INTEROFFICE *MEMO*

TO: NDA 21861
FROM: C. Joseph Sun, Ph. D., Supervisory Pharmacologist, HFD-570
DATE: September 13, 2005

I concur with pharmacologist's recommendation that pharmacology and toxicology of olopatadine have been adequately studied and evaluated. However, the safety of the intranasal formulation containing the inactive ingredient (Povidone) has not been adequately demonstrated. Therefore, the intranasal formulation of the product is not approvable from a preclinical standpoint.

Pharmacology: The action of olopatadine is a typical antihistamine that blocks H_1 receptors as evidenced by *in vitro* receptor binding studies and *in vivo* allergic bronchospasm or histamine-induced bronchoconstriction animal models.

General toxicity: Chronic oral toxicity studies have been conducted with olopatadine in rats and dogs up to 52 weeks in duration. In rats, target organs of toxicity include the kidneys, heart, liver, eyes, urinary bladder and pancreas. In dogs, target organs of toxicity included the kidneys, spleen, liver, heart, bone marrow and eyes. Intranasal formulation of olopatadine did not cause any notable toxicity in the 6-month rat and 9-month dog intranasal studies. However, the formulation that contained the excipient Povidone was only tested for the first two months of the 6-month rat study. In the 6-month intranasal bridging study in rats for the Povidone, olfactory epithelial degeneration and respiratory turbinate epithelial vacuolization were observed at all the doses tested in a dose-responsive manner with regard to incidence and severity. As such, there was no NOAEL identified. Consequently, a safety assessment of intranasal use of the excipient Povidone in the formulation can not be conducted.

Reproductive toxicity: Olopatadine did not impair fertility in rats and was not terotogenic in rats and rabbits. Fetal deaths at birth were reported in rats and rabbits and decreased pup survival after delivery was observed in rats. Therefore, pregnancy category C is appropriate.

Geotoxicity: Olopatadine was not genotoxic in the standard battery of assays (Ames test, chromosome aberration assay in Chinese hamster lung cells and *in vivo* mouse micronucleus test).

Carcinogenicity: In two oral carcinogenicity studies in mice and rats, olopatadine did not induce any tumors.

Labeling: Carcinogenesis, mutagenesis and impairment of fertility section and pregnancy section should be revised as suggested to incorporate the above-mentioned nonclinical findings of olopatadine.

Outstanding preclinical issue: All issues regarding olopatadine raised during the drug development have been resolved. However, based on the results of the 6-month rat study of Povodine that showed local nasal effects without identifying a NOAEL, Povidone is not considered safe to use as an excipient in the proposed intransal formulation. To provide a safety assessment of the intended intranasal formulation, a 6-month intranasal rat study using either the intended formulation or Povidone itself is required. The study should identify a NOAEL that would provide an adequate safety margin for the intended clinical formulation.

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/s/

Joseph Sun
9/13/2005 04:06:00 PM
PHARMACOLOGIST

Drug: **Olopatadine**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric				0	3	0	25	0
Adult	>12	2.4	2	4.8	50	0.096	37	3.552

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
rat	oral	200	6	1200	337.84	---	340	---
mouse	oral	500	3	1500	422.3	---	420	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
Repro/Fertility:								
rat	oral	50	6	300	84.459	N/A	85	N/A
rat	oral	400	6	2400	675.68	N/A	680	N/A
extra			---	---	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
Teratogenicity:								
rat	oral	20	6	120	33.784	N/A	35	N/A
rat	oral	60	6	360	101.35	N/A	100	N/A
rat	oral	600	6	3600	1013.5	N/A	1,000	N/A
rabbit	oral	400	12	4800	1351.4	N/A	1,400	N/A
extra			---	---	---	N/A	---	N/A
Overdosage:								
rat	intranasal	3.6	6	21.6	6.0811	---	6	---
mouse	oral male	1150	3	3450	971.28	---	970	---
mouse	oral female	1830	3	5490	1545.6	---	1,500	---
dog	oral	5000	20	1E+05	28153	---	28,000	---
Overdosage:								
rat	oral	3870	6	23220	6537.2	---	6,500	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
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/s/

Gary Bond
8/26/2005 03:05:23 PM
PHARMACOLOGIST

Joseph Sun
8/26/2005 03:11:20 PM
PHARMACOLOGIST
I concur.

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Chemistry Consult

NDA: 21-861

Date of Consult Request: February 2, 2005

Date of Submission: December 21, 2004

Reviewer: Gary P. Bond, Ph.D., DABT

Date Completed: June 14, 2005

Sponsor: Alcon Inc.

Drug Name: Patanase® (olapatadine HCl)

Class: antihistamine and mast cell stabilizer

Route of administration: intranasal

Daily Dose: 0.6% olapatadine as single doses of 2x 100 ul spray/nostril BID

Response to Chemistry Consult as Requested by Craig M. Bertha

Description of the Consult

This consult request is for evaluation of the acceptability of the allowance of (b) (4) (relative to olapatadine) of degradant (b) (4) (relative to olapatadine) of (b) (4) (b) (4) are structurally related, structural alert (b) (4) degradants of olapatadine.

Review and Evaluation:

During the course of the development, (b) (4) a structural alert, and another degradant of olapatadine, the non-structural alert degradant (b) were evaluated for genotoxicity. *In vitro* Ames bacterial mutation assays, mouse lymphoma assays (MLA), and Syrian hamster embryo assays (SHE) were conducted on (b) (4) as individual test articles. *In vivo* mouse micronucleus assays were conducted on (b) (4) in which they were each individually administered along with olapatadine at an approximate ratio of (b) (4) olapatadine and (b) (4) degradant. No studies were conducted with (b) (4) Seven genotoxicity assays for (b) (4) were reviewed (study summaries follow).

1) Study title: Bacterial Reverse Mutation Study Using (b) (4) a Degradation Product of AL-4943A (Olopatadine)

Key findings:

- No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation up to the limit dose of 5000 ug/plate where toxicity was observed (an extremely reduced background lawn with no revertants)
- (b) (4) was not genotoxic in the Ames Bacterial Mutation test

Study no: Alcon TR 019:30:0203
Volume # and page #: 57 and pages 1-78
Conducting laboratory and location: (b) (4)

Date of study initiation: December 11, 2002 (February 12, 2003 report date)
GLP compliance: yes (USFDA, USEPA, UK, Japan, OECD)
QA reports: yes (x) no ( )
Drug, lot # and % purity: 10258:002 and 99.6%
Formulation/vehicle: yellow powder/water

Methods:

Strains/species/cell line: Salmonella typhimurium TA98, TA 100, TA1535, TA1537
Escherichia coli WP2uvrA

Dose selection criteria:

Basis of dose selection: guidelines (top dose of 5000 ug/plate or precipitate)

Range finding studies: 1.5, 5, 15, 50, 150, 500, 1500, & 5000 ug/plate with toxicity at 5000 but no precipitate

Test agent stability: stable at room temperature in the dark with desiccant

Metabolic activation system: Aroclor 1254-induced male Sprague-Dawley rat liver S9 microsomes

Controls:

Vehicle: sterile water for test groups and positive control sodium azide; dimethyl sulfoxide for other positive controls

Negative controls: sterile water

Positive controls: range finding & main study

strain	S9 mix (-)		S9 mix (+)	
	positive control article	dose (ug/plate)	Positive control article	dose (ug/plate)
TA98	2NF	1	2AA	1
TA100	SA	1		1
TA1535	SA	1		1
TA1537	9AA	75		1
WP2uvrA	MMS	1000		10

- SA (sodium azide); 9AA (9-aminoacridine); 2AA (2-aminoanthracene); 2NF (2-nitrofluorene); MMS (methylmethansulfonate)

Comments: dosing solution analyzed by HPLC

Exposure conditions:

Incubation and sampling times: plate incorporation method with 48-72 hour incubation

Doses used in definitive study: 75, 200, 600, 1800, & 5000 ug/plate

Study design: initial toxicity-mutagenicity test +/- S9 and + controls and main (confirmatory) test

Analysis:

No. of replicates: 2/strain/dose for initial toxicity-mutagenicity test; 3/strain/dose for confirmatory test

Counting method: bacterial suspensions by spectrophotometer for turbidity; colony analyzer for revertants or manual when precipitate dictates for revertants and lawn condition

Criteria for positive results: mean number of revertant colonies for two plates exhibit dose dependent increase over two increasing concentrations and maximum value at least ≥ 3x that of vehicle control (strains TA1535 & TA1537) and ≥ 2x that of vehicle control (other strains)

Results:

Study validity: valid
- tester strain genotypes: ampicillin, crystal violet, tetracycline, and UV sensitivity or resistance, as appropriate
- initial and confirmatory assays agree
- no bacterial proliferation in sterility test (sham and S9 mixes and the test article dilutions must contain at most one contaminant colony per plate)
- at least 3 nontoxic dose levels
- toxicity or mutagenicity at top dose or test up to 5000 ug/plate, precipitate at top dose or tested up to 5000 ug/plate
- positive controls at least 3x negative controls
- mean values vehicle and positive controls within ± 2SD of historical values

Study outcome:

- Toxicity (an extremely reduced background lawn with no revertants) but no precipitate at limit dose of 5000 ug/plate
- No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation in a valid test
- (b) (4) was not genotoxic in the Ames Bacterial Mutation test

2) Study title: Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with (b) (4)

Key findings:

- No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation in a valid test
- (b) (4) was not genotoxic in the Ames Bacterial Mutation test

Study no: Alcon TDOC-0000652
Volume # and page #: 58 and pages 1-59
Conducting laboratory and location: (b) (4)

Date of study initiation: June 30, 2003 (November 23, 2003 report date)
GLP compliance: yes (USFDA, Japanese MHLW, OECD)
QA reports: yes (x) no ( )
Drug, lot # and % purity: M-Ref 9502 and 99.8%
Formulation/vehicle: yellow powder/dimethyl sulfoxide (DMSO)

Methods:

Strains/species/cell line: Salmonella typhimurium TA98, TA 100, TA1535, TA1537
Escherichia coli WP2uvrA
Dose selection criteria:
Basis of dose selection: previous study data
Range finding studies: none (doses from previous study)
Test agent stability: stable – stored frozen an -10 to -30oC
Metabolic activation system: Aroclor 1254-induced male Sprague-Dawley rat liver S9 microsomes
Controls:
Vehicle: sterile water for test groups and positive control sodium azide; dimethyl sulfoxide for other positive controls
Negative controls: sterile water
Positive controls: range finding & main study

strain	S9 mix (-)		S9 mix (+)	
	positive control article	dose (ug/plate)	Positive control article	dose (ug/plate)
TA98	2NF	1	B[a]P	2.5
TA100	SA	2	2AA	2.5
TA1535	SA	2		2.5
TA1537	ICR-191	2.0		2.5
WP2uvrA	4NQO	0.4		25.0

- SA (sodium azide); 2AA (2-aminoanthracene); 2NF (2-nitrofluorene); B[a]P (benzo[a]pyrene); 4NQO (4-nitroquinoline-1-oxide); ICR-191
Comments: dosing solution analyzed by HPLC

Exposure conditions:

Incubation and sampling times: preincubation method with 52±4 hours incubation

Doses used in mutagenicity Assay: 157, 313, 625, 1250, 2500, & 5000 ug/plate

Doses used in definitive study: 33.3, 100, 333, 1000, 3330, & 5000 ug/plate

Study design: initial mutagenicity test +/- S9 and + controls and main (confirmatory) test

Analysis:

No. of replicates: 2/strain/dose for initial toxicity-mutagenicity test; 3/strain/dose for confirmatory test

Counting method: bacterial suspensions by spectrophotometer for turbidity; colony analyzer for revertants or manual when precipitate dictates for revertants and lawn condition

Criteria for positive results: mean number of revertant colonies for two plates exhibit dose dependent increase over two increasing concentrations and maximum value at least ≥ 3x that of vehicle control (strains TA1535 & TA1537) and ≥ 2x that of vehicle control (other strains)

Results:

Study validity: valid

- tester strain genotypes: ampicillin, crystal violet, tetracycline, and UV sensitivity or resistance, as appropriate
- initial and confirmatory assays agree
- no bacterial proliferation in sterility test (sham and S9 mixes and the test article dilutions must contain at most one contaminant colony per plate)
- at least 3 nontoxic dose levels
- toxicity or mutagenicity at top dose or test up to 5000 ug/plate, precipitate at top dose, or tested up to 5000 ug/plate
- positive controls at least 3x negative controls
- mean values vehicle and positive controls within ± 2SD of historical values

Study outcome:

- no toxicity and no precipitate at limit dose of 5000 ug/plate
- No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation in a valid test
- (b) (4) was not genotoxic in the Ames Bacterial Mutation test

3) Study title: In Vitro Mammalian Cell Gene Mutation Test (L5178Y/TK$^{+/-}$ Mouse Lymphoma Assay) using (b) (4) a Degradation Product of AL-4943A (Olopatadine)

Key findings:

- in the presence of S9 microsomes for a 4 hour exposure, the initial mutagenicity assay and independent repeat mutagenicity assays were positive as ≥100 mutants per 106 clonable cells over that of the solvent control were observed
- (b) (4) was positive in the mouse lymphoma assay in the presence of S9 microsomes in a valid study

Study no.: Alcon TR 018:30:0203
Volume #, and page #: 57, pages 1-59
Conducting laboratory and location: (b) (4)

Date of study initiation: December 10, 2002 (March 8, 2003 report date)
GLP compliance: yes (USFDA, USEPA, UK, JAPAN, OECD)
QA reports: yes (x) no ( )
Drug - lot #,and % purity: ERM 10277:001 and 99.6%

Methods

Strains/species/cell line: L5178Y/TK$^{+/-}$ Mouse Lymphoma cells

Doses used in definitive study:
- preliminary toxicity assay at nine concentrations +/-S9 microsomes from 0.5-3100 ug/mL
- initial mutagenicity test at 10, 15, 20, 25, 30, 40, & 50 ug/mL (4 hour –S9); 50, 75, 100, 110, & 125 ug/mL (4 hour +S9), and 7.5, 10, 12.5, 15, 20, & 25 ug/mL (24 hour –S9)
- independent repeat assay at 50, 100, 110, 120, 125, & 130 ug/mL (4 hour +S9 only)

Basis of dose selection: relative growth of high dose between 10-20%

Negative controls: sterile water (vehicle for test groups)

Positive controls:
- methyl methane sulfonate in –S9 groups for 4 hour exposure at 1000 and 2000 ug/mL and for 24 hour exposure at 250 and 500 ug/mL
- 7,12-dimethyl-benz(a)anthracene in +S9 groups at 250 and 400 ug/mL

Incubation and sampling times: duplicate samples for initial and independent repeat assays

Results:

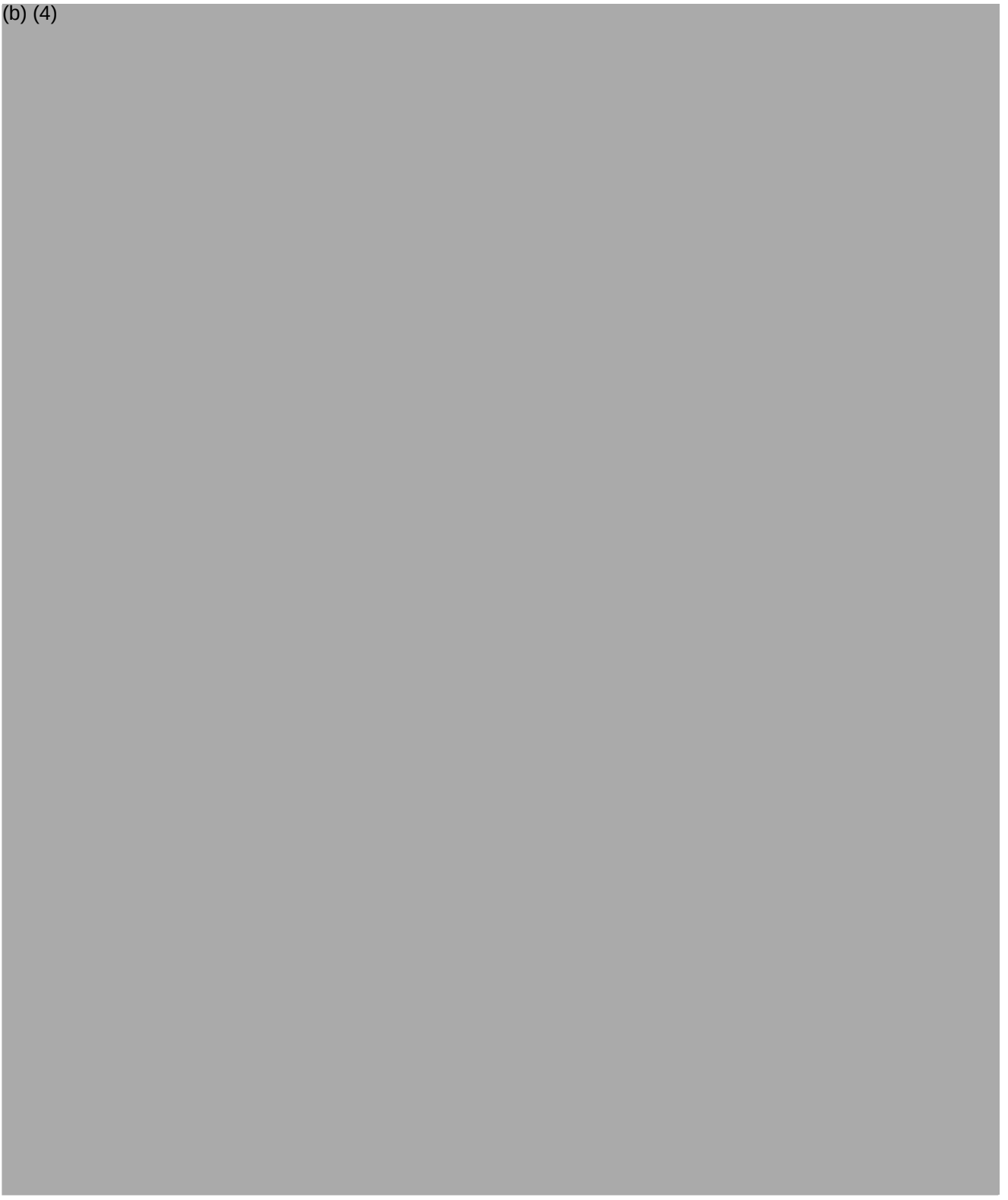
Study validity:
- valid per guidelines
- control ≥ 50% viability and positive response at > 100 mutant colonies per 106

cells more than control

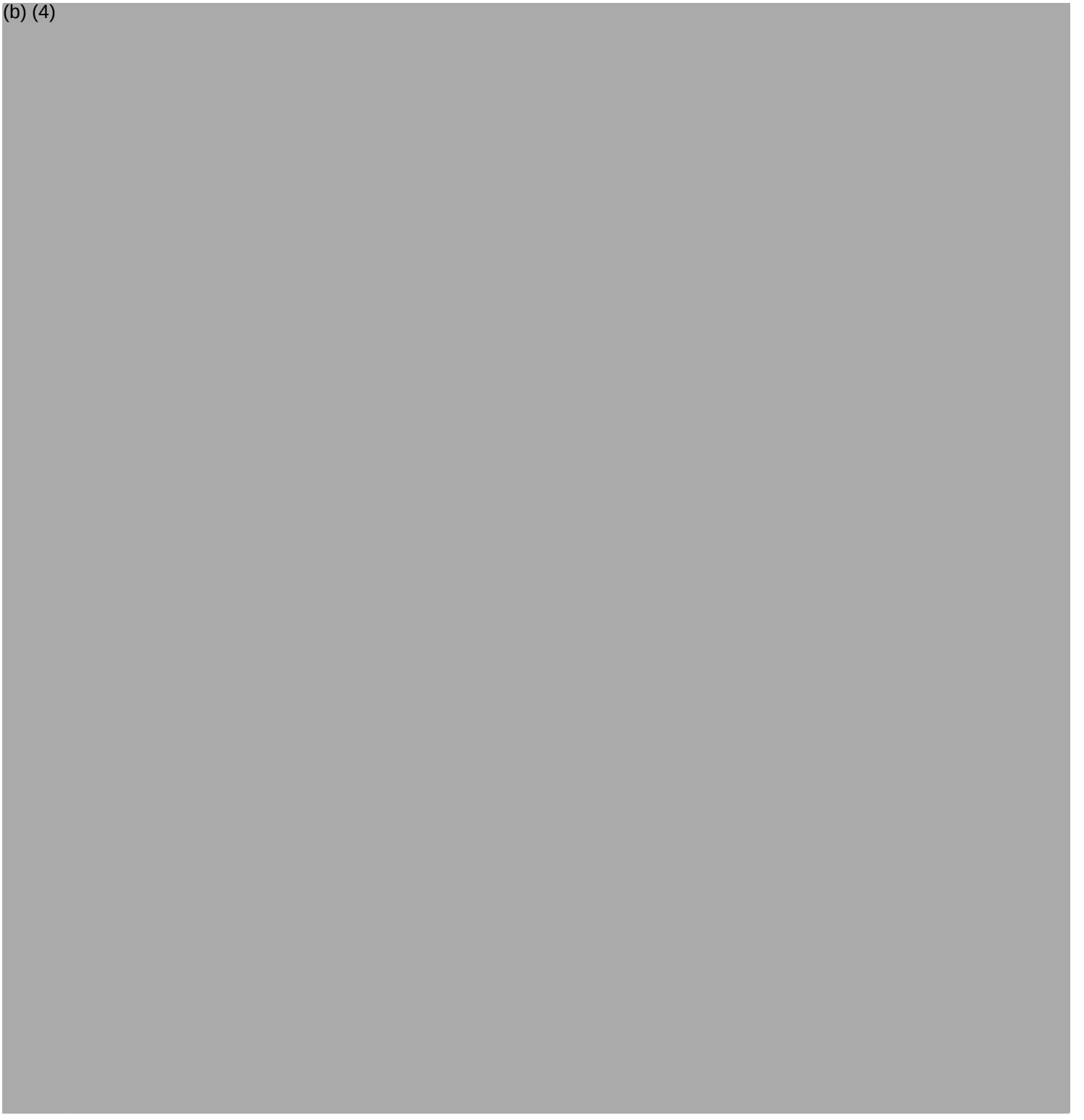
Study outcome:

- 4 hour –S9 - initial mutagenicity assay equivocal (see table)
- 24 hour –S9 - extended treatment assay negative (see table)
- 4 hour +S9 - initial mutagenicity assay and independent repeat mutagenicity assays were positive as ≥100 mutants per 106 clonable cells over that of the solvent control were observed (see tables)
- (b) (4) was positive in the mouse lymphoma assay in the presence of S9 microsomes in a valid study

(b) (4)

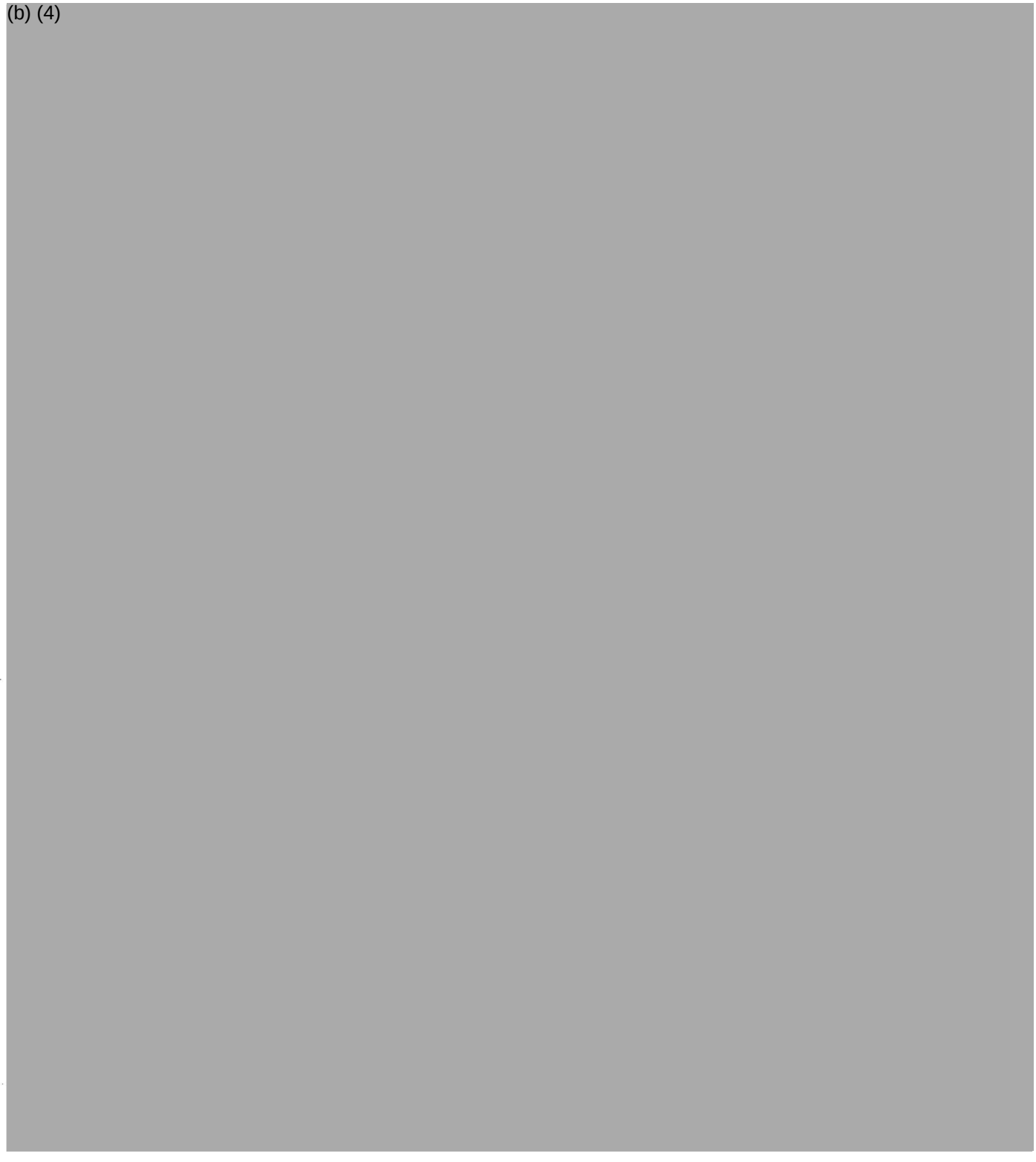


(b) (4)

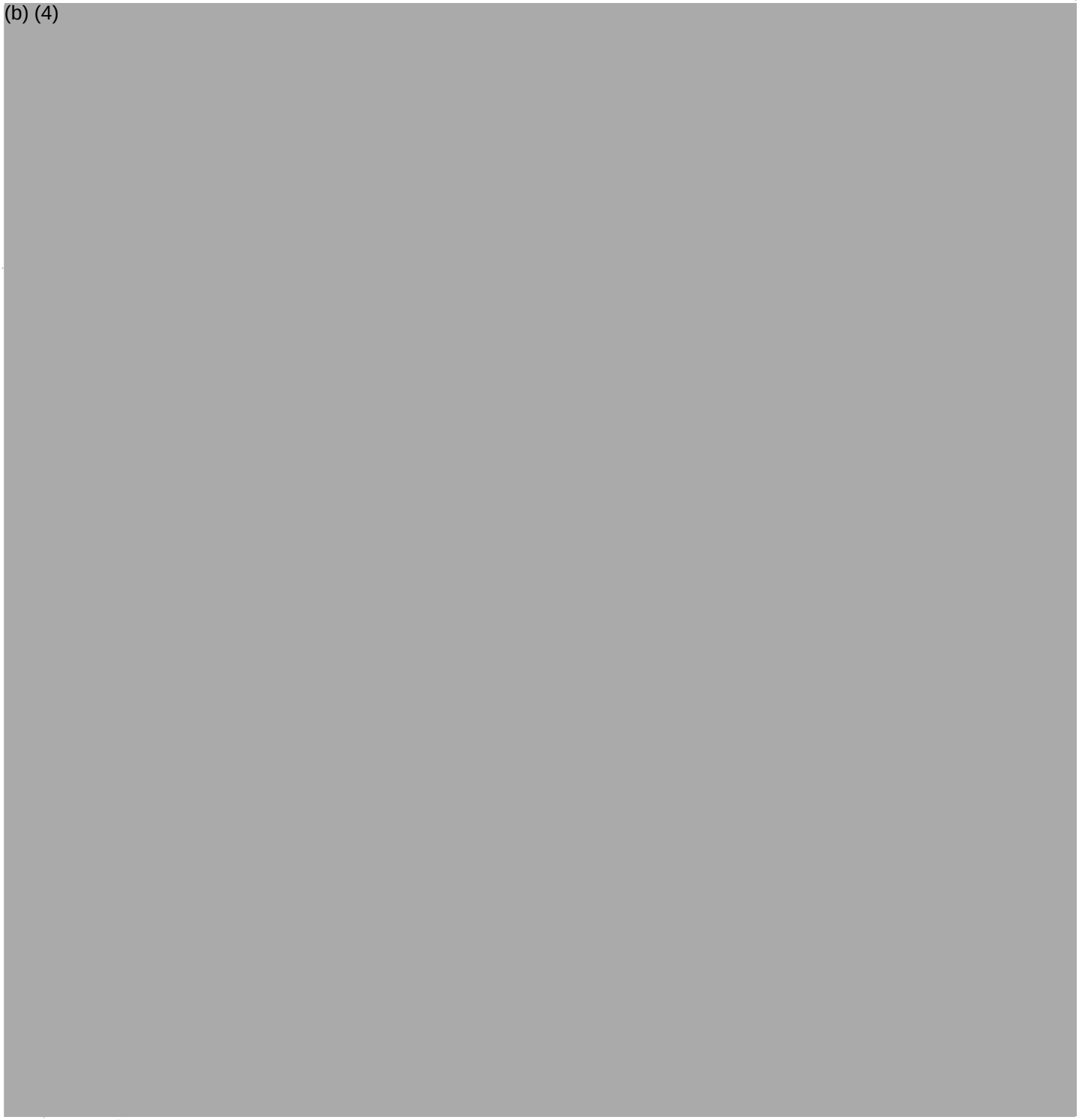


(b) (4)

(b) (4)



(b) (4)



4) Study title: In Vitro Mammalian Cell Gene Mutation Test (L5178Y/TK$^{+/-}$ Mouse Lymphoma Assay) using (b) (4) a Degradation Product of AL-4943A (Olopatadine)

Key findings:

- in the presence of S9 microsomes for a 4 hour exposure, the initial mutagenicity assay and independent repeat mutagenicity assays were positive as ≥100 mutants per 106 clonable cells over that of the solvent control were observed with an increase in the frequency of small colonies
- (b) (4) was positive in the mouse lymphoma assay in the presence of S9 microsomes in a valid study

Study no.: Alcon TR 017:30:0203
Volume #, and page #: 57, pages 1-59
Conducting laboratory and location: (b) (4)

Date of study initiation: November 11, 2002 (January 22, 2003 report date)
GLP compliance: yes (USFDA, USEPA, UK, JAPAN, OECD)
QA reports: yes (x) no ( )
Drug - lot #,and % purity: ERM 10277:001 and 99.6%

Methods

Strains/species/cell line: L5178Y/TK$^{+/-}$ Mouse Lymphoma cells

Doses used in definitive study:
- preliminary toxicity assay at nine concentrations +/-S9 microsomes from 0.5-3100 ug/mL
- initial mutagenicity test at 10, 15, 20, 25, 30, 40, & 50 ug/mL (4 hour –S9); 50, 75, 100, 110, & 125 ug/mL (4 hour +S9), and 7.5, 10, 12.5, 15, 20, & 25 ug/mL (24 hour –S9)
- independent repeat assay at 50, 100, 110, 120, 125, & 130 ug/mL (4 hour +S9 only)

Basis of dose selection: relative growth of high dose between 10-20%

Negative controls: sterile water (vehicle for test groups)

Positive controls:
- methyl methane sulfonate in –S9 groups for 4 hour exposure at 1000 and 2000 ug/mL and for 24 hour exposure at 250 and 500 ug/mL
- 7,12-dimethyl-benz(a)anthracene in +S9 groups at 250 and 400 ug/mL

Incubation and sampling times: duplicate samples for initial and independent repeat assays

Results:

Study validity:
- valid per guidelines

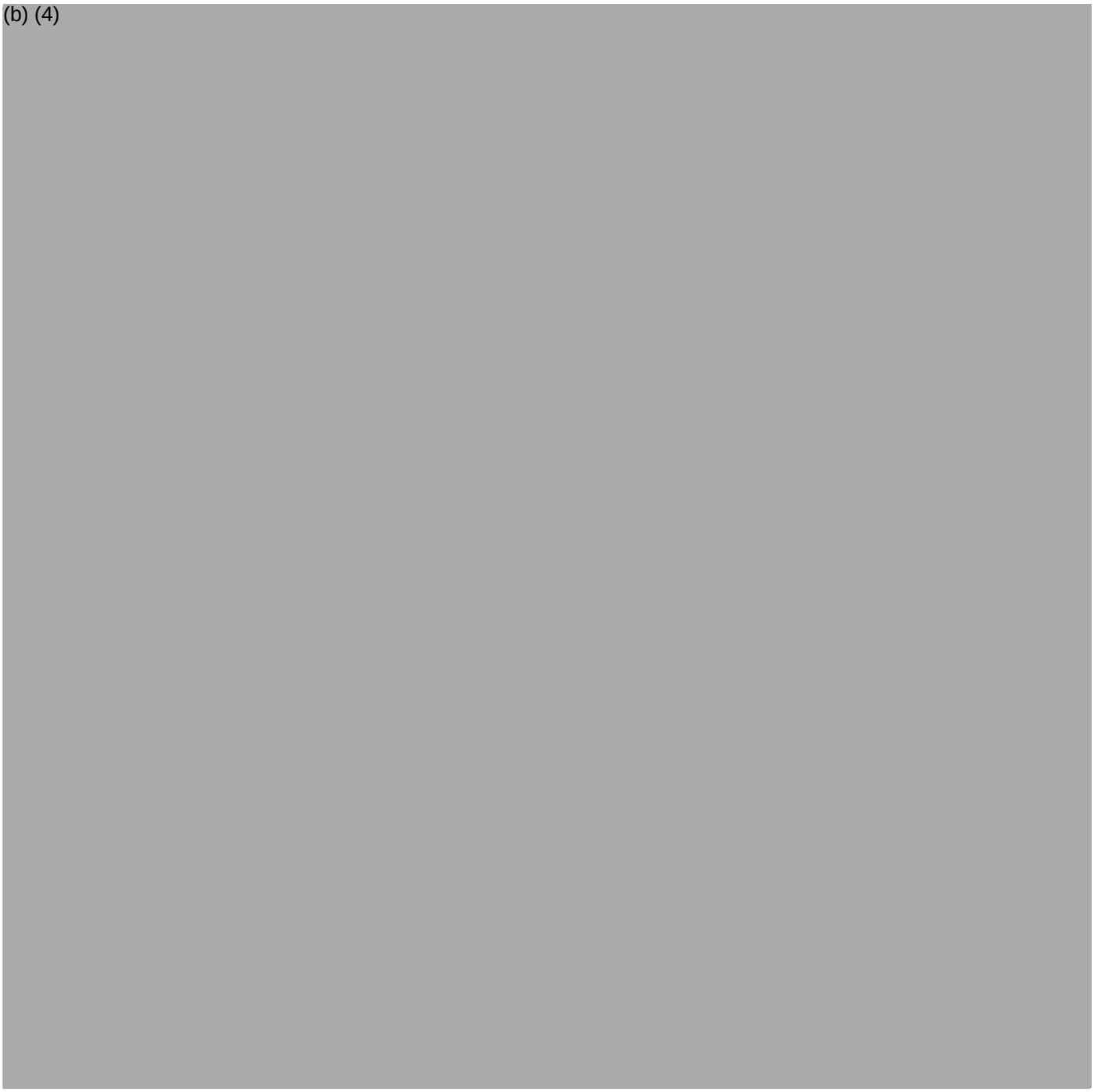
- control ≥ 50% viability and positive response at > 100 mutant colonies per 106 cells more than control

Study outcome:

- 4 hour –S9 - initial mutagenicity assay equivocal (see table)
- 24 hour –S9 - extended treatment assay negative (see table)
- 4 hour +S9 - initial mutagenicity assay and independent repeat mutagenicity assays were positive as ≥100 mutants per 106 clonable cells over that of the solvent control were observed(see tables)
- (b) (4) was positive in the mouse lymphoma assay in the presence of S9 microsomes in a valid study

(b) (4)

(b) (4)



(b) (4)

(b) (4)

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5) Study title: Exploratory Dose Ranging/Screening Assay of AR (b) (4) and AS (b) (4) in the Syrian Hamster Embryo Cell Assay – degradants of Olopatadine

Key findings:

- Olopatadine degradants (b) (4) and (b) (4) were tested in tested in non-GLP SHE cell assay
- statistically significant increases in morphological transformation at 2 doses of (b) (4) (LD and HD) with increase in MD not statistically significant