Jacobson-Kram, Ph.D.

Chair, Executive CAC

cc:\
/Division File, DAVP
/JFarrelly, DAVP
/IYuen, DAVP
/MZeballos DAVP
/ASeifried, ONDIO/Pharm Tox

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ita Yuen
10/11/2007 03:28:52 PM
PHARMACOLOGIST

Hanan Ghantous
10/11/2007 03:38:43 PM
PHARMACOLOGIST

Comments on N22-145 Raltegravir
From A. Jacobs
10/5/07

1. There are no pharm/tox approval issues and the pregnancy category seems appropriate.

2. Labeling: I have not seen the entire labeling

Under pregnancy: the route of exposure should be given and it should be described that the study in rats was a combined embryofetal/peripostnatal study.

Results from the peri-postnatal part of the study could be described somewhere in the labeling (now under nonclinical tox?).

3. The discussion of ongoing carcinogenicity studies should have been eliminated from the review, since results are uninterpretable at this point. It is unclear if the protocol ever went to the exec-cac, since I couldn't find it in DFS. If the protocol went to the exec-CAC, the minutes should have been be appended to the NDA review.

Other comments, including a number of editorial comments were discussed with the Pharm/tox Supervisor

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Abby Jacobs
10/5/2007 09:10:41 AM
PHARMACOLOGIST

Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: QT Study Review

IND or NDA	NDA 22145
Brand Name	Isentress
Generic Name	Raltegravir potassium (MK-0518)
Sponsor	Merck & Co.
Indication	Treatment of HIV
Dosage Form	Oral tablet
Therapeutic Dose	400 mg bid
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	MTD not identified
Application Submission Date	13 April 2007
Review Classification	Priority NDA Review (6 month)
Date Consult Received	24 April 2007
Date Consult Due	11 June 2007
Clinical Division	DAP / HFD 530
PDUFA Date	12 October 2007

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

A supratherapeutic dose of 1600 mg raltegravir was evaluated in this single-dose 'thorough QT study.' The mean Cmax in 12/30 (40%) subjects was 19.6 μM which is 4-fold higher than the mean steady state Cmax when 400 mg bid (of the to-be-marketed formulation) was administered to patients in study 004. The concentration range sufficiently covers the expected increases in raltegravir plasma concentration due to the known drug-drug interactions (Table 2).

For the primary analysis, the maximum mean change and upper 1-sided 95% confidence interval were -0.2 msec and 3 msec, respectively. However, drug effects on QT were only assessed for 12 hours after dosing. Some drugs (e.g., pentamidine) cause a delayed prolongation of the QT interval; i.e., at a time well after Tmax. A delayed effect of raltegravir on the QT interval at a time point later than 12 hours can not be excluded.

1.2 ADDITIONAL QT-IRT COMMENTS

- Merck in the current study included ECG samples only up to 12 hour in the analysis. Therefore, the effect of raltegravir on the QT interval at later time points can not be evaluated.
- Merck analyzed raltegravir concentrations only in a subset of the subjects (N=12, 40%). During our review, we found there were no differences in the drug effects on QT interval between subjects with and without serum concentration data

(see table 1 below). However, we can not be as confident in this analysis as we would have been had Merck provided the appropriate serum concentrations at Tmax for all subjects.

To evaluate whether there was a difference in the drug effect on the QT interval, we performed a two group t-test to compare the QTcF interval at each time point between Group 1, which consists of 12 subjects for whom serum concentrations are reported, and Group 2, which consists of 26 subjects for whom serum concentration were not reported. The findings are shown in Table 1. Statistically, there is no significant difference of the QTcF interval between the two groups (all the P-values > 0.05).

Table 1: T-test Results for the Two-Group Comparison

time	Mean of Group 1	Mean of Group 2	Difference (Group 1 - Group 2)	P-values of T-test
0.5	-1.82	-3.84	2.02	0.67
1	-1.44	-7.87	6.43	0.11
2	-2.57	-2.63	0.06	0.99
3	-0.81	0.52	-1.33	0.74
4	-3.49	-1.28	-2.21	0.67
6	-1.32	-4.03	2.71	0.48
12	-3.26	-1.59	-1.67	0.66

2 PROPOSED LABEL

The sponsor did not propose any labeling for QT. We have made labeling recommendations for the Clinical Pharmacology section of the label to reflect the findings of the thorough QT study. These recommendations are suggestions for labeling only and we defer all final labeling decisions to the review division.

3 BACKGROUND

3.1 INDICATION

Treatment of HIV

3.2 DRUG CLASS

HIV integrase inhibitor

3.3 MARKET APPROVAL STATUS

The sponsor is seeking marketing approval of raltegravir potassium (MK-0518) for the treatment of HIV in this NDA submission

3.4 PRECLINICAL INFORMATION

According to the sponsor:

"Overall, the non-clinical results suggest that the risk for QT interval prolongation in humans at therapeutic concentrations is likely to be very low.

MK-0518 was administered as a single dose to conscious beagle dogs by oral gavage to determine its effects on the cardiovascular system via radiotelemetry. Each of the 4 dogs received a single dose of 5, 15, or 45 mg/kg of MK-0518 and vehicle in a Latin square crossover design with ≥1-week washout period between doses. No treatment-related effects were observed following administration of 5, 15, or 45 mg/kg of MK-0518 for systolic, diastolic, or mean blood pressure or for heart rate, PR interval, QRS interval, QT interval, or rate corrected (Fredericia, QT/RR1/3) QT interval (QTcf), or physical signs. The mean plasma drug concentrations approximately 1 hour postdose were 3.62 – 0.681, 10.1 – 2.04, 20.6 – 2.98 μM for 5-, 15-, and 45-mg/kg doses, respectively. In conclusion, the no-effect dose level for cardiovascular effects following single oral administration of MK-0518 was ≥45 mg/kg.

The cardiovascular effects of MK-0518 at rising cumulative doses of 1, 3, and 5 mg/kg IV were examined in 3 pentobarbital-anesthetized, vagotomized, and ventilated dogs. The vehicle for this study was 20% dimethylacetamide/80% water and volume of injection of each dose was 10 mL over 30 minutes. There was no effect of MK-0518 on mean arterial pressure or heart rate over this dose range and findings were consistent with vehicle administration. Electrocardiographic evaluation of MK-0518 indicated that this agent had no effect on the PR, QRS, and QTc intervals and all findings were similar to vehicle infusion. Plasma blood levels at the end of infusion of the 1-, 3-, and 5-mg/kg doses were 6.6 – 1.3, 15.6 – 2.2, and 17.5 – 1.6 μM, respectively."

3.5 PREVIOUS CLINICAL EXPERIENCE

As of 01-Apr-2007, approximately 361 healthy male and female subjects have been administered MK-0518 in 23 phase 1 studies in single doses up to 1600 mg and up to 800 mg twice daily for up to 14 days. The sponsor states "There were no consistent treatment-related changes in…electrocardiogram (ECG) safety parameters when MK-0518 was given alone or in combination with other therapies in comparison to placebo (page 47 Summary of Clinical Safety)." No deaths and only 1 SAE, a hypersensitivity rash, were reported in the phase 1 program. No subjects discontinued drug due to a cardiac adverse event.

Approximately 875 AIDS patients (both treatment experienced and treatment naïve) have been either randomized to MK-0518 or given open label MK-0518 in 4 phase 2 and 3 studies, generally at a dose of 400 mg bid combined with optimal background therapy, for up to 78 weeks. No subjects are reported to have died or discontinued due to cardiac adverse events. One subject is reported to have an SAE of syncope and none of seizures. In the 20 Apr 2007 IB and the Integrated Summary of Safety included in this NDA submission, the sponsor does not report any discontinuation due to QTc prolongation or any events suggestive of torsade de pointes occurring in any subject in a clinical trial of MK-0518.

3.6 CLINICAL PHARMACOLOGY

Table 2 Highlights of Clinical Pharmacology (Data Compiled by the Sponsor)

Therapeutic dose	400 mg twice daily	
Maximum tolerated dose	MTD was not clinically identified; all doses tested were well tolerated.	
Principal adverse events	The most common (reported by ≥5% of the subjects/patients) drug-related clinical adverse experiences were the following: headache, dizziness, nausea, and chromaturia. The adverse experience of chromaturia was seen in only one study, the rifampin drug interaction study, reported while subjects were on rifampin alone. This adverse experience is consistent with the safety profile of rifampin.	
Maximum dose tested	Single Dose	Phase I lactose formulation and Phase II/III/FMI formulation 1600 mg
	Multiple Dose	Phase I lactose formulation 800 mg q12 hr x 10 days
Exposures Achieved at Maximum Tested Dose	Single Dose	Phase I lactose formulation GM (95% CI): Cmax = 19.63 μM (11.72, 32.89) $AUC_{0\text{-}12\ hr}$ = 63.05 μM•hr (41.82, 95.05)
	Multiple Dose	Phase I lactose formulation GM (95% CI): Cmax = 19.73 μM (14.21, 27.40) $AUC_{0\text{-}12\ hr}$ = 45.27 μM•hr (36.09, 56.78)
Range of linear PK	Phase II/III/FMI formulation: AUC and Cmax 100 to 1600 mg	
Accumulation at steady state	Phase I lactose formulation 100 to 600 mg q12 hr: CmaxSS/SD = 0.72 to 1.17 (0.98 for 400 mg bid) $AUC_{0\text{-}12}$ hrSS/SD = 0.91 to 1.17 (1.05 for 400 mg bid)	
Metabolites	Phenolic hydroxyl glucuronide derivative of MK-0518 (inactive)	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability was not determined. Clinical ADME results indicate that absolute bioavailability is greater than 32%.
	Tmax	• Phase I lactose formulation (10 to 1600 mg): 1 hour (0.5 to 1.3 hrs) Phase II/III/FMI formulation (100 to 1600 mg): 3.2 hours (2.5 to 3.4 hrs) • Pharmacokinetics of the glucuronide metabolite were not assessed.
Distribution	Vd/F or Vd	Estimate from population PK model (2-compartment model): Vc/F = 139 L Vp/F = 148 L
	% bound	83% (in vitro)
Elimination	Route	• Major: metabolism (glucuronidation mediated by UGT1A1); in ADME study 32% of dose recovered in urine as glucuronide (23%) and parent (9%), and 51% recovered in feces as parent (much of the parent in feces was likely derived from hydrolysis of the glucuronide metabolite secreted in bile) • Minor: Renal excretion (9% of dose excreted unchanged in urine)
	Terminal t½	• 100 to 1600 mg Phase II/III/FMI formulation α =.92 hrs (0.86 to 0.96 hrs); β=9.5 hrs (8.7 to 11.3 hrs) • Pharmacokinetics of the glucuronide metabolite were not assessed.

<table>
<tr><td></td><td>CL/F or CL</td><td>Estimate from population PK model:
CL/F = 67.6 L/hr [Note: this value is likely an overestimate, because of a systematic bias of the model to underpredict the highest concentration data. In animals a moderate clearance value was obtained.]</td></tr>
<tr><td rowspan="4">Intrinsic Factors</td><td>Age</td><td>No clinically meaningful effect of age on PK.</td></tr>
<tr><td>Sex</td><td>No clinically meaningful effect of gender on PK.</td></tr>
<tr><td>Race</td><td>No clinically meaningful effect of race on PK.</td></tr>
<tr><td>Hepatic & Renal Impairment</td><td>No clinically meaningful effect of moderate hepatic impairment or severe renal impairment on PK.</td></tr>
<tr><td rowspan="2">Extrinsic Factors</td><td>Drug interactions</td><td>
<table>
<tr><th>Coadministered Drug</th><th>AUC GMR† (90% CI)†</th><th>C_{max} GMR† (90% CI)†</th></tr>
<tr><td>Atazanavir</td><td>1.72 (1.47, 2.02)</td><td>1.53 (1.11, 2.12)</td></tr>
<tr><td>Atazanavir and Ritonavir</td><td>1.41 (1.12, 1.78)</td><td>1.24 (0.87, 1.77)</td></tr>
<tr><td>Ritonavir</td><td>0.84 (0.70, 1.01)</td><td>0.76 (0.55, 1.04)</td></tr>
<tr><td>Efavirenz</td><td>0.64 (0.52, 0.80)</td><td>0.64 (0.41, 0.98)</td></tr>
<tr><td>Rifampin</td><td>0.60 (0.39, 0.91)</td><td>0.62 (0.37, 1.04)</td></tr>
<tr><td>Tipranavir and Ritonavir</td><td>0.76 (0.49, 1.19)</td><td>0.82 (0.46, 1.46)</td></tr>
<tr><td>TMC125</td><td>0.90 (0.68, 1.18)</td><td>0.89 (0.68, 1.15)</td></tr>
<tr><td>Tenofovir</td><td>1.49 (1.15, 1.94)</td><td>1.64 (1.16, 2.32)</td></tr>
<tr><td>Tenofovir</td><td>1.41 (1.11, 1.79)</td><td>1.33 (0.96, 1.85)</td></tr>
</table>
</td></tr>
<tr><td>Food Effects</td><td>Phase I lactose formulation - High-fat meal GMR (fed/fasted) (90% CI):
Cmax = 0.82 (0.58, 1.16)
$AUC_{0-\infty}$ = 0.98 (0.84, 1.14)
Phase I lactose formulation - Moderate-fat meal GMR (fed/fasted) (90% CI):
Cmax = 0.66 (0.47, 0.92)
$AUC_{0-\infty}$ = 0.79 (0.68, 0.92)
Phase II/III FMI formulation - High-fat meal GMR (fed/fasted) (90% CI):
Cmax = 0.66 (0.44, 0.98)
$AUC_{0-\infty}$ = 1.19 (0.91, 1.54)
Overall, no clinically important effect of food on Cmax and AUC.</td></tr>
<tr><td>Expected High Clinical Exposure Scenario</td><td colspan="2">Co-administration of MK-0518 with atazanavir or tenofovir may increase Cmax and AUC by ~1.65- and 1.75-fold, respectively. The supra-therapeutic dose administered in the TQT study adequately covered this range of increase in Cmax and AUC.</td></tr>
</table>

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor conducted a 'thorough QT study' based on E14 guidance.

4.2 TQT STUDY

4.2.1 Title

A Double-Blind, Randomized, Placebo-Controlled, Double- Dummy, 3-Period, Single-Dose Crossover Study to Assess the Effect of MK-0518 on QTc Interval in Healthy Volunteers

4.2.2 Protocol Number

MK-0518 Protocol 024

4.2.3 Objectives

- To evaluate effects of a supra-therapeutic dose of MK-0518 on the QTcF interval.
- To demonstrate sensitivity of a QTc assay using moxifloxacin as a positive control.

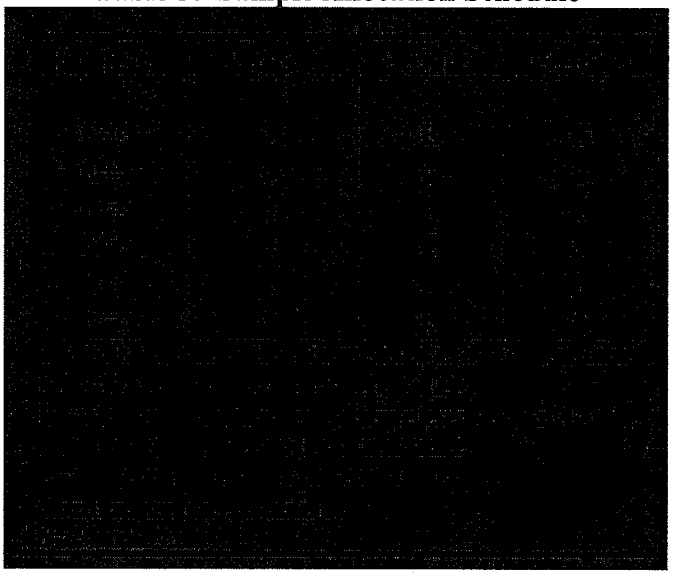
4.2.4 Design

4.2.4.1 Description

Study 024 was designed as a randomized, double-blind, placebo-controlled, double-dummy, 3-period, 6-sequence, balanced crossover thorough QT study in healthy volunteers. During each treatment period a single oral dose of 1600 mg MK-0518, 400 mg moxifloxacin, or placebo was administered; there was a 7-day washout interval between periods.

The allocation of subjects to the treatment groups is show in below.

Table 3: Sample Allocation Schedule



4.2.4.2 Sponsor's Justification for Design

This study was designed based on the E14 guidance and included: (1) use of a positive control (moxifloxacin), (2) characterization of the response relationship using exposures that are multiples above the expected therapeutic concentrations, (3) reducing variability in the measurement of the QTcF interval using replicate ECGs and a centralized core laboratory to measure QTcF interval manually, and (4) utilizing the 10 ms cutpoint as the threshold below which the upper arm of the 95% one-sided confidence interval (of the placebo-corrected change in QTc interval from baseline) must fall in order for the study to be considered negative.

A crossover design was chosen because MK-0518 and moxifloxacin act rapidly and reversibly, and have a relatively short terminal half-life, and because a crossover study allows each subject to serve as their own control.

The primary endpoint of this study is based on the E14 guidance which specifies that the primary endpoint of the study should be the placebo corrected change in QTc from baseline. The definition of baseline values was based on experience gained in prior studies which demonstrated that the overall variability across the different time points resulted in greater variability when time-matched baselines were used as compared to when predose baseline values were utilized. Based upon this finding, the baseline value for QTc interval was defined as the average of 5 replicate baseline QTc intervals from the predose ECGs. The primary hypothesis compares the change in QTc interval from predose baseline values between active and placebo treatment, consistent with the guidance.

4.2.4.3 Controls

The sponsor used 400 mg moxifloxacin tablet as positive control.

4.2.4.4 Blinding

All study drugs, both MK-0518 and moxifloxacin, were administered blindly using a double-dummy design. In addition, ECGs were interpreted in a core ECG laboratory by cardiologists who were blind to allocation, subject, and time of the ECG. All of the ECGs for an individual subject were interpreted by the same cardiologist.

4.2.5 Study Subjects

Healthy, non-smoking males and non pregnant females between the ages of 18 and 45 years who were within 30% of their ideal body weight and without abnormalities on ECG

4.2.6 Dosing Regimens

4.2.6.1 Treatment Arms

The three treatment arms were as follows:

Treatment A = 1600 mg MK-0518 (administered as 8 x 200 mg MK-0518 tablet + 1 moxifloxacin placebo tablet)

Treatment B = 400 mg moxifloxacin (administered as 1 x 400 mg moxifloxacin + 8 MK-0518 placebo tablets)

Treatment C = placebo(administered as 8 MK-0518 placebo tablets + 1 moxifloxacin placebo tablet)

4.2.6.2 Sponsor's Justification for Doses

In accordance with the E14 guidance, this study utilized a dose that provides substantial multiples above the highest anticipated clinical exposures. The most likely clinical dose of the poloxamer tablet formulation is 400 mg BID which, based on prior pharmacokinetic data from Protocol 007, would be expected to provide a Cmax of ~ 4.5 μM. Based on prior pharmacokinetic data from Protocol 001, a single 1600 mg dose of the Phase I lactose formulation of MK-0518 would be expected to result in a geometric mean Cmax 36 μM, a geometric mean AUC0-∞ of 95.6±21.8 μM•hr, and a median Tmax of 1.0 hours. This supratherapeutic dose of the Phase I lactose formulation of MK-0518 would therefore provide a ~ 8-fold margin over the expected clinical Cmax. This margin is anticipated to be generally representative of the target patient populations. These margins are also reassuring in the context of the limited vulnerability of MK-0518 to metabolic inhibition.

Preclinical pharmacokinetic and metabolism studies show that MK-0518 is a low to intermediate clearance compound. MK-0518 is primarily eliminated by glucuronide conjugation. In both rats and dogs, the major metabolite formed is the glucuronide derivative of the parent compound. MK-0518 is not a potent inhibitor of human liver microsomal cytochromes P-450 (CYP) or of uridine diphosphate glucuronosyl tranferase-1A1 (UGT1A1). Since MK-0518 is primarily excreted via glucuronidation, exposures of MK-0518 are not expected to increase in the presence of metabolic inhibition of CYP enzymes or in patients with renal insufficiency. The coadministration of MK-0518 and atazanavir (which is a UGT1A1 inhibitor) resulted in a ~50% increase in the Cmax of MK-0518. With respect to renal elimination of MK-0518, less than 14% of the dose was excreted unchanged into urine after oral dosing. The majority of the excretion into urine occurred in the first 4 hours after dosing, which is consistent with the shape of the plasma concentration profile.

4.2.6.3 Instructions with regard to meals

The tested formulations were given in fast condition.

4.2.6.4 Study Assessments

Table 4: Highlights of Schedule of Interventions (Day -1 and Day 0 for each treatment period)

Study Day	-1	1
Intervention	No treatment	Single dose / day
12-Lead ECGs	Record ECGs[#1] (Baseline)	Record ECGs[#2]
PK Samples for drug	None collected	Collected [#3 (for Moxi), #4 (for MK-0518)]

[#1] Baseline assessment
[#2] Day 1: predose, 0.5, 1, 2, 3, 4, 6 and 12 hr postdose
[#3] (For Moxifloxacin): Blood samples for archive, predose, 1, 2, 3 and 4 hr postdose
[#4] (For MK-0518): Blood samples for archive, predose, 0.5, 1, 2, 3, and 4 hr postdose

4.2.6.5 Sponsor's justification for sampling schedule

The choice of time points was based on the plasma concentration profile of the Phase I lactose formulation of MK-0518. ECGs will be collected predose and at 30 minutes, 1, 2, 3, 4, 6, and 12 hours postdose. The time point at 12 hours postdose was chosen to assess the effect of MK-0518 at lower plasma concentrations and to assess for the unlikely possibility of hysteresis in this potential pharmacodynamic endpoint. Because the metabolism of MK-0518 is primarily via glucuronidation, it is extremely unlikely that a metabolite of MK-0518 would have significant effects on QTcf. One benefit of using a ——— H-12 digital Holter recorder is the potential for the core ECG laboratory to extract ECGs at other intermediate timepoints should analysis of the data suggest the possibility an increase in QTcF intervals at any time point.

4.2.6.6 Baseline

The Sponsor based the definition of baseline values on experience gained in prior studies which demonstrated that the overall variability across the different time points resulted in greater variability when time-matched baselines were used as compared to when predose baseline values were utilized. Therefore, the Sponsor did not use time-matched baseline.

Based upon the above finding, the Sponsor defined the baseline value for QTc interval for each subject during each period as the average of 5 replicate baseline QTc intervals from the predose ECGs (electrocardiograms), i.e., any measurements taken prior to administration of MK-0518, placebo, or moxifloxacin.

4.2.7 ECG Collection

ECG readings were recorded by a standard 12-lead method and with a ——— H-12 Holter-recorder. Subjects rested quietly in a supine position at least 10 minutes prior to and 5 minutes following each prescribed ECG time point.

QTcF intervals were measured from digital 12-lead ECGs recorded on a H- 12——— digital Holter recorder and subsequently extracted by a core laboratory according to the time points specified in the protocol. Five replicates ECGs were extracted from each timepoint and the ECG intervals averaged to reduce the variability of the measurement and to increase precision of the estimate.

ECGs were interpreted by cardiologists blinded to allocation, subject, and the time of the ECG using computerized digital equipment to assist with the measurement of ECG intervals. All of the ECGs for an individual subject were interpreted by the same cardiologist.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Thirty-one (31) healthy male and female subjects were enrolled into the study, and thirty (30) subjects completed the study per protocol. The demographic and baseline characteristics are presented in Table 5.

Table 5: Demographic and Baseline Characteristics

AN	Gender	Race	Age (yr)	Height (cm)	Weight (kg)
0331	Male	black	25	184.1	70.0
0332	Male	black	22	185.4	96.4
0333	Male	Hispanic	19	177.8	60.5
0334	Male	black	28	181.6	97.3
0335	Male	black	45	187.9	91.8
0336	Male	white	44	180.3	87.7
0337	Male	black	25	179.0	80.9
0338	Male	Hispanic	36	175.2	77.3
0339	Male	black	27	175.2	91.4
0340	Male	black	35	180.3	80.5
0341	Female	Hispanic	34	156.9	51.8
0342	Female	white	31	160.0	49.5
0343	Female	white	42	167.6	70.9
0344	Female	Hispanic	34	162.5	54.1
0345	Female	Hispanic	30	167.6	63.2
0346	Female	white	45	171.4	56.4
0347	Female	Asian	31	164.5	65.9
0348	Female	black	30	167.6	81.0
0349	Female	black	28	172.7	65.5
0350	Female	Hispanic	35	160.0	74.5
0351	Female	black	19	165.1	63.6
0352	Female	Hispanic	38	164.5	67.3
0353	Male	white	43	179.0	91.4
0354	Male	black	38	177.8	82.3
0355	Male	white	32	198.1	103.2
0356	Male	Hispanic	36	182.8	100.0
0357	Female	black	31	160.0	74.0
0358	Female	black	20	167.6	51.4
0359	Male	black	19	180.3	60.9
0360	Male	black	36	177.8	89.3
1332	Male	white	42	177.8	70.0
N:			31	31	31
Overall range:			19 to 45	156.9 to 198.1	49.5 to 103.2
Overall arithmetic mean:			32.3	173.8	74.8
Male N:			17	17	17
Range:			19 to 45	175.2 to 198.1	60.5 to 103.2
Arithmetic mean:			32.5	181.2	84.2
Female N:			14	14	14
Range:			19 to 45	156.9 to 172.7	49.5 to 81.0
Arithmetic mean:			32.0	164.9	63.5
AN=Allocation number.					

Data Source: [16.4.1]

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Applicant's primary analysis was based on a mixed-effects ANOVA (analysis of variance) model appropriate for a three-period, three-treatment crossover design, with period, treatment, time, and treatment-by-time interaction as fixed effects and with subject as a random effect. All confidence intervals were computed using the least squares means and variance components from this mixed-effects ANOVA model.

Table 6 shows the Applicant's results on the placebo-adjusted mean change from baseline for raltegravir (MK-0518) and for moxifloxacin (see last two columns) along with the two-sided 90% confidence intervals based on the mixed effects model.

Table 6: Applicant's Results—Placebo-corrected Mean Change from Baseline in QTcf intervals based on Mixed Effects Model

Estimated Means and Confidence Intervals on the Effect of Placebo, MK-0518, and Moxifloxican on the QTcf Interval (msec) in Young, Healthy, Male and Female Subjects

Treatment	Time	Mean[†]		Mean CFB[‡]		Placebo-Adjusted Mean CFB[‡]	
		N[§]	Estimate (95% CI)	N[§]	Estimate (95% CI)	N[§]	Estimate (90% CI)
Placebo	Predose	30	404.0 (397.5, 410.5)				
	30 Minutes	31	403.1 (396.6, 409.6)	30	-0.3 (-3.5, 2.9)		
	1 Hour	31	405.1 (398.6, 411.6)	30	1.9 (-1.4, 5.1)		
	2 Hours	31	403.7 (397.2, 410.2)	30	0.2 (-3.0, 3.5)		
	3 Hours	31	400.5 (394.0, 407.0)	30	-2.7 (-6.0, 0.5)		
	4 Hours	31	401.8 (395.3, 408.3)	30	-1.5 (-4.7, 1.7)		
	6 Hours	31	398.3 (391.8, 404.8)	30	-5.4 (-8.6, -2.1)		
	12 Hours	31	395.4 (388.9, 402.0)	30	-8.0 (-11.2, -4.8)		
MK-0518	Predose	29	402.3 (395.7, 408.8)				
	30 Minutes	29	399.6 (393.0, 406.1)	29	-3.3 (-6.5, 0.0)	28	-2.9 (-6.5, 0.6)
	1 Hour	29	400.3 (393.8, 406.8)	29	-2.5 (-5.8, 0.7)	28	-4.4 (-8.0, -0.8)
	2 Hours	30	399.6 (393.1, 406.1)	29	-3.2 (-6.5, 0.0)	28	-3.5 (-7.0, 0.1)
	3 Hours	30	399.8 (393.3, 406.3)	29	-3.2 (-6.4, 0.1)	28	-0.4 (-4.0, 3.1)
	4 Hours	30	399.2 (392.7, 405.7)	29	-3.9 (-7.2, -0.7)	28	-2.4 (-6.0, 1.2)
	6 Hours	30	394.5 (387.9, 401.0)	29	-8.5 (-11.7, -5.2)	28	-3.1 (-6.7, 0.5)
	12 Hours	30	391.0 (384.5, 397.6)	29	-11.5 (-14.8, -8.3)	28	-3.6 (-7.2, 0.0)
Moxifloxacin	Predose	29	406.2 (399.6, 412.7)				
	30 Minutes	29	406.2 (399.7, 412.7)	29	0.3 (-3.0, 3.6)	28	0.6 (-3.0, 4.2)
	1 Hour	30	410.6 (404.0, 417.1)	29	4.5 (1.2, 7.8)	28	2.6 (-1.0, 6.2)
	2 Hours	30	412.5 (406.0, 419.0)	29	6.7 (3.4, 10.0)	28	6.4 (2.9, 10.0)
	3 Hours	30	414.1 (407.6, 420.7)	29	8.4 (5.1, 11.6)	28	11.1 (7.5, 14.7)
	4 Hours	30	412.0 (405.5, 418.5)	29	6.5 (3.2, 9.7)	28	8.0 (4.4, 11.6)
	6 Hours	30	404.2 (397.6, 410.7)	29	-1.9 (-5.2, 1.3)	28	3.4 (-0.2, 7.0)
	12 Hours	30	399.1 (392.6, 405.6)	29	-7.0 (-10.3, -3.8)	28	0.9 (-2.7, 4.5)

CFB= Change-from-baseline. CI=Confidence Interval.

[†] Inference arising from an ANOVA model with the raw ECG values as the dependent variable. Mean Square Error=52.8 msec^2.

[‡] Inference arising from an ANOVA model with the ECG CFB values as the dependent variable. Mean Square Error=67.1 msec^2.

[§] Number of subjects with data available; some data points missing.

Data Source: [16.1.9; 16.4.4]

Source: Applicant's Table 11-2 on Page 47

4.2.8.2.2 Categorical Analysis

Table 7 shows the number of subjects with QTcF greater than 450 msec, 480 msec, or 500 msec. Similarly, Table 8 shows the number of subjects with change from baseline in QTcf ≤30 msec, between 30 to 60 msec, or > 60 msec. The Applicant reported that there were no raltegravir (MK-0518) values with QTcF values > 450 msec at any time point post-dose, and no changes from baseline values for MK-0518 that were > 30 msec.

Table 7: Frequency of QTcF ≤450 msec, 450 msec < QTcF ≤ 480 msec, 480 msec < QTcF ≤ 500 msec, or QTcF > 500 msec

Treatment	Time	Count (Percent)			
		QTc ≤ 450	450 < QTc ≤ 480	480 < QTc ≤ 500	500 < QTc
Placebo	Predose	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	30 Minutes	31 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1 Hour	31 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2 Hours	31 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3 Hours	31 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4 Hours	31 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	6 Hours	31 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	12 Hours	31 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
MK-0518	Predose	29 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	30 Minutes	29 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1 Hour	29 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2 Hours	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3 Hours	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4 Hours	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	6 Hours	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	12 Hours	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moxifloxacin	Predose	29 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	30 Minutes	29 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1 Hour	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2 Hours	29 (96.7)	1 (3.3)	0 (0.0)	0 (0.0)
	3 Hours	29 (96.7)	1 (3.3)	0 (0.0)	0 (0.0)
	4 Hours	29 (96.7)	1 (3.3)	0 (0.0)	0 (0.0)
	6 Hours	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	12 Hours	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data Source: {22 39}

Appears This Way
On Original

Table 8: Frequency of ΔQTcF ≤30 msec, 30 msec < QTcF ≤ 60 msec, or QTcF > 60 msec

Categorical Tabulation of Change-From-Baseline QTcf (msec) values by Treatment and Time Point after Administration of Placebo, MK-0518, or Moxifloxican to Young, Healthy, Male and Female Subjects

Treatment	Time	Count (Percent)		
		QTc CFB ≤ 30	30 < QTc CFB ≤ 60	60 < QTc CFB
Placebo	30 Minutes	30 (96.8)	0 (0.0)	0 (0.0)
	1 Hour	30 (96.8)	0 (0.0)	0 (0.0)
	2 Hours	30 (96.8)	0 (0.0)	0 (0.0)
	3 Hours	30 (96.8)	0 (0.0)	0 (0.0)
	4 Hours	30 (96.8)	0 (0.0)	0 (0.0)
	6 Hours	30 (96.8)	0 (0.0)	0 (0.0)
	12 Hours	30 (96.8)	0 (0.0)	0 (0.0)
MK-0518	30 Minutes	29 (100.0)	0 (0.0)	0 (0.0)
	1 Hour	29 (100.0)	0 (0.0)	0 (0.0)
	2 Hours	29 (96.7)	0 (0.0)	0 (0.0)
	3 Hours	29 (96.7)	0 (0.0)	0 (0.0)
	4 Hours	29 (96.7)	0 (0.0)	0 (0.0)
	6 Hours	29 (96.7)	0 (0.0)	0 (0.0)
	12 Hours	29 (96.7)	0 (0.0)	0 (0.0)
Moxifloxacin	30 Minutes	29 (100.0)	0 (0.0)	0 (0.0)
	1 Hour	29 (96.7)	0 (0.0)	0 (0.0)
	2 Hours	29 (96.7)	0 (0.0)	0 (0.0)
	3 Hours	28 (93.3)	1 (3.3)	0 (0.0)
	4 Hours	28 (93.3)	1 (3.3)	0 (0.0)
	6 Hours	29 (96.7)	0 (0.0)	0 (0.0)
	12 Hours	29 (96.7)	0 (0.0)	0 (0.0)

CFB= Change-from-baseline.

Data Source: [16.1.9; 16.4.4]

4.2.8.2.3 Assay Sensitivity

Table 9 shows the Applicant's results on the placebo-adjusted mean change from baseline for raltegravir (MK-0518) and for moxifloxacin (see last two columns) along with the two-sided 90% confidence intervals based on the mixed effects model. Figure 1 shows the placebo-adjusted mean changes from baseline in QTcF and 90% confidence intervals for raltegravir (MK-0581) and moxifloxacin.

Appears This Way
On Original

Table 9: Applicant's Results—Placebo-corrected Mean Change from Baseline in QTcf intervals based on Mixed Effects Model

Treatment	Time	Mean[†]		Mean CFB[‡]		Placebo-Adjusted Mean CFB[‡]	
		N[§]	Estimate (95% CI)	N[§]	Estimate (95% CI)	N[§]	Estimate (90% CI)
Placebo	Predose	30	404.0 (397.5, 410.5)				
	30 Minutes	31	403.1 (396.6, 409.6)	30	-0.3 (-3.5, 2.9)		
	1 Hour	31	405.1 (398.6, 411.6)	30	1.9 (-1.4, 5.1)		
	2 Hours	31	403.7 (397.2, 410.2)	30	0.2 (-3.0, 3.5)		
	3 Hours	31	400.5 (394.0, 407.0)	30	-2.7 (-6.0, 0.5)		
	4 Hours	31	401.8 (395.3, 408.3)	30	-1.5 (-4.7, 1.7)		
	6 Hours	31	398.3 (391.8, 404.8)	30	-5.4 (-8.6, -2.1)		
	12 Hours	31	395.4 (388.9, 402.0)	30	-8.0 (-11.2, -4.8)		
MK-0518	Predose	29	402.3 (395.7, 408.8)				
	30 Minutes	29	399.6 (393.0, 406.1)	29	-3.3 (-6.5, 0.0)	28	-2.9 (-6.5, 0.6)
	1 Hour	29	400.3 (393.8, 406.8)	29	-2.5 (-5.8, 0.7)	28	-4.4 (-8.0, -0.8)
	2 Hours	30	399.6 (393.1, 406.1)	29	-3.2 (-6.5, 0.0)	28	-3.5 (-7.0, 0.1)
	3 Hours	30	399.8 (393.3, 406.3)	29	-3.2 (-6.4, 0.1)	28	-0.4 (-4.0, 3.1)
	4 Hours	30	399.2 (392.7, 405.7)	29	-3.9 (-7.2, -0.7)	28	-2.4 (-6.0, 1.2)
	6 Hours	30	394.5 (387.9, 401.0)	29	-8.5 (-11.7, -5.2)	28	-3.1 (-6.7, 0.5)
	12 Hours	30	391.0 (384.5, 397.6)	29	-11.5 (-14.8, -8.3)	28	-3.6 (-7.2, 0.0)
Moxifloxacin	Predose	29	406.2 (399.6, 412.7)				
	30 Minutes	29	406.2 (399.7, 412.7)	29	0.3 (-3.0, 3.6)	28	0.6 (-3.0, 4.2)
	1 Hour	30	410.6 (404.0, 417.1)	29	4.5 (1.2, 7.8)	28	2.6 (-1.0, 6.2)
	2 Hours	30	412.5 (406.0, 419.0)	29	6.7 (3.4, 10.0)	28	6.4 (2.9, 10.0)
	3 Hours	30	414.1 (407.6, 420.7)	29	8.4 (5.1, 11.6)	28	11.1 (7.5, 14.7)
	4 Hours	30	412.0 (405.5, 418.5)	29	6.5 (3.2, 9.7)	28	8.0 (4.4, 11.6)
	6 Hours	30	404.2 (397.6, 410.7)	29	-1.9 (-5.2, 1.3)	28	3.4 (-0.2, 7.0)
	12 Hours	30	399.1 (392.6, 405.6)	29	-7.0 (-10.3, -3.8)	28	0.9 (-2.7, 4.5)

CFB= Change-from-baseline. CI=Confidence Interval.

[†] Inference arising from an ANOVA model with the raw ECG values as the dependent variable. Mean Square Error=52.8 msec^2.

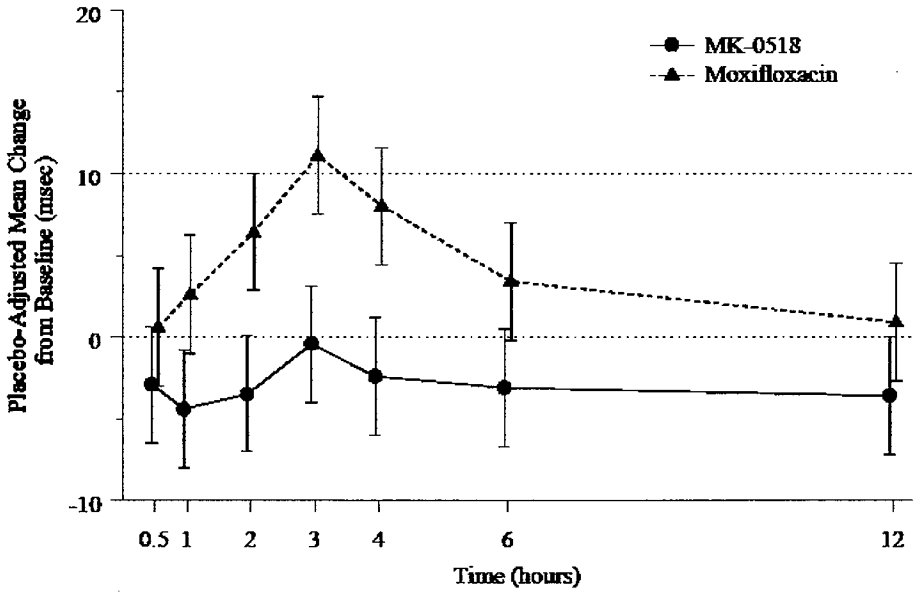
[‡] Inference arising from an ANOVA model with the ECG CFB values as the dependent variable. Mean Square Error=67.1 msec^2.

[§] Number of subjects with data available; some data points missing.

Data Source: [16.1.9; 16.4.4]

Source: Applicant's Table 11-2 on Page 47

Figure 1: Applicant's Figure on Placebo-Adjusted Mean Change from Baseline in QTcF and 90% Confidence Intervals for raltegravir (MK-0518) and moxifloxacin (Based on Mixed Effects Model)



4.2.8.3 Safety Analysis

31 subjects enrolled and 30 completed the study. There were no deaths, SAEs, ventricular arrhythmias, syncope, or seizures reported.

Fifteen subjects reported a total of 26 adverse experiences, all of which except one (a toothache) were considered mild or moderate in intensity by the investigator. No cardiac AEs are reported.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Plasma samples from a subset of 12 subjects treated by MK-0518 were analyzed for MK-0518 concentrations. Plasma samples from moxifloxacin treated group were collected for archive but not assayed.

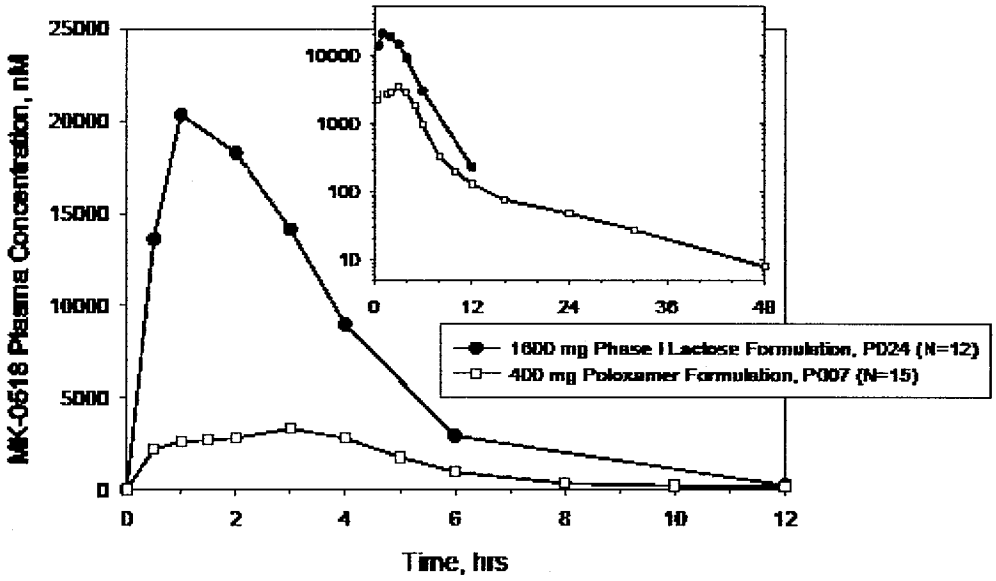
The mean plasma concentration-time profile for the 12 subjects is shown in Figure 2. For comparison, the mean plasma concentration-time profile for subjects who received a single oral dose of 400 mg of the poloxamer formulation in Part I of Protocol 007 is also shown Individual values of the MK-0518 plasma pharmacokinetic parameters for these subjects are shown in Table 11-7. The geometric mean AUC and Cmax values are somewhat lower than the values that were projected based on prior pharmacokinetic data from Protocol 001, but exposure to MK-0518 in this study remains well above that anticipated for a 400 mg dose of the final market image formulation.

Table 10. Sponsor's Table: Summary of PK Paramters in A Subset of Subjects

Pharmacokinetic Parameter	N	Geometric Mean	95% Confidence Interval for Geometric Mean
C_{max} (μM)[†]	12	19.63	(11.72, 32.89)
$AUC_{0-12 hr}$ (μM-hr)[†]	12	63.05	(41.82, 95.05)
[†] Analysis performed on the log scale and back transformed prior to reporting.			

[Ref. 5.3.4.1: P024]

Figure 2: Mean concentration-time profiles for young, healthy, male and female subjects administered single oral dose of MK-0518



4.2.8.4.2 Exposure-Response Analysis

The sponsor did not conduct exposure-response analysis.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

We performed independent analyses based on the mean change in QTcF of the drug and placebo after baseline adjustment at each time point. Table 11 shows the delta-delta QTcF mean change as well as the 2-sided 90% confidence interval. We used normal distribution approximation. As indicated in the table, all the point estimates are below zero and all the upper bounds below 10 ms, which indicates that there is no statistically significant difference of the drug and placebo in terms of QT prolongation.

Table 11 FDA Reviewer's Analysis of Delta-delta QTcF Mean Change at Each Time Point

Treatment	Time	# of Subj.	Mean ddQTcF	SD of ddQTcF	CI Low	CI High
MK-0518	0.5	29	-2.68	11.06	-6.06	0.70

MK-0518	1	29	-4.20	9.71	-7.16	-1.23
MK-0518	2	29	-2.60	11.34	-6.06	0.87
MK-0518	3	29	-0.24	10.87	-3.56	3.08
MK-0518	4	29	-2.54	13.73	-6.74	1.65
MK-0518	6	29	-2.48	10.01	-5.54	0.58
MK-0518	12	29	-2.55	9.48	-5.44	0.35
Moxifloxacin*	0.5	29	0.35	10.88	-2.97	3.68
moxifloxacin	1	29	2.70	12.16	-1.02	6.41
moxifloxacin	2	29	6.75	11.67	3.19	10.32
moxifloxacin	3	29	10.85	13.41	6.75	14.94
moxifloxacin	4	29	7.73	13.91	3.48	11.98
moxifloxacin	6	29	4.10	13.07	0.11	8.09
moxifloxacin	12	29	1.40	12.02	-2.27	5.07

*We did not perform multiple endpoint adjustment for moxifloaxacin comparison.

For the categorical analysis, even though the sponsor claims that there was no subject whose QTc was greater than 450 msec, we found that subject #344 had QTcF>450 msec. This subject was a 34 year old Hispanic female. Below are the time points at which her QTcF was > 450 msec:

- While on moxifloxacin (Period 1), QTcF was > 450 msec at 0.5, 2, 3, 4 and 6 hours post-dose
- While on Placebo (Period 2), QTcF was > 450 msec at 6 hours postdose
- While on raltegravir MK-0518 (Period 3), QTcF was > 450 msec at 1, 3, and 4 hours post-dose

5.2 Clinical Pharmacology Assessments

No additional assessments were performed by the reviewer.

5.3 Medical Assessments

The sponsor does not report any adverse events which appear to be related to QT prolongation or torsade de pointes. No cardiac adverse events are reported.

One subject (332) withdrew consent on day 16. The sponsor reports that subject had completed one treatment period, during which he was administered placebo for both moxifloxacin and MK-0518. The sponsor reports this withdrawal was not due to an AE but the subject had had hives on day 10 and was treated for 3 days with diphenhydramine. This subject was replaced by subject 1332.

6 APPENDIX

6.1 TABLE OF STUDY ASSESSMENTS

Schedule of Clinical Observations and Laboratory Measurements, as Stated in the Protocol

	Hours Postdose (Dosing Day)											
Procedure	Prestudy	Predose	0	0.5	1	2	3	4	6	8	12	Poststudy[†]
Review of entry criteria/informed consent	X											
Medical history	X											
Hepatitis/HIV tests (at the discretion of the investigator)	X											
Vital signs (BP, HR, RR, oral temperature)[‡]	X	X				X						X
Physical examination (including body weight)	X											X
Moniture 12-lead Holter recorder[‡]		X										
ECG time points[‖]		X	X							X		
Standard 12-lead ECG[¶]	X	X				X		X				X
Standard meal[#]								X		X	X	
Laboratory safety tests[††]	X	X[†††]										X
Urine for drug screen	X	X										
Serum/urine β-hCG (females only)[‡‡]	X	X										X
Serum FSH test[‡‡‡]	X											
Administration of MK-0518/moxifloxacin/placebo[¶¶]			X									
Blood for MK-0518 for archive[‖‖]		X		X	X	X	X	X	X		X	
Blood for moxifloxacin for archive[##]		X			X	X	X	X				

	Hours Postdose (Dosing Day)											
Procedure	Prestudy	Predose	0	0.5	1	2	3	4	6	8	12	Poststudy[†]
Genetic analysis consent form[***]		X										
Blood sample for genetic analysis[***]		X										

† Ten to 14 days after the last test drug administration.

‡ Vital signs to be obtained in the supine position after resting for 10 minutes. Respiratory rate and oral temperature to be recorded at prestudy and poststudy only.

‡ Following the predose procedures, subjects must rest quietly in a supine position for 30 minutes prior to dosing and will be hooked up to the ECG Holter recorder 15 minutes prior to dosing.

‖ ECGs will be extracted by the ECG core laboratory at the prescribed ECG time points: predose, 0.5, 1, 2, 3, 4, 6, and 12 hours postdose. However, ECGs may be extracted at additional time points post-hoc. Therefore, in order to prepare subjects so that ECG data can be collected with minimal artifact, subjects must rest quietly in a supine position at least 10 minutes prior to and 5 minutes following the time points listed (hours postdose): ¼, 1, 1¼, 2, 2¾, 3, 3¾, 4, 4¾, 5, 5¾, 6, 7, 8, 9, 10, 11, and 12 hours postdose.

¶ A 12-lead ECG will be performed and reviewed by the investigator at predose, 2, and 4 hours postdose for safety evaluation.

The menu of the 4-, and 8-hour meals and 12-hour snack will be at the discretion of the investigator but must be standardized across all subjects. Meals will be served following the ECG time points. Meals must be consumed within 30 minutes.

†† Laboratory safety tests (hematology/blood chemistry/urinalysis) are performed after an 8-hour fast.

‡‡ A serum β-hCG pregnancy test will be performed at pre- and poststudy. A urine pregnancy test will be favored at predose but a serum pregnancy test may be performed at the discretion of the investigator.

‡‡‡ Female subjects of nonreproductive potential who are postmenopausal and had last menses within 3 years.

¶¶ Administered with approximately 240 mL of water.

‖‖ Blood for MK-0518 plasma concentrations for archive will be collected at predose, 0.5, 1, 2, 3, 4, 6, and 12 hours postdose.

Blood for moxifloxacin plasma concentrations for archive will be collected at predose, 1, 2, 3, and 4 hours postdose.

*** The consent form for genetic analysis and blood sample will be obtained on the day of randomization (Period 1 only).

††† Except urinalysis.

Data Source: [16.1.1.1]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christine Garnett
7/10/2007 03:19:09 PM
PHARMACOLOGIST
Hao Zhu was the clinical pharmacology reviewer.

Joanne Zhang
7/10/2007 03:31:33 PM
BIOMETRICS

Stephen Grant
7/10/2007 03:33:20 PM
MEDICAL OFFICER

Norman Stockbridge
7/10/2007 05:18:02 PM
MEDICAL OFFICER