5. Carcinogenicity Update

5.1 Long-Term Studies

Studies of approximately 2-years duration to assess the carcinogenic potential of MK-0518 are ongoing in rats and mice. The in-life phase of these studies is scheduled to be completed in [redacted]20[redacted] with final study reports planned to be completed in [redacted]20[redacted] This memorandum provides a current update of key observations on these ongoing studies. In addition, the attached tables include a listing of all neoplastic changes irrespective of the potential relationship to treatment.

Importantly, results provided in this update should be considered preliminary as the tumor evaluation has only occurred on animals which have died through Drug Week 76 of these ongoing studies. Total mortality in the rat and mouse studies is currently 23% and 27%, respectively; control and treated combined. Therefore, the preliminary data provided on tumor incidence represents an evaluation of less than 1/3 of all animals on each study. Furthermore, there are differences in mortality among the groups that should be considered when evaluating the incidence of histomorphologic changes.

106-Week Oral Carcinogenicity Study in Rats

Status

The MK-0518 carcinogenicity study in rats is currently in Drug Week 82. The doses of 50, 150, and 300 mg/kg/day in males and 50, 300 and 600 mg/kg/day in females were selected as the maximum tolerated dose in males and the maximum feasible dose in females based on data from range finding studies. In high-dose males there is a 12% decrease in mean body weight gain, relative to concurrent controls. Audible respiratory sounds were noted in females at 600 mg/kg/day, in males and females at 300 mg/kg/day, and in males at 150 mg/kg/day from Drug Week 4, 7, 12, and 15 onwards, respectively. Almost all females at 600 mg/kg/day, and approximately half the animals at 150 mg/kg/day and 300 mg/kg/day presented at least once with this finding. Similar audible respiratory sounds were observed in animals on the previous 27-week oral toxicity study in rats and were considered to result from inflammation and irritation to the nose and nasopharynx as discussed below.

Mortality

Current total mortality through Drug Week 81 is provided in the table below. The majority of these early deaths were considered to be due to intubation (dosing) accidents or aspiration of dosing material. It is likely that the cause of these dosing accidents and aspirations resulted from animals struggling during oral gavage dosing as MK-0518 is believed to have poor palatability based on the high incidence of salivation seen in rats

and has demonstrated to be an irritant to mucosal surfaces evidenced by the nasal and nasopharyngeal inflammation observed in both the rat 27-week toxicity study and the ongoing rat and mouse carcinogenicity studies.

Total Mortality in Rats through Drug Week 81
(Incidence, n=50 sex/group)

Dose Group (mg/kg/day)	Number Dead (Percent)	
	Females	Males
Control 1	7 (14)	8 (16)
Control 2	4 (8)	10 (20)
50	9 (18)	11 (22)
150	-	15 (30)
300	13 (26)	16 (32)
600	23 (46)	-
Total Mortality through Drug Week 81: 116/500 rats (23%)		
- = Not applicable		

(Carcinogenicity study in progress)

Tumor Incidence and other notable Histomorphologic Observations

Histomorphologic examination has been completed on all animals necropsied through Drug Week 76. A complete listing of tumors diagnosed on these animals is provided in Attachment 1 (Rat Summary of Primary Tumors).

The table below summarizes notable neoplasms and histomorphologic changes on the ongoing study. As expected, following chronic irritation and inflammation to the nose/nasopharynx, epithelial hyperplasia and squamous metaplasia have been observed in many of these animals. Five squamous cell carcinomas of the nose/nasopharynx have been identified in high dose female animals which are considered to be the expected outcome of chronic irritation and inflammation secondarily associated with the dosing procedure. Further, one chondrosarcoma of the nose has been observed in one mid dose male rat.

MK-0518: 106-Week Oral Carcinogenicity Study in Rats
Draft Unaudited Histopathology Results of Relevant Findings of the Nose/Nasopharynx Through Drug Week 76

	MK-0518 (mg/kg/day)									
	Females (n=50/group)					Males (n=50/group)				
	Ctrl1	Ctrl2	50	300	600	Ctrl1	Ctrl2	50	150	300
# animals necropsied	7	5	11	15	24	8	10	12	15	17
# animals examined (through Drug Week 76)	5	4	7	12	19	8	9	11	13	16
NASOPHARYNX										
Inflammation	-	-	-	10	17	1	-	2	7	12
Metaplasia, squamous	-	-	-	-	11	-	-	-	-	5
Respiratory epithelium, hyperplasia	-	-	-	2	1	-	-	-	2	3
Squamous cell carcinoma	-	-	-	-	4	-	-	-	-	-
NOSE										
Inflammation	-	-	-	10	19	-	-	-	8	14
Metaplasia, squamous	-	-	-	3	8	-	-	-	5	7
Squamous cell carcinoma	-	-	-	-	1	-	-	-	-	-
Chondrosarcoma	-	-	-	-	-	-	-	-	1	-

- = histomorphologic change was not observed

As discussed in the textbook Pathology of the Fisher Rat [Ref. 4.3: 235], chemicals characterized as irritants induce lesions by regional epithelial cytotoxicity which is "probably related to regional deposition of the material in the nose." The text further describes "the sequence of events following such exposure generally proceeds through (1) an initial period of tissue degeneration or necrosis, (2) rapid cell proliferation and migration to repair defects in the epithelial lining, and (3) restoration of the normal appearance or adaptation (metaplasia) depending on the degree of damage and the presence or absence of continued toxic exposure. These changes are often accompanied by an acute or chronic inflammatory response." Additionally, the text describes that

experimental studies have established that regions of the upper respiratory tract (e.g., trachea) "often responds to irritants with goblet cell hyperplasia, metaplasia, dysplasia, or neoplasia." The current literature supports the mechanism of the nasal and nasopharyngeal tumors to be due to chronic irritation and inflammation. Furthermore, MK-0518 was negative in all genetic toxicology studies.

105-Week Oral Carcinogenicity Study in Mice

Status

The MK-0518 carcinogenicity study in mice is currently in Drug Week 82. The doses of 50, 250, and 400 mg/kg/day in females and 50, 100 and 250 mg/kg/day in males were selected as the maximum tolerated doses in females and males based on data from range finding studies. In females at 250 and 400 mkd, there is a decrease in body weight gain of -43% and -68%, respectively, relative to concurrent controls. In males at 250 mkd, there is a decrease in body weight gain of -53% relative to concurrent controls.

Transient audible respiratory sounds in females and males at 250 mg/kg/day and in females at 400 mg/kg/day have been observed. This observation was also observed in the ongoing rat carcinogenicity study and also is likely due to inflammation and irritation of the nose and nasopharynx as discussed below.

Mortality

Current total mortality through Drug Week 81 is provided in the table below. The majority of the deaths in the high dose females were caused by inflammation of the nose and nasopharynx consistent with aspiration and/or dosing procedure.

Total Mortality in Mice through Drug Week 81
(Incidence, n = 50 sex/group)

DoseGroup (mg/kg/day)	Number Dead (percent)	
	Females	Males
Control 1	13 (26)	12 (24)
Control 2	8 (16)	12 (24)
50	8 (16)	14 (28)
100	-	15 (30)
250	14 (28)	9 (18)
400	28 (56)	-
Total Mortality through Drug Week 81: 133/500 mice (27%)		
- = Not applicable.		

(Carcinogenicity study in progress)

Tumor Incidence and other Notable Histomorphologic Observations

Histomorphologic examination has been completed on all animals necropsied through Drug Week 76. To date, no neoplasms of the nose or nasopharynx have been observed in the mouse carcinogenicity study. Histomorphologic changes in the nose, nasopharynx and trachea including chronic inflammation, epithelial hyperplasia and metaplasia have been observed which are consistent with those described in the rat. A complete listing of neoplasms diagnosed on these animals is provided in Attachment 2 (Mouse Summary of Primary Tumors).

MK-0518: 105-Week Oral Carcinogenicity Study in Mice
Histopathology Results of in the Nose and Nasopharynx
Through Drug Week 76

	MK-0518 (mg/kg/day)									
	Females (n=50/group)					Males (n=50/group)				
	Ctrl1	Ctrl2	50	250	400	Ctrl1	Ctrl2	50	100	250
# animals necropsied	13	8	9	14	28	12	13	14	16	10
# animals examined (through Drug Week 76)	12	7	6	11	27	9	12	13	14	9
NASOPHARYNX										
Inflammation	-	-	3	2	16	-	-	3	1	6
Metaplasia, squamous	-	-	4	3	16	-	-	1	1	5
Squamous cell Carcinoma	-	-	-	-	-	-	-	-	-	-
NOSE										
Inflammation	-	1	3	4	22	2	-	2	3	7
Metaplasia, squamous	-	-	3	4	16	1	-	1	2	5
Squamous cell Carcinoma	-	-	-	-	-	-	-	-	-	-
TRACHEA										
Inflammation	-	-	-	3	10	2	-	-	-	1
Hyperplasia, epithelial	-	-	1	3	9	1	-	-	-	1
Squamous cell Carcinoma	-	-	-	-	-	-	-	-	-	-

- = histomorphologic change was not observed

Conclusion

In conclusion, both the rat and mouse carcinogenicity studies have completed 81 weeks of in life assessment. Expected effects of drug irritation to nose and nasopharynx have

been observed in both rats and mice. Additionally, in the female rat, squamous cell carcinomas of the nose and nasopharynx were observed and are considered to represent the expected consequence of chronic irritation and inflammation. There were no tumors in mice. Based on available histomorphologic data through Study Week 76, there is no evidence of any other preneoplastic or neoplastic change in the ongoing rat and mouse carcinogenicity studies that is considered to be related to drug treatment.

Attachment 1
Rat: Summary of Primary Tumors

TABLE B-3. MK-0518: One-Hundred-Six-Week Oral Carcinogenicity Study in Rats. TT #05-6040
Summary of Primary Neoplasms - Through DW76

Group Number	Female 1	2	3	4	5	6	Male 1	2	3	4	5	6
NUMBER NECROPSIED	7	5	11	-	15	24	8	10	12	15	17	-
NO. EXAMINED MICROSCOPICALLY	5	4	7	-	12	19	8	9	11	13	16	-
Brain												
Malignant Astrocytoma	-	-	-	-	-	-	1	-	-	-	-	-
Malignant Oligodendroglioma	-	-	-	-	-	-	-	1	-	-	-	-
Pituitary												
Pars Distalis, Benign Adenoma	2	-	-	-	1	-	1	2	1	-	-	-
Skin												
Malignant Fibrosarcoma	-	-	-	-	1	-	-	-	-	-	-	-
Mammary Gland												
Benign Fibroadenoma	-	-	1	-	-	1	-	-	-	-	-	-
Thyroid												
Parafollicular Cell, Benign Adenoma	-	-	-	-	-	-	-	-	-	1	-	-
Uterus												
Malignant Adenocarcinoma, Endometrial	-	-	-	-	-	1	-	-	-	-	-	-
Benign Polyp	-	1	-	-	2	-	-	-	-	-	-	-
Malignant Endometrial Stromal sarcoma	-	-	1	-	-	-	-	-	-	-	-	-
Vagina												
Malignant Sarcoma	1	-	-	-	-	-	-	-	-	-	-	-
Ovary												
Malignant Granulosa Cell Tumor	-	-	-	-	1	-	-	-	-	-	-	-
Pharynx												
Nasopharynx, Malignant Squamous Cell Carcinoma	-	-	-	-	-	4	-	-	-	-	-	-
Nose												
Malignant Chondrosarcoma	-	-	-	-	-	-	-	-	-	1	-	-
Malignant Squamous Cell Carcinoma	-	-	-	-	-	1	-	-	-	-	-	-
Primary Site Undetermined												
Malignant Hemangiosarcoma	-	-	1	-	-	-	-	-	-	-	-	-
Malignant Lymphoma, Lymphocytic	-	-	-	-	-	1	-	-	-	-	-	-

KEY: GROUP 1 = Control 1
GROUP 2 = Control 2
GROUP 3 = 50 mg/kg/day
GROUP 4 = 150 mg/kg/day (Males Only)
GROUP 5 = 300 mg/kg/day
GROUP 6 = 600 mg/kg/day (Females Only)
- = NOT PRESENT.

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Attachment 2
Mice: Summary of Primary Tumors

TABLE B-3. L-000900612: One-Hundred-Five-Week Oral Carcinogenicity Study in Mice. TT #05-1117
Summary Incidence of Primary Neoplasms - Through DW76

Group Number	Female 1	2	3	4	5	6	Male 1	2	3	4	5	6
NUMBER NECROPSIED	13	8	9	-	14	28	12	13	14	16	10	-
NO. EXAMINED MICROSCOPICALLY	13	7	6	-	11	27	9	12	13	14	9	-
Brain												
Malignant Meningioma	-	-	-	-	-	-	-	-	-	-	1	-
Harderian Glands												
Benign Adenoma	-	1	-	-	-	-	1	1	-	1	-	-
Skin												
Malignant Fibrosarcoma	-	-	-	-	-	-	-	-	-	-	1	-
Malignant Hemangiosarcoma	-	-	-	-	-	-	1	-	-	-	-	-
Malignant Sarcoma, Undifferentiated	-	-	-	-	-	-	-	1	-	-	-	-
Malignant Schwannoma	-	-	-	-	-	-	-	-	1	-	-	-
Mammary Gland												
Malignant Adenocarcinoma	-	1	-	-	-	-	-	-	-	-	-	-
Liver												
Malignant Hemangiosarcoma	-	1	-	-	1	-	-	-	1	-	-	-
Benign Hepatocellular adenoma	-	-	-	-	-	-	-	-	2	-	1	-
Malignant Hepatocellular carcinoma	-	-	-	-	-	-	-	-	1	2	-	-
Lung												
Malignant Adenocarcinoma	-	-	-	-	-	-	-	1	1	2	1	-
Benign Adenoma	1	-	-	-	-	1	-	1	1	3	-	-
Primary Site Undetermined												
Malignant Histiocytic Sarcoma	-	-	-	-	-	-	1	-	-	-	-	-
Malignant Leukemia, Erythroid	-	-	-	-	-	-	-	-	-	-	1	-
Malignant Leukemia, Myeloid	-	-	-	-	-	-	-	1	-	-	-	-
Malignant Lymphoma, Lymphoblastic	3	-	-	-	1	-	-	-	-	-	-	-
Malignant Lymphoma, Lymphocytic	2	1	2	-	-	-	-	1	1	-	-	-
Malignant Lymphoma, Pleomorphic	1	-	-	-	-	-	-	-	1	-	-	-

KEY: GROUP 1 = Control 1
GROUP 2 = Control 2
GROUP 3 = 50 mg/kg/day
GROUP 4 = 100 mg/kg/day (Males Only)
GROUP 5 = 250 mg/kg/day
GROUP 6 = 400 mg/kg/day (Females Only)
- = NOT PRESENT.

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